Design of a Domain Information Model for a Medication Profile to support Patient Care and Clinical Research

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Declaration

I, Julie Margaret James, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Dedication and Acknowledgements

Many, many folk have supported me as I have travelled along the road of this thesis journey, and for this, I offer my heartfelt thanks:

- ❖ My two supervisors, Dipak and Jane, for their expertise, but even more, their constant and unflagging encouragement
- ❖ My family – Hugh and the children, for their love and belief in me, and specifically their patience and giving me the space to work
- ❖ My evaluators – for your time and effort in doing the evaluation and giving your insightful comments, and especially to Colin for the initial reality checking
- ❖ The wider informatics community – thank you for inspiring me!

May the favour of the Lord our God rest upon us;
Establish the work of my hands for me, yes, establish the work of my hands

Psalm 90

In the realm of ideas everything depends on enthusiasm….in the real world all rests on perseverance

Goethe

Abstract

Use of medicines is the commonest intervention in healthcare. Information about an individual's medication use over their lifetime, managed as a coherent whole but presented appropriately for context, is central to providing good quality care.

Considerable investment continues to be made in specifying the information structures underpinning electronic health systems to provide clinicians with patient information to support care provision, yet medication errors continue to occur at unacceptable rates. At the same time, the quantity of healthcare information - which includes medication information – is increasing, and there is growing interest in "secondary uses" of this, particularly to support clinical research. Unfortunately, for both primary and secondary uses, the requirements for the data elements that are needed for medication information are poorly specified, despite a variety of major national and international initiatives and effort. The process for population of those data elements with high quality, consistent, trustworthy information that can be presented to the use cases efficiently and clearly is even more poorly specified.

By gathering requirements from processes within clinical research *alongside* the requirements from the processes of patient care, an integrated data element view of a patient's medication use over their lifetime has been described; this is termed the patient's Medication Profile. Examination of the care processes that provide the data to populate that integrated view elicits the method and rules for the realisation of the Medication Profile. These together are provided in a formally scoped fully specified information model which defines the data elements of the Medication Profile (the static model) and the processes and rules to instantiate it (the dynamic model).

The Medication Profile, populated with data based on the rules and processes of the dynamic model, is evaluated against test scenarios to assess its success to support use cases from both clinical care and clinical research. This evaluation indicated that the model provided both sufficiency of information coverage and clarity in the information presented.

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Chapter 1: Introduction

This chapter presents the background and rationale for the thesis. It provides an initial overview of the situation with regard to information - and specifically electronic health record information - about a patient's medications, about the use of this information for patient care and about the secondary uses of this information in clinical research, and from this demonstrates why this work to formally define a Medication Profile is necessary and valuable. This leads into the description of the Aims and Objectives of the thesis in Chapter 2.

Everyone uses medicines

In the provision of healthcare, the administration of one or more medicines is the commonest intervention used in the care of patients; a prescribed medicine is the most frequent treatment provided for patients in the United Kingdom's National Health Service[1]. In addition to medicines prescribed as treatment for or prophylaxis of symptoms or conditions, almost all surgical interventions use medicines in the process of managing the patient through the procedure, whether in anaesthesia, in analgesia, and/or in prophylaxis or treatment of infection. Many diagnostic investigations use medicines either as part of the investigative process, for example contrast media used in imaging investigations and/or in the care of the patient during the process, for example in sedation for endoscopic procedures. Almost every member of the population has received at least one vaccination with a medicinal product and most people have received courses of vaccines at various points in their lifetime. Patients themselves are increasingly encouraged to take some responsibility for their own health, which may include purchase and administration of medicines without requiring prescription and in some cases without reference to the advice of a healthcare professional. Almost everyone in the world has used a medicine at some point in their life, and is likely to do so again in their future.

A cradle to grave record of medication information

In addition to the increasingly widespread use of medicines, the delivery patterns for healthcare are also changing rapidly. Patients are no longer cared for by one or two primary care professionals who are familiar with all aspects of their care – including their medication. Care is now delivered in many different ways, through multi-disciplinary care teams in different care settings, through out-of-hours facilities and in situations without any direct contact such as telemedicine. Patients themselves are mobile: travelling widely for business, pleasure, and maybe even migrating considerable distances between locations with the seasons (the so called 'snowbirds'). The information about the use of medicines by an individual (the basic data of what, when, why, how much, for how long) is therefore likely to be recorded

in a variety of disparate places throughout (possibly multiple) healthcare services. This information is rarely if ever brought together into a comprehensive and cohesive set of information about the medication of an individual a patient.

This truly complete and coherent set of medication information appears to be somewhat challenging to compile and maintain. Various initiatives have been undertaken to date and are reviewed fully in a later chapter; these have concentrated on various forms of recent (i.e. recently comprehensive) history, although without defining such concepts formally and without a documented foundation in the evidence on safety or quality of care. This limited view carries risk, since it is clear it will miss a considerable amount, particularly about immunisation, the majority of which occurs in the early years of life. The ideal is to have information about the lifetime use of medicines as a true longitudinal whole. In the UK, where every baby has a vitamin K medicine administered within moments of their birth, clearly such a record must cover the 'cradle to the grave'.

Without this comprehensive and coherent medication record, it is hard for healthcare professionals to provide high quality and safe ongoing care for a patient. Without the full picture, preventable adverse drug reactions become harder to avoid[2], it is not possible to ascertain whether drug interactions are likely, whether treatment side effect profiles may be overlapping, or to judge the success or otherwise of a previous exposure to a medicine or class of medicines.

The risks of continuing without this comprehensive and coherent medication record are so great it is difficult to comprehend why the situation continues. One concerning estimate is that that around 150 deaths occurred as a result of medication errors in England and Wales in the year of 2001[3], another is that errors in prescribing have been estimated to cost £400million in the UK annually; this is equivalent to the cost of running four district general hospitals[4]. The FDA state that medication errors cause at least one death every day and injure approximately 1.3million people annually in the United States[5], at an estimated cost of at least $3.5billion[6]. Every year nearly 10,000 people are reported to have experienced serious adverse reactions to drugs in the NHS[7]. Yet the behaviour of the medicines themselves is largely predictable, so many adverse reactions could be avoided or minimised by healthcare professionals having access to good information about both the medicine and the context of its use in the individual patient. This context includes the patient's medication history, and particularly, the medicines they are currently using and the justification for those[8]. However unfortunately, it has been estimated that medications are accurately recorded for as few as 5.3% of patients[9].

Requirements from patient care and electronic health records

There has been and continues to be much local, national and international emphasis on designing, building, populating and maintaining electronic health records (EHRs) for patients, to improve the quality of the care that they receive.

National initiatives include:

- the NHS in England, through the National Programme for Information Technology (NPfIT) and its successors, Connecting for Health (CfH)[10] and the Health and Social Care Information Centre[11]

- in the USA, through Healthcare Information Technology Standards Panel (HITSP)[12] and the 'Meaningful Use' initiative for electronic health records which flows from the American Reinvestment & Recovery Act (ARRA)[13]

- in Australia, through the National eHealth Transition Authority (NeHTA)[14]

- in the Netherlands, through NICTIZ (Nationaal ICT Instituut in de Zorg)[15]

- in Singapore, through the Ministry of Health and Holdings (MOHH[16]) and

- in European Commission initiatives such as epSOS (European Patients Smart Open Services)[17]

All of these initiatives have within them a focus on the prescribing and/or recording of medication information, highlighting the central importance of medication information in the development of eHealth services and acknowledging its centrality to the delivery of safe, high quality and cost-efficient patient care.

Within these initiatives, the concepts of 'medication history', 'past medication' and 'current medication' are often used but rarely if ever defined, either informally or formally as information concepts. For example, the Integrated Care Records Service Output-Based Specification from NHS England[18] has a concept of a 'Patient Medication Profile' to which information may be added by the patient, the patient's practitioner, or through uploads from pharmacy fulfilment files (dispensing records) [311.17.1]. This profile may be edited (additions, changes and deletions) and reviewed by authorised users [311.17.7-9]. From this profile, an application is required to create a 'dynamic list of medications (current and past) for the patient, which may be filtered, sorted and grouped by the user' [311.17.6]. So although this specification has a clear requirement for the concepts of 'current and past medication

information' to be available for a user, there is no definition of exactly what these concepts are, or where or how to find or generate them.

The ASTM Standard Specification for Continuity of Care Record (CCR)[19] is a little better in its descriptions. It is one of the most detailed specifications of its type, describing itself as a patient health summary standard. It has been developed by a significant range of stakeholders in the domain, based in the US. It claims to be a 'core data set of the most relevant administrative, demographic, and clinical information facts about a patient's healthcare, covering one or more healthcare encounters' [page 8]. This aims to provide the means by which one healthcare practitioner, system, or setting can aggregate together all of the pertinent data about a patient and share it with another practitioner, system, or setting, to support the ongoing care of that patient. Its data set includes a summary of the patient's health status (for example, problems, medications, and allergies), some information about their insurance plan(s), and any care plan(s). It contains a significant amount of detail about medications, most particularly in its section 5.1.2.9, which deals with a patient's current medications and pertinent medication history. This section states that: 'at a minimum, the currently active medications should be listed, with an entire medication history as an option, particularly when the CCR is used for comprehensive data export'; however, no definition or even description is given for what 'currently active medications' actually consist of.

The terms 'current medication' and 'past medication history' have for many years been regularly used in the common parlance of clinical practice, for example in admission and referral correspondence, where 'current medication' is listed, along with 'previous medication (history)' in order to provide some relevant information about the patient's current and possibly previous treatments. These two concepts, the latter being described as 'relevant previous medications' are the two sub-headings in the Medication record section of the Royal College of Physicians approved Hospital admission record: headings and definitions[20]. However, in the formal literature search supporting this thesis, it was confirmed that these concepts have had very little formal investigation or definition. Clearly, pragmatic definitions do exist in order that various aspects of clinical applications can function at all, in particular for medication decision support. For example, one national general practice computer system defines current medication as 'all currently authorised repeat prescriptions and any acute prescriptions generated in the last six months'[21]. In an era of evidence based practice and with health informatics being a formal discipline both academically and professionally, a lack of formal definition for such critical concepts should not continue.

In addition, either as part of the development and implementation of EHR applications or as standalone systems, the use of information technology to support the medication process (prescribing, dispensing and administration) in all sectors of care is growing, with the aim of improving the quality (safety, efficacy and value for money) of medicines use[1]. The increasing use of decision support is very welcome. However, without access to the relevant supporting clinical information about the patient, and in particular the comprehensive and cohesive information about the medication the patient is already using, has used in the past, and which they may have access to in the foreseeable future, the decision support that is integral to support a safer medication process[22] cannot function to its full potential[23]. The availability of that comprehensive and cohesive information in a clear, robust, standardised and useable format is therefore critical to this quality improvement for medication use in patient care, yet the definition of what this actually consists of remains unclear and without that clarity it cannot be provided.

Requirements for secondary uses – clinical research

In recent years, there has been a growing interest in exploiting the rich source of data that EHR systems could provide for so-called secondary uses: clinical research, public health, epidemiology and health service management; if and when suitable privacy and ethical considerations are fully respected. This naturally includes medication information, as well as information about diagnoses, procedures and investigations. This interest is currently expressing itself in a large number of projects that are developing models and policies to effectively utilise this longitudinal data from cohorts of patients. The following are examples of these projects; each has a multi-million dollar/euro budget and multi-year time-span.

- EHR4CR (focus on using EHRs to support four scenarios that are current bottlenecks in clinical research)[24]

- TRANSFoRm (focus on translating knowledge from research into clinical practice, and data from clinical practice into formal studies – particularly in primary care)[25]

- OMOP (focus on using EHR data to detect and monitor safety risks for existing medicinal products)[26]

- EURECA (focus on re-use of EHR data in clinical trials)[27]

- SALUS (focus on using EHR in pharmacovigilance)[28]

The proliferation of these projects intimate that there are substantial challenges to be overcome in order to extract the value from this data for clinical research, public health or service management most effectively. These challenges include the incompatibility of the standards used in healthcare and in research, particularly in terms of their purpose and therefore their models, and the patchy implementation of these standards. It is clear that there urgently needs to be a formally documented evidence-based set of information requirements, and particularly the medication data elements, that should be available to clinical research from EHRs.

Clinical research, as opposed to the broader term of medical research, is defined as 'studies for the formal assessment of the utility, impact, or other pharmacological, physiological, or psychological effects of a medicinal product, procedure, process, or device on a human, plus all associated regulatory artefacts required for or derived from this effort, including data specifically associated with post-marketing adverse event reporting'. This definition is derived from the definition of the domain of the BRIDG model[29] and used in particular because it references the artefacts of clinical research, such as protocols and the eligibility criteria they contain, and it explicitly references post-marketing adverse event reporting, which is a large part of the process of pharmacovigilance. Within clinical research, currently used standards focus on the syntactic structuring or formatting of study data in its collection (CDASH[30]), presentation for submission (SDTM[31]) and presentation for analysis (ADaM[32]). These standards are not semantic standards whose aim would be to ensure the preservation of meaning of the data across time and space such that it can be exploited to support multiple use cases.

Clinical research is more than the management of study data. There are processes that occur before a study can be conducted that are concerned with developing the study protocol and recruiting subjects into studies, and processes that must continue after formal studies have concluded, to continue to monitor the safety of the medication. There are several specific processes where information about the administration of medicinal products to individual patients or to cohorts of patients is of value. These include in the authoring of a Clinical Development Plan (CDP), in the patient recruitment process (both for protocol feasibility testing and in the actual recruitment of individual sites and subjects), in the gathering of clinical information for a subject throughout a study (the so-called clinical report form (CRF) process), and in safety assessment – the pharmacovigilance process. Two of these processes (the study feasibility/patient recruitment process and the pharmacovigilance process) are examined in detail in this thesis to ascertain the requirements they place on the information held in a patient's Medication Profile. These two processes have been selected as there is evidence that there are issues within these that better

medication information would help to solve, and very pragmatically because the raw material for the examination is available, either through personal contact (from the EHR4CR project[24], see below) or in the public domain. Examination of other processes would be equally valuable, but currently out of scope for this thesis due to resources both of time and availability of materials: formal CDPs are relatively new constructs[33] and as such a representative set is not available for study; CRFs are proprietary both to each study and to each organisation that conducts the study. However, relating to this latter, a specification for data elements used in the submission of raw clinical trial data, the Study Data Tabulation Model (SDTM)[31], does exist and its content has been included in the pharmacovigilance work, as explained in that part.

Various strategies are being adopted in order to minimise study delays and ever-increasing costs due to problems with patient recruitment, and there are various development projects underway including several of those mentioned above that are investigating the use of EHR data in clinical research, and particularly in protocol feasibility studies and patient recruitment support. These developments involve the use of clinical data warehouses or registries against which queries derived from study eligibility criteria are run. As presented in Chapter 5 (1), a review of eligibility criteria showed that a significant proportion include medication information and therefore the importance of this type of data being available to query.

At the opposite end of the clinical research spectrum is pharmacovigilance, the ongoing process to evaluation the safety of medicines. Pharmacovigilance is a multi-stranded process and the various strands are reflected in the World Health Organisation's definition of pharmacovigilance as: 'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'[34] [page 1]. Detection in this context includes the gathering of adverse event information, including events that occur within clinical trials (which may be in the pre-or post-marketing authorisation periods) or by spontaneous reporting by patients, carers or clinicians in the post marketing authorisation period, or by active surveillance of health records. The assessment of information gathered to gain the requisite understanding of adverse drug events is complex; finding that a medicinal product is responsible for a particular adverse event has been likened to finding a needle in a haystack[35]. The process usually involves significant analysis of vast amounts of data, both from the adverse events themselves and comparison with one or more background datasets which are sometimes taken directly from general healthcare and sometimes from a larger adverse event database, as adverse events must be differentiated from normal clinical events. Having gained an understanding of a medication adverse event, this

understanding should be translated into prevention of (further) adverse events by a set of actions, which may include altering recommended dosage regimens, adding contra-indications, special precautions or warnings for use or, in severe cases, by withdrawing the medicine from use.

The concept of pharmacovigilance and the management of medication adverse events has recently been broadened to include adverse events that are not related to the pharmacology or pharmaceutics of the medicinal product but which are caused by external factors related to the medicinal product, such as issues with the packaging or labelling of the product. An example of this is the case where an adverse event occurs due to incorrect dose quantity being administered; on analysis it might be found that the description of the strength of the medicine on the packaging lacks the necessary clarity[36].

Adverse drug reactions have an enormous economic cost, in terms of the direct costs to the healthcare system of treating the adverse events, in the loss of revenues if/when a medicinal product must be prematurely withdrawn from the market and in terms of any litigation arising from inadequate safety information for the sponsoring pharmaceutical company. One large UK-based observational study from 2004 found an adverse drug reaction prevalence of 6.5% with a projected cost to the health services of managing these reactions being £466m[37]. This same study points out that much of the research in this area of setting a rate for adverse drug events is over 20 years' old, and expresses the authors' disappointment that their findings show that the prevalence has not decreased with time and understanding. There have been many other studies and systematic reviews of studies into the prevalence of adverse drug reactions; one of the most recent of these reviews found an overall average of approximately 5.3% of hospital admissions were associated with adverse drug reactions, with lower rates for children and higher rates for elderly patients[38]. In terms of lost revenues and litigation costs, when rofecoxib (Vioxx, Merck) was withdrawn in 2004, its loss was expected to reduce the company's profit by around 20%[39] and one observer estimated legal costs to be between $12 billion and $38 billion[40]. When Bayer withdrew celecoxin (Baycol, Lipobay), one report suggested losses of between €600m and €650m[41]. There are also the less tangible but none the less real costs of loss of confidence in the company and in the sector that follow such a withdrawal. Therefore managing the safety of medicinal products through pharmacovigilance is extremely important, both for the health of individuals and populations, and for the economic health of the pharmaceutical industry.

The backbone of pharmacovigilance remains the collection of data about adverse events as they are suspected of occurring. Various forms for clinicians and the

general public to use to report suspected adverse events have been authored by the agencies responsible to governments for the safety of medicinal products, and these can be taken as providing a set of requirements for the actual data elements deemed to be of use in pharmacovigilance. Currently, this data must be gathered together and provided to the form by the reporter, but in the future, if the enabling technology and security/permissions were in place, it could be obtained directly by interrogation of the relevant electronic health record, particularly for the medication information. It is imperative therefore, that the medication information that is available from EHRs and their medication records supports the data elements that pharmacovigilance requires, ensuring the ongoing safe use of medicines.

A high quality comprehensive and cohesive Medication Profile

It is clear that high quality comprehensive and cohesive medication information is a vital component of electronic health records, for use in the provision of care to individuals and also for secondary use of that information in clinical research to promote better and safer medication development for the future. It is also clear that there is no evidence based formal definition of what that high quality comprehensive and cohesive medication information should explicitly be, what it should contain and how it should be maintained. Humans have an innate ability to perceive and understand within their framework of culture and experience that computers cannot have. However, this ability is itself shaped by our own individual representation or mental map of our world (called 'schema' in psychology) which varies due to both internal and external factors. So to use of concepts such as 'current medication' or 'previous medication (history)' that are essentially formally undefined and therefore open to interpretation, even amongst humans with similar professional training, is of concern. Of yet greater concern is that computers cannot 'intuit, they cannot make assumptions and act on these. Even the most sophisticated reasoners[a] running on ontologic structures can only provide logical extensions to their existing knowledge, which must be represented in quite sophisticated patterns in order to for the reasoner to perform. The healthcare environment, both human and machine, cannot continue to make guesses as to what is or what is not within a patient's medication record, and therefore how that content should be managed. It must be systematically reviewed from many perspectives in order to provide as comprehensive a picture as possible, which is then formally defined and described.

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[a] A "reasoner" is a piece of software that is able to infer logical consequences from a set of asserted facts or axioms, as presented to it by an ontology

This thesis will demonstrate that, by investigating and gathering requirements from the process of clinical research *alongside* the requirements from the process of patient care and blending these requirements together, an integrated view of how a patient's medication should be recorded in healthcare systems, from beginning to end, can be produced. This formal definition of the gold standard comprehensive cradle to grave Medication Profile, if and when it would be implemented within systems, provides the solid foundation from which to conduct the safe and high quality performance of the processes of patient care and clinical research. Clinicians and the decision support systems that assist them would have the full set of information they need to optimally manage the medication process for each patient, and in particular to prevent those errors that continue to occur in patient care due to the lack of this information. Clinical research would have the full set of information it needs to optimally test protocols and select patients for study recruitment, and to monitor the ongoing safety profile of medications in use through pharmacovigilance. Having such a gold standard Medication Profile would also avoid the costly re-specification that continues to be seen in the national and international e-health initiatives and allow resources to be channelled to improving the actual implementation, so that the benefits of this high quality comprehensive and cohesive Medication Profile can be realised.

Chapter 2: Aims and Objectives

Overall Aim

The aim of the thesis is to develop a formal specification for a patient's comprehensive and cohesive Medication Profile that, when implemented, can meet the evidence based requirements placed upon it to support high quality care for that patient, whilst also providing information to support valuable secondary use cases in clinical research for the wider community.

Objectives

In order to achieve this aim, the following objectives were set:

- To specify the information (data elements) needed for the Medication Profile to function effectively to support the use cases, alongside the evidence for their validity, and processes for the population of those data elements

  o for the provision of safe high quality care to the individual patient

    - through record keeping

    - through the various processes that are undertaken in medication use, and the decision support that assists these processes

  o for secondary uses in clinical research

    - for protocol feasibility testing and patient recruitment

    - for pharmacovigilance

- To investigate, define and validate the scope or boundary of the Medication Profile

- To collate the gathered requirements into a cohesive set that transcends the limitations of individual healthcare cultures and practices

- To formally define the gathered data element requirements and their management through space and time using informatics best practice, to produce an information model with both static and dynamic and rules-based components, and therefore to give a complete formal domain information model of the Medication Profile

- o Because of the fundamental nature of the medication concepts being examined, this definitional work should provide value even in contexts where there are not electronic medication information systems to implement them

- To undertake an evaluation of the formal domain information model defined above by developing some test scenarios which reflect the instantiation of various aspects of the model (using the dynamic processes to populate the static elements) to be submitted to a range of reviewers for evaluation and to provide a report of the consolidated response to that evaluation

In addition to the objectives outlined above, this work aims to meld together the academic discipline of a thesis, with literature review and investigation and analysis, with the practical and formal discipline of the informatics/systems development process. This includes using informatics methods such as static and dynamic information models described using the Unified Modelling Language (UML2) standard[42] from the Object Management Group, and a formal description of rules-based information management processes, in such a way as to produce something that is truly evidence-based but practically implementable in the development of the healthcare systems of tomorrow.

The objectives focus on gathering requirements from two specific areas, but in doing so this by definition excludes others. Two areas that, like clinical research, are secondary users of medication information and from which requirements could have been gathered if time were unlimited are pharmacoepidemiology and pharmacoeconomics. These disciplines rely heavily on pooled data from populations and in that sense will have similar requirements to those from protocol feasibility testing in clinical research.

Thesis Structure

- **Introduction**: setting the context for the research

- **Aims, Objectives, Structure**

- **Literature Review**: formally investigating, documenting and discussing what is already known in the domain for the definition and maintenance of a Medication Profile

- **General Methodology**: description of the overarching method of research. Note that supplementary method details and supplementary relevant literature

are provided within each of the Requirement chapters, so that the context of each requirements area is coherently presented

- **Requirements from Patient Care**: investigation, description and discussion of the requirements for Medication Profile information for the provision of high quality patient care:

  - Patient Care Record specifications

  - Safe Medication Processes and Decision Support

- **Requirements from Clinical Research**: investigation, description and discussion of the requirements for Medication Profile information from the clinical research process:

  - Patient Recruitment and Protocol Feasibility Testing

  - Pharmacovigilance

- **Consolidated Results Summary**: Presentation of the consolidated results of the investigations, which form the formal requirements for the Medication Profile model

- **Scoping the Boundary of the Medication Profile**: investigation, description and discussion of the various types of products whose use the Medication Profile should encompass

- **The Medication Profile Model**: presentation of the formal domain information model (static and dynamic – data elements and business processes) that form, populate and maintain the Medication Profile to meet the requirements from patient care and clinical research

- **Evaluation of the Medication Profile Model**: investigation, description and themed discussion of an evaluation of the Medication Profile model by a range of users, based on a set of test scenarios

- **Overall Discussion of the Research**: a review and critique of the findings of the research in terms of the fulfilment or otherwise of the aims and objectives, and including Recommendations for future work and further research

Introduction and Problem Statement

Aims and Objectives

General Methodology

Literature Review

Requirements Chapters

Patient Recruitment and Feasibility

Pharmaco-vigilance

Patient Record and Communications Specifications

Safe Medication Processes and Decision Support

Consolidated Requirements

Definition of Scope of the Medication Profile

THE MEDICATION PROFILE DOMAIN ANALYSIS MODEL

Static model

Dynamic model

Medication Profile Model Evaluation

Overall Discussion and Recommendations

Figure 1: Diagrammatic Representation of Thesis Structure

General Methodology

The literature review confirmed that although the concept of a 'Medication Profile' is used widely, there is little if any formal definition of this is and what this should contain. This deficit exists in terms of the types of products whose usage information should be included, in the data elements describing the use of those products by the patient, and in how that data element information should be managed over time using the medication process and the activities that it contains. This latter is particularly given that use of medications is often a long-term activity. The objectives below therefore aim to address this deficit.

Objective 1: Investigate and document the requirements

The first objective of the thesis was to investigate and document the specific information required for the Medication Profile to function effectively to support the use cases, alongside the evidence for their validity. Requirements gathering is a formal process which is part of business analysis and which seeks to document what is needed for a system to function in a safe and useful way. There are a variety of requirements gathering and requirements validation techniques that can be employed, including workshops, prototyping (user centred design), questionnaires, process observation etc. However, all of these produce opinion-based or context-based requirements, not least because their primary aim is usually to produce a system that the users accept and will want to use. But, when designing a system whose primary function is to store and manage data and to then provide that data in meaningful display to users or to another system in response to specific queries, opinion as to what that data should be or how it should be managed is not enough. One of the best known hierarchies of evidence is that produced, and most recently revised in 2009, by the Centre for Evidence-Based Medicine[43] is the 'Levels of Evidence'; this states that 'expert opinion without critical appraisal' is the lowest (of 5) levels of evidence. Therefore, a more robust requirements gathering exercise than the usual user/opinion focussed business analysis must be undertaken. The search for and gathering of the requirements of a Medication Profile to serve both patient care and clinical research was conducted by:

1. Examining a set of specifications from national and international health record and summary care record development projects and programmes for their requirements for medication related information. By examining a set of specifications and amalgamating the results, the vagaries of cultural practice and individual expert opinion are reduced, giving a set of generic requirements to support patient care

2. Examining the various medication focused processes that occur in the provision of healthcare to patients, and the medication information requirements for systems that provide decision support to these processes to ensure their quality and safety. Unfortunately, much of the detailed information for such processes is commercially confidential; however the author is able to leverage many years' experience of working in this area, both nationally and internationally, to document these requirements

3. Examining a set of eligibility criteria from a range of protocols for recently undertaken clinical studies for their requirements for medication related information. By examining a set of criteria and amalgamating their results, an overall view of the requirements for the types and patterns of medication information is produced that would be applicable for all clinical trials, and which, if the information in patients' Medication Profiles were available to match those patterns, would be specifically useful to support patient recruitment and protocol feasibility testing

4. Examining a set of pharmacovigilance reporting forms from a number of national medicines regulatory agencies for their requirements for medication related information to support suspected adverse reaction reports. Again by examining a set of forms, the vagaries of different cultures are reduced to give a generic set of requirements which need to be captured, and therefore which should be available from individual patient's Medication Profiles

Objective 2: Define the scope of the Medication Profile

The second objective of the thesis was to investigate and document the scope of the Medication Profile, to set a boundary around the types of things that a Medication Profile system should contain. Although medicinal products are tightly defined based on regulation, there are types of products that could be considered as on the margins of this; for example, the few types of products that in the past have been categorised as medicinal products but which now are managed as medical devices. Having clarity with regard to whether information about the use of the types of borderline products is included in the Medication Profile is important in order to fulfil the overall aim of producing a robust information model of the domain. This product boundary is defined by:

- examining each of the different types of medicinal products and each of the borderline product types

- documenting these, with supporting regulatory definitions from international standards where available

- documenting the roles such products play in the medication process and how and where they play them

From this, each product type can be ruled within the scope of the domain covered by the Medication Profile, or out of that scope.

Objective 3: Collate the requirements superset

Having undertaken the requirements gathering from the individual areas under study, these are collated together to produce a cohesive superset of requirements that transcends the limitations of individual healthcare cultures and practices and transcends the individual areas of practice. This superset is then subjected to a weighting exercise to give a relative sense of overall priority and importance of the individual requirements within the overall. This provides the summarised requirements to go forward into the modelling process.

Objective 4: Develop a Domain Information Model for the Medication Profile

The objective of the modelling process is to formally define the data elements from the requirements gathering process described above and to define a management process for these to robustly maintain their value to the use cases through space and time. This was undertaken using informatics best practice, to produce a domain information model for the Medication Profile system consisting of

- static models – using classes, attributes and relationships to describe the data elements of the domain

- dynamic models – describing the business processes that occur in the domain and the different patterns of how these processes can relate together

- rules-based components – describing the logic of how to populate the static models using information as it is generated by the different business processes that occur

Objective 5: Evaluate the Domain Information Model using test cases

The final objective was to evaluate the outworking of the formal domain information model by applying it to produce some test scenarios. This was

undertaken by creating storyboards for some imaginary individual patients and clinicians who are involved in a set of scenarios that reflect the original use cases of providing safe patient care using medication and in supporting clinical research and pharmacovigilance. These evaluation scenarios contain exemplar displays of relevant sections of the patient's Medication Profile, populated with data from the processes described in the storyboards, which reflect the data elements and processes in the Model, and with the data managed using the rules described in the Model. A set of questions accompanied each scenario, inviting reviewers to evaluate whether the information presented in the sections of Medication Profile was accurate given the storyboard and acceptable to fulfil the use case as described in the scenario. The set of scenarios were then distributed, with a covering letter, to a range of reviewers from those healthcare professions most intimately involved with the medication process (doctors, nurses and pharmacists) working in both patient care and clinical research, and to a range of health informatics professionals with medication management experience, who may or may not have originally been healthcare professionals. An opportunity to provide general comments on the scenarios was also provided. The responses and comments from the evaluations were collated together and the general themes identified. These were then examined for their validation or otherwise of the model of the Medication Profile.

Biographic details of the author

In addition to the writing of this thesis, the author has extensive experience in the field of health informatics and particularly in medication information. This experience, which is particularly relevant to the information present in the second part of chapter 5, where little information is present in the public domain, includes:

- 10 years working in the Knowledgebase Services department of First DataBank[44], a leading provider of medicines decision support systems (data and algorithms), culminating in leading the department
- 15 years working as a consultant in informatics including
- a 5 year project with the British National Formulary[45] to transform their paper publication into a knowledgebase for active decision support
- a 3 year (ongoing) project with the Irish Pharmacy Union[46], working as a consultant for the redevelopment of the Product File to support Irish healthcare processes, and redevelopment of the decision support provided with the Product File
- a 4 year project to develop the international standard for identification of medicinal products for the national and international regulatory agencies

These roles included responsibility for the following:

- The editorial policies that governed the data collection and/or data management
- The structures within the information model, terminology model or knowledgebase that hold the data to allow it to be used most effectively in processes and algorithms
- The logic that governs the processing and/or algorithms that use the data and provide further information
- The implementation guidance for deployment of the systems within clinical care and/or clinical research
- The testing of implementations to ensure their correct functioning

In addition, the author has spent 20 years working in international standards bodies to develop standards and specifications for medicines and medicines related processes. These bodies are:

- Health Level 7 (HL7)[47],
- ISO TC 215[48] (specifically WG6 Pharmacy and Medicines and WG2 Systems and Device Interoperability)
- IHE – Integrating the Healthcare Enterprise – Pharmacy domain[49]

In working to develop the standards and specifications in the organisations above, various skills and expertise are needed, including understanding of how the different healthcare cultures (legal, ethical, regulatory and practical aspects) of different nations affect the

- medication processes that need to be supported
- business architectures that the processes and systems need to work within
- data structures that must be populated and shared
- communications that need to flow

Having gained that understanding, standards and specifications are developed that define and describe the same things in the same way whilst respecting and supporting the national and regional differences as appropriate.

Chapter 3: Literature Review

Introduction and initial investigation

As a precursor and in preparation to undertaking a comprehensive literature review, an initial investigation into the use and understanding of the term 'medication profile' as used in the literature was undertaken. This initial keyword search found that the term was used extensively, often in very clinically focussed studies of a disease area, to generically describe 'information about a patient's medication use'[50,51,52,53]. Rarely was any formal definition of what the term actually meant given either explicitly or implicitly, confirming the need for the research and informing the full search strategy. The detail of this initial investigation is described in Appendix 1.

Methodology and search strategy

Scope of the search

The search strategy used the two most appropriate citation databases for this domain: MEDLINE[54] and EMBASE[55] (the latter having a slant towards drug therapy, research and pharmacovigilance)[56], using the OVID tooling. EMBASE covers approximately 2700 journals that are not within scope of MEDLINE, but are likely to have information about a 'Medication Profile', as can be seen from the significant differences in search returns for the two databases given below.

Specialist citation databases such as PsychINFO[57], concentrating on psychology and the behavioural and social sciences, and CINAHL[58] (Cumulative Index to Nursing and Allied Health Literature) were not used. These have a precise focus on their particular areas of practice and therefore it is not expected that they will cover medication summary information topics, and it is unlikely that data element definition and requirements for management of data elements for medication would be within their remit. Whilst it is possible that there might be description of medication information requirements that are specific to these specialist areas that would not be present in the more general clinical literature, the probability of this based on the evidence from the general searches was deemed to be too small for the effort that would have been required and the time resource available. Regional citation databases such as IndMED[59] and LILACS[60] were not searched due to resource/access constraint and English language focus for this work.

The searches, which were revised and updated in January 2016, covered all In-Process and Other Non-Indexed Citations from 1946 to January 2016, with no other search filters applied.

Search terms

A thesaurus of search terms was developed, focused on the terms used to describe medication information for a patient as found to be associated with describing a 'medication profile' in the initial literature review and using the search term matching in the search databases.

Keyword search terms

This thesis uses the term 'medication' consistently and exclusively, because it closely links to the formally defined regulatory concept of 'medicinal product' with its therapeutic intent. It avoids the negative connotations that can be associated with the term 'drug' (as in misuse of substances for so called recreational purposes). However, the keyword search used both 'medication' and 'drug'; this is because unfortunately there is no single term applied consistently in the literature, as the search results confirm. When combined with the qualifiers of 'past' and 'current', the terms 'drug' and 'medication' appear to have been used in indexing synonymously as the number of hits for each was identical, as was an 'and' search for the combination of these terms.

Table 1: Keyword search terms

Medication profile	Drug profile
Medication record	Drug record
Medication history	Drug history
Medication histories	Drug histories
Current medication	Current drugs
Past medication	Past drugs

Controlled Vocabulary Tree search terms - MEDLINE

Although nominating the most appropriate index terms should maximise the likelihood of retrieving relevant publications, the accuracy of the search, for example in MEDLINE, critically depends upon how those terms are semantically indexed and organised within the database itself. MEDLINE uses the Medical Subject Heading (MeSH)[61] system to produce its controlled vocabulary for assisted searching. The terms described above were entered and the maps offered by the search engine were evaluated. A significant number of the search maps offered were not well related to or just too general for the topic (e.g. the keyword map for 'medication profile' includes the controlled terms of 'aged', 'middle aged' and 'computers'). Others were condition specific and therefore unhelpful (e.g. the keyword map for 'current medication' gives the controlled terms of 'aged', 'middle aged', 'adult', 'asthma', 'migraine disorders', 'endocarditis bacterial', 'heart defects, congenital', 'antipsychotic agents', 'angiotensin-converting enzyme inhibitors' and

'hypoglycaemic agents'). The selection of MeSH terms for searching was therefore informed by those mapped terms that appeared helpful (such as 'Drug Prescription', mapped to 'medication profile') and was augmented by studying the MeSH hierarchy and scope statements directly to find any additional concepts of relevance. For example, although 'Drug Prescription' was a mapped search term as discussed above, its scope statement: 'The use of DRUGS to treat a DISEASE or its symptoms. One example is the use of ANTINEOPLASTIC AGENTS to treat CANCER' is too broad to be useful to the objectives of the literature search focussing on the perception and definition of a Medication Profile. Similarly, although the term 'Medical Records Systems, Computerized' and its accompanying scope statement of 'Computer-based systems for input, storage, display, retrieval, and printing of information contained in a patient's medical record' is in some senses appropriate, the term is too broad to be useful; the focus needs to be specifically on the 'medication' part of a patient's overall health record. Unfortunately, the scope for the narrower term 'Clinical Pharmacy Information Systems' covers 'Information systems, usually computer-assisted, designed to store, manipulate, and retrieve information for planning, organizing, directing, and controlling **administrative activities** associated with the provision and utilization of clinical pharmacy services' and clearly focuses on organisational activities for service provision and use rather than the clinical information needed to provide those services, which would include the patient's Medication Profile.

The term 'Medicine' was also investigated in the MeSH controlled vocabulary. The scope statement for the term is 'The art and science of studying, performing research on, preventing, diagnosing, and treating disease, as well as the maintenance of health'. This statement includes a note, which adds 'medicine only as a field, profession or discipline: differentiate from DELIVERY OF HEALTH CARE where the patient is emphasized; very general; it is divided broadly into experimental medicine (= BIOMEDICAL RESEARCH) & CLINICAL MEDICINE, a specialty devoted to the diagnosis & management of human patients; / legislation & jurisprudence = LEGISLATION, MEDICAL or JURISPRUDENCE or FORENSIC MEDICINE; LEGAL MEDICINE see FORENSIC MEDICINE is also available'. The children of the term, of which there are many, realise that scope statement in that they are all types of specialities within the discipline of medicinal practice such as 'Disaster Medicine', 'Preventative Medicine', 'Internal Medicine', 'Military Medicine', 'Sports Medicine' 'Reproductive Medicine', 'Tropical Medicine' and 'Traditional Medicine'. There is no sense that the controlled term has any association with 'medicine' as a product used for therapeutic effect. There were, however, two intriguing terms as children of the parent term 'Medicine' that merited some further investigation: 'Herbal Medicine' and 'Medicine chest'. The scope statement for the former is 'The study of medicines

derived from botanical sources' and as such relates to the disciplines of pharmacology and pharmacognosy rather than health informatics. The scope statement for the latter is 'Boxes in which physicians kept their drugs and other medications, medical instruments and supplies, manuals, etc. As a carrying case or convenient storage receptacle, or a kind of portable pharmacy, the medicine chest was indispensable to the itinerant physician. The chest was usually larger and sturdier than a doctor's kit or bag. NOTE: do not confuse with the modern medicine cabinet: may be used for doctor's bags'; so it is clear that this child search term is describing a storage entity for medicinal products and instruments/supplies rather than a health informatics topic concerned with recording information about the administration of medicinal products to patients, although quite how that manages to be a child concept (i.e. a specialisation) of the parent 'Medicine' concept is unclear.

The terms that after definitional review were selected for the controlled vocabulary search are shown diagrammatically in their relative position in the MeSH hierarchy, in two separate drawings (Figures 2 and 3), one from each of the two top level concepts that are the parents for all the search terms; the terms selected for use in the search are shown in **bold type**. Terms that were considered but not included as search terms are shown in *italics*. The table that follows provides the formal MeSH definitions of the terms selected for the search term thesaurus.

Analytical, Diagnostic and Therapeutic Techniques and Equipment

Therapeutics

Drug Therapy

    Drug Prescriptions

    Inappropriate Prescribing

    Medication Errors

        Medication Reconciliation

        Near Miss, Healthcare

    Polypharmacy

        Deprescription

    Self Medication

Investigative Techniques

    Epidemiologic Methods

        Data Collection

            Records as Topic

                Medical Records

                    Medical Records Systems, Computerized

                        Electronic Health Records

Diagnosis

    Diagnostic Techniques and Procedures

        Medical History Taking

Figure 2: MeSH Term Tree from the parent concept Analytical, Diagnostic and Therapeutic Techniques and Equipment
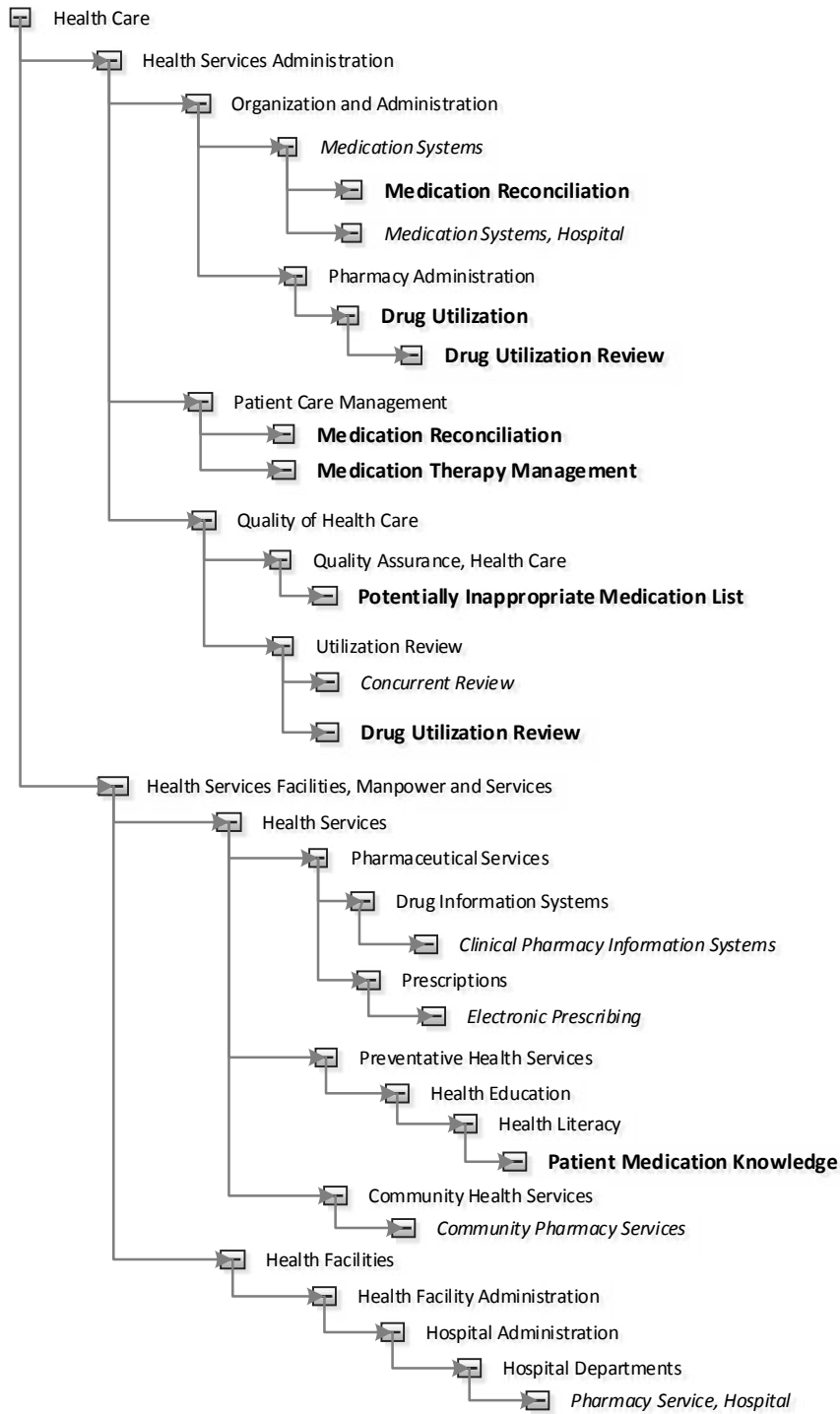
Figure 3: MeSH Term Tree from the parent concept Healthcare

Table 2: MeSH controlled vocabulary search terms and their scope statements

MeSH Term	MeSH Scope Statement
Inappropriate Prescribing	The practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist
Medication Errors	Errors in prescribing, dispensing, or administering medication with the result that the patient fails to receive the correct drug or the indicated proper drug dosage
Medication Reconciliation	The formal process of obtaining **a complete and accurate list** of each patient's current home medications including name, dosage, frequency, and route of administration, and comparing admission, transfer, and/or discharge medication orders to that list. The reconciliation is done to avoid medication errors
Deprescription	Directions written to discontinue use of PRESCRIPTION DRUGS in order to reduce unnecessary and/or excessive medications (see POLYPHARMACY), DRUG SIDE EFFECTS and ADVERSE DRUG REACTION
Drug Utilization	The utilization of drugs as reported in individual hospital studies, FDA studies, marketing, or consumption, etc. This includes drug stockpiling, and **patient drug profiles**

Table 2 (cont.): MeSH controlled vocabulary search terms and their scope statements

MeSH Term	MeSH Scope Statement
Drug Utilization Review	Formal programs for assessing drug prescription against some standard. Drug utilization review may consider clinical appropriateness, cost effectiveness, and, in some cases, outcomes. Review is usually retrospective, but some analysis may be done before drugs are dispensed (as in computer systems which advise physicians when prescriptions are entered). Drug utilization review is mandated for Medicaid programs beginning in 1993
Medication Therapy Management	Assistance in managing and monitoring drug therapy for patients receiving treatment for cancer or chronic conditions such as asthma and diabetes, consulting with patients and their families on the proper use of medication; conducting wellness and disease prevention programs to improve public health; overseeing medication use in a variety of settings
Potentially Inappropriate Medication List	A list, criteria, or screening tool designed to improve PATIENT SAFETY by determining an individual's exposure to potentially inappropriate drugs. They are designed to prevent MEDICATION ERRORS by INAPPROPRIATE PRESCRIBING. Analysis for a list includes factors such as DOSE-RESPONSE RELATIONSHIP, DRUG; DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS; AGE FACTORS; GENDER; and existing medical conditions
Patient Medication Knowledge	Patient health knowledge related to medications including what is being used and why as well as instructions and precautions

Controlled Vocabulary Tree search terms - EMBASE

EMBASE has its own controlled vocabulary tree (Emtree) for assisted searching that is different from MEDLINE. As with MEDLINE, the set of search terms that match to the keyword search terms include those that are not well related to or just too general for the topic (e.g. in EMBASE the keyword map for 'medication profile' includes the controlled terms of 'patient', 'pharmacy' and 'nilotinib' (a specific immunomodulatory agent)). Other matched search terms were condition specific and therefore unhelpful (e.g. the keyword map for 'drug record' includes the controlled terms of 'acute heart infarction', 'college' and 'cataract'). The EMBASE search term scope statements contain only a list of all the terms that are covered by the search term (i.e. its children in the hierarchy); there is no formal textual definition of the search term provided. This severely limits the value of the controlled vocabulary as a search tool for the purpose of finding additional literature focused on the concept of a Medication Profile. In view of this, tree search terms from EMBASE were deemed to offer no additional value to this literature search.

Comment on Search Terms

The MeSH and EMBASE search terms demonstrate the confusion that persists in the definition of the vital concept of a patient's Medication Profile. Whilst it is not relevant to this thesis to conduct a full critique of the search terms provided by these two fundamental research databases, it is relevant to comment that their lack of rigor and consistency in term definition is perpetuating the problem of a clear understanding of the concept of a patient's Medication Profile throughout all aspects of healthcare.

An example of the issues can be seen in the scope for the MeSH term 'Drug Utilization', which is defined as 'The utilization of drugs as reported in individual hospital studies, FDA studies, marketing, or consumption, etc. This includes drug stockpiling, *and patient drug profiles*' where, it might be assumed 'patient drug profiles' might refer to the concept of a patient's longitudinal record of medication use, i.e. their Medication Profile. But there is, unfortunately, room for ambiguity; 'patient drug profiles' might equally refer to the concept of the information provided to support the use of a medicinal product in clinical care: the Summary of Product Characteristics in Europe or the Product Label in North America. The child concept of 'Drug Utilization', 'Drug Utilization Review', is scoped as 'Formal programs for assessing drug prescription against some standard. Drug utilization review may consider clinical appropriateness, cost effectiveness, and, in some cases, outcomes. Review is usually retrospective, but some analysis may be done before drugs are dispensed (as in computer systems that advise physicians when prescriptions are

entered). Drug utilization review is mandated for Medicaid programs beginning in 1993'. Within this scope there is no mention, nor even a hint of the requirement for a patient Medication Profile, unless one accepts the implicit requirement that clinical appropriateness cannot be assessed without the overall medication context that the Profile provides.

Another example is the term 'Potentially Inappropriate Medication List' which looked very promising as a search term and as such has been included in the search thesaurus. However, the scope statement is disappointing: 'A list, criteria, or screening tool designed to improve patient safety by determining an individual's exposure to potentially inappropriate drugs. They are designed to prevent medication errors by inappropriate prescribing. Analysis for a list includes factors such as dose-response relationship, drug; drug-related side effects and adverse reactions; age factors; gender; and existing medical conditions'. Although the scope explicitly states 'existing medical conditions' as being an important factor in preventing medication errors it does not mention existing or past medication use. Similarly the term 'Medication Systems, Hospital' which is scoped as 'Overall systems, traditional or automated, to provide medication to patients in hospitals. Elements of the system are: handling the physician's order, transcription of the order by nurse and/or pharmacist, filling the medication order, transfer to the nursing unit, and administration to the patient' does not mention anything about the facility to or importance of storing and then sharing any of the information from the core medication processes of prescribing, dispensing and administration that the system is required to perform, even though it does explicitly mention the somewhat clinically less important process of medication transportation.

Although both 'drug' and 'medication' appear in the MeSH and EMBASE controlled vocabulary, the term 'drug' is only used in those terms with longstanding and widely used application ('Drug Information Systems', 'Drug Utilization' and 'Drug Utilization Review'), although the term 'Drug Therapy' is a major heading, probably due to its longstanding position within Therapeutics. Further confusion appears in that various authors have used the term 'medication profile' to describe the characteristics of a medicinal product itself, yet had their articles matched to more clinically focussed search terms. Two have been picked out as exemplar: one focussing on information for clinicians such as pharmacology, pharmacokinetic properties, efficacy, and tolerability[62] and the second on information of interest and consideration to patients in order to ascertain their treatment preferences: time on the market, dose frequency, side effect list[63]. Several authors used the concept of a 'medication profile' to mean something closer to either a drug utilisation profile (the pattern of medicines from a particular therapeutic group used in a particular cohort of patients) or to a medication

regimen – a set of medications used together for a particular indication. French *et al*[64] applied the concept of a 'medication profile' to a cohort of patients when investigating the use of medication by blast victims. The concept was one of a drug utilisation profile for the cohort; how many patients used medicines from the particular therapeutic classes in a particular time frame post injury. The study did also use the term 'profile' when describing medication for individual patients too. Another study[65] applied the term to a drug utilisation profile for a cohort of patients, whilst investigating syncope and comparing cardiovascular medication use and central nervous system medication use between groups. Reichelmann *et al*[66] used the concept of a medication profile as the set of medications used to optimise symptom management in palliative care.

If the conduct of a good systematic search of the literature is not routinely achievable and comparatively reproducible on a regular basis, it is impossible to track and harmonise development in this critical domain. For this thesis, having built a thesaurus of search terms as rigorously as possible based on the hierarchies and definitions, it has been necessary to review the large number of retrieved results from their application quite extensively to find the literature that is truly relevant to the area of study.

Method for reviewing the selected papers

After de-duplication, title and abstract screening was undertaken on the papers retrieved through the above search strategy, to arrive at the final set of papers to be studied in detail. These were examined to elicit their contribution to the description of, population of and requirements for a Medication Profile. Based on the initial investigation, it was clear that although the literature in this area appears extensive, close examination shows that not to be the case and therefore a methodological review or quantitative examination would not be as valuable as a narrative discussion. The discussion of the papers examined was structured around themes from the papers themselves, which were assembled during the initial reading process:

- Systematic reviews in the domain
- The 'gold standard medication list' and medication reconciliation
- Medication information in transfer of care
- Personal medication records
- Data sources for medication information
- Medication systems and medication information

Results

Keyword search terms

The following gives the number of papers found (total and de-duplicated) for each of the keyword search processed through MEDLINE and EMBASE.

Table 3: Number of papers found in keyword searches

Keyword Search	MEDLINE TOTAL	MEDLINE Duplicates Resolved	MEDLINE ONLY Duplicates Resolved	EMBASE TOTAL	EMBASE Duplicates Resolved	EMBASE ONLY Duplicates Resolved	BOTH	BOTH Duplicates Resolved
Medication profile	137	133	15	231	225	107	118	118
Drug profile	221	211	12	492	484	285	200	199
Medication record	89	85	7	181	173	95	81	78
Drug record	19	18	0	28	27	9	18	18
Current medication	551	551	61	1024	987	497	490	490
Past medication	28	25	1	64	61	37	27	24
Medication history	840	836	102	1698 (1701)	1657	923	738	734
Medication histories	269	269	22	458	436	189	247	247
Drug history	825	825	111	1390	1356	642	714	714
Drug histories	167	161	27	224	214	80	137	134

Note that although when run as a full search, the total for 'Medication history' in EMBASE was 1701 articles, but due to institutional limits this full set could not be accessed; all divisions used always returned a total of 1698 articles, so this is given as the pragmatic total returned by the search query.

The number of papers in the search ranged from manageable numbers for some search terms such as 'past medication', to very high numbers such as for 'medication history', a pattern mirrored in both databases. To develop a more focused set of results for further investigation, the search terms were combined in a Cartesian square using the 'AND' operator. The results are presented in the table below. Whilst there were one or two very useful sets of hits in combination with the 'medication history' and 'medication histories' search term in both databases, many of the other combinations gave either a very small number or nothing at all. This re-enforced the sense that the searching and indexing in this domain is less than ideal in supporting systematic evaluation of the literature for the concept of a Medication Profile.

Table 4: Number of papers found in keyword search combination ('AND' operator)

MEDLINE \ EMBASE	Medication profile	Drug profile	Medication record	Drug record	Current medication	Past medication	Medication history	Medication histories	Drug history	Drug histories
Medication profile		2	1	1	3	0	5	3	0	0
Drug profile	1		1	0	1	0	1	0	0	0
Medication record	1	0		0	3	0	7	2	4	0
Drug record	0	0	0		0	0	0	0	0	0
Current medication	2	0	2	0		3	22	9	4	4
Past medication	0	0	0	0	3		16	1	1	0
Medication history	3	0	3	0	9	3		137	23	5
Medication histories	3	0	1	0	3	0	69		6	3
Drug history	0	0	0	0	1	1	8	3		22
Drug histories	0	0	0	0	0	0	2	1	9	

Controlled Vocabulary Tree search terms

As discussed above, search using selected controlled vocabulary terms was only sensible to do with search terms from MEDLINE, selected as described.

The results of this are given below, accompanied by the specific sub-set exclusions that were applied to the search.

Table 5: Number of papers found for the MeSH controlled vocabulary search (MEDLINE)

MeSH Term Search	MEDLINE TOTAL	Exclusions
Inappropriate Prescribing	489	History: Legislation & Jurisprudence; Statistics & Numerical Data; Veterinary
Medication Errors	6626	Legislation & Jurisprudence; Veterinary
Medication Reconciliation	192	Statistics & Numerical Data; Organization & Administration
De-prescriptions	6	
Drug Utilization	3532	Legislation & Jurisprudence; Statistics & Numerical Data; Organization & Administration
Drug Utilization Review	585	Legislation & Jurisprudence; Statistics & Numerical Data; Organization & Administration
Medication Therapy Management	297	History; Legislation & Jurisprudence; Statistics & Numerical Data; Organization & Administration
Potentially Inappropriate Medication List	3	
Patient Medication Knowledge	13	Statistics & Numerical Data; Organization & Administration

To focus the search more appropriately, particularly for the MeSH controlled terms with a large number of hits, pairings of the terms were combined using the 'AND' operator using a Cartesian square pattern and the results shown below.

Table 6: Number of papers found for the MeSH controlled vocabulary search combination ('AND' operator) (MEDLINE)

MEDLINE	Inappropriate Prescribing	Medication Errors	Medication Reconciliation	De-prescriptions	Drug Utilization	Drug Utilization Review	Medication Therapy Management	Potentially Inappropriate Medication List	Patient Medication Knowledge
Inappropriate Prescribing									
Medication Errors	34								
Medication Reconciliation	7	71							
De-prescriptions	2	0	0						
Drug Utilization	24	37	1	0					
Drug Utilization Review	14	30	7	0	16				
Medication Therapy Management	1	20	6	0	3	2			
Potentially Inappropriate Medication List	0	0	0	0	1	0	0		
Patient Medication Knowledge	0	1	1	0	0	0	1	0	

Results summary

The results of the three searches, the keyword searches from MEDLINE and EMBASE and the controlled vocabulary search from MEDLINE, with each search having the AND operator applied using the Cartesian square pattern, were combined and de-duplicated. This gave 128 papers from the MEDLINE keyword search, 290 from the EMBASE keyword search and 279 from the MEDLINE controlled vocabulary search, such that a set of 697 papers and articles were assembled. This initial set of the 697 papers was screened by title, reducing it to 281 papers. These were then screened by abstract, selecting those relevant to the exploration of the perception and definition of medication information for a 'Medication Profile' and its value to healthcare, and in particular what the data objects in it are/should be, the use cases it must support and how 'current medication' and 'medication history' relate to or within it. This abstract screening provided a final set of 59 papers to be reviewed. A diagrammatic representation of this process is shown in the flow diagram below.
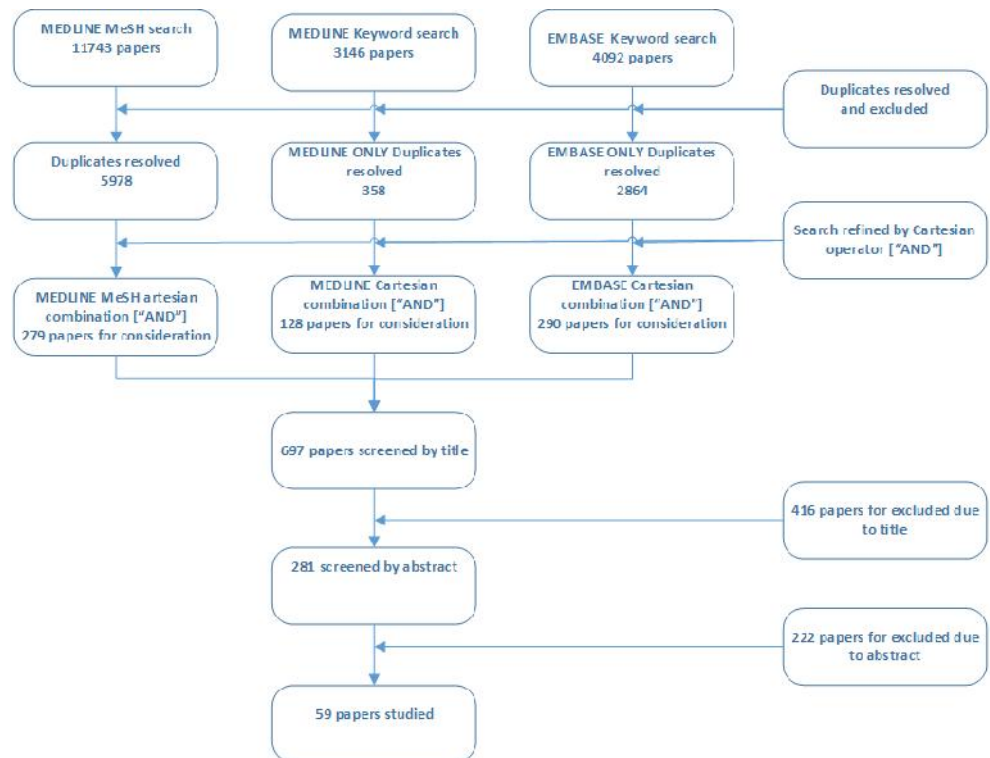
Figure 4: Flow diagram of paper selection for review

Discussion of the Literature

Systematic reviews and general discussion

Firstly, and following on from the challenges encountered in the literature searching itself which have been described above, it is noteworthy that there are extremely few systematic reviews of medication management and particularly the informatics of medication management in the literature, and those that do exist demonstrate the difficulty in finding relevant literature through searching. A review by Bayoumi et al[67] initially found 813 citations for a systematic review of medication reconciliation processes, but these were reduced to just 5 to actually review. A study by Kostas et al[68] also on the topic of medication reconciliation found 746 citations, but these were reduced to 35 and then to only 19 when constrained on their main focus of 'older patients'. This study described the concept of a 'best possible medication history' (BPMH) as a basis from which to conduct medication reconciliation process. Kostas and team describe a BPMH as a 'comprehensive list of prescription and non-prescription medications used by patients, which incorporates all available information sources, including patients' medication lists, prescription vials, outpatient records, pharmacy records (and phone call if necessary) and patient interview, among others'. They list eight possible types of sources of data to populate that list: 1) medication histories, which involved patient-generated information, including patient interviews, often in combination with other sources (e.g. prescription bottles and outpatient pharmacy); 2) hospital orders, which included inpatient and discharge medication orders; 3) medication administration records, which included inpatient drug administration records; 4) inpatient medical records, which included admission histories and physicals, progress notes and discharge summaries; 5) outpatient medical records, which included primary care notes and medication lists in outpatient medical records; 6) outpatient prescriptions or pharmacy records, which often included references to the patient's actual medication bottles or phone calls to pharmacies; 7) home reviews, which included a visit to the patient's home; and 8) the patient's own list, which included a patient-supplied, written medication list. The review concentrated on the types of data sources used to collate a BPMH, not the data elements that would comprise it, although implicitly, since omission of dosage form and route information was taken as a 'discrepancy' one can assume that these two data elements are indeed components of it. The review concludes that there is currently an absence of a gold standard medication list, which is a challenge, and that the literature on the topic remains deficient.

A review by Hogan-Murphy et al[69] looking more broadly at medication management systems and their implementation found 2566 references through searching, but these were reduced to 5 for actual inclusion. That review stated that two of the

studies had demonstrated that electronic systems had improved access to a patient's drug history and that it was 'easier to alter patient's drug list' but there was no definition of what those concepts (drug history or patient's drug list) actually meant in terms of the data elements to be provided. A similar lack of definition was found in a scoping review by Bassi et al[70] that sought to identify studies that were using information technology in medication reconciliation and determine how this is used to facilitate the process. Although this review looked at systems and functionality ranging from medication information sharing using e-mail through to managing medication safety by use of decision support tools, there was a marked absence of any description of actual medication data elements used or required by the systems or functionality.

Halapy and Kertland[71] wrote a general discussion of problems with medication histories (although the concept of 'medication history' itself is not defined in detail). They used focus groups to study the topic from the perspective of the patient and the healthcare professional. Patients were found to be unanimous in their opinion that all healthcare professionals caring for them should have access to complete medication histories to provide high quality care and expressed no reluctance to have that information available. Patients themselves knew they needed to be able to provide information about their medication to healthcare professionals, otherwise it might compromise the care being provided to them, and they used a variety of methods to achieve that: lists (either handwritten or computer generated) or bringing the actual medicines themselves. Patients were supportive of the use of information technology to achieve this goal of having their medication information available, and 'some form of a central computerised solution was suggested frequently, such as a single network listing medications captured through the patient's (health insurance) number, a smart card for electronic records, or some other mode of recording medications in patients' hospital records'. Healthcare professionals all agreed that accurate medication histories were important and they did provide a list of data elements that could be included: names of medications, indications, directions for use, and duration of therapy; they also described scope, to include both prescription and non-prescription medications. In this study, healthcare professionals suggested that some other types of information, which have been explicitly excluded in this research, would be useful in a medication history and these included allergy and adverse reaction information and insurance eligibility. The authors noted that patients and health care professionals both agreed that recording medication history information in electronic databases, to facilitate appropriate sharing of information among health care providers, was an important process. They also noted that an electronic system would improve availability of information about a patient's medication, particularly out of routine hours, and would help to address concerns

about inaccuracy or incompleteness of medication history. This reinforces the motivation for this research, to provide an evidence based static and dynamic information to populate and maintain that database of medication information (in a sense a synonym for the Medication Profile) in a comprehensive, high quality and consistent manner.

Introducing the gold standard medication information concept

The concept of 'best possible' or a 'gold standard' when related to concepts such as medication history or medication list or current/active medication list to give the concept of a 'gold standard medication list' that does appear frequently in the literature, although rarely with a formal definition. The *process* that is used to obtain what is described as the best possible or a gold standard tends to form the focus of study, usually in the context of finding a baseline from which to conduct a medication reconciliation process, rather than defining the information elements that provide the structure to hold the gold standard information. Both are important, but focussing on one to the exclusion of the other means that the foundations are unbalanced and any construction is at risk.

The gold standard medication list and medication reconciliation

Medication reconciliation itself as a process does have a formal definition: it is 'a process of identifying the most accurate list of all medications a patient is taking—including name, dosage, frequency, and route—and using this list to provide correct medications for patients anywhere within the health care system'[72]. It its goal is also articulated: 'to improve patient safety by minimizing errors that could harm patients'[73], and stated in more detail as 'complete, accurate, and current medication information for all patients and everyone involved in their care by seeking to prevent omissions, duplications, dosing errors, and potential adverse interactions among a person's medications'. However, it is acknowledged that this is not as easy as it sounds. In March 2010, the Joint Commission issued a statement that noted that many organisations had struggled to develop and implement effective and efficient processes to achieve the recommended standards for medication reconciliation and therefore they temporarily suspended the requirement. And as of July 2011, rather than being a separate Patient Safety Goal, medication reconciliation was brought under the umbrella of the National Patient Safety Goal #3[74], Improving the safety of using medications. This requires that organisations maintain and communicate accurate medication information and also that they undertake to compare the medication information the patient brought to the hospital with the medications ordered for the patient by the hospital in order to identify and resolve discrepancies.

To do medication reconciliation effectively requires the development of an accurate list, which must therefore be complete, of all medications a patient is currently taking, then, as described by Feldman et al[75], updating the list and repeating the comparison and reconciliation process whenever medication changes are made. It also includes communicating the reconciled list to all appropriate clinicians, especially to the next provider of care, and providing the list and effectively communicating its contents to the individual and the individual's family caregivers. This essence of having complete and accurate data about medications available to all, including the patient and carers to improve safety, is articulating part of the heart of this research. It also highlights the urgent need for the research, since apart from the statement about 'including name, dosage, frequency, and route', there are no formal definitions of exactly the data that should be involved, of what 'currently taking' truly means and indeed what the scope is for 'complete'. Implicitly, 'all medications' can be assumed to include those beyond simply prescribed medications, as further elucidated by Steeb and Webster[76] in their work on optimising medication reconciliation, where they described a medication list to include 'all medications as defined by accrediting organizations such as the Joint Commission, including, at a minimum, prescription medications; sample medications; vitamins and nutraceuticals; over-the-counter (OTC) drugs; complementary and alternative medications; radioactive medications; respiratory therapy–related medications; parenteral nutrition; blood derivatives; intravenous solutions (plain or with additives); investigational agents; and any product designated by the Food and Drug Administration as a drug'. They provided a definition for their concept of a medication list as 'a record of current medications that an individual carries across the continuum of care to stimulate conversation between the individual and his or her health care providers regarding the patient's current medications'. Unfortunately, they did not provide a definition for the qualifier of 'current', and although they stated that they felt that there was inadequate standardisation of the data elements of the medication record, they did not offer any view as to what that standard set of data elements should be. There was a clear sense from Steeb and Webster that, in their culture and practice (the United States in 2012) the holder of this list should be the patient, as they saw fundamental barriers to incorporating this list into the patient's health record that only legislation and regulation would overcome.

Back in 2004, Collins et al[77] started looking at the gold standard and noted that previously, researchers had assumed the gold standard medication history to be the medication information from the patient at the time, but they felt there were problems with this assumption. These included that patients cannot always recall all the information about their medication currently (names, dosage instructions) and that patients who are intentionally non-compliant with a regimen may be reluctant to

express this. The study confirmed earlier research that showed that physician-acquired medication histories contained inaccuracies and that pharmacist-conducted medication histories are likely to be more accurate, in that they identify a greater proportion of the medicines patients are taking. It also highlighted that the patient's health record should have clearer and more complete medication information. Although Collins et al concluded that there was indeed no gold standard medication history available and therefore further work was needed, even at this early stage there is a mismatch in definition and understanding which pervades the domain and makes solid progress difficult. This study implicitly assumes the concept of a gold standard medication history to be what others might actually term a current medication (list) since it is concerned with the medication of the patient at this point in time, not in times past.

Nearly 10 years and much research later, and focusing in a particular clinical area, Prins et al[78] also concluded that there still is no gold standard for obtaining an accurate medication history, either in terms of the structure of that history or in terms of the process to gather it. Their research compared information about the use of medications at home for older patients admitted to a psychiatric hospital and found it to be different from that recorded in the usual process for over three quarters of patients, with nearly a quarter of patients suffering clinical consequences as a result of the differences. It is therefore vital that these concepts are at last properly and formally defined using best informatics practice to support the provision of clinical care.

Fitzgerald[79], writing an article on the importance of an accurate drug history in the prevention of medication errors, gave quite a broad scope for what he considered the medication history should be, not simply as a list of a patient's medication and the associated dosage information but also to include additional but related information such as information about adherence to therapy, previous hypersensitivity reactions and adverse effects, noting that these latter were often poorly documented in patient records and particularly on medication charts. Ryan et al[80] studied the concept of correctness of medication information, such that the medications reported for the patient are indeed the ones the patient is taking, with no falsely included medications. Completeness of the information was also examined, stating that medication name, dose (quantity) and frequency (of administration) should always be included for each reported medication. In this study, if medication information was both correct and complete it was deemed to be accurate.

Medication information in transfer of care

Much of the available information in the literature about description of medication information comes from studies that have concentrated on particular points of transition in the care process, as a different set of healthcare professionals take responsibility for the care of the patient and need information, particularly medication information, to provide that care safely and well.

Medication information at transfer into secondary care (admission)

The transition into secondary care, either directly or through an emergency department, is a particular focus in the literature. This is because more than half of all hospital medication errors occur at the interfaces of care, with over one-quarter of all hospital prescribing errors attributed to incomplete medication histories obtained at the time of admission[81]. An early systematic review by Tam et al[82], which initially found 343 potentially relevant studies but which finally reviewed just 22, looked at admission to hospital and the errors in 'medication history' that were occurring. This study found significant heterogeneity in methods/sources used to obtain the comprehensive medication histories, but gave no detail of either the definition of the period that a history might cover, nor the data elements that comprised those histories other than by implication from the error types. These included incorrect dose (quantity), (product) strength, (dosage) frequency and errors of omission or commission in the inclusion or otherwise of particular medicinal products in the listing. Similarly, an early study from Andersen et al[83] looked at a patient's medication history on admission to a medical ward, but based on the description that these were 'the medications that the patients are reporting to consume or the medications that they keep at home' this is really a concept that should be termed the patient's current medication. This study, and a similar one by Rees et al[84] which was also looking at discrepancies in drug history on admission to a medical unit, had comparable findings to that of Prins discussed above, in that it found that approximately 70% of the patients had some sort of discrepancy in their medication list.

A study by Kaushal et al[85] was a qualitative assessment of the use of a model health information exchange project for a network of emergency departments in which claims data from pharmacy benefit managers (PBMs) were made available at the point of care to clinicians in emergency departments, to provide information on patients' medications. Although the information provided was felt to improve clinicians' knowledge of patients' medications, they did not believe it decreased the time required to obtain a medication list from which to continue to provide care. The authors felt this mismatch of value was probably due to a belief that the source

information was incomplete, particularly since psychiatric and HIV medications, mail order medications and medications dispensed in other countries were not included. The study also noted that any system providing medication information at the point of care needs to be carefully designed and implemented, especially into the workflow.

This theme of use of the patient's medication information in the workflow was also studied by Vawdrey et al[86], using a coded, longitudinal medication list known as the 'Outpatient Medication Profile' (OMP). This study acknowledged that, in their context, there was no gold standard medication list. Although it might be assumed the OMP could become that gold standard, there was a strong sense that further analysis was necessary to assess the validity of that, and also to explore the possibility of synchronising data with external pharmacy information and other data sources. This study is one of very few that describe any sense of a longitudinal record of medication use for an individual patient, or to note explicitly the use of coded data elements within that record.

A study by Cohen et al[87] on the availability of medication information for elderly patients to support the initial interventions made by physicians in the emergency department concluded that even if the names of medications a patient may have taken immediately before arrival at the emergency department were available, a complete list of the patient's medications with details of the dosage, route, and frequency of medications was unlikely to be provided. They felt that these elements, accurately supplied, would be very valuable to support the initial interventions necessary during the initial period of acute stabilization. Another study that focussed on medication reconciliation in the emergency department context was that by de Winter et al[88]; this was a quantitative analysis of discrepancies in medication histories obtained in that emergency care context which found a 59% discrepancy rate (against a reported rate in other studies ranging from 10% to 96%). Whilst no explicit list of the data elements for which discrepancies were measured was provided, the statement that 'correct dose, frequency and route of administration were responsible for the greatest number of discrepancies' implies that these data elements were considered, as well as omission or commission of the medicinal product itself.   At the other end of the age spectrum, Dersch-Mills, Hugel, and Nystrom[89] looked at medication information on admission for paediatric patients, a cohort that generally does not require much medication therapy, and in their study just under a quarter of patients took no medications at all, and approximately half took no prescribed medications. This study used the concept of a best possible medication history against which to calculate completeness, and although the content of this was not explicitly stated, it can be gathered by implication from the

completeness scoring system, which had one scoring point for each of: the name of the medication, the dose (amount per dose), and the frequency of dosing, with complete correctness being three points or a 100% score. The scope of the best possible medication history was also implicit, in that the study noted 'the informed interviewer consistently included over-the-counter products, herbal products, and vitamins, in addition to prescription medications, in her questioning'.

Owusu-Ankomah et al[90] investigated the overlooking of various types of medicines when documenting a patient's medication on admission to an acute medical unit. This omission is important because incomplete medication histories at the time of admission account for approximately 27% of hospital prescribing errors and increase the risk of drug interactions. Use of over-the-counter complementary and alternative medicines in particular is poorly documented at hospital admission and prescribed drugs that are commonly overlooked included oral contraceptive medications, -adrenoceptor agonist inhalation products and topically administered medicines such as steroid, antihistamine or emollient products. The authors suggested that reasons for poor documentation may include lack of time or perceived lack of importance of these medications and concluded that lack of documentation of non-prescribed medications and overlooked medicines may result in omission of indicated treatments or failure to predict interactions or correctly identify adverse events. Fitzsimons, Grimes and Galvin[91] also observed that ideally, pre-admission medication lists (in their terms, 'PAMLs' or 'GS-PAML' (gold-standard PAML, equivalent to Pippins 'gold standard' medication list described below) should not merely list the medications prescribed or dispensed to the patient, but reflect what the patient was actually using prior to admission, taking into account not just non-prescribed medications, but also any known non-compliance with any medication regimen. In their study, only 17% of PAMLs had no discrepancy when compared to the GS-PAML, constructed by amalgamation and reconciliation of various information sources including general practice referral letters, community pharmacy and where appropriate, nursing home information. Their conclusion was that this high discrepancy rate illustrates the complexity of the problem of identifying the patient's actual (current, pre-admission) medication use and medication history (no definition given). They also noted that their finding that the community pharmacy provided information most frequently in agreement with the GS-PAML was inconsistent with findings from the UK, where the GP was identified as the most accurate source, adding yet more evidence to the need for formal definition of how to structure and manage this information in this safety critical area.

In terms of internal transfer within an institution such as a hospital, Lee et al[92] showed that clinically significant medication discrepancies occur commonly at the point of

internal hospital transfer of patients. Their conclusion was that a 'structured, collaborative, and clearly defined medication reconciliation process is needed' to prevent such transfer discrepancies and therefore to reduce the risk of patient harm. They did not, however, postulate as to what that structure and clear definition might be.

Dharas and Dean Franklin[93] investigated the information that patients themselves contributed at a point of transfer of care, by comparing and contrasting patients admitted for elective surgery and through emergency medication admission. Overall, 63% of patients contributed information about their regular medication (no definition of regular was given), but it was noted that those admitted electively contributed more than those admitted as an emergency, and particularly those admitted through the accident and emergency department. This points to the clear requirement for a Medication Profile to be available to all, especially to support unscheduled care. In a similar vein, Dooley, van de Vreede and Tan[94] studied the accuracy of a patient-completed questionnaire for medication history used in a pre-admission surgical assessment and found that it was inaccurate in four out of five patients. This study also used the concept of a gold standard for the patient's medication history, but other than stating that this was the pharmacist's assessment of the patient's medication, no other description of that gold standard was provided.

Medication information in shared care (outpatients)

The availability and accuracy of medication information has also been studied in outpatient clinics, a context which could be described more as a situation of shared care than of a transfer of care. Ashjian et al[95] studied medication information at a haematology/oncology outpatient clinic, finding the medication information discrepancy rate to be similar to other studies, at 88% of patients' records. This study was clear in that it explicitly described the scope of patient's medication list (to include prescription and non-prescription products, including herbal and dietary supplements) and was also explicit about some of the data elements examined (drug (description), dose (quantity), route, frequency and indication). Pasetka et al[96] also studied medication history in an outpatient oncology setting; no detail of their definitions is given but their conclusion was that approximately a third of patients in this medication critical area of practice did not have a documented medication history of any type.

Seden, Back and Khoo[97] also reviewed medication history information in an outpatient clinic setting, again for a medication critical speciality: human immunodeficiency virus (HIV) treatment. Their focus was identification of drug-drug interactions, which they acknowledge relies upon having a comprehensive and

current medication history. No definition of this or of the data elements it should contain was given, but the understanding that a range of non-prescription medications such as herbal medicines, vitamins or supplements and so-called recreational drugs may impact anti-retroviral therapy indicates that the scope of their medication history concept would include these products. In the United Kingdom, Darley, Bell and Pammi[98] also investigated communication specifically related to HIV treatment, particularly between primary and secondary care environments and the NHS England Summary Care Record[99] (SCR), which is intended to provide patient information to support better care for patients across care boundaries. Less than a quarter of patients (23%) had a mention of their anti-retro-viral (ARV) therapy on their SCR, less than 10% of patients' SCR had complete ARV information. In contrast, just over half of the hospital records had all current medication listed, including all ARV. The findings of this study are in many senses extremely disappointing, given that the SCR explicitly includes medication information as a priority[100] (possibly its only priority currently). This highlights the need for this research to provide not just the data element definition but also the dynamic model of processes and rules for population of the data elements, to make initiatives such as the SCR for medication actually work in reality.

Another study in a (preoperative) clinic setting, by Lee and Nishimura et al[101] found discrepancies in 94% of patients' personal medication lists, with further analysis noting that polypharmacy was a significant factor in increasing the likelihood of inaccuracy in medication information. This study did describe its data elements: the name, dose (quantity), and frequency were included, but there is no mention of route of administration as a data element. The scope was described as including all prescription and non-prescription medications or dietary supplements.

Personal medication records

Most of the situations described so far have focussed on one or more medication lists being managed by one or more types of healthcare professional, either with or without the support of information management systems. The literature also describes the concept of a personal medication record, a record of medication information that is held and managed by the patient themselves, for example as described by Burns[102] as part of an overall medication therapy management service. This service has five core elements, of which four are relevant to the management of medication information for an individual: medication therapy review (MTR), management of a personal medication record (PMR), development and execution of a medication-related action plan (MAP), documentation and follow-up; with the fifth being actual intervention and/or referral. This work by Burns is unusual in that it

provides good description of what it expects in the (personal) medication record, both in terms of scope (all prescription and non-prescription medications, herbal products, and other dietary supplements) and in terms of the data elements: for each medication, name and dosage instructions for use, indication, start/stop date and any special instructions. It also requires information about the healthcare professional responsible for that medication. Because the focus is on the provision of an overall medication therapy management service, various other information was required in the record, including allergy/adverse reaction information and metadata about when the PMR was updated and by whom. Even more unusually, there is some sense of the management of this record over time to keep the record current and accurate, although this is, possibly unreasonably, delegated to the patient. The patient is instructed to update the PMR each time they receive a new medication (prescription or non-prescription or herbal product) or has a current medication discontinued or a medication has a dosage instruction or other regimen change. However, there was the sense that ideally, the pharmacist, physician or other health care professional should actively assist the patient with the management of the PMR. The author concludes that widespread use of the PMR would support uniformity of information provided to all healthcare professionals and therefore improve the care they provided to patients yet because it is patient held and managed, it is not tied to any particular provider's system or specification, and could be used by all. Given the other research in this area, this is undoubtedly true, but no healthcare culture has yet successfully implemented and had widespread uptake of a patient managed medication record, despite several large initiatives including GoogleHealth[103] (cancelled end of 2011) and Microsoft HealthVault[104]. But the sentiments, and particularly the explicit description of the nature of the scope and components of the record are very much what this research is focussing on.

There have been some smaller research-led initiatives in the area of personal medication records. Zeng, Bodenreider and Nelson[105] describe a stand-alone web-based application called MyMedicationList that was provided by the US National Library of Medicine as an initial trial of something that could also be integrated as a medication module within a PHR (personal health record system), not least because of its standards base. MyMedicationList was composed of the data elements from the ASTM Continuity of Care Record[19] and was implemented through the Continuity of Care Document (CCD) standard, to provide human readability as well as computer process-ability, and as such can be argued to have a defined and standardised dataset, at least within the US healthcare culture. The authors argue that this means that it is 'semantically complete' and rich enough to represent all medication information, including medication name, interval (start/stop time), quantity,

frequency, patient instruction, indication, available generic substitute of a branded drug, prescriber and supplier.

Multiple data sources for a gold standard medication list

The theme of the multiple data sources that might or might not contribute to a gold standard medication list is one that many have looked at. Pippins et al[106] looked at what they considered to be all available sources of information, including subject and family/caregiver interviews, prescription pill bottles, outpatient electronic medical records, previous hospital discharge orders, outpatient providers, and outpatient pharmacies in order to develop a pre-admission medication history. The data elements that they collected from this set of sources were not listed explicitly, but can be implied by looking at the types of discrepancies that they noted. These included dose per administration (dose quantity), since to have '100mg bid' instead of '200mg bid' was considered a discrepancy; dose frequency, since to have '100 mg bid' instead of '100 mg tid' was also considered a discrepancy, and indeed the authors explicitly state that to have '100 mg bid' instead of '200 mg qd' (or 'od/once daily' in UK/Europe) would be a discrepancy in dose *and* frequency even though the total daily dose is the same. Route of administration information and substitution information (whether it is appropriate to exchange a medication for a different one within the same therapeutic class) were collected.

Kramer et al[107] used four different sources of information, home medication profile report, home medication reconciliation report, discharge medication reconciliation report, and patient discharge medication profile, and sought to use information technology to integrate these sources into a system to generate forms to support and to report the results of the medication reconciliation process on admission. These forms were then placed in the patient's notes or given to the patient on discharge. Although no explicit description of the data elements collected was given, the copies of the forms provided showed that in addition to the full medicinal product name, dose quantity, route of administration and dose frequency were collected, and an additional 'Comments' space looked to be regularly used to describe the indication for the medication.

Karkov *et al*[108] also undertook to investigate the number and type of discrepancies between four medication sources and to assess their potential clinical significance to the patient, in a very small study (9 patients) undertaken on patients admitted to hospital with hip fracture. The four sources were the patients themselves, the Danish Personal Electronic Medication Profile (PEM)[109] that records all prescriptions dispensed to a patient, the general practitioner and the in-home care provider. In this study, a discrepancy was defined as any disagreement or omission of

information between the four sources mentioned concerning name, form, strength and dose for each medication with which the patient is being treated, therefore implicitly providing what the study considered to be the component data elements for the gold standard.

Phansalkar et al[110] also addressed the fragmentation of medication information across the healthcare domain, and the difficulties that this poses. They examined various sources and their qualities, concluding that each source had both positives and negatives in terms of their contribution to a gold-standard medication list (in their case, for use at admission to hospital). Information directly from patients and/or their carers may not always be accurate but it is likely to be the most comprehensive in scope (going beyond prescription medications) and may also reveal adherence issues. Medication information obtained from an EHR system in secondary care may provide greater detail on the dosage instructions for the medication, but have no sense of whether the patient has actually had the prescription supplied and is therefore using the medication. Pharmacy dispensing databases, either directly or via insurance claims provide objective information on medication supply, but may not have all the dosage instructions information. The conclusion, not unnaturally, was that the gold-standard medication list is likely to be obtained by a combination of all sources, but the study gave no indication as to how that combination should be undertaken.

Similarly to the National Library of Medicines' MyMedicationList, Simonaitis et al[111] have also looked at the Continuity of Care Document standard as a vehicle to share medication history information to primary care clinicians. Three different sources for medication information were queried, one providing dispense information, and two providing dispense information indirectly through insurance claims. Using the structures in the CCD, the following information was extracted and provided back to prescribers: the medication name (as the RxNorm[112] Clinical Drug Name), the dosage instructions (no individual components described), the quantity dispensed and the date dispensed, which pharmacy dispensed it and also who prescribed it (name). The information was found to be helpful to the primary care clinicians and complemented medication information that they already had, by adding to it. The researchers in this study started to describe – although not to attempt to solve - some of the issues of a dynamic model for populating medication information, such as when a change is made for a patient to move from lisinopril 10mg tablets to 20mg tablets, is this a new medication or a continuation of an existing one? They also investigated how to recognise two different reports of the same medication process from two different sources.

Medication systems and the gold standard medication list

There have been several studies on various aspects of information technology in supporting the gold standard medication list.

Some of these studies have investigated particular local or national initiatives: one of these is the study by Price et al[113] from Canada, which used the term adopted in this thesis, that of Medication Profile and although it did not provide a clear and formal definition of the term, it appears that it was intended to mean the patient's current medication list (no definition of currency was given). The study itself extracted patient medication profiles from a provincial repository of dispensing information (the PharmaNet system) and compared them to a Best Possible Medication Histories (BPMH) gathered by pharmacist led patient interview. The study found that most of a patient's medications were listed on their Medication Profile, but discrepancies were occurring because of a missing 'current' flag, with insulin, salbutamol and codeine being most frequently discrepant in this manner. Discrepancies in dose (quantity) or dose frequency accounted for a further quarter of recorded discrepancies, followed by discontinued medications still being listed as current, and inaccuracies in route of administration information. So although no data element components were formally described for the Medication Profile, these are implicitly understood to be included, with the discontinuation information being equivalent to a 'medication course ceased date'. Over-the-counter medications were rarely described in the PharmaNet system, relying as it does on dispensing information, but specialist clinic medications (such as anti-retrovirals) and other hospital dispensed medications were also missing. The authors concluded that using a system providing dispensing information only is insufficient for completing a medication history, a term that was itself undefined yet clearly different in the authors' minds from that of medication profile, and they suggested that information from other health records must be incorporated to generate a Best Possible Medication History (BPMH).

Another Canadian study by Fernandes et al[114] also looked at the use of a provincial database of prescription information, which was provided through a system called the drug profile viewer (DPV). Note that, similarly to the other Canadian study by Price et al, this study also used the concept of a profile that is formally undefined, but appears to be similar to the Medication Profile concept used in this research. The premise of the study was that the DPV information could add value (quality and efficiency) to a BPMH, and from the results, which found that discrepancies in the BPMH were significantly reduced after the introduction of information from the DPV, the premise was found to be supported.

Tulloch and Evans[115] also studied a provincial database of dispensing records in the Canadian healthcare culture, the Pharmaceutical Information Program (PIP) from the Saskatchewan Drug Plan and its use in providing a drug profile for patients admitted to hospital, particularly to support medication reconciliation on admission. Similar to other Canadian provincial medication databases, information about hospital medications, cancer medications, tuberculosis medications, investigational medications, over-the-counter medications and herbal products are not covered. The focus of the study was to compare the PIP profile to a BPMH, obtained by a pharmacist on admission. Similarly to the study by Price et al above, this study by Tulloch and Evans found most discrepancies occurred because of medications being wrongly categorised in the PIP profile. This was most particularly medication being incorrectly given the status of inactive (the discrepant medication was listed on the 4-month PIP history in 88 (87%) of the 101 cases of this discrepancy, but incorrectly appeared as inactive in 49 (49%) cases). Differences in description of the dosage instructions and medications missing from the PIP profile were the next most likely discrepancies. The differences in dosage instructions had the consequence of affecting adherence calculations, especially where active status was calculated based on dispensing date and dosage regimen; in this culture, the dispensing pharmacy must enter the number of days' supply for each medication, which is often based on a best guess for usage. The authors also noted that dispensing date might be different from the date that the patient actually retrieved the medication from the pharmacy, or the date at which they commenced using that supply. This study has started to tackle the dynamic modelling of information in the domain, looking at how dynamic information components, particularly status, should be populated and starts to document the problems in this area that must be overcome to provide a fully defined and formally managed high quality comprehensive Medication Profile for each patient.

Although most of the research in this section originates in North America, the issues are global; an investigation in Taiwan by Lee et al[116] also used information from a medication usage database from a national insurance source to provide a baseline list against which to work. Unfortunately, there was no description of the actual data elements taken from the database and brought into the list.

In each of the studies above, the information flow was unidirectional and at a single point in time, from the provincial dispensing database to the user of the information at the point of admission to hospital care. A study by Remen and Grimsmo[117] from Norway looked at a situation where there are several versions of medication information available in an EHR application from different sources, external (e.g. in referral communications) and internal (e.g. from past episodes in hospital). Their

investigation found that clinicians were searching for up-to-date information about the patient's medication use, expressing a marked preference for limited and summarised medication information to be available in emergency situations. They postulated that this would be best obtained from a record of recently dispensed prescriptions, which in effect is exactly what the Canadian studies had been using in their unidirectional and single-point-in-time information flow from the provincial dispensing databases.

Bell et al[118] studied the views of a panel of technical experts in relation to the concept of medication history (RxH) obtained from health insurance claims data, in the context of electronic prescribing. They looked particularly at the need for an accurate medication history for prescribing decision support, especially in a healthcare culture of distributed care with a single patient having multiple prescribers. It was noted that some vendors of prescribing decision support systems admitted to having given up on reconciling medication history data from multiple sources and used only the prescription data originated on their software for alerting. Others were matching using more complex reconciliation, based initially on codes (the National Drug Code - NDC) and failing that, using text string matching for medication names, but with inconsistent success. One vendor was quoted as saying: 'In order for medication history to be used effectively, it should be available in a consistent manner for the majority of the patients being managed by a provider or practice. In areas of scarce PBM (Pharmacy Benefits Management) coverage, for example, providers do not find this information useful even when available'. There was an overall sense from the panel that the current information structures are likely to be adequate, but the value of the medication history information is undermined by its inconsistent availability and by problems with its usability, particularly in terms of reconciliation from different sources. Crossen et al[119] also studied this same RxH concept from a physician's perspective, reporting that this group found the RxH information to be inaccurate or incomplete and therefore they continued to rely on patients to provide medication information to support their care. It was felt that unless medication information can be offered to prescribers in their systems consistently and reliably, it was actually of little value. The authors concluded that the remedy for the root cause of inaccurate and incomplete medication information was to have standardisation for the information, and it is exactly these issues, of consistency of both structure and population of that structure that this research is aiming to address.

Elliott et al[120] also studied prescriber's opinions of a system to provide medication information based on dispensing information into an electronic health record system. Overall, the majority of respondents to the survey felt that the information provided was useful, particularly when wanting information to assess adherence and to

support a medication reconciliation process. All of the respondents felt that in order to be useful in clinical practice, medication information needed to be both complete and accurate, underlining the need for the gold standard Medication Profile to be made available to all to support high quality delivery of care to patients, as proposed by this research.

Given some of the issues described above with collecting and sharing data and particularly data about ARV medication, some functionality developed by Cushman et al[121] is particularly interesting. This was a web-based application to create and then display ARV medication histories (only). Patients and clinicians reviewed medication use together at each clinic visit using the tool, which also included medication images to facilitate obtaining accurate information. The authors stated that this gathered data was subject to quality control checks, particularly to confirm clinically unlikely regimens, but they provided no information as to the data elements or algorithms used to do this. Implicitly, there is also a sense of a dynamic model underpinning the application, although again it is not described, because the raw data is dynamically transformed into medication instances (where a medication instance is an uninterrupted period of use for a particular drug) which can then be displayed graphically by the application. This type of display is only possible when the dynamic (process) model from which to manage the information has been described within the system. The authors anticipate that the use of the tool would improve the accuracy and efficiency of medication data collection (in the clinics).

Zhu and Cimino[122] acknowledged what much of the literature has demonstrated: that a system that accurately presents medication information that has been obtained from the range of different data sources that manage medication and which properly deals with changes in medication use over time, to provide clinicians with reliable summary of patient medication information at the point of care and in real time, should reduce errors and improve quality of and patient safety; indeed the heart of the motivation for this research. From this foundation, they performed an evaluation of a prototype application that provided a visualisation of a patient's medication information in a set of timelines, using open source software called Timeline, working as a complementary application in an overall EHR system. A web-based tool collected medication lists from various sources including clinic notes, admission notes and discharge summaries, the outpatient medication order entry system and the inpatient pharmacy system. The core data elements used in this tool were medication name, dose (quantity), route (of administration), frequency, data source, context, prescription time, start time, stop time, and usage status. Unfortunately, to generate the gold-standard medication information required a significant amount of human intervention in order to be presented in the Timeline application; two experts

read each information record individually and produced the overall amalgamation. It is therefore clear that the system design did not address management of a dynamic model such that accurate amalgamated information could be generated automatically using logic rules. The authors did conclude that their work had great potential, and that it would be feasible to implement a medication summarisation tool into clinicians' daily practice. Unfortunately, the focus of their future work appeared to be improving the graphical user interface rather than investigating further and more accurate generation of medication information; this is likely to seriously hinder the value of their work as the level of human intervention required to generate the gold-standard medication information seems insupportable in the wider world.

Again working alongside the main functionality of an EHR, Wolver and Aggarwal[123] investigated views about and use of what they termed the External Medication History (EMH) to support electronic prescribing. There is no detail as to what the EMH actually contained in terms of scope or data element components; the work focussed on patients' and healthcare professionals' views of its value. The authors found the EMH was used to check compliance, to confirm or reconcile dosage instructions information and to confirm that the most up to date medications were on the patient's medication profile within the EHR, which raises questions as to where, if anywhere, a gold standard medication profile would be available for a patient in their healthcare environment. There is an implicit sense from the patient survey that the EMH was actually primary care dispensing information, since patients stated that they 'knew their providers could see if they were filling their medications', and as such, the environment for this study is similar to the several Canadian studies discussed above.

Duran-Garcia et al[124] looked at the role of information technology to bring together the information needed to produce a best possible medication history from multiple and fragmented data sources, including primary care prescription information, discharge prescriptions, outpatient prescriptions and patient interview. Yet again, the actual data elements that would be necessary to form that best possible medication history, or to maintain it over time, were not described.

Whilst the majority of studies have shown an improvement in medication information quality with the use of information technology, Schnipper et al[125] noted that, although the quality and availability of medication information had improved in their study due to the introduction of a medication reconciliation improvement process, after the introduction of an electronic medication record as part of an EMR system, medication information discrepancies actually increased in number at admission. They felt this was because the system itself had disrupted the medication reconciliation process

and made medication information harder to document. They advised that any introduction of the use of information technology must be managed carefully so as not to reduce data quality, even in the interim.

Stoop et al[126] looked at the information technology of medication information from a different perspective: that of the social and political environment in which the system is developed, implemented and used by healthcare providers. The Dutch OZIS system, which provides shared access to the patient's medication (dispensing) data, has been accepted because, they hypothesise, its introduction coincided with increasing need for medication information to provide high quality pharmaceutical care out of hours and to a range of patients not necessarily within their usual practice. This different perspective is not part of the heart of this thesis, but any implementation of the information models from this thesis should be mindful of the conclusions from Stoop et al, that the success or failure of information technology in health care is just as much about the social and political context in which the system is used as it is about the 'intrinsic value' of the system itself.

Finally, a study by Lesselroth et al[127], published in a journal specialising in methodology, was interesting in that its objectives included developing an in-depth understanding of the workflow and information flow in admission medication reconciliation; in other words, a dynamic model for the process. From this they looked to design medication reconciliation support technology using a combination of software development methodologies such as rapid-cycle prototyping and human-centred design (also known as user centred design). However, despite the authors stating these objectives, documenting their use of tools such as storyboards and concentrating on the process, no formal process or data element models appear to have been to be described, and although a proof of concept application was developed, the authors reported it did suffer from usability issues. This study is particularly interesting to this research work, which aims to blend together the formal software development paradigms, such as the use of analysis tools from the Unified Modelling Language and Business Process Modelling Notation with the academic discipline of a thesis, since in some senses this study by Lesselroth seemed to take a similar approach.

Conclusion

Although there is a wealth of literature available that acknowledges the critical value of an individual's medication information (both history and current use) in order to provide safe and effective ongoing care to patients, and a wealth of studies describing methods to collect and share medication information, there is a dearth of literature that formally describes any of the key concepts or informatics components

that are needed to provide correct, complete and accurate medication information for patients, either for their own care or for wider secondary uses such as clinical research. The formal definition of a high quality comprehensive and cohesive Medication Profile for use in the provision of care to individuals and also for secondary use of that information in clinical research to promote better and safer medication development for the future is therefore urgently required.

Key literature findings that have directed this research

- Many studies have emphasised the importance of a consolidated and reconciled medication list derived from multiple sources to underpin the safe use of medicines in patients, especially at points of transfer of care or in shared care environments

- The phrases 'current medication' and 'medication history' are frequently used to describe a medication list or medication record and are often even given the qualifier of 'best possible' or 'gold standard' but they are almost never defined and never justified

- Several studies have reported that issues with identifying 'current medication' are a major source of medication discrepancies

- Studies that have attempted to consolidate medication lists from multiple sources have found this to increase the overall quality of the medication information but have found the process to be resource intensive; this implies that a scalable and computable approach to integrating medication information sources is needed and may improve patient safety

- Few studies that have designed systems to capture, communicate, integrate or reconcile medication have been explicit about the details (data items) that were used

- Few studies have addressed any of the issues regarding maintenance of population of data elements over time or the processes that might be used to support this within a system, other than to repeat a reconciliation process at every transfer of care

- Many studies have noted that the scope of the medication list, the inclusion or otherwise of prescription and non-prescription medication and related healthcare products, is a key issue in terms of discrepancies of information; none have addressed this issue of scope directly

- Few studies have addressed the issue of how to record and share changes in therapy, especially when these changes do not affect the main therapeutic intent (e.g. dosage instructions changes)

Chapter 4: Requirements for the Medication Profile from Patient Care

Part 1: Electronic Health Records and Electronic Patient Summaries

Introduction

As healthcare computing has developed and health informatics has matured as a discipline, a 'holy grail' has emerged: the specification for the delivery of an electronic comprehensive longitudinal cradle-to-grave documentation of an individual person's health and wellbeing, available at all times to inform and support all healthcare professionals that provide care for that individual; the Electronic Health Record (EHR). This chronicle of a person's health status and the interventions made to support that status would be ordered and presented in such a way as to be most useful for all those supporting that person by the provision of health care to them. Within an EHR, all information about the medications, including immunisations, that a person has received, is receiving or is planned/scheduled to receive would be present as a section, providing a 'Medication Profile' for that patient.

One of the key goals of a central electronic health record is that it should be semantically interoperable[128]. This means it should be able to share its information with any and all other systems used by the healthcare professional, be they critical support systems such as artificial ventilation systems, investigative or monitoring systems such as x-ray systems, electrocardiograms, medication systems, care record systems (medical, nursing or ancillary such as physiotherapy or dietetics) and systems providing report information such as laboratory systems. Semantic interoperability is a widely used phrase in health informatics to indicate that systems are able to share information in such a way as the meaning of the information is usefully and accurately preserved through both time and space; information entered in system A at time point X can be shared with system B at some later time and the meaning of that information remains the same[129]. In the medication domain, semantic interoperability would be demonstrated by the prescribing section of a general practitioner's care record system sharing its information, as part of a referral, with a clinic application in a local hospital. The clinic application would receive the information about the prescriptions for the referred patient and it can understand the information such that it can then present this information usefully to the clinic staff, so that they can see and understand the medication(s) ordered, the dosage instructions for the medication(s) and the time frame of them, even if that time frame was some years previously. The system should present the information in such a way as to be clear that, unless there is additional supporting information (possibly

from elsewhere), the prescription is an order *only*, and unaccompanied by any related dispensing or administration information is not a guarantee that the patient received the medication, only that it was prescribed. In addition to presenting the information usefully to humans, who can make sensible interpretations and often intuitively fill in information gaps, semantic interoperability would allow the information about the prescriptions for the referred patient to be safely usefully used within the clinic system in the hospital, such as for use in decision support (drug interaction checking etc.).

There have been various initiatives, both national and international, in the last 10-15 years that have aimed to produce a specification for a semantically interoperable electronic health record; the major such initiatives are described in the section below. However, in the last 5 years, the focus has shifted away from attempts to specify a full longitudinal EHR towards specification of an interoperable Patient Summary. This summary is a synopsis of the most pertinent points of a patient's health status and an outline of their current situation, with the focus to inform and support all healthcare professionals that provide care for that individual. Medication retains a key position in the summary, in that, as shown below, all summaries include information about a patient's medication in some form or other. Some of these specifications directly list and/or describe the data elements that they require; others describe the functionality that they require systems to provide using a summary. However, in order to provide functionality, there has to be a fundamental understanding of the data elements that are need to support that functionality. Therefore, studying these specifications should give a clear set of requirements for the data elements needed for a Medication Profile, and a set of functionality that a Medication Profile should support.

Overview of EHR Specifications and their Medication information

The following overview starts locally, with the vision of the English NHS, which was the first of the national initiatives that produced a specification for an overarching electronic health record, then moves to take a European view, and finally looks at what is specified in the United States. There have also been initiatives other realms, for example Australia and New Zealand; the Australian initiative in particular looking to achieve something of a mixture of NHS England's ICRS[18] using the international EN ISO 13606 EHR structure[130] together with some elements of the HL7 Clinical Document Architecture[131].

Information for Health (NHS England)

The NHS in England was one of the first health services to bring the EHR into focus by the publication, in September 1998, of 'Information for Health'[132]. The purpose of

the EHR was to ensure that patients received the best possible care, and to support healthcare professionals in delivering that care, through provision of lifelong electronic health records for every person in the country and for all NHS clinicians to have round-the-clock access to those records.

Information for Health resulted in the development of an output-based specification for the Integrated Care Record Service (ICRS)[18], which had two parts: part one for National Services and part two for Local Services. The National Services were to include a clinical 'spine' which was to provide core services such as a person demographics service, terminology services, messaging services (including e-Booking and the Electronic Transfer of Prescriptions service for primary care) and a clinical summary. This latter was to provide summary or status information such as (a) medication summary (previous and current medication). In addition to the status information, the spine summary was also to provide event-based information, one of which was 'medication events'. This would result in the provision of full medication records (being) available, promoting prompt recognition of conflicts and potential problems, as well as giving insight into patient compliance with drug regimens. Indeed the Clinical Spine Applications Service actually used the phrase 'Medication Profile' for one of its components.

The Local Services were to be where 'deep, rich clinical functionality and clinical data resides to support the end-to-end process of care delivery across a broad range of settings' (page 6). In all three of the exemplar scenarios described in Part Two, prescribing, dispensing and administration of medicines played a crucial role in the patient care, highlighting the importance of medication both in general patient care and in the information technology strategy to support it. Following a general introduction which includes some overall requirements, the specification is split into over twenty sections, each focussing on a set of clinical functionality that a local system should perform, such as managing clinic referrals and appointments, reporting of (laboratory) results, maternity care, decision support and prescribing and pharmacy (medication management). Within each section, there are overview and scope sections, followed by the desired benefits and outcomes expected by using the functionality, both generally and specifically for patients and clinicians. There is then a table of detailed requirements statements, for example 'When the current prescription course has ended, it shall disappear from the current list although still be present within the medication history' (113.5.5). Section 113 of the ICRS describes all the requirements for 'Prescribing and pharmacy' reiterating the statement that 'prescribing and administering drugs to patients is a key care process' and that 'if inadequately informed, can also cause serious risks to patient safety'.

Comment

Within Information for Health, although its clinical summary was to include '(a) medication summary (previous and current)' and the Spine was to gather 'medication events', no definition or description of exactly what either of these really entailed was provided.   This meant that the specification was open to a wide range of interpretations as to what would or would not be a sufficient summary, and how that summary could be generated from the currently available event-based information sources and those that might possibly be available in the future.   Differing interpretations of a goal mean that it was almost impossible to achieve it, and that indeed unfortunately was the case for the medication summary as described in the Information for Health specification.

CEN/ISO EN 13606, Health informatics - Electronic Health Record Communication

In the wider European community, rather than defining a specification on the basis of its outputs, the focus was on developing a specification for the architecture of an EHR, the structure it should have to support its goal of being a cradle-to-grave record of a patient's health status and clinical care that could be communicated between systems.   This effort centred on EN ISO 13606: the Electronic Health Record Communication specification[130].

13606 defines a rigorous and stable information architecture from which to communicate part or all of the EHR of a single subject of care (patient) in order to support the interoperability of systems that need to communicate (access, transfer, add or modify) EHR data via electronic messages or as distributed objects.   It stresses the importance of being faithful to preserve the original clinical meaning of the data as intended by its author and of reflecting the confidentiality of that data as intended by both the author and patient.   As such, it has a generic reference information model to represent the information structure (record components, with items of content), which is then populated to describe the actual instances of clinical information.   However, it does not provide definition of any individual clinical data elements that would populate that reference information model; these are the 'archetypes': constraints and legal combinations of the classes of the reference information model (specifying particular record component names, data-types and prescribed value ranges and values) that then can be used to describe the things of importance in particular clinical domains, organisations, and operational contexts. Archetypes, once defined and verified, can be stored in a repository (library) for use by a healthcare enterprise. This library would form a metadata repository for that enterprise, and the meaningful shared clinical semantics of the enterprise are then metadata and terminology focussed rather than model (pattern) focussed.

Comment

In terms of information to support a Medication Profile, 13606 does not and would not explicitly reference medication data elements at all; that would be a task for an archetype repository for an enterprise. Because the current incarnation of an archetype repository is enterprise-based, even though this was not its original intention, there is a risk that different archetype repositories, even though based on 13606, would design different medication archetypes, depending on the functional use cases to be supported. Although semantically interoperable communication within the enterprise should be possible, as soon as communication outside the enterprise is required, point-to-point information transform (mapping) will be required with all its attendant risks of loss of information or unintended addition of meaning.

There are a number of initiatives currently looking at the development of archetypes, or their close relation, detailed clinical models. The openEHR Foundation[133] provides 'a set of archetypes for clinical use in an international setting' though its archetype repository[134] (Clinical Knowledge Manager - CKM). Searching in the CKM for 'medication' offers 36 archetypes (as of January 2015) that include 24 that reference medication information (e.g. an archetype for recording an adverse reaction) and 12 whose focus is directly on medication information (e.g. an archetype to describe an amount of medication). None of the medication-focused archetypes is standard in that their status is either 'draft' or 'team review', although one composition archetype, which could be used to describe a medication list (in conjunction with other more specific medication archetypes) has the status of 'published'. Unfortunately, there is currently no formal quality process that could move these archetypes to what could be considered a standard status. The data elements present in these archetypes have therefore not been considered for inclusion in the analysis below because they cannot be considered a published and authoritative. The same would be true for the detailed clinical models produced by openCIMI (Clinical Information Modeling Initiative)[135].

HL7 EHR-S FM

In the USA and to a lesser extent in Canada, the focus has been on a functional specification for the EHR, the operations that clinicians and others would undertake that should be supported by the information in the EHR. This focus centred on the HL7 Electronic Health Record System Functional Model (EHR-S FM)[136]. The HL7 EHR-S FM specifies sets of functions, divided into seven functional areas, which an EHR system should support. It also gives a standardised description of each function so that there can be a common understanding of what the function actually entails. Finally, it creates domain Functional Profiles that go across the functional areas and create subsets that constrain individual functions as required or desired

in a way that is deemed appropriate for use in various contexts of care (primary, secondary). The specification is clear that implementation of it 'is not sufficient to provide a longitudinal health record'. It does however aim that 'information exchange enabled by (it will) support the population of clinical documents, event summaries and in the future will enable a longitudinal health record'.

The HL7 EHR-S Functional Model also provides a Glossary, so that concepts referenced in the requirements statements can be understood. Also in the Glossary, there is a definition of that most elusive concept, a patient's 'Current Medication': 'A medication that a patient is using, either on a regular basis or on an ad hoc basis (e.g., "two pills as needed for pain"). A medication that has been dispensed to a patient and whose administration has not yet been completed or finished according to the medication's intended duration, dose, frequency, and quantity.'

Section CP.6 in the EHR-SFM describes Medication focused functionality, 'the functionality required to support the safe administration of medications or immunizations to a patient based on medical requirement and orders within the system. This includes presenting providers with the list of medications or immunizations that are to be administered to a patient, necessary administration information, and capture all required and relevant administration details'. The specification then gives a long set of formal requirements statements that a system could claim conformance to, for example: 'The system SHALL provide the ability to render the list of medications that are to be administered' and 'The system SHALL provide the ability to render the list of medications that are to be administered including all administration directions/instructions (SIG)'.

Comment
Although the HL7 EHR-S Functional Model is primarily about functionality, it does by implication provide some data element requirements, as the functions mentioned list (although do not define) particular items of information, for example to describe dosage instructions. The Glossary goes some way to address the definition necessary for implementation of such a functionality-based specification, much more so than the NHS ICRS. However, it can be argued that in health informatics, the relationship between concepts is as important to their definition as a textual description, and therefore although the Glossary in the HL7 EHR-SFM is useful, it is not sufficient to support its implementation in such a way that conformant systems would be semantically interoperable.

Within the HL7 EHR-SFM, in the initial overview section (section 4) the example used following the section descriptions is 'Manage Medication List'. This highlights

how often a medication management activity is a poster child in healthcare informatics generally and in this specification in particular. In the Glossary, there is a specific clarification section (section 7.6.4 Clarification of Terms) that deals with distinction of 'nuanced' or 'troublesome' terms and it has just one entry: to discuss the difference between a 'medication order' and a 'prescription order' – again showing just how complex the whole medication domain is deemed to be. The outcome of this clarification was that, for the EHR-S Functional Model 'prescription' was to be used only to refer to the *document* from an authorised practitioner that is required for ordering of medications because of jurisdictional legislation, before the medication can be supplied. 'Medication order' is a wider term, covering the use of all medicines, and is the preferred term in the HL7 EHR-S Functional Model.

Overview of Patient Summary Specifications and their medication information

None of the EHR initiatives has solved the problem of how to share health information, and specifically information about medication, although they have obviously contributed to the field. In more recent years, the focus of standardisation has shifted away from trying to specify the EHR or parts of it in terms of functionality or in terms of record architecture, towards patient summary interoperability specifications, of which European Patient Summary Guidelines[137] and the Continuity of Care Record[19] have been two of the most prominent. The aim of both of these interoperability specifications is to describe a core set of information that systems should be able to share between them to support basic patient care, then, over time gradually enrich these specifications to (hopefully) lead towards a shareable cradle to grave record.

The Continuity of Care Record (CCR) (USA)

The Continuity of Care Record (CCR) describes a core set of the most relevant administrative, demographic, and clinical information about a patient's healthcare, which may be derived from one or more healthcare encounters. Its purpose is to provide a mechanism for one healthcare practitioner and/or system to aggregate all of the pertinent data about a patient and forward it to another practitioner and/or system to support the continuity of care for that patient. The colloquial phrase often used is to share 'a snapshot in time' from one system and therefore one practitioner to another for a specific patient. The intent of the CCR is to enhance patient safety by reducing errors and to reduce the cost of care by enhancing efficiency of health information exchange. It aims to do this by assuring at least a minimum standard of health information transportability when a patient is referred, transferred, or is otherwise seen by, another healthcare provider.

After its introduction describing its scope and purpose, and a large glossary section, the CCR specification expresses its intended significance and benefits to patients and clinicians from its use. It is in this section (4.2) that the CCR summarises the information that it considers is essential for the delivery of good patient care, which, when provided can 'serve as a necessary bridge to a different environment, often with new practitioners who know little about the patient'. It is here that medication information is listed, along with allergies, current and recent past diagnoses, most recent healthcare assessments and services, advance directives, and the recommendations of practitioners who last treated the patient. The main focus of the specification then follows, describing the CCR itself, and the sections of the body of the record. Section 5.1.2.9 Medications should contain 'a patient's current medications and pertinent medication history' and that 'At a minimum, the currently active medications should be listed, with an entire medication history as an option, particularly when the CCR is used for comprehensive data export'. There then follows, as an Annex, a description of the xml schema elements (tags) that make up the CCR, with their definition and description, examples and optionality, and in a second Annex, some implementation guidance with exemplar completed xml snippets for various sections.

Comment

Despite having listed medication information as essential to support good patient care, the CCR specification somewhat contradicts itself in its focus on the criticality of medication information, as in the detail of the specification in the xml data objects, the Medication data object is stated as 'optional' in any one CCR for any one patient in any one context. But it then says, in the same line, 'At a minimum, the currently active medications should be listed, with an entire Medication History as an option, particularly when the CCR is used for comprehensive data export'. This paradox of such specifications, trying to be flexible enough and generic enough to please everyone and therefore not risking mandating everything, does risk the value of the specification and makes useful and conformant implementation difficult.

Just as with the HL7 EHR-SFM, medication information plays a poster child role in the CCR; for example, when describing the requirement to validate critical information from the CCR before further action, 'current medications' are given as the example (section 1.6); and in the examples of data objects in the CCR, given in the Appendix (A2.3.1.4) the first example is of amoxicillin as a medication object. In describing medication information, the CCR relies heavily on an existing US-based Community Pharmacy standards organisation, the National Council for Prescription Drug Programs (NCPDP)[138] and on two US-based identification systems for medicinal products: the National Drug Code[139], managed by the Food and Drugs

Administration and RxNorm, a metathesaurus managed by the National Library of Medicine[112]. However, the CCR does provide a significant amount of detail on the data elements that it specifies are part of the Medication section, and these have been analysed in detail in the Results section below.

The European Patient Summary Guidelines

The European Patient Summary Guidelines have their primary focus to support the objective of continuity of care and patient safety across borders, as stated in Article 14 (2) (b) (i) of the Directive on patients' rights in cross-border healthcare[140]. The Guidelines focus on defining the data elements needed to safely provide emergency or unplanned care in a cross-border context. They also have a secondary purpose of being available as reference material for member states; the Guidelines acknowledge that 'advanced and elaborate Patient Summaries exist in some member states' (page 3) but for other states, the Guidelines serve as a baseline for development. This means that they describe not only what data is to be included in the Patient Summary but also that they provide the ability to assess the implications of adopting a patient summary in practice, especially in terms of organisational, technical and semantic requirements. The aim of the Guidelines is that member states should commit to implementing the dataset in whatever systems are or will be developed in their jurisdictions. Semantic interoperability is highly desirable for the Patient Summary, and towards that aim, the Guidelines offer a 'a non-exhaustive list of data that are to be included in patients' summaries and that can be shared between health professionals to enable continuity of care and patient safety across borders' (page 5). The Patient Summary should be useful in any clinical encounter, but it is likely to be most useful when the health professional and patient do not share the same language and where, as an unplanned encounter, no information is readily available. Following on from its introduction, giving its scope and purpose and describing its context in the European e-health landscape, the Guidelines provide a set of exemplar use cases, showing when the Patient Summary would be used, not just textual descriptions of the event, but also how the systems providing information to each other would interact.

The Guidelines then move to the Dataset itself, which consists of 'essential and understandable health information' that is made available 'at the point of care to deliver safe patient care during unscheduled care [and planned care]' but which should have its 'maximal impact in unscheduled care' (page 9). This then constitutes the minimum essential dataset needed to provide safe ongoing care for the patient, especially for unscheduled care. The Guidelines list in detail the sets of variables (data elements) that should be present in the Summary and giving definition of and comments about them, and qualifying them as 'basic' or 'extended'. Each field in

the dataset was defined while 'keeping in mind the medical perspective and the clinical purpose' (page 17). Implementation of the Guidelines is the responsibility of the member states, although some guidance is given in the sections following the dataset description, including how shared communication of the dataset might be implemented technically, by the use of 13606 or the HL7 Continuity of Care Document (the HL7 implementation of the CCR) or by the use of an IHE Profile for Patient Care Coordination[141]. Within the dataset there is a section called Medication Summary which should contain a 'list of current medicines' and which define the individual variables that would fulfil that summary (page 12). These data elements have been analysed in detail in the Results section below.

Comment

The Medication Summary is listed as 'basic' and therefore is considered by the Guidelines to be core information within the Patient Summary. The Guidelines themselves identify areas where further work is required, and pick out in particular the need for shared controlled terminology to be used to support the value sets for each data element in the dataset. This was the only specification to do this, and reflects the very broad and multi-lingual nature of the healthcare enterprise being addressed.

Methodology

As described in the Introduction, there is no one single gold standard specification for a description how a patient's medication information should be described in a Medication Profile to support patient care, whether that Profile be in a longitudinal health record or in a patient summary. The aim of the investigation was therefore analyse a set of the recognised national and international electronic health record and health record summary specifications to document the data elements about medicines that these require. A data element that is present in all of the specifications could be considered *essential,* a first class requirement on the Medication Profile, whereas a data element present in only one of the specifications may be considered a less important optional requirement in terms of the use case of supporting patient care. There was not scope in this research to undertake an exhaustive international survey of all available specifications, but this is not considered an important limitation given their similarity. The specifications were current and publically available during the period of this study, which was January to April 2015.

Each specification was examined in turn and the medication sections identified. From within these sections, the data elements requested were noted. The starting point for the medication data elements was usually a description of the medication itself (e.g., a section entitled 'medicinal product'). The semantics (meaning) of each

medication data element in each specification was determined, by examination of its name, its description and critically, any examples of the instantiated data element that were provided. For instance, the data element named in CCR as <Dose> and described as 'This is the dose to be administered, not the dispensed dose' can only be identified as the thing that it really is (Dose Quantity) by looking at the example given: 'A simple dose example would be "250mg"'. Each data element was then given its own name and definition, independent of any one of the examined specifications. These definitions were based on or adapted from the relevant ISO definitional standards[142] for the data element; if no ISO standard is available, a data element name and description has been made up, as semantically robustly as possible.

The extraction of data elements was crosschecked by the author by undertaking a separate second pass through each specification. The research supervisor independently checked the extraction for a sample of various parts of the specifications. Due to the heterogeneity of the format of the specifications and the variation in granularity of the data elements themselves, an iterative approach was used to develop a meaningful description of the Results in tabular form.

Results

Four specifications were examined to ascertain the data elements that each required in their medication records; the details of the specifications shown below in Table 7 following.

Table 7: Description of the EHR and patient summary specifications examined

Specification Short Name	Specification Full Name	Owner
CCR	Standard Specification for Continuity of Care Record	ASTM International
HL7 EHR SFM	HL7 Electronic Health Record System Functional Model	Health Level 7 International
EuPS	Guidelines on minimum/non-exhaustive patient summary dataset for electronic exchange in accordance with the cross-border directive 2011/24/EU; Release 1	European Commission
NHS ICRS	Integrated Care Records Service Output Based Specification Parts 1 and 2	NHS National Programme for Information Technology (NHS England)

High Level Data Elements

Table 8 below describes and compares the high level data medication information required by each of the specifications. The Data Element Definition provides a standardised meaning for the data element, then for each specification, its stated requirements for that data element are provided.

Table 8: Definition of and comparison of the high level data elements of medication information from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Medication (Medicinal Product)	Description of the medicinal product itself (independent of the activity it is used it – be that prescribing, dispensing, (self) administration, statement about)	'list and describe the patient's current medications and pertinent medication history'	'The system SHALL provide the ability to render the list of medications that are to be administered' 'The system SHALL provide the ability to render the medication administration history including administering provider, date, and time.'	'List of current medicines'	'Medications must be able to be added to the patient profile by a patient or a patient's practitioner, or electronically through uploads from pharmacy fulfilment files.'
Medication 'Activity'	Description of the role in the Medication Process that the medicinal product played (e.g. being prescribed, administered, or statemented)	'list and describe the patient's current medications and pertinent medication history'	'The system SHALL provide the ability to render the list of medications that are to be administered'	'All prescribed medicines whose period of time indicated for the treatment has not yet expired, whether it has been dispensed or not'	*Not required*

Table 8 (cont.): Definition of and comparison of the high level data elements of medication information from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Information Date/Time	Description of the time when the information about the medication was made or recorded	*Not required*	'Appropriate time stamps for all medication related activity are generated.'	*Not required*	*Not required*
Status	Indication of the state (standing, nature) of the item of medication information with reference to the role in Medication Process – and whether it could be considered current or historic, and whether it has been reviewed	'Defines the <Status> of the <Product>. [Active, On Hold, Prior History No Longer Active]'	'The system SHOULD provide the ability to tag the medications that are to be administered by the patient (i.e. self-administered).' 'The system SHOULD provide the ability to capture an acknowledgement from a user that a medication order has been reviewed including capturing the date, time and user credentials.'	'All prescribed medicines whose period of time indicated for the treatment has not yet expired whether it has been dispensed or not'	*Not required*

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Table 8 (cont.): Definition of and comparison of the high level data elements of medication information from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Dosage instructions	Description of the full set of information that supports the correct administration of a medication to a patient in order for it to have its therapeutic effect[143]	'<Directions> is the instructions (SIG) component describing the intended patient use of the <Product>. <Directions> contains an XML string defined as follows below. Can be used to map a single SIG or a complex recurring SIG like a tapered dose or sliding scale. Recurring SIG segments are represented by repeating the <Directions> tag and its children.'	'The system SHALL provide the ability to capture, maintain and render medication administration details as discrete data, including:(1) the medication name, strength and dose;(2) date and time of administration;(3) route and site;(4) administering provider (5) observations, reactions and complications (6) reason medication not given, and/or medication related activity not performed; according to scope of practice, organizational policy, and/or jurisdictional law. '	*Some individual items of dosage instructions information described in the dosage instructions table below*	'Dose' and 'Route'

Table 8 (cont.): Definition of and comparison of the high level data elements of medication information from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Course of Therapy Timing	Description of the dates and/or timing information when the medication was used by the patient as a whole (synonymous with a 'regimen timing') Often considered part of the full dosage instructions set	'Used to define dates and times relevant to the patient and the Product.' This can be an exact DateTime, an age, an approximate DateTime, or a DateTime range.'	*Not required*	*Not required*	*Not required*
Dispensing / Repeat (Refill) Information	Description of information needed for correct dispensing of a medicinal product to a patient/carer, including labelling and repeat information	'<FulfillmentInstructions> for the <Product>, which in the case of medications are the instructions to the dispensing pharmacist or nurse. Label In Spanish, Dispense As Written. <Refill> Defines the number of <Refills> and any constraints on <Refills>. Includes <Number>, <Quantity>, <DateTime>, to define 'Last Refill,, and <Comment> for any specific <Refill> alerts or comments.	'The system SHOULD provide the ability to render medications as dispensed (including dose and quantity of dispensed units of medication).'	*Not required*	*Not required*

Table 8 (cont.): Definition of and comparison of the high level data elements of medication information from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Regimen	Description of any order or pattern between items of medication information that is important – e.g. for a treatment regimen	'<SeriesNumber> Defines the <SeriesNumber> of the <Product>, for use when there is a series of medication administrations. Enoxaparin, chemotherapy, etc.'	*Not required*	*Not required*	*Not required*

Note that all bar one of the specifications describe the role that the Medication is playing in the overall Medication Process. This is done by indicating whether the Medication is/was prescribed (ordered) (i.e. from a prescription), or was dispensed or administered (i.e. is an administration record) or whether a statement about Medication administration is being made (i.e. 'medication was taken from this time to this time'). The exception is the NHS ICRS, which implicitly assumes that all information will be in the form of Medication statements, and therefore describes who should add statement information rather than what statements should be made.

Only the CCR and HL7 SFM mention data elements that are specifically to support dispense information – such as refill numbers and repeat dispensing time information.

The CCR supported some methodology to relate together different medications as part of a regimen or programme of therapy (as with cancer chemotherapy). However, the mechanism to implement this is not clear from the single numeric data element. The CCR also included 'Course of Therapy Timing' as a high-level data element; this would normally be considered part of the more granular dosage instructions.

Low Level Data Elements

Medication

The first high-level data element required in all specifications was identification of the medication itself. In Table 9 below, the detail of the granular data elements required by each specification to fully describe a medication is provided. As in the previous table, the Data Element Definition provides a standardised meaning for the granular data element, then for each specification, its stated requirements for that data element are given. If a standard definition for the data element is available, that is used and reference.

Table 9: Definition of and comparison of the data elements for description of medications from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Medication (medicinal product) code (often referred to as 'ID')	A machine-readable identifier - a 'code' from a coding system to identify the medicinal product. e.g. an NHS dm+d code or an RxNorm code	Instance of IDType, which includes child elements <Type>, <ID>, and <IssuedBy>.	'The system SHALL provide the ability to capture and maintain the medication identification number of the drug administered to the patient (e.g., NDC number, lot numbers, expiration date).'	*Not required*	'The medications must be able to be either entered as coded drugs…..'
Product Name	The human readable designation for the medication – either as the 'preferred name' from the coding system used or a free text product appellation – brand or generic	'<ProductName> Defines the generic name for prescriptions and over-the-counter medications and non-proprietary name for non-medication products. An NDC Code or RxNorm Code (preferred) should be used when <Product> is used to describe a medication. <BrandName> For the medications that are branded, It defines the <BrandName> of the <Product>. One should also provide the generic name of the medication as <ProductName> above. <Manufacturer> Defines the <Manufacturer> of the <Product>.'	'The system SHALL provide the ability to capture, maintain and render medication administration details as discrete data, including: (1) the medication name, strength '	*Not required*	'The medications must be able to be either entered as coded drugs, using the drug search, or as free text if the item is not in the formulary (e.g., herbs, vitamins, etc.). Medication name; generic name (if applicable);'

Table 9 (cont.): Definition of and comparison of the data elements for description of medications from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Active Ingredient Substance (plus code)	The chemical/biologic/mineral matter of defined composition present in the medicinal product that produces or contributes to the therapeutic effect of the medicinal product[144]	*Not required*	*Not required*	'Substance that alone or in combination with one or more other ingredients produces the intended activity of a medicinal product. Example: 'paracetamol'. Brand name if a biological medicinal product or when justified by the health professional (ref. Commission Directive 2012/52/EU). Code that identifies the active ingredient'	*Not required*
Strength Note: CCR has 'size' included in Strength; this is not appropriate except for device products	The amount of active ingredient substance(s) present in single administration unit of the medicinal product[144]	'Strength> Defines the predefined strength of the <Product>. MeasureType with <Value>, <Units>, and <Code>. <Units> has children <Unit> and <Code>. <Form> <Concentration> MeasureType with <Value>, <Units>, and <Code>. <Units> has children <Unit> and <Code>. <Size> (e.g. small, medium, large)'	'The system SHALL provide the ability to capture, maintain and render medication administration details as discrete data, including: (1) the medication name, strength'	'Content of the active ingredient expressed quantifiably per dosage unit, per unit of volume or per unit of weight, according to the pharmaceutical dose form. Example: 500 mg per tablet'	*Not required*

Table 9 (cont.): Definition of and comparison of the data elements for description of medications from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS	NHS ICRS
Dose Form	The physical manifestation of the medicinal product that contains the active ingredient(s) and/or inactive ingredient(s) that are intended to be delivered to the patient[144]	'<Form> - dose form'	'Form in which a pharmaceutical product is presented in the medicinal product packaging (e.g. tablet, syrup)'	*Not required*	'Dosage form'
Diluent or Vehicle	Any substance used with the medicinal product to support its administration to the patient, as in a diluent or carrier substance	'Used to define a <Vehicle> used to deliver the <Product> such as an IV solution. D5W, normal saline, etc. Note: is in dosage instructions section in the CCR specification'	*Not required*	*Not required*	*Not required*
Quantity	The amount of medicinal product being referred to (for dispensing/supply) Note: this is not the dose quantity	'Quantity> MeasureType with <Value>, <Units>, and <Code>. '	*Not required*	*Not required*	*Not required*

Note that the HL7 SFM is the only specification to include data elements for the lot number (batch number) and expiry information for the medicinal product.

Dosage instructions

The other information for which the majority of specifications described requirements for significantly more granular data elements detail is that of dosage instructions. Table 10 below shows this for three of the four specifications; the NHS ICRS had only a minimal requirement for 'Dose' (no further explanation) and 'Route' data elements, so it has not been given its own column in this detailed table. As in the previous tables, the Data Element Definition provides a standardised meaning for the granular data element, then for each specification, its stated requirements for that data element are given. If a standard definition for the data element is available, that is used and reference.

Table 10: Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Dose Quantity	Describes the 'amount' of the described medication that is to be administered to the patient at a single point in time (i.e. a single dosage administration act)[143143]	'<Dose> This is the dose to be administered, not the dispensed dose. Dispensed dose is found under <Strength>, above. This is the dose portion of the SIG which can define a fixed dose or can repeat to define a variable dose, dose range, or dose options. This is the numeric or text expression of the dose. A simple dose example would be '250mg' where the value in this field would be '250'.'	the medication name, strength and **dose**	Number of units per intake that the patient is taking. Example: 1 tablet

Table 10 (cont.): Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Rate of Administration	Describes information about the 'delivery speed' with which a specified amount of a medication should be administered to a patient per unit of time[143]	'Dose also includes: Also contains <Rate> and for multiple or variable doses. <DoseSequencePosition> and <MultipleDoseModifier>.' '<DoseCalculation> This segment is used to express a dose as a calculation, such as '40mg/kg/day divided into 3 doses'. This segment is used in conjunction with <Dose> to allow the expression of a dose as a calculation. Also used to express doses to be calculated by nurses based on physiological parameters, such as Dopamine, Nipride, etc. Amoxicillin for a child is dosed at approximately 40mg/kg/day/2 to 3 doses. For a 9kg child, an appropriate dose would be 125mg tid. To express this, the prescribing physician would put '125mg' in the <Dose> (and 'tid' in <Frequency>) and '40mg/kg/day/3 doses' in <DoseCalculation>. This allows the pharmacist to look at the dose (125mg tid) and do a secondary patient safety check against the desired dosing of '40mg/kg/day/3 doses"	*Not required*	*Not required*

Table 10 (cont.): Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Route of Administration	Describes which way that the administered medication should take to get into the body or into contact with the body[143]	'<Route> Used to define the <Route> of administration. po, pr, sl, etc.'	'route and site;'	*Not required*
Site of Administration	Describes the specific area of the body 'where' the medication is to be administered[143]	'<Site> Used to define the physical location on the patient for use, implantation, or administration, where specified. Right gluteus, left deltoid, Hickman catheter, etc.'	'route and site;'	*Not required*
Method of administration	Describes 'how' the medication should be administered - the particular way of carrying out or accomplishing the substance administration[143]	'DeliveryMethod> The textual representation of the Dose Delivery Method. This is the method in which the dose is delivered (describes how the dose is administered/consumed). Defines the method: take, apply, swish, swallow, inject, insert, chew, use, give, sprinkle, mix, dissolve'	*Not required*	*Not required*

Table 10 (cont.): Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Dose Timing	Describes fully the 'when' for medication to be (or was) administered to the patient[143]	'<AdministrationTiming> This is used to define a specific administration or use time. Can repeat for more than one administration time. Can be a text string (Morning, Evening, Before Meals, 1 Hour After Meals, 3 Hours After Meals, Before Bed) or an exact time.'	'date and time of administration' 'Date when patient needs to start taking the medicine prescribed'	'Date of onset of Treatment: Date when patient needs to start taking the medicine prescribed'
Frequency	Describes when the medication (expressed as the dose quantity) is to be (or was) administered to the patient *using a measured time pattern* (twice per 24 hours, once per 2 weeks, every 6 hours)[145]	'<Frequency> Used to define a <Product> frequency of use/administration qd, bid, tid, qid, qod, etc.' '<Interval> Used to define a <Product> interval of use/administration. q15m, q2h, q4h, q12h'	*Not required*	'Frequency of Intakes: Frequency of intakes per hour/day/week/month. Example: every 24 hours'
Duration of Therapy	Describes how long the course of therapy of that medication is to be or was[143]	'<Duration> Used to define the <Duration> of use or administration of a product. x 10 days'	*Not required*	'Duration of Treatment Example: 14 days'

Table 10 (cont.): Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Dosage Upper Bound	Describes a limit for the amount of medication that can be administered during a particular timing period[143]	'<DoseRestriction> This segment can repeat for more than one dose restriction. This is the dose restriction segment of the SIG which defines a maximum or dose imit. 'Not to exceed 10 Tablets in 24 Hours' or '1000 mg/kg/hr'.'	*Not required*	*Not required*
Indication	Describes the intended (therapeutic) use and reason for the medication being administered[146]	'<Indication> Defines the <Indications> for the use of the <Product>. This can be a <Description> or a <Problem> or a link to a <Problem> within the CCR, or one or more <PhysiologicalParameter>. It also includes a PRN designator.'	*Not required*	'The service shall facilitate the documentation against patients or individual drugs of: the reasons / indications for drug therapy initiation and the reasons for an individual drug choice and/or the reason for rejection of a particular drug;'

Table 10 (cont.): Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Non-administration Reason	Describes the cause or motivation why a medication was not administered to the patient as according to the described dosage instructions	*Not required*	'reason medication not given, and/or medication related activity not performed; according to scope of practice, organizational policy, and/or jurisdictional law.'	*Not required*
Discontinuation	Describes information about when the medication administration (is to be) ceased	<StopIndicator> Used to express a hard stop, such as the last SIG sequence in a tapering dose, where the last sequence is 'then D/C' or where the therapy/drug is used to treat a condition and that treatment is for a fixed duration with a hard stop, such as antibiotic treatment, etc. An instance of CodedDescriptionType. Can have the value Yes or the tags will not exist and there will be no content (the null instance of a <StopIndicator>).	*Not required*	*Not required*

Table 10 (cont.): Definition of and comparison of the data elements for description of dosage instructions from the EHR and patient summary specifications

Data Element Name	Data Element Definition	CCR	HL7 EHR SFM	EuPS
Clause Sequence	Describes the (ordinal) position of a particular clause (set of dosage instructions) within a full set of dosage instructions for a single medication; should be used with the conjunction 'then' [145]	\<DirectionSequencePosition\> Used when the \<Direction\> repeats (multiple SIGs) such as with an insulin sliding scale or tapering dose, etc.	*Not required*	*Not required*
Clause Conjunction	Describes the relationship between of two dosage instructions clauses (within a full set of dosage instructions for a single medication (or, then, and)[143]	\<MultipleDirectionModifier\> Defines the relationship between multiple directions (SIGs). Used with the values AND, OR, or THEN to express when there is more than one SIG as to whether all the SIGs must apply (AND) or if any of the SIGs can apply (OR) or if the SIGs are sequential (THEN), in the sequence defined by \<DirectionSequencePosition\>.	*Not required*	*Not required*
Additional Instructions	Describes any other additional instructive information about the administration of the medicine; it is usually non-quantitative in its nature[143]	\<PatientInstructions\> Defines the \<PatientInstructions\> for the \<Product\> that are not covered under \<Directions\> - in other words \<PatientInstructions\> that are not traditionally part of the SIG. Take with water.	*Not required*	*Not required*

Discussion

High level Data Elements

All specifications have a description of the medication (medicinal product) being referenced. Whilst this would seem to be almost an absolute requirement – how could information about a patient's medication be described without describing the medication? – this is not necessarily so. In the clinical research domain, medication has been described less directly, by reference to its membership of a therapeutic group, or by its indications, as will be seen in the following chapter.

Only the EHR SFM explicitly mentions a timestamp for the system capture of medication information. To know when something occurred seems such a key requirement that possibly the other specifications consider such information to be metadata about the medication information and therefore do not explicitly describe it in the detail of the specification. For example, the EN ISO 13606 model requires the capture of that time stamp for all information, which would include medication information, if that was part of the archetype being used).

All but the NHS ICRS have some way to indicate whether the described role of the Medication is current (active) information or historic (no longer active) information. From the description and examples in the specifications, 'current' information is implicitly taken to be medication that the patient is actively using at the time the information was recorded (for example, a current prescription implies that the patient may have received a supply as dispensing information is available and therefore is assumed to be administering it at that time). 'Historic' information concerns medication information that was used at some time before the time when the information was recorded. 'Current' and 'historic' as terms here are given their meaning in the context of administration of medication, not in the context of medication information that is relevant to clinical decision-making. It is concerning that there is no explicit definition of 'current' and/or 'historic' given formally, since these are informatics specifications and implicit definition is always at risk of misinterpretation.

All the specifications mention dosage instructions in some way, ranging from just the two elements of 'Dose' and 'Route' in the NHS ICRS through to very granular and detailed data elements in the CCR. The CCR also has a specific Course of Therapy Timing data element at this high level, which, from its description, indicates that it allows this timing to be expressed not just as a set of actual dates but as relative timing, by specifying the age of the patient when the medication statement is/was relevant. For example, it would support a statement such as 'phenytoin was taken [by this patient] from age 5-9 years'.

Low level Data Elements

Medication

All but the EuPS have requirements for a machine-readable code to describe the Medication and a human readable display name as separate data elements. Note that most system implementations (and especially all those using the ISO 21090 healthcare datatypes[147]) this would be implemented in systems as a single data element with a complex datatype, thereby not splitting the machine-readable and human readable elements for the same thing. It is likely that the EuPS does not have this requirement because there is no applicable pan-European Medicinal Product code system that is able to satisfy this requirement; the Horizon 2020[148] openMedicine initiative[149] from the European Commission has specifically set up a project to address this need. Because of this lack of a pan-European Medicinal Product code system, the EuPS specification has an active ingredient data element, allowing the use of the international non-proprietary name for medicinal substances, which is applicable throughout Europe.

All but the NHS ICRS have a description of the product strength as a separate data element, even though this is likely to be in the medication display name obtained from a code system. This is also true for information about the product dose form, and here the EuPS is somewhat illogical in that it does not require this data element, so the Summary would contain information about active ingredient(s) and strength(s) but not the dose form that these would be formulated into for use by the patient. However, some medicinal product code systems do have the additional facility to describe the product in an abstract way, without dose form and strength information, so specifications have to allow for that variability. Unfortunately, without guidance and examples (which none of the specifications gave), there is a risk that an inappropriate combination of data elements are populated, or worse, populating the data elements with contradictory information, making the medication information less than fully useful. For example, if the Product was described as 'amoxicillin 250mg powder for solution for injection' but the dose form was given as 'oral solution' there is a clear inconsistency in the information which cannot but cast some level of doubt on the accuracy of the information overall.

The CCR also has data elements to support information about diluent(s)/vehicle(s) to be used with the Medication and for quantity; all of these are 'instructional' information that would specifically support dispensing activity, which is consistent with CCR also having repeat and refill information.

Description of a medication is not the subject of this thesis, but the medication (medicinal product) does have to be described in sufficient detail for the information in the Medication Profile to make clinical sense, to support the linking together of

information from the different medication processes and to support the distinction of the various types of courses of therapy. With the implementation of the ISO 11615 specification[144] to provide a full international code system for all authorised and investigational medicinal products, a human readable product name and machine-readable code should suffice; however, dose form, strength and diluent vehicle information may be needed (together) to describe magisterial products.

Dosage instructions

The lower level data elements in the dosage instructions section describe in machine-readable detail when and how the medication is being, was or should be administered to the patient.

The minimal requirements specified in the NHS ICRS for dosage instructions were for a 'Dose' data element, with no further explanation of what this should be, and no examples provided, and a 'Route' data element. It is here assumed that 'Dose' means at a minimum the Dose Quantity, but possibly also some aspects of Dose Timing. This is very poorly specified, especially for such an important document for the English NHS (at its time) and as such meant that the specification was un-implementable for any system, and particularly a system that was envisaged to be a central care record.

Dose Quantity

This data element is included by all three of the specifications that provide granular data elements for dosage instructions. However, to make that statement, one must make the assumption, for the HL7 S-FM, that 'Dose' is indeed dose quantity. For continuous administrations, such as intravenous infusions or gases administered through masks or similar devices, a rate of administration may be given rather than a dose quantity (specified as a quantity per time period). Only the CCR specification had a rate of administration data element.

Route, Site and Method of Administration

The CCR, HL7 S-FM and the NHS ICRS all included a route of administration data element; the EuPS did not include this. Occasionally, specifications may assume that route of administration information can be imputed by knowing the dose form of the medication itself (for example, tablets are normally for oral administration, eye drops for ophthalmic administration etc.) however the EuPS does not specify a dose form data element.

The CCR and the HL7 S-FM both had a data element for site of administration, whereas only the CCR specified method of administration information. Both of

these data elements are necessary only in a proportionally small number of sets of dosage instructions. For example site is given when laterality is important (e.g. left eye for eye drops), in situations where similar products are to be used at different sites (e.g. different strength topical steroid products on different body sites) and when the medication itself needs a particular site (e.g. cytotoxic medication that should be administered through a specific usually central vein). Similarly, method of administration is only important when there are choices (infusion or injection) or when it is unclear (for example that a tablet should be chewed before swallowing).

Timing

All of the specifications had some timing information, particularly information as to when the medication should/did start, except for the NHS ICRS, unless one assumes that the 'Dose' was meant to include it.   The CCR and the EuPS specify data elements for both a frequency of (single dose) administration and the duration of the therapy, and no specification had a data element for dose duration (for continuous administrations where the quantity is specified by rate) or for the duration of a cycle of therapy (for example the 28 day cycle of an oral contraceptive medication, in which medication is only administered for 21 days, or for chemotherapy cycles).

None of the specifications made any mention of implementing the data elements in such a way as to allow partial timing information to be recorded – for example, supporting timing of 'early-2008 until mid-2010'. This facility can be very useful for recording generic statements made by patients or carers when gathering or verifying a medication history.

Other Data Elements

The CCR and the EuPS specified a data element to capture the indication for the use of the mediation.

The EuPS also specified a data element to describe a reason for a medication not being administered.   It is not clear whether this is to be used for total non-administration (this therapy was prescribed but never dispensed or administered for this reason) or non-administration of a single dose (the 10pm dose was not administered, as the patient was asleep) or would be suitable for both.   The CCR specified a 'stop indicator' – when the medication should be discontinued (as opposed to when it was discontinued which would be part of the duration of therapy information). Neither of these data elements as described would be suitable to capture discontinuation reason information (e.g. medication discontinued due to intolerance or ineffectiveness).

The CCR had a data element to describe 'additional instructions' which are mainly aimed at dispensing and labelling, and as such are relevant only to that one part of the medication process and not to summary information.

The CCR was also the only specification to describe dosage instructions clause information, the sequence in the high-level data elements and the conjunction of these, and therefore was the only specification that could support the description of complex dosage instructions. This indicates the depth of the CCR specification through its requirement to support complex dosage instructions in a machine-readable way. This is in contrast to the other specifications that, it is assumed, expect complex dosage instructions to be given in human readable text only. Given that only machine-readable dosage instructions are candidates for dosage checking functionality and that in the spectrum of health information, even complex dosage instructions are highly structured, it would seem reasonable to have the facility to specify and implement machine readability of dosage instructions at some level of complexity.

Limitations of this study

All of the specifications that have been described and analysed here have been authored following a similar process, by the brainstorming a set of either invited or volunteer experts, and for some of these there is little if any transparency in that development process. Only the HL7 EHR-S FM actually provides any reference to its development process in its content: in the Scenarios section [5.5.1] it states:

> 'Dr. Smith and interested colleagues review an Ambulatory Care registered profile to see how the use setting and scenario illustrate the EHR functions related to their practice; they look at the Ambulatory Care prioritization of the individual functions that a *group of experts working with HL7 have identified*. They both begin by looking at an Acute Care balloted profile to see how a group of experts working with HL7 have identified how an EHR-S could be used within a hospital.'

For both 13606 and the HL7 EHR-S FM there has been a ballot process, in accordance with the procedures of the relevant standards development organisation, and indeed the HL7 EHR-S FM states: 'committee members and interested industry participants have formally reviewed and balloted [the normative content] following the HL7 procedures' [section 1.1, Table 1]. For all the other specifications, the development and consultation process is far from transparent, and therefore likely to be based on the professional opinion of those (invited to be) involved.

Decisions made in healthcare, whether at the highest levels of policy for a nation or group of nations, or at the lowest (but most personally important) level of the care of an individual person in a family, should be made with consideration of the best available evidence as to the validity, safety and efficacy of the course of action decided upon. That evidence is therefore foundational and in itself should be validated, and there is a growing recognition that not all evidence is equally valid. Initial work on evidence validation assessed the evidence of interventions made to sustain or improve health, and this have led to the understanding that the randomised controlled study provides one of the most valid levels of evidence[150]. However, in recent years understanding has developed to take a broader view of evidence, so that rather than looking at single studies, a systematic review of all studies is undertaken, with each contributing study being evaluated for quality before its contribution to the overall set of evidence is evaluated[151]. However, randomised controlled studies are not appropriate research methods in all situations, other methods can be more appropriate; so these need then to be evaluated for the risk of error and/or bias in their results. This has led to the description of hierarchies of evidence to allow different research methodologies to be categorised in terms of the probable validity of their results as evidence[152].

One of the best-known hierarchies of evidence is that produced and most recently revised 2009 by the Centre for Evidence-Based Medicine[153] - the 'Levels of Evidence'. In all areas, and specifically relevant here in the category of 'Economic and decision analyses', expert opinion, and particularly expert opinion without critical appraisal is specified as the lowest level of evidence (of 5). The CEBM also wisely opines: 'What are we to do when the irresistible force of the need to offer clinical advice meets with the immovable object of flawed evidence? All we can do is our best: give the advice, but alert the advisees to the flaws in the evidence on which it is based'. That same caveat should surely apply to all these specifications; however, by having undertaken a systematic comparison and analysis of them, it is possible that the outcome, i.e. the requirements described in this chapter, could then be considered as closer to a systematic review, which would move it evidence to level 3a.

Recommendations for further work

Specifications in EHRs and patient summaries, particularly for medication information, should be authored in open and transparent processes, based on best available evidence of need, as opposed to continuing to be authored based on (limited) expert opinion. Using this work as a basis, further evaluation of the evidence to support the requirements for data in EHRs and patient summaries should be undertaken, nationally and internationally. This should allow development

of specifications and systems that truly serve the needs of patients and healthcare professionals using the limited resources available for that development. All specifications should clearly and fully define the concepts they use, providing full examples.

Conclusion

Based on the assessment of current specifications for EHRs and patient summaries, the data elements that essential to be present and populated in a Medication Profile, in that they are required by the majority of the specifications, should be as follows:

- A description of the medication itself, preferably from a robust medicinal product terminology, but if that is not available, through description of active ingredient substance(s) and strength(s) and dose form
- A description of the status of the medication (active/current/ongoing, concluded/past)
- Basic data elements from the dosage instructions; at a minimum the
    - Dose quantity
    - Course of therapy timing; the date of starting (and stopping, if relevant) the medication
    - Route of administration

Data elements that should be present in a Medication Profile, based on their presence in one or more of these widely available EHRs and patient summaries are as follows:

- Other elements of dosage instructions
    - Site and method of administration
    - Individual dose frequency
- Indication for the medication
- Discontinuation information, including reason
- Dosage instructions clauses, with their attendant sequence and conjunction indicators

Information to supporting dispensing and active administration are pertinent to those processes only and are not necessary as part of a Medication Profile.

Part 2: Safe Medication Processes and Medication Decision Support

Introduction

The administration of a medicine to a patient is by far the most common therapeutic intervention made by healthcare professionals as they seek to change the course of events of a healthcare condition for the benefit of the patient concerned[1]. It is also, after staff costs, the most resource intensive; in the year 2014/2014, the NHS in England spent £14.4 billion on medicines[154] that is approximately 15% of the total budget[155]. Using medicines safely and reducing risks has been and is of continuing concern to individual healthcare professionals, to their employers and related organisations, to national responsible authorities and internationally.   Increasing patient safety by improving the safe administration of medicines to patients has rightly become a focus in both the provision of healthcare itself and the development of information technology applications to support the provision of that care. But it is clear that in current practice, medication errors continue to occur with disturbing frequency and that information deficits are a major contributor to adverse medication events[156].

In any examination of improving patient safety with regard to medication use, there are two distinct types of unsafe situations that are to be avoided; these are:

- Adverse drug reactions, which are defined by the World Health Organisation as 'any response to a drug which is noxious, unintended and occurs at doses used for prophylaxis, diagnosis or therapy' (p 42)[157]
- Medication errors, whose definition by the National Co-ordinating Council for Medication Error Reporting and Prevention has been adopted by the NHS National Patient Safety Agency and is 'any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of health professional, patient or consumer'[158], are mistakes which occur in one or more of the processes of prescribing, dispensing and administration of a medicine which produces an unintended and (potentially) harmful outcome

The European Medicines Agency now also provides a definition of medication error, including it within its definition of an adverse drug reaction: 'unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer'[159]. It notes that these are the most common single preventable cause of adverse events in medication practice. The EMA is now includes the reporting of adverse events due to medication error in the national pharmacovigilance databases and onward to the Eudravigilance

system, to support analysis of such events to take forward into risk management planning[157]. The understanding of adverse drug reactions per se, the science of pharmacovigilance, is discussed in relation to the Medication Profile in detail in Chapter 5(2) of this thesis. This chapter focusses medication safety in terms of systems available for the avoidance of adverse drug reactions occurring in the medication process, and for the avoidance of medication errors.

In the UK, there was an entire NHS report focussed on the safe use of medicines: 'Building a Safer NHS for Patients: Improving Medication Safety' published by the Department of Health**Error! Bookmark not defined.**. There is a growing body of research and consequent understanding about when medication safety is compromised and when medication errors and adverse events may occur. One of the key statements made within the report relates to the use of information technology generally in improving medication safety (page 11): 'The electronic national care record is central to this strategy and will ensure that any health professional treating a patient will have access to essential clinical information, including the medicines they are taking. This will provide increased safety in the prescribing, dispensing and administration of medicines'. This, coupled with the premise, expanded further on in that section of the document, that because a significant number of serious medication errors involve a failure to receive, recognise, interpret or act appropriately on the medication and/or patient data, and therefore that well designed and implemented information management systems could have potential to reduce the scope for human mistakes and lapses and possibly even to eliminate completely some types of error, show the strongly held belief at the highest levels that having an electronic care record will indeed make a major contribution to improving medication safety. However, although the report discussed the lack of exploitation of opportunities to improve medication safety provided by information technology only a few actual recommendations were made.

Unfortunately, despite reports such as this, there is little if any *evidence* in the literature of the value of information technology applications. In the key report on evidence-based safety improvement practices by Shojania et al[160] only two information technology based medication safety applications – computerised physician order entry (CPOE) with clinical decision support systems (CDSS) and using medicine bar coding – were discussed, although the former was cited as an opportunity for research. In their reflection on this situation, Leape et al comment that research into the efficacy of system change, particularly change involving such applications as CPOE, is difficult and expensive to conduct[161]. A systematic review to investigate the effects of CPOE and CDSS on medication safety was undertaken by Kaushal et al[22] and did find evidence that these systems can substantially reduce medication error rates, but most of the studies looked at home-grown systems, often

concentrating on specific therapeutic areas (e.g. antibiotic prescribing). This is in contrast to the rather broader levels of CDSS functionality described in a recent report by a JAMIA Clinical Decision Support Workgroup[162], which includes drug allergy checking, drug interaction checking, and other clinical information display (such as contra-indication information) in its basic functionality level, moving on to more advanced functionality such as weight-based dose checking for paediatrics, pro-active disease management alerts, and drug-lab alerts[23]. Note that in the UK, the term CPOE would be more readily understood as 'electronic prescribing', sometimes also written as eRx. Within the Building a Safer NHS for Patients report, electronic prescribing systems linked to the patient record are seen as valuable in reducing the risk of many prescribing errors (page 45)[1], and the use of decision support is implicit (for example, in the recommendation 'that all drug allergies should be recorded on the computer in a way that will trigger an alert if an attempt is made to prescribe these drugs in future' (page 71)[1], behaviour that is an almost universal standard to medication decision support applications; however no specific discussion of decision support per se is given.

In order for CDSS to function successfully and provide alerts to clinicians to warn against possible unsafe activity, they require in addition to their own knowledgebase and algorithms, inputs from the medication activity being supported, and these include inputs from the Medication Profile. The aim of this chapter is to describe the information requirements that CDSS place on the Medication Profile in order to support a safe medication process.

In addition to the activities of the medication process having potential for error and therefore the requirement for the use of decision support, these same activities also, somewhat paradoxically, are themselves the source of data for the Medication Profile. As such, these activities form the foundations of the dynamic model part of the domain analysis model discussed in detail in Chapter 9.

Methodology

As discussed in the Introduction, there is little literature available that focusses on the data requirements for provision of clinical decision support to support the medication process. In the paper by Kuperman et al[162], which is a review of decision support in order entry systems, various modules of decision support are discussed, but mostly in terms of evidence for their use rather than in terms of the requirements for them to function; it does however include a set of recommendations for drug knowledgebase vendors, acknowledging that they are the core providers of the functionality needed to improve safety.

In most healthcare cultures knowledgebase providers are commercial organisations or specialist (and quasi-commercial) sections of professional bodies (such as Z-Index[163], the medication knowledgebase provider for Dutch healthcare, which is affiliated to the professional society for pharmacists in the Netherlands, the Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP[164] and the British National Formulary[45]). These bodies rarely if ever publish their data structures, not least because to do so could be commercially unwise, despite requests to do otherwise in the literature[165]. However, the author has had considerable experience in this area, and this section has been written based on knowledge and experience gathered in roles over the preceding 20 years. This experience is described in detail in the General Methodology.

Analysis methodology adopted

To elicit the requirements placed on the Medication Profile by the decision support systems that provide support for the ongoing safe use of medication, each of the various activities that occur in the medication process were examined. There are three separate but interrelated activities that occur in the medication process: prescribing, dispensing and administration. These involve various healthcare staff from different professions, as well as the patient themselves and sometimes a carer also. This complexity is a well-known distinctive of medicines use[3], which has the potential both to be beneficial or detrimental to the final result of the activity. Using the knowledge and experience described above and evidence from the literature (as cited in the text below), each medication activity was described highlighting where and how errors and issues may occur and also describing the types or modules of decision support can be offered to mitigate against those errors occurring. Then, the data elements from the Medication Profile required by these modules were described. Note that in all of the decision support modules discussed, the usual process is to alert the clinician if, and only if, an issue is detected, and in which case both the reason for the alert and the medication triggering it would be provided. In addition to this, all clinicians have the responsibility to review the patient's Medication Profile before taking a medication related action.

As well as the inherent complexity of the medicines process itself, the complexity of care provision arrangements (shared care) are also a source of potential problems.

A summary table of the data elements from the Medication Profile required by the activities and decision support modules that these use was produced.

Results

Errors in prescribing - the medication selection activity

To prescribe is defined as to 'give directions, either orally or in writing, for the preparation and administration of a remedy to be used in the treatment of any disease'[166]. In order for the prescriber to be able to 'give directions', there a decision process must have occurred in the mind of the prescriber as to selection of the medicine itself (the therapeutic product) and selection of an appropriate set of dosage instructions to ensure its correct use. Then, the directions themselves must be given either directly to the patient or to another healthcare professional who is involved in the medication process. It is a matter of both law and ethics that all prescriptions for particular types of medicines are written, but some medicines are prescribed verbally, principally those which may be purchased over-the-counter and self-administered or administered by a carer; this activity, particularly if undertaken in a pharmacy, is often referred to as counter prescribing[167]. Note that counter prescribing is sometimes described as a dispensing activity rather than as a prescribing activity[168], the activity being primary viewed as the supply of the medication rather than the selection and communication of the appropriate medication and dosage instructions.

Within the single activity of prescribing, there are two distinct sub-activities in which error may occur, the medication and dosage instructions selection process and the communication process. For the purpose of this study, which focuses on the requirements placed on the Medication Profile to support a safer medication process, it is the former that is of most importance in the prescribing process. Management of the communication process, and systems that support that (verbal, written or electronic), are outside of the scope of this examination, however some discussion of them is given in the chapter on patient record and summary specifications, where the data elements required for prescription information are described in those specifications.

Errors in the medication and dosage instructions selection process within prescribing may occur when there is insufficient knowledge of the patient, the medicine or both[1], or when insufficient attention is paid to the knowledge available. An accurate medication history is essential for safe prescribing[1], making the availability of medication history information an important requirement on the Medication Profile. Indeed, lack of this knowledge about the patient or failure to access this knowledge when it is needed has been identified as one of the major causes of medication prescribing errors[169].

Repeat prescribing

Due to the chronic nature of many of the conditions for which medicines are prescribed, the medication and dosage instructions selection process is likely to be performed once but the prescription itself may be repeated many times, often over years, and sometimes without review. Repeat prescribing, the re-issue of a prescription for supply of a medicine or medicines previously authorised, has been identified as a significant source of error, not least because if an error occurs, it may be repeated for a prolonged period[170]. Repeat prescribing should be undertaken in the framework of a regular, protocol-based review and monitoring process[171],[172] in which the Medication Profile of the patient plays a prominent part. Particularly for those medications with known bioequivalence issues, patients should be stabilised on a particular product from a single manufacturer and encouraged to continue to use that product. Having the facility to accommodate that manufactured product description is therefore a requirement, in addition to any generic description.

Drug interactions

When a patient is using more than one medicine concurrently (or in close proximity of time) there is a potential for the effects of one medicine to interact, either desirably or undesirably, with the effects of the second medicine. If the effect is undesirable, it is known as a drug interaction. Drug interactions are either pharmacodynamic or pharmacokinetic in nature and are deemed to occur between a two drugs in a pair; three-way or four-way interactions are not evaluated. In all cases of a drug interaction, it is the concurrent presence of the medicine in the body of the patient that is the cause of the interaction. This is because some medicines continue to have a presence in the body for some significant time after the last administration (e.g. amiodarone, which has a plasma half-life in the order of 50 days[173]), use of medicines in the preceding period must also be considered when interaction checking. It is also important to consider route of administration, as medications that are applied topically and whose action is only topical should not be considered for drug interaction checking.

There are many drug interaction checking applications available from drug knowledgebase suppliers which will perform this assessment of a newly prescribed medication against the patient's existing medication and alert the prescriber to possible problems with drug interactions. All of these can only operate if they are provided with the necessary information regarding current (now) medication use and medication use from the recent past so that these can be considered with the newly prescribed medicine and evaluated for the possibility of interactions occurring. The recent past should be at least 180 days, taking amiodarone as a worst case, as the half-life for this is one of the longest of all[174], and 180 days represents at least three

half-lives, such that elimination should have reduced to in the order of 10% of therapeutic steady state levels.

Using combinations of medicines concurrently that are known to interact does not necessarily result in undesirable clinical manifestation, particularly if the use of the medicines is managed carefully[175]. There may be overriding clinical reasons to use medicines that are known to interact, therefore the risk is accepted and managed as much as possible; or the interaction itself may be considered clinically insignificant in some groups of patients. For example, the well-known pharmacodynamic interaction between a thiazide diuretic such as bendroflumethiazide and an ACE inhibitor such as enalapril which results in increasing hypotensive effect is commonly exploited in clinical practice in the step-wise treatment of hypertension[176]. Therefore, even if a drug interaction is present, its actual potential for harm to the patient must be separately evaluated on the basis of the patient's clinical condition. This evaluation may itself draw on information from the Medication Profile. For example, a patient taking bendroflumethiazide is prescribed digoxin; this pair of medicines has a drug interaction that puts the patient at increased risk of cardiac toxicity from the digoxin due to the hypokalaemic potential of the thiazide diuretic. However, further examination of the Medication Profile may reveal that the patient is also taking amiloride, a potassium sparing diuretic, which will mitigate the hypokalaemic effect of the bendroflumethiazide and therefore mitigate the potential for harm of the drug interaction.

Duplicate therapy

Without knowledge of the medication that a patient is already using, a clinician might unintentionally prescribe the same medication causing the patient to be overdosed, or a medication from the same therapeutic class, risking toxicity similar to an overdose situation. This risk is particularly great when healthcare is being provided from a variety of different provider situations and access to a complete Medication Profile is restricted or unavailable. It is also a risk with the use of over-the-counter medicines, especially as more medicines move from being available only by prescription to being available from a pharmacy. Although all such sales should be supervised and require investigation of the patient's Medication Profile, not all patients will be able to give that information comprehensively. Example scenarios might be: a patient with active cardiovascular disease has heard that there is a medicine to control cholesterol levels that can be acquired over the counter so they purchase some Zocor Heart-Pro, unaware that they are already receiving statin therapy from their GP in the form of pravastatin tablets; a patient taking already one

NSAID[b] preparation as an anti-inflammatory and then being advised to take a medication such as ibuprofen, also an NSAID, as an analgesic, again not realising there is a duplication occurring because different words are used.

The risk of duplicate therapy occurring should be completely eliminated if a patient's Medication Profile were available for consideration for all prescribers, including those managing over the counter sales of medicines, and a duplicate therapy checking module was used to alert practitioners if prescription or sale of a medication is a duplicate therapy risk.

Contra-indication/caution checking – using implied morbidity

Despite the ideal of every prescriber having access to a patient's medical record, at least in summary, this is still not the norm. In particular, much emergency healthcare is provided 'blind', or on the basis of the information that can be obtained from the patient or relative at the time. Patients or their carers can usually give some information about the medicines being taken, even if they are completely unable to give any information about the indications for those medicines; for example: a significantly greater proportion of parents of special needs children were able to list their child's medications than to describe their child's medical condition[177]. Therefore, this medication information, a verbal summary of a Medication Profile, can give significant information to a clinician about the patient's clinical state, which in turn may be used to promote medication safety[178].

Two examples to demonstrate this use case are described: A patient on holiday presenting at an Emergency Department with a fractured limb is likely to be prescribed an NSAID for short term pain relief; if questioning reveals the patient has recently taken a course of a proton-pump inhibitor medicine such as omeprazole, it is prudent to assume that the patient has suffered some gastro-intestinal reflux or ulceration and therefore to avoid the use of an NSAID. In the self-care domain, a patient seeks advice and treatment for a verruca in a community pharmacy; the pharmacist has no access to the patient's medical record, but asks about general health, which the patient says 'is good'. The pharmacist thinks that a topical salicylic acid preparation is indicated, and despite this being a topical preparation and therefore having no drug interactions issues, makes the standard check in all counter prescribing about 'Any other medication use?'. The patient mentions that they take glipizide, which immediately alerts the pharmacist to the fact that the patient suffers from type II diabetes mellitus, which the patient did not mention in response to the question about general health because their view of their health is that it is good, the

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[b] Non-steroidal anti-inflammatory drug

medication controls the diabetes mellitus, and they are happy. Use of topical salicylic acid is contra-indicated in diabetic patients; this contra-indication for this patient is detected from information about the content of the patient's Medication Profile, not from their medical history/current condition.

Symptom management

Almost all medicines have some side effects; these are usually minor and manageable. Occasionally, the severity of a side effect outweighs the benefits of the medicine and treatment must be changed. Side effects usually manifest themselves as one or more symptoms, and it may or may not be easy to differentiate these symptoms as side effects of a medicine rather than as symptoms of a condition. Knowing the content of a patient's Medication Profile is an important piece of information in this investigative process. For example, if a patient presents with dry cough, if they are known to be taking an ACE[c] inhibitor, the dry cough is possibly a side effect of this rather than a presenting symptom of another condition. The management of the symptom will then probably involve management of the patient's current medication, rather than initiating new therapy for the new symptom.

Dose range checking

Dose range checking allows the dosage instructions information given with a medication to be checked for suitability for the patient (correct daily dose quantity, frequency and duration of course). Without indication information, a dose range check is a somewhat blunt instrument, as some medications have distinctly different dosage patterns or ranges depending on indication (e.g. methotrexate for chemotherapy or for rheumatic disease suppression, proton pump inhibitors for gastro-oesophageal reflux disease or for Zollinger-Ellison syndrome). Having indication information available with any prescription or available in the Medication Profile would significantly increase the sensitivity of dose range checking, making it a more effective tool for medication safety. Advanced dose range checking would also take into account other medications being administered concurrently, for example, administration of carbamazepine often lowers the plasma concentration of valproate, such that a larger dose of the latter is required. For truly useful and sensitive dose range checking, current medication information should be available, from the Medication Profile.

[c] Angiotensin converting enzyme (inhibitor)

Care pathways

Many chronic conditions are now being managed using a care pathway, 'a multidisciplinary outline of anticipated care, placed in an appropriate timeframe, to help a patient with a specific condition or set of symptoms move progressively through a clinical experience to positive outcomes'[179]. A pathway is a structured and documented evidence-based set of goals, clinical milestones and therapeutic interventions that are appropriate to provide at those milestones, with the supporting documentation and communication[180]. Many of the interventions provided will involve one or more medications.

Using care pathways is becoming a key feature of the provision of higher quality and more standardised and cost effective care, which by its very nature, should be safer care. Although the pathways themselves are documented, systems to document an individual's progress through a pathway are rare, and yet successful the use of these clinical pathways or patient trajectories is dependent on up to date and correct information being available[181]. That information includes the medication interventions have been used, their indication for use, and whether that use was successful or unsuccessful for that patient, so that at any particular pathway milestone to know where to go next along the path, it is the Medication Profile that must be referenced.

The nature of the care of chronic conditions using care pathways is such that including information in the Medication Profile about medications that are planned to be administered would also be useful.

Laboratory test checking

Medicinal products may interact with laboratory tests such that test results provided may be misleading. Decision support alerts can be produced to highlight this when appropriate. This form of decision support requires, as each test is ordered or result is processed, information on the medications being taken by an individual, which can be provided by the Medication Profile.

Allergy checking

Allergy checking is a major contributor to safety events involving medication. Recording of allergy information has been deliberately excluded from this analysis because it is argued that rather than managing allergy information as part of a Medication Profile, it should be managed as a separate and distinct topic in an individual's more general health profile or problem list. An individual may be allergic to a range of items other than medicinal products, including foods and cosmetics and natural substances such as rubber or venom. The allergy checking process requires information about the allergy itself (causative agent, severity, etc.) and information

about actions being taken (e.g. prescriptions being written or medications dispensed) rather than information from the Medication Profile per se.

Errors in dispensing - the prescription fulfilment activity

To dispense is defined as to 'to give out medicine and other necessities to the sick; to fill a medical prescription'[166]. The dispenser fills the prescription by providing a medicinal product that fits the description given by the prescriber to the patient or their carer(s) and by providing a label for the medicine that describes the prescriber's instructions for the dosage instructions of the medicine in a way that the patient/carer can understand and follow. There is also a professional responsibility on the part of the dispensing pharmacist to ensure that the prescription as dispensed is safe for the patient as well as following the prescriber's intentions.

In many healthcare environments, dispensing is a process that takes place separately and remotely from the prescribing process; the healthcare professionals concerned may well not have access to the medical record nor to the decision-making processes that have led to the particular prescription. Despite this, particularly in healthcare cultures such as the Netherlands or the United States, it is the community pharmacy that is likely to have the most comprehensive record of a patient's Medication Profile, and many of the checks that have been discussed above in relation to prescribing will operate at the time of dispensing, most particularly the detection and avoidance of drug interactions and duplicate therapy issues.

The majority of dispensing errors, 60% in one recent study[182], occur due to incorrect selection of the medicine to be dispensed, against which knowledge of the patient's Medication Profile would contribute little, but there are some types of dispensing errors that could be avoided if the Medication Profile information was available to support safety checking.

Supporting the labelling process

Incorrect labelling of an otherwise correct medicine for dispensing may lead to confusion of the patient, such that the medicine is administered incorrectly (over or under-dosage, with the attendant risks in these cases) or may be omitted completely. Having access to the patient's Medication Profile, and allowing this to provide information into the dispensing label generation process reduces the likelihood of labelling errors by providing information against which to cross check (for example for the system to highlight if a repeat dispensing is showing a different strength of a medication or a different set of dosage instructions). If label generation were then

also linked to bar-coded checking of the item to which the label is attached, then incorrect medicine selection errors can also be significantly reduced.

However, having access to the Medication Profile and allowing information from this to flow into the dispensing/labelling process must never be seen as a substitute for reading the prescription against which the dispensing is authorised. The prescriber may have altered the presentation and/or the dosage instructions such that the prescription is intentionally slightly different from the previous one shown in the Medication Profile, and the new information must be used correctly, not accidentally overwritten with previously applicable information. Providing 'reason for change' information for any therapy change is particularly helpful to support good dispensing practice.

Clarifying safety concerns

Having access to the Medication Profile to support the dispensing process is useful to clarify safety concerns about a prescribed medicine. In the prescribing safety section, the management of drug interactions was discussed; this is also an issue in the dispensing process. If a dispensing shows an interaction either between two medicines that are part of it, or between its medicine and those within the Medication Profile, by examination of the Medication Profile the dispenser may assess the interaction. This will focus on whether the interaction is new, whether the interaction is likely to be significant such that it should be referred back to the prescriber, or whether it has been present previously and is being managed or is deemed not clinically significant.

Supporting the compounding process

Despite increasing rarity, there are still occasions when a medicine must be compounded in an extemporaneously prepared formulation for a specific patient. This is acknowledged to be a process with a greater degree of risk than dispensing of licensed formulated medicines, and as such has specific guidance attached to it[183]. Having the formula (ingredient substances and strengths) for an extemporaneously prepared medicine available as part of a Medication Profile or as an easily accessible addendum to it provides continuity, ensuring a medicine is always compounded in a specific way for a specific patient. This avoids risks of toxicity or under-dosage due to changes in bioavailability from different compounding methods (e.g. the use of different suspending agents). It also avoids constant recalculation of strengths and volumes at each dispensing, which is a known area of risk and is particularly the case for medicines dispensed for children[184], where it is known that errors can also be more serious[185].

Errors in administration - the giving activity

Whereas the concepts of prescribing and dispensing can be defined within the healthcare domain, the final step in the medicines management process, the administration, is a concept that has much wider linguistic use, and as such does not have a precise definition within the healthcare domain. But its use has implicit understanding of the process of giving the medicine into or onto the patient's physical body where it can have its therapeutic effect.

This giving activity should be performed in accordance with the dosage instructions given by the prescriber, covering the quantity to give, the timing (frequency and duration) of when to give it, the route of administration (way in/on to the body), the method (how to do it) and site (where on the body to do it) of administration if required. There may be a device to use to assist in the administration, and there may be some manipulation of the medicine itself to be performed (e.g. dilution).

By far the majority of medicine administration occurs in the patient's home environment, unsupervised and unrecorded by any healthcare professional. There is an assumption that all the effort and checks that occur in the prescribing and dispensing processes to ensure that the patient receives the right medicine, with the right dosage instructions to give the required therapeutic effect have been effective. Any errors that occur in self-administration – misunderstanding, misinterpreting or simply forgetting - are rarely detected, unless they give rise to a significant health issue.

In situations where medicines administration is undertaken by a healthcare professional, it is known that errors do occur, but the majority of these occur in the activity of administration (e.g. wrong administration technique, missed doses etc.) and therefore knowledge of the patient's Medication Profile would provide little mitigation of these.

In care homes, where medicines administration is undertaken by the home staff, medication administration records (MARs) are often used to manage the administration process. The management of MARs themselves such that they provide accurate information to support the administration process has been identified as a risk for error[1]. Having real-time access to the current medication section of a Medication Profile with which to verify, or possibly even to produce MAR sheets would reduce the risk of this type of error occurring.

Errors in the communication process – shared care environments

There is now an ever more disparate care environment; whereas in years gone by patients were cared for by a single general practitioner, used a single community

pharmacist, and if necessary received care in a single district general hospital, they now may receive care from a number of sources within and between the traditional distinctions of primary, secondary, tertiary and social care. This care may be delivered contemporaneously or sequentially, but in either case, the interfacing between the care environments is a source of risk for medication error, as discussed in many of the papers in the Literature Review. Having an accurate shared view of a patient's Medication Profile can make a key contribution to error reduction in this complex care environment.

As the delivery of healthcare changes, with more and more chronic conditions and complex care protocols being managed in a shared care environment, the importance of having a shared Medication Profile increases. A central source of truth to which all those involved in the provision of care can refer reduces the likelihood of the errors that might otherwise occur; as evidenced in the Literature Review, this is the point at which most medication reconciliation effort is concentrated; more than half of all medication errors occurring in secondary care occur at a care interface, with over a quarter attributed to incomplete medication information obtained on admission[115]. Building a Safer NHS for Patients noted that effective communications are critically important when patients move from one care setting to another and that many medication errors occur at such 'handover points'[1]. Serious errors have occurred because of poor communications between primary and secondary care. Accurate information about current therapy is essential when patients are admitted to hospital to enable an accurate clinical assessment and to plan future treatment. And on discharge, the patient's drug regimen and treatment plan need to be communicated in a timely and reliable way to ensure safe and seamless transfer of care back to the primary care team.

Evidence for this requirement for shared access to a patient's Mediation Profile can be seen from four therapeutic areas discussed below; the first three are well known, the fourth is now just emerging.

1. Despite the narrow therapeutic index of oral anticoagulants, the management of patients requiring oral anticoagulation through pharmacist- or nurse-led clinics is now widespread. Oral anticoagulants are well-known for being involved in a large number of drug interactions, the majority of which will increase the anticoagulant effects of the medicine, putting the patient at risk of excessive bleeding. It is vital that all those involved in the care of these patients have access to the patient's Medication Profile, so that the risk of introducing drug interactions is minimised.
2. Methotrexate as used for its immunosuppressant properties as opposed to cytotoxic properties is unfortunately well known for problems in

communication for shared care such that it has been the subject of repeated National Patient Safety Agency alerts[186], having a single central Medication Profile that included indication information would significantly reduce the errors around methotrexate dosing.

3. Opiate analgesia is another area of concern for communication in shared care. Many terminal care patients are cared for by a multi-disciplinary team; part of this care involves opiate analgesia and considerable effort is expended to tailor the opiate regimen to the patient's individual need. This regimen may involve using both immediate release and extended release formulations of opiate products. Confusion can occur between these formulations across the team such that the dose of what should have been the extended release formulation as prescribed and administered as an immediate release formulation. If this happens, severe overdose effects can occur.

4. Amphotericin treatment errors are also increasing[187], as patients on this therapy are moved from hospital to the community and having intravenous infusions supplied from a home healthcare organisation; confusion as to whether the patient should receive the standard amphotericin formulation or a lipid formulation, with their attendant significant difference in dose, has led to individuals experiencing severe overdose.

A different paradigm in shared care is in terms of out of hours and emergency care provision. Changes to how primary care is provided and the development of out-of-hours service centres and walk-in clinics increase the importance of access to a Medication Profile for the healthcare practitioners working in these environments for current medication, with its indication, and recent past medication. The NHS Summary Care Record in the UK and the Continuity of Care specification in the US (discussed in detail in the Chapter 5(1)) both contain medication information specifically to support such care.

Results summary

Table 11 following provides a summary of the data element requirements that each of the activities of the medication process and their decision support modules place on the Medication Profile.

Table 11: Summary of the Medication Profile data element requirements from the medication process activities and their decision support modules

		Medication Profile data elements					
		All current ('now') medication	Recent past medication	All past medication	Indication	Dose instructions	Ingredient substance and strength
Prescribing activity	Drug interaction checking	✓	✓	x	x	x	x
	Duplicate therapy checking	✓	x	x	x	x	x
	Contraindication and caution checking; implied morbidity	✓	x	x	x	x	x
	Symptom management	✓	✓	x	x	x	x

Table 11 (cont.): Summary of the Medication Profile data element requirements from the medication process activities and their decision support modules

		All current ('now') medication	Recent past medication	All past medication	Indication	Dose instructions	Ingredient substance and strength
Prescribing activity	Dose range checking	✓	x	x	✓	✓	x
	Care pathways	✓	x	✓	✓	x	x
	Laboratory test checking	✓	x	x	x	x	x
Dispensing activity	Label checking	✓	x	x	x	✓	✓
	Compounding	x	x	x	x	x	✓
Administration activity	MAR sheets	✓	x	x	x	✓	x
Shared care		✓	✓	x	✓	✓	✓

Discussion

In each of the three major activities of the medication process and in the communication process, there are various types of decision support functionality that can contribute to safer medication use. All of these place some requirement on information from the Medication Profile

Access

The first requirement, which might almost be missed as it can be seen as implicit, is access to the Medication Profile, is a significant issue for some healthcare professions. Most prescribers have access to *their own* records, which will have a section that records medication information and fulfils a Medication Profile type role. However, this will contain only the information from their own activities. A general practice system will contain records of prescriptions generated in that practice, and possibly may not even reference administrations occurring in different sections, which would have to be searched for separately (e.g. vaccinations given by the practice nurse may be in a separate record)). Information received from other healthcare providers, such as secondary care institutions, will remain in document form (even if electronic) and medication information will probably only 'transfer' to the proxy medication profile if a prescription is required. Short-term therapy (e.g. a course of antibiotics given during a hospital stay) is likely to remain as isolated information. Most hospitals do not currently have a comprehensive health information system; prescribing and administration of medicines may be maintained in a single system (even if on paper) but dispensing will be managed separately (and electronically). Again, the system will record only the activities it is responsible for, and not activities that have occurred elsewhere (e.g. in a theatre or in an investigative unit such as radiology). Community pharmacists also maintain their own medication records based on the prescriptions they have dispensed for patients, and possibly of over-the-counter sales made to specific patients. They may also have records of medication reconciliation activities performed, some of which may be shared records with the general practice responsible for the patient. Some linked community pharmacies may also now share records amongst their membership (with the permission of the patient concerned).

All of these activity-based records are no substitute for a comprehensive Medication Profile, which is a central shared repository of information that should be accessible by all who need to. Providing access to a comprehensive Medication Profile has both technological and political considerations; neither are topics for the focus of this research. Since a comprehensive Medication Profile is designed specifically to meet the needs of all the healthcare professionals providing care for a patient, and having

such an artefact designed and made available for implementation, it would seem sensible to create the necessary infrastructure and political willingness to allow it to be made available to all those it seeks to serve.

In their special article on the use of information technology in improving patient safety, Bates and Gawande[188] stated that a 'good information technology infrastructure is vital, and that an electronic record and computerised physician order entry are fundamental areas for implementation to improve safety. To provide high quality healthcare requires everybody to 'be on the same page' – to have the same information available, and the single biggest reason for medication error was not having all the necessary information to hand'. A key phrase in that is 'all the necessary information to hand', implying that access to and availability of this information must be seamless within the business process; any interruption to the workflow to obtain the information would be considered a major barrier to its acceptance and use. An example of this is a Medication Profile implementation in Canada that takes so long (several minutes) to download the information that clinicians find it unacceptable to use[189]. These usability issues therefore form non-functional requirements on implementation of the Medication Profile within systems and the architecture, both technical and business, of those systems.

Medicinal product description

The second requirement is a good description of the medication being used; each of the all current (now) medication, the recent past medication and all past medication needs to be described in a way that all those involved can easily recognise and understand. To facilitate this, the medication terms should be drawn from a robust terminology of medicinal products that conforms to the *Cimino desiderata[190]*, the best practice for healthcare terminology. Implicit in the concept of terminology is that it is a code system[191] – a managed collection of designations (the human readable/recognisable descriptions, including synonyms, of the concept) and one or more codes (the machine-readable identification of the concept). For decision support, the code is implicitly important, because this is what can most quickly and easily be processed by algorithms.

In the development of CPOE and DSS, there is a clear requirement for standards in terminologies used; the requirement for a 'convenient, usable standard dictionary for medication ordering' is identified by Teich et al[23], along with standards for identification of doses, allergies etc.. In 'Information for Health'[132], the report that commissioned the UK Clinical Products Reference Source, the forerunner of the NHS dm+d[192], there is the oft quoted comment about the 'lack of standardisation in the UK in describing medicines, appliances and medical devices, in how such

descriptions are organised, and in linking knowledge required for decision support to these descriptions'.

In the report on Improving Medication Safety, Building a Safer NHS for Patients[1], drug name confusion is sited as a cause of medication error in prescribing (3.1.18), dispensing (3.2.5) and administration. This is a recurring theme found in medication error research[8,193]. It has been reported that roughly one in every four errors reported to the Medication Error Reporting Progam (MERP, run by the Institute for Safe Medication Practices and the United States Pharmacopoeia) involves a pair of medicines whose names look or sound alike[194]. The American Society of Health-System Pharmacists has produced a series of recommendations for preventing medication errors in cancer chemotherapy, which include having standardisation of prescribing vocabulary 'including drug names'[195]. Similarly, a study assessing the impact of various patterns of label information on nurses' and physicians' ability to select the correct strength of a liquid parenteral showed that error frequency was reduced when a standardised format of information was used[196]. In addition, the use of 'Tall Man' lettering and/or colour has also been shown to reduce errors in drug name confusion[197], although this has tended to concentrate on medicine labelling, it is suggested that it could have applicability in computer applications[198]. In collecting medication error information, the European Medicines Agency are now also actively looking at the potential for medication errors associated with the name of a medicine, and naming is routinely assessed by the EMA's Name Review Group, whose mandate includes the assessment of medicinal product names from a safety and public health point of view prior to marketing authorisation.

The problem of a having a good description of a medicinal product is one that has been recently addressed by the Identification of Medicinal Products suite of standards that have progressed through the international standardisation process and are manifest in the Identification of Medicinal Products (IDMP) suite of standards. These are ISO 11615 (Medicinal Products)[144], 11616 (Pharmaceutical Products)[199] and the accompanying standards to describe Substances, Dose Forms, Routes of Administration, Dose Units and Package Descriptions. The implementation of this suite of standards, which is being led by the European Medicines Agency and the US Food and Drugs Administration, will provide unique identification for all authorised and developmental medicinal products globally. Having this foundation, from the key source of such information (i.e. the regulatory agencies) provides a very solid basis from which to work forward into clinical care. Indeed, it is on this premise the Horizon 2020 openMedicine[149] initiative is working, specifically for the use of cross-border prescribing and dispensing, and since these are two of the three main activities in the medication process, if these can be

supported, the description of the medicinal product should by implication be accurate and clear such that it would be useful in a Medication Profile. In addition, the ISO technical specification that is currently in development, for Medicinal Product Dictionaries[200] lists use cases and requirements for such a terminology.

So at this time, for the first time, it would appear that the perfect storm is occurring for development and implementation for standardised medicinal product terminology at both national and international level, which will meet the requirement for clear identification of current and past medicinal products in the Medication Profile.

Dosage instructions description and indication

The third requirement is a full and unambiguous description of the dosage instructions and indication information so that these can be correctly communicated to the patient and, in a machine-readable form can be used in dose range checking.

Currently, there is no formal definitional standard for the representation of dosage instructions, although there is some work in the ISO community, in the form of TS 17251, the Requirements for a Syntax to Exchange Structured Dose Information for Medicinal Products[142]. This work is currently strongly influenced by the work of the National Council for Prescription Drug Programs (NCPDP)[138138] in the USA, which is being used in the Meaningful Use legislation, although it also has its roots in the work done in HL7 on a structured dose syntax that was originally produced for the English NHS. In other parts of this work, where dosage instructions are referenced, it is the HL7/NHS Dose Syntax structure and definitions that are used, as these have been developed to support all aspects of dosage information and particularly for machine processing with dosage checking. The full HL7/NHS Dose Syntax is described in an Appendix to this thesis, as it was developed by the author of this thesis.

For dose range check to function appropriately, the minimum information requirement is either a single dose quantity and a single dose frequency or a daily dose quantity, and the route of administration. The route of administration may be explicitly stated as part of the dosage instructions, or it may be implied information; implied either from the product being dose checked, for example a dose check on the product 'Methotrexate 2.5mg tablets' implies oral administration, or the dose quantity may be stated as 'two tablets' with the tablets implying oral administration. Course duration is helpful for a course length check but this check is less frequently used than a dose range check.

For dose range checking to be useful in a wide range of circumstances and particularly not to generate unnecessary alerts, which are well known to be an issue

to users[201], information on the indication for use is required. This is rarely, if ever provided, but would be a very valuable data element in a comprehensive Medication Profile to support safety checking. Indication information would also be valuable as part of care pathway medication documentation, and in that context, when a particular medication is discontinued due to either intolerance or lack of efficacy that information should be present, in addition to the date of the discontinuation (which is a standard part of the course of therapy detail).

For several of the decision support modules, if the description of the medication(s) involved are provided only at a high level, particularly without dose form information (e.g. 'amoxicillin' rather than 'amoxicillin 250mg capsules'), even if the description comes from a robust and coded controlled terminology, then the dosage instructions information becomes important to the decision support algorithms. Both drug interaction checking algorithms and duplicate therapy algorithms will process medications administered systemically differently from those administered topically to avoid inappropriate alerting; for example: a patient *may* use two NSAID medications if one is topical and the other is administered systemically.

Cradle to grave lifespan

The fourth requirement of a comprehensive Medication Profile is that it covers all medication activity for an individual, from cradle to grave. So often, as discussed in the Access section above, records exist for activity occurring only in that system. This is improving in the UK, with the ability to transfer general practice computer records from one surgery to another when a patient moves[202], but no such system is available for hospital records, for example, or for community pharmacy records. Only a single, central shared Medication Profile will be able to provide information about both current medication use and the historic medication use that is needed for drug interaction checking; the current, past and planned medication use information for care pathway intervention selection and, until other medical information is shared and available (diagnoses and conditions), implied morbidity information for contra-indication checking.

Limitations of this study

One of the main limitations of this study is the lack of published information on how medication decision support works within systems that support medication activities, and therefore the requirements gathered from it are confined to those that are available or are known personally to the author. This limitation could be overcome if more information were publically available, or alternatively if an assessment of

medication decision support functionality and its requirements such as is presented here were formally reviewed by other experts in the field.

Recommendations for further work

Further efforts should be undertaken to provide good evidence for the effectiveness of the various different modules of medication decision support, particularly of the type provided by the commercial knowledgebase vendors that underpins most of the systems used by clinicians day to day. Having an understanding of the most effective functionality and the requirements that these place on the Medication Profile would support prioritisation of those requirements to systems that particular data to be gathered, stored and shared.

Conclusion

It is clear that having knowledge of and access to information about an individual's comprehensive and shared Medication Profile, containing current, past and planned medication information can play a significant part in making the overall process of medicines use safer for patients. Without this, important safety checks that can be provided by information technology, such as drug interaction checking, are not possible.

Based on the assessment of the various decision support functionality that supports the activities of the medication process, the data elements that essential to be present and populated in a Medication Profile:

- A description of the medication itself, preferably from a robust and machine readable (coded) medicinal product terminology
- A description of the status of the medication (current, past, with a sense of how far in the past a medication was last used – see below for course of therapy timing)
- Basic data elements from the dosage instructions for dose range checking and to support other functionality if the medication is not fully described
  - o Dose quantity and dose frequency – to calculate the total daily dose
  - o Course of therapy timing; the date of starting (and stopping, if relevant) the medication
  - o Route of administration
  - o Indication for the medication

Chapter 5: Requirements for the Medication Profile from Clinical Research

Part 1: Patient Recruitment and Protocol Feasibility Studies

Introduction

The complexity of the clinical studies required to bring a new therapeutic entity to market has increased over time, with detailed requirements for information to demonstrate both safety and efficacy being required by the regulatory agencies[203]. In 1970 it was estimated that 1600 subjects were required per trial; in 2000 this figure had risen to 6345. Similarly more trials are required per New Drug Application (NDA); 30 trials in 1970 as opposed to 70 in 2000[204]. In the United States in 2004, the average for a new therapeutic entity was for it to be tested in more than 4000 patients across 37 different clinical trials before receiving FDA Approval[205].

Patients are selected as suitable for recruitment into a clinical trial based on eligibility criteria that are formally documented as part of the protocol for a study. Finding these patients is known to be difficult[206], and success in recruitment appears to be variable: levels of study participation vary according to condition/disease; it is estimated that 3% of all cancer patients have participated in a study of some sort, whereas 80%+ of paediatric cancer patients have participated in studies[207]. This is despite the fact that generally, patients appear to be willing to participate in studies, although only a small proportion of patients – less than 10% - actually have participated in a study[208]. Interestingly, given the above, a fairly small proportion of time is being invested 'in the field' to actually finding potential patients: clinical research coordinators generally devote only 13% of their day to finding subjects (8% to 'subject recruitment activities' and 5% to 'searching medical records for potential study subjects')[209]. Up to 25% of sites within a trial enrol less than 5% of the total number of patients, with 10-15% of sites not enrolling a single patient[210]. Patient recruitment is often the rate-limiting step for many clinical studies. Up to a third of the overall trial process is taken up by patient recruitment, and almost half of all trial delays are caused by patient recruitment problems[211]. This not unnaturally has a significant effect on the cost of clinical trials, estimated at €710-790 billion in 2007 with an annual growth rate of 10.2-13.6 % since 2003[212]. Delays to the process to obtain a market authorisation may cost millions both in sales, estimates range from between $600,000 for a small or niche product to $8million for a blockbuster drug per day in lost sales[213] and in additional trial costs. It is estimated that $1.3-8.0 million additional costs are incurred for each day a trial runs over time[204].

Various strategies are being adopted in order to minimise trial delays and ever increasing costs due to problems with patient recruitment; there are various developments underway, including the EU Innovative Medicines Initiative (IMI)[214] project EHR4CR[24] that are investigating the use of electronic health record data in clinical research, and particularly in protocol feasibility studies and patient recruitment support.

Protocol feasibility testing

Although no formal definition of protocol feasibility testing exists, it can be described as a process of comprehensive review and analysis of all aspects of the protocol; it is undertaken to minimise barriers to successful completion of the study in terms of science, safety, quality, or operability. It is frequently performed by the use of checklists of questions to test, for example, the appropriateness of the eligibility criteria to select the patient population to be recruited and to determine which of the criteria may be the most challenging to fulfill.   Eligibility criteria are themselves defined as 'the medical or social standards determining whether a person may or may not be allowed to enter a clinical trial; they are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions'[215].

Objective testing of the eligibility criteria aspect of protocol feasibility may be undertaken by decomposing the probable inclusion and exclusion criteria from the draft protocol and using their content to construct queries that are then run against a suitably large cohort of patient information containing the types of data items described in the criteria. This patient information may be in a registry, constructed for the purpose as described above or in a clinical data warehouse derived from one or more EHR systems. Once a study has been designed, protocol feasibility studies may also be conducted to ascertain whether a site is likely to be able to fulfil its recruitment quota of study subjects for that trial based on the eligibility criteria, by running the eligibility criteria queries against the clinical data warehouse of that particular site. If the site does not show close to the required number of likely subjects, then the effort and expense of setting up the trial in that site can be avoided, as can the delay in the study as a whole that would occur when that site would not be contributing recruited subjects to the overall total.

Patient recruitment strategies

As described above, fulfilling the recruitment requirements for the increasing number of trials being conducted is a challenge, especially as the number of investigational sites has not increased proportionally, thereby increasing pressure on the available

patient pool for any one site. There has been a trend to conduct more trials from contracted small clinical research centres in addition to using the large centralised research hospitals/institutions. This increases the size of the pool of patients who have the potential to become trial subjects, but it also increases the risks in variability of the application of the trial eligibility criteria, which can cause problems in results reconciliation.

Another approach to improving recruitment is to use referral sites; this involves contracting with various organisations to find patients that match the eligibility criteria, then identified patients are referred to central clinical research centres in institutions for further screening, and if accepted, are managed in the trial from these centres. This approach shares the same benefits for recruitment as described above, a bigger pool to work through, but by using the central sites for conducting the trial, the risk of variability, both in patient selection and in the actual conduct of the trial, is reduced.

An alternative strategy that is being used by some pharmaceutical companies and some of the larger contract research organisations and business intelligence organisations is to invest, often quite heavily, in the development and maintenance of patient registries. These are defined as 'an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specific outcomes for a population defined by a particular disease, condition, or exposure, that serves as a predetermined scientific, clinical or policy purpose' [216] . Constructing a registry involves building databases from vast quantities of pre-existing information, usually by combining information from numbers of smaller databases or warehouses, for example information on all the patients and investigators and trial sites that the company has had contact with in previous studies. Registry data can then be queried to locate potential patients for new trials. Some registries are disease-based whereas some are more general. Whilst these registries have value in supporting the recruitment process (and for protocol feasibility testing), they can be expensive to produce due to differences in structure, description and granularity of data and it is extremely hard to keep them accurate and up-to-date. The use of registries can mean that patients are used in multiple trials, which in itself becomes a problem, since many trials now specifically exclude patients who have been subjects in other trials recently.

Any of this data, in a clinical data warehouse or in a patient registry, can be interrogated with queries based on the eligibility criteria to identify individual patients who may be suitable for recruitment. Because this filtering process is conducted by algorithmic querying, it has several benefits. It eliminates the human variability of

interpretation of the eligibility criteria and it is applied across the complete cohort of patients, rather than being applied selectively to those the investigator deems reasonable to consider initially; this primary selection in itself may introduce bias or result in some eligible subjects being overlooked.

In order that the processes described above can perform well for protocol feasibility testing and patient recruitment, it is important that the data, be it in a registry or a clinical data warehouse, has the necessary elements to support the queries. A cursory review of almost any set of eligibility criteria shows that a proportion of them include medication information. Analyses of eligibility criteria to date, and specifically analysis of computability to support clinical research, have primarily focused on the semantic structuring of the criteria, rather than on their clinical content[217]; the analysis that has been done on content appears to have been a by-product of the structural analysis[218]. This structural analysis has investigated for example, the proportion of criteria that describe temporal data (when something occurred) without any particular interest as to what sort of thing (for example, procedure, diagnosis or medication administration) was that was being described temporally. Van Spall et al[219] undertook a systematic review of the description of exclusion criteria (only) in published randomised controlled trials; 54.1% of the trials examined had medication-related reasons for exclusion, meaning that over half of all trials studied required at least some medication-related information for eligibility assessment. Ross et al[218] conducted an analysis to characterise eligibility criteria into three categories, one of which was a treatment or intervention on the participant, which is presumed to include medication, and to quantify their patterns and the complexity of these patterns. There is little or no analysis of the clinical content itself, and none that looks particularly at medication information. This means that there is no standardised information as to the data items that are necessary to support for protocol feasibility testing and patient recruitment actually are.

The aim of this study was therefore to analyse a set of study eligibility criteria and to specifically investigate in detail the medication-related data elements which could be used as parameters to query a patient's Medication Profile to assess their suitability for entry into a trial (patient recruitment) or to query a set of Medication Profiles in a data warehouse to assess whether the eligibility criteria as described would yield a reasonable cohort of patients as potential subjects (protocol feasibility). These medication-related data elements then become information requirements that a Medication Profile should ideally meet, in order to be able to support these two uses in the Clinical Research domain. A subsidiary aim was to have some sense of the value, in terms of frequency of use, of each of these data elements, such that an assessment of their importance for the particular use case can be made. If a

parameter is used in many eligibility criteria, the value of its presence in the Medication Profile is high and vice versa.

Methodology

This analysis studied eligibility criteria from 41 clinical trials conducted in Europe by nine different pharmaceutical companies provided to the EHR4CR project[24] specifically for use in protocol feasibility and patient recruitment studies. There were 1112 individual eligibility criteria from the protocols for these trials, which had been submitted to the project by the participating pharmaceutical companies specifically for research into improving protocol feasibility and patient recruitment.

Note: there was considerable variability in what each trial considered a single eligibility criterion to be. For some trials, a single criterion might contain a number of related parameters, for example, the following was considered as a single criterion in its study:

'Laboratory values (within 1 week prior to the first dose of Drug X): - Absolute neutrophil count = 1500/mm3. - Platelets = 100,000/mm3. - Creatinine = 1.5 times upper limit of normal (ULN) or creatine clearance rate = 60 mL/min. - PT international normalized ratio (INR) and partial thromboplastin time (PTT) within normal limits. - Hemoglobin = 10 mg/dL. - Total bilirubin = 1.5 times the ULN. - Aspartate aminotransferase and alanine aminotransferase = 2.5 times above ULN. - Alkaline phosphatase = 2.5 times above ULN'

This is in contrast to another trial where the following five parameters were detailed as five separate criteria:

'Hemoglobin   9.0 g/dL independent of transfusion; Platelet count   100,000/µL; Serum albumin   3.0 g/dL; Serum creatinine < 1.5 x ULN or a calculated creatinine clearance   60 mL/min; Serum potassium   3.5 mmol/L'

Since the investigation was seeking a more of a qualitative understanding of the requirements that eligibility criteria place on the Medication Profile than a truly quantitative measure, no attempt was made to normalise the pattern of eligibility criteria such that each describes one and only one parameter. The eligibility criteria have been used and counted exactly as they were supplied in the protocol.

Each of the eligibility criteria from the protocols was extracted into a spreadsheet from where it was examined, and those whose parameter(s) involved medication information were identified for further detailed study. This comprised identifying the how the medication was described, and any medication data elements and additional contextual information (for example, medication used for a particular diagnosis or indication, or medication allergy information) that might be expected to be available from the Medication Profile.

Eligibility criteria that described adverse events to medication occurring during the study (i.e. after a subject has been recruited into the trial) were not included for detailed evaluation, since these would not be relevant for protocol feasibility testing or patient recruitment. An example of such a criterion is:

'Any other hemorrhage/bleeding event > CTCAE Grade 3
within 4 weeks of first dose of study drug'

Eligibility criteria that described adverse events to medication that occurred prior to the study, and therefore which might be expected to be in documented in a patient's Medication Profile and which therefore could be used for protocol feasibility testing and/or patient recruitment applications were identified and studied, and were categorised as medication related information.

Each item of descriptive data was categorised, with definitions for data elements being provided based on or adapted from the relevant ISO definitional standards[142] for the data element; if no ISO standard is available, a data element name and description has been made up, as semantically robustly as possible.

The identification of the relevant eligibility criteria, the description of medication the data elements and the categorisation of additional context was crosschecked by the author by undertaking a separate second pass through each protocol. The research supervisor independently checked the extraction for a sample of various protocols. For the categorisation, an iterative approach was used to develop a meaningful description for the Results in tabular form.

To provide a comparison to the medication information based data elements, eligibility criteria whose description and data element(s) involved laboratory test information were also identified. Laboratory test information was defined as biochemistry and haematology tests only; observables such as blood pressure measurement, pathology and microbiology information were not included. Laboratory test information was chosen as a comparator for medication information

as like medication information, it is highly structured with little additional free text and is similarly stored in patient records.

Results

As shown graphically in Figure 5 below, of the 1112 eligibility criteria, 201 made a direct reference to medication that a potential subject may be taking or may have taken. In addition, 79 eligibility criteria described medication related information (allergy to medication, adverse events from medication administration) that should be available from an extended Medication Profile, or that could be queried by inference. As a comparison to the medication-related eligibility criteria, 99 eligibility criteria that involved laboratory test information were identified; of these 39 were inclusion criteria and 60 were exclusion criteria. Two inclusion criteria contained both laboratory test information and medication information as they were both criteria describing a number of parameters (and therefore are counted in both categories in Figure 5).
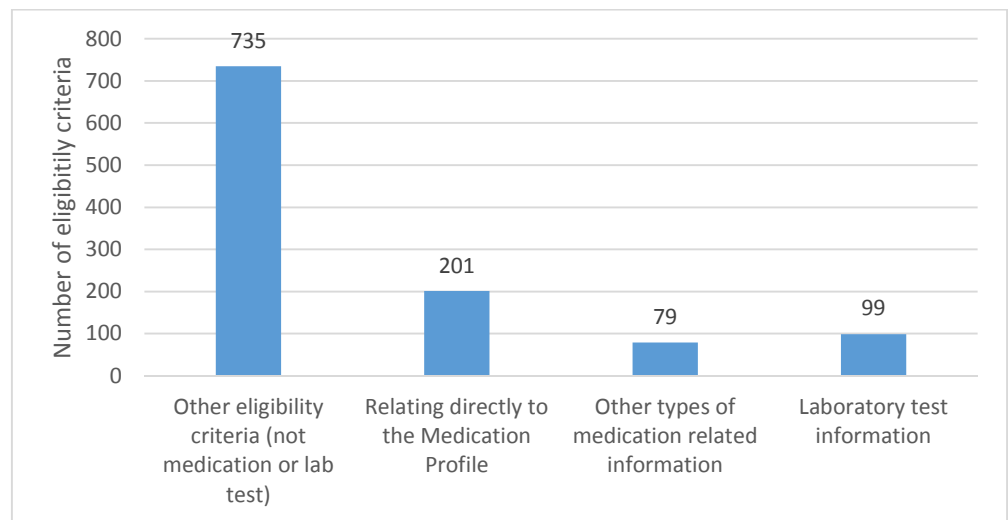
Figure 5: Bar chart showing proportions of medication-based and laboratory test based eligibility criteria

Identifying the medications in eligibility criteria

Only 10 of the 201 eligibility criteria explicitly described a specific medication by name; all the others used a class description referring to characteristics or use of the medicines in that class. These class descriptions were categorised into five groups as shown in Figure 6 below.
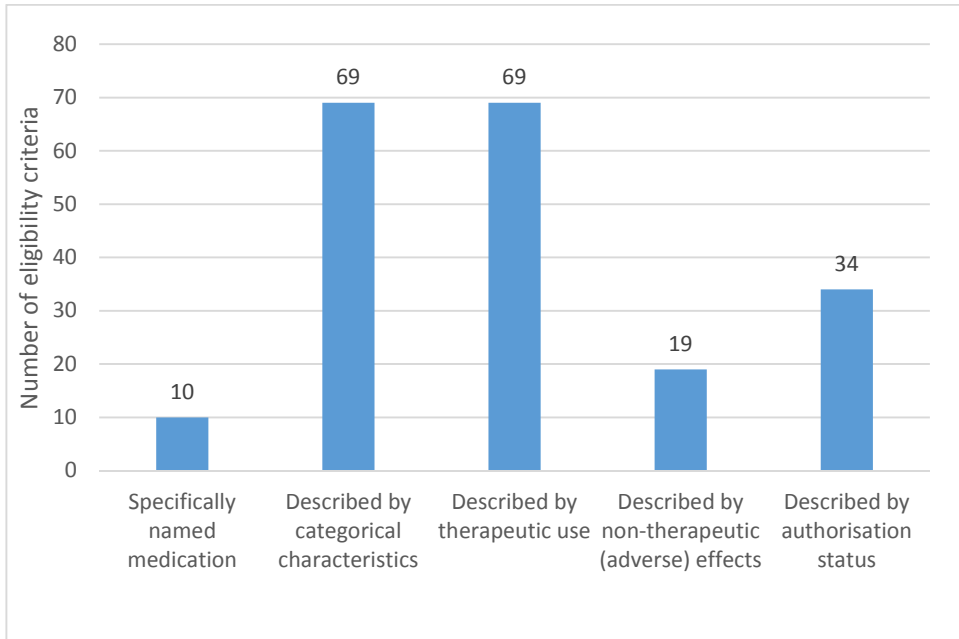
Figure 6: Bar chart showing the different categories of medication description in eligibility criteria

Categorical characteristics

Medications were described on the basis of their categorical characteristics, for example whether they are in the chemical group of 'bisphosphonates' or 'anthracyclines' or share a common mechanism of action, for example 'beta-blockers' or 'glucocorticosteroids'. These grouping features are part of the categorical information about medicines, information is always and necessarily true for that medicine.

Example:

> *'Chronic treatment with a non-steroidal anti-inflammatory drug'*

Therapeutic use

Medications were also described and identified as a group based on their therapeutic use, for example whether they are used to treat hypertension or in cancer chemotherapy. This information is not part of categorical medicinal product information, it is contextual and it changes over time. For example: for many years aspirin (acetylsalicylic acid) was used only as an analgesic and antipyretic, then it was discovered to have antithrombotic properties and so is now additionally used as secondary prevention therapy after myocardial infarction, stroke and a variety of other cardiovascular events, so its therapeutic use has changed over time.

Example:

> *'Patients receiving antipsychotics who are not on stable doses of atypical antipsychotics for four weeks prior to baseline'*

Non-therapeutic (adverse) effects

Just as medications can be described and identified as a group according to their therapeutic use, they can also be grouped by particularly significant non-therapeutic effects; these are usually considered unwanted and undesirable and are therefore often known as adverse effects. This information is also contextual and changes over time, especially as experience with the use of the medications grows.

Example:

> *'Any concomitant medication known to prolong the QT interval'*

Authorisation status

Medications in eligibility criteria were described and identified as a group by their authorisation status, whether or not they have a formal marketing authorisation. This is information about medicinal products at a point in time within their overall development lifecycle.

Example:

> *'Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment'*

Medication information and its context of use in eligibility criteria

The 201 eligibility criteria containing information relating directly to the Medication Profile were examined in more detail to ascertain the information that would be required from the Medication Profile to query correctly for potential subjects. Figure 7 describes the results of this, focusing particularly on the context of the medication use, and whether that information was used in an inclusion or exclusion criterion.
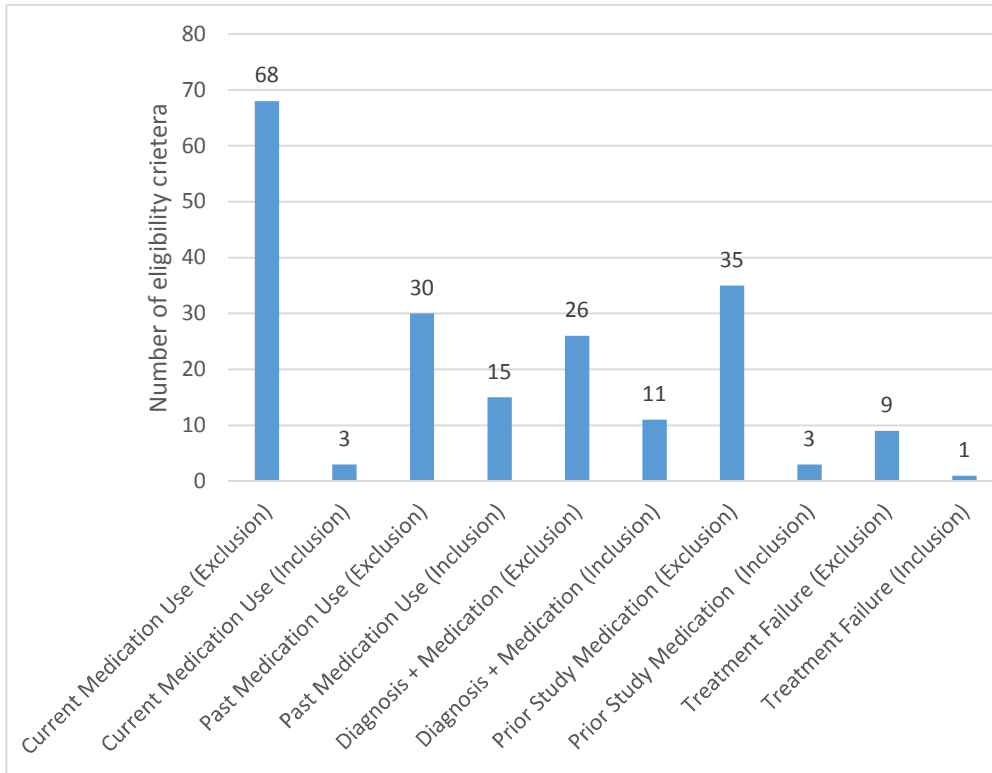
Figure 7: Bar chart showing the contextual medication information present in eligibility criteria

Current medication use

Current medication use is defined as those eligibility criteria that identify that a medication (or group of medications which might be defined by therapeutic category or by shared indication) being taken by a patient/potential subject at the time of recruitment into a study using words and where identified by phrases such as '(current) use of' or 'concomitant administration of' . The large majority of these were exclusion criteria with just 2 being inclusion criteria.

Example:

> *'Currently on any medication to treat high blood pressure'*

Included in the current medication use category are those eligibility criteria where there was some indication of the timing of the medication administration in relation to the current point in time or to a particular point in the study such as randomisation, and for which it is likely that the medication would (still) be being used 'in the present'.

Example:

> *'Treatment with oral neuroleptics within 4 weeks prior to the screening visit'*

Past medication use

Past medication use is the category of eligibility criteria that describe a medication (or group of medications) that has been taken in the past and are no longer being

taken (words and phrases such as 'prior administration or' or 'history of'). Some eligibility criteria were not explicit in their reference to past medication use, for example the criterion:

> *'At least one but not more than 2 cytotoxic chemotherapy regimens for metastatic castration-resistant prostate cancer'*

This criterion implies that the chemotherapy must have occurred previously to the current point in time, and would therefore be recorded as past medication. The past medication use criteria were split with two thirds being exclusion criteria and one third being inclusion criteria.

Example:

> *'History of prior exposure to carisbamate'*

Diagnosis with medication use qualifier

The set of eligibility criteria described in the group of 'Diagnosis + Medication' are those where the primary criterion is that the subject has the condition/symptom described (a diagnosis) with a supplementary qualification identifying a medication. The subject must have both the condition/symptom (diagnosis) **and** be using or have used the treating medication to fulfil the criterion.

Example:

> *'Cardiac arrhythmias requiring anti-arrhythmic therapy'*

Prior study medication

Prior study medication is the category of eligibility criteria that describe the use by a patient of a study agent in a previous study; the overwhelming majority (35) were exclusion criteria, but there were 3 that were inclusion criteria (such that the patient would be eligible as a subject for a follow-on trial).

Example:

> *'Investigational drug therapy outside of this trial during or within 4 weeks of study entry'*

Treatment failure

There were 10 eligibility criteria that concerned treatment failure which was recognised by phrases such as 'inadequate response to', 'resistance/resistant to' and 'relapse after'; with just one exception these were all inclusion criteria.

Example:

> *'History of inadequate response to at least 1 AED[d]….'*

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[d] AED = anti-epileptic drug

Medication information and dosage instructions information in eligibility criteria

Dosage instructions information is information about dose quantity (individual dose quantity, daily dose quantity or cumulative ('lifetime') dose quantity), about timing of administration (frequency of individual administrations or duration of the course of therapy or start/stop dates) and about route of administration. Indication information is not considered a core component of the dosage instructions information but is assessed with them as provision of the reason for the medication can be given as part of the instructions. Figure 8 shows the dosage instructions data elements that were present in medication based eligibility criteria.
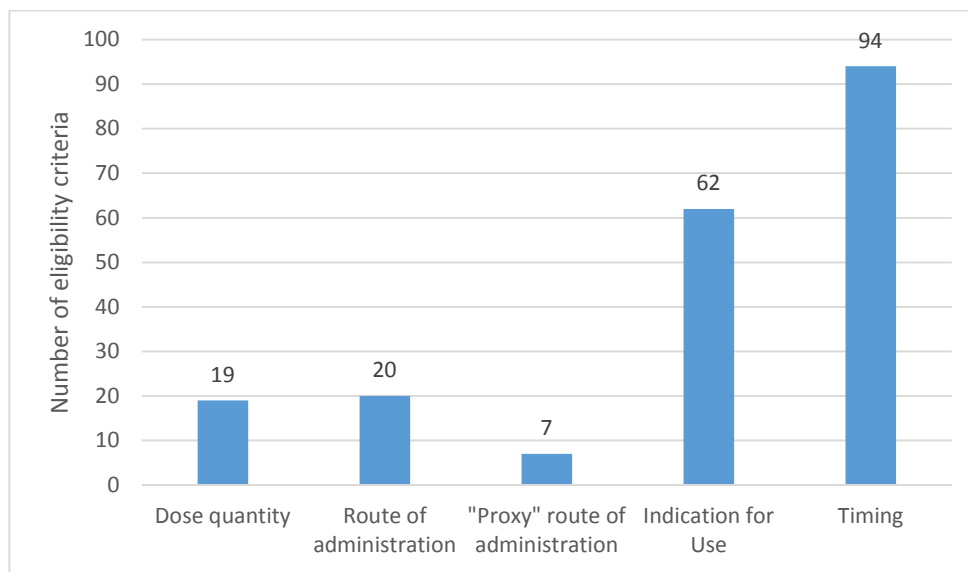
Figure 8: Bar chart showing the dosage instructions data elements for medication information present in eligibility criteria

Dose quantity

Less than 10% of the medication focussed eligibility criteria made any reference to dose quantity information and of those half criteria did not specify a dose quantity per se, but specified 'stable dosage' or 'changing dosage' as part of their description, implying that dose quantity would need to be queried.

Example:

> 'Low dose warfarin (1 mg po qd) is permitted if the INR (International normalized ratio) is < 1.5. Low-dose aspirin is permitted (100 mg daily).'

Route of administration

A similarly small percentage of the eligibility criteria specifically referenced one or more routes of administration for medications directly (oral, intravenous) and a further 7 criteria referenced route of administration by the proxy grouper concept of 'systemic', which implies oral or parenteral routes of administration (as opposed to topical routes).

Example:

'Patients that required any use of IV vasodilators'

Indication for use

However more than a quarter of all medication focussed eligibility criteria described the indication for use of the medication that the patient was administering as part of their content.

Example:

'Patients in whom anticoagulant treatment for their index PE or DVT should be continued'

Timing

Almost half of medication based eligibility criteria described some element of the timing of the medication administration. Of these, 73 were 'within' and 11 were 'prior to' a certain point, usually a milestone in the study lifecycle, such as screening, randomisation or first dose of study medication. The others were 'for at least… before'. Some eligibility criteria, particularly those describing use of another investigational agent, also stated a time period in terms of 'within x days or 5 half-lives, whichever is longer'.

Example:

'History of felbamate treatment within the past 3 months'

Other types of medication related information

The 79 eligibility criteria that referenced medication related information that might possibly be included in a Medication Profile or related to information within it were categorised as described and shown in Figure 9.
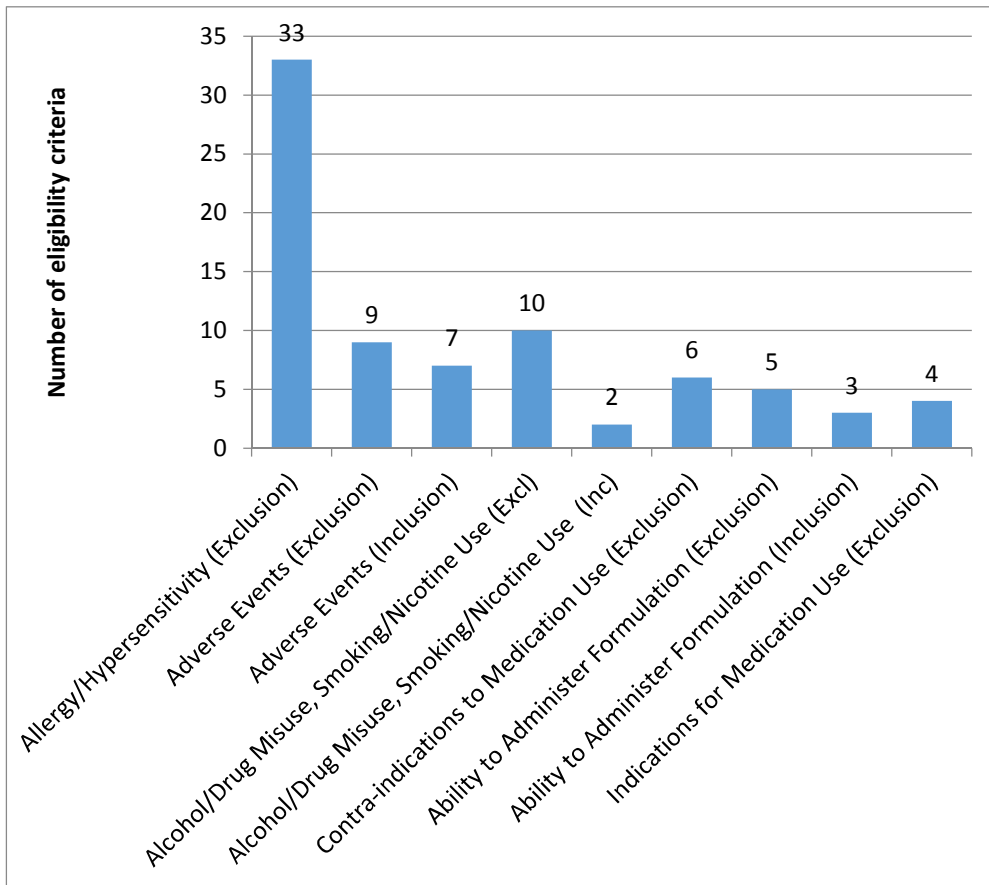
Figure 9: Bar chart showing categories of medication related information present in eligibility criteria

Allergy/hypersensitivity

All the eligibility criteria that described allergy or hypersensitivity to a medication or an excipient were exclusion criteria.

Example:

> *'History of hypersensitivity to docetaxel, or polysorbate 80'*

Adverse events

Eligibility criteria describing adverse events to a medication or type of medication were mostly exclusion criteria. Note that an allergy could be considered an adverse event and also included in this category, but in this analysis was classified separately if specifically described (as above).

Example:

> *'Unresolved or unstable serious adverse events from prior adjuvant chemotherapy or radiotherapy'*

Alcohol and substance misuse, smoking status and nicotine use

There were 12 eligibility criteria looking at current or past substance and alcohol misuse, either directly or by referencing screening and/or current or past smoking status and nicotine use. Two criteria were listed as inclusion criteria, but they

specified a negative result which semantically means that they were effectively exclusion criteria.

Example:

'Current alcohol dependence or drug abuse'

Contra-indications to medication use

All the eligibility criteria that described contra-indications to a medication or group of medications were exclusion criteria.

Example:

'Contraindications to the use of corticosteroid treatment'

Ability to administer medication formulation

Some eligibility criteria described the subject's ability or otherwise to administer/have administered the medication in a particular formulation.

Example:

'Patients unable to swallow oral medications'

Indications for medication Use

All the eligibility criteria which described the subject being having the required indication for a treatment with a medication or group of medications were exclusion criteria; in these criteria the indication for medication use is used as a proxy for a set of diagnoses.

Example:

'Indication for anticoagulant therapy for a condition other than atrial fibrillation (e.g., VTE[e])'

Discussion

Importance of Medication Profile information in eligibility criteria

The results of the analysis show that just over 18% of the 1112 examined eligibility criteria from the 41 clinical trials referred to medication information. This proportion is approximately double the proportion of examined eligibility criteria that referred to laboratory test information, which provides good evidence of the value of using a patient's Medication Profile for protocol feasibility studies and in the development of computer platforms and tools to support patient recruitment. It also reinforces that the correct types of information and data elements need to be present in that Medication Profile.

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[e] VTE = venous thromboembolism

This 18% is considerably lower than an analysis conducted by Ross et al[218], which found, of 1000 eligibility criteria studied, 'criteria specifying treatments or interventions participant has received or will receive' accounted for 34% of the total; however no clear definition of the difference between a 'treatment' and an 'intervention' is provided in that analysis. The proportion of eligibility criteria referencing laboratory data was also lower in the Ross analysis; 9% as opposed to 23%; this suggests that the categorisation in this analysis was more granular than that of Ross et al.

Current medication and past medication

The results show the relatively high level of importance of a subject's current medication as compared to the medication history. Almost twice as many eligibility criteria referred to medication being administered 'now' (and including prior to and 'now') compared to those that referred to medication having been administered in the past and which are no longer being administered. In the context of eligibility criteria, the 'now' may be any specified point in the trial process – randomisation, first administration of the investigational product etc. However, if the number of eligibility criteria that focus on previous administration of a study agent, which is a type of past medication, were included, this would give roughly equal value to knowledge of current and past medication. This is important, because in the healthcare delivery domain the current medication is deemed the more important, with the longitudinal record of lesser importance.

Investigational product use

A notable group of eligibility criteria were those that refer to previous administration of a study agent, or which reference the authorisation status of products that have been previously administered (which includes use of an authorised medication outside of its approved indications). This is significant because of the recent growth in the use of study registries, which accompanied by the concentration of clinical research in a smaller number of large centres, means that the re-use of potential subjects is becoming a problem.

To interrogate Medication Profile information correctly for use of study agents or other non-approved drugs, it should be possible to identify these. There are two possibilities. One is to incorporate the use of a medicines knowledgebase that has wide coverage of study agents as part of the query application (see below) that could be used to compare all the medicines in a patient's Profile with their authorisation status in the country of use. Unfortunately, most medicines knowledgebases do not have full coverage of investigational agents because information about these is not

widely available and putting such information, even in a limited way, has sometimes been deemed advertising, which is not permitted for unauthorised medicines. Even though there is a move from the regulatory agencies to increase the availability of information on investigational products and an acceptance that inclusion of basic information about an unlicensed product in a knowledgebase is not advertising, it is likely to be some several years before such information is widely available and is useable in a computable way. Even if the information were available, the comparison of each medicine in a Profile against an authorisation status is a considerable task, especially for protocol feasibility testing when a large volume of potential patients' information is being queried. The second possibility is to indicate directly into the Medication Profile when a patient is taking an investigational agent. This is not, to the writer's understanding, currently done in any formal way by any medication recording system (PMR or EHR) used in patient care, but on the evidence of this analysis would appear to be useful.

Identifying medicines – knowledgebase requirement

Only a very small number, less than 3%, of eligibility criteria that focus on the subject's use of medicines directly describe the medicines themselves; all the rest describe medicines in groups either by categorical characteristics or by therapeutic use, or by non-therapeutic effect. This is significant for any process that wishes to use Medication Profile information in protocol feasibility studies and/or in tooling to support patient recruitment in that it introduces a requirement for knowledge about medicines to be used. A medicines knowledgebase, such as those that support medication decision support in patient care should have the categorical information and the therapeutic use information readily available and in a format that would be straightforward to process to provide the additional information for querying of these eligibility criteria. A knowledgebase of this type will use the Summary of Product Characteristics (SmPC) as one of its primary sources. In that document, which is laid out in standard sections[220] the categorical characteristics of a medicine are described in the 'Pharmacodynamic properties' section (5.1) usually by direct reference to a formal characteristics classification such as the ATC[221]. Therapeutic use is similarly described in the 'Therapeutic indications' section (4.1).

Although non-therapeutic effect information of the types seen in the eligibility criteria is available for medicinal products as part of this authorisation information, it is not as organised and as accessible as the categorical characteristics or indications information, nor is it standardised. For although there is a section in an SmPC labelled 'Undesirable effects' (section 4.8) this merely lists all unwanted effects that the medication has been found to cause or suspected of causing. For newer

medicines, these effects are at least grouped together in categories based on the MedDRA System Organ Class[222] hierarchy and therefore it is possible to identify those of relevance to an eligibility criterion more easily, say by looking at the cardiac disorders for QT interval prolongation. This type of adverse effect information may alternatively be described elsewhere, as in the 'Special warnings and precautions for use' section (4.4). Information about enzyme modulation caused by a medicinal product may be even more dispersed in a single SmPC. It may appear in the 'Posology and method of administration' section (4.2), because it is seen as a requirement for dosage adjustment. It may appear in the 'Special warnings and precautions for use' section (4.4) as information about co-administration and it will almost certainly also appear (again) in the 'Interaction with other medicinal products and other forms of interaction' section (4.5). Therefore, although the raw data is usually available, even if somewhat scattered in location, it has to be processed into knowledge for use in practice. This can introduce a concerning lack of consistency. For example, there is no documented standard set of medicines acknowledged as those that prolong the QT interval in a clinically relevant manner. An illustration of this is that the British National Formulary lists QT interval prolongation as side effect of macrolide antibiotics[223] but does not do so for quinolone antibiotics although such effects have been documented[224] and are noted in SmPC. The same lack of consistency exists for information about for cytochrome P450 isoenzyme modulators, and is more complicated as there are several individual isoenzymes to consider. Knowledgebases currently take this raw data on enzyme modulation and apply it in the maintenance of their drug interaction modules, rather than provide it directly as information about the medicinal products that are CYP modulators[225]. Recognising this issue, some clinical trial protocols will document lists of medications that in its context are considered to carry these risks, for example:

'*Any concomitant medications that may cause QTc prolongation or induce Torsades de Pointes (see Appendix D for the lists of medications in Table 1 and Table 2) or induce CYP3A4 function*' and '*Concomitant use of CYP3A4 inhibitors or inducers. See Section 5.3.2 for list of prohibited medications.*'[226]

The lack of consistency means is information must be managed on a study-by-study basis, and cannot necessarily be applied to other studies that have not provided such information.

There were a small number of eligibility criteria that described alcohol and/or substance misuse and/or nicotine use. Whilst not directly part of the Medication Profile, there is information that could contribute to this. Medications used specifically in the management of substance misuse, alcohol misuse and nicotine

replacement therapy are likely to be documented in a Profile and, by using a knowledgebase to identify these and then querying against that set, some assessment of a potential subject's suitability against this type of eligibility criteria could be made using information in the Medication Profile.

A knowledgebase could be used to provide information to assist in querying for the small number of eligibility criteria that reference contra-indications to medications, by listing these contra-indications as conditions and then the patient record querying for evidence their presence directly. However, this is a considerable amount of processing for a relatively small number of eligibility criteria; it would be more constructive to protocol feasibility studies and patient recruitment support to list the conditions themselves, rather than use a medication's contra-indications as a proxy.

Dosage instructions

The proportion of medication eligibility criteria that describe dosage instruction information showed some clear patterns. Less than 10% required dose quantity or route of administration information. However, nearly half of all eligibility criteria that describe use of medicines also reference when the course of therapy occurred, either that it was currently in progress or when in the past it had occurred and ceased, as already described in the classification of those eligibility criteria that reference either current medication or past medication.

Given the complexity that can easily develop in describing dosage instructions information in a machine-readable way, these results indicate that there is little value to be obtained by attempting complex querying of this information within the Medication Profile for protocol feasibility studies and patient recruitment tooling. But the results show that it is important for protocol feasibility studies and patient recruitment tooling to be able to ascertain the basic timing of the course of therapy (i.e. start and stop dates), even if the detail of the dose quantity, frequency of administration or route of administration within that course is not provided in any machine-readable/query-able way.

Indication for treatment and discontinuation

A significant proportion (almost a third) of eligibility criteria that include medicinal product use also require evaluation of the indication for the use of the medication, but this information is rarely directly recorded in a medication process and therefore is presently unlikely to be directly available in a clinical data warehouse or EHR system. The information may well be present implicitly: the patient was diagnosed with breast cancer at point X and three weeks later doxorubicin is administered; it is

almost certain that the doxorubicin would be indicated for the treatment of the breast cancer. Whilst a clinician reviewing a patient with a complete health record can make that connection straightforwardly, if they can find the data, an application querying a clinical data warehouse or EHR system would find that an extremely complex task to accomplish successfully given the current state of such systems. Even a clinician may find this type of inference difficult for those medications with a diverse set of therapeutic uses; being clear of the indication for the use of amitriptyline, whose primary use has been as an antidepressant but is now as likely to be used as an analgesic in post herpetic neuralgia or as a prophylactic against migraine, is a much more tricky task.

Indication information in an eligibility criterion is subtly different from the combination of a particular diagnosis with a medication qualifier, although each describes a medication and a condition/symptom being treated. The latter is somewhat easier to query for in a clinical data warehouse or EHR system; the diagnosis can be queried directly, and if found, then the qualifying medication can then be investigated, again directly. Since both mechanisms achieve roughly the same ends, potential subjects with a particular diagnosis also taking a particular medication that is related to that diagnosis, wording eligibility criteria in the pattern of 'diagnosis + medication qualifier' is likely to be more efficient for querying in protocol feasibility studies and patient recruitment tooling than using the 'medication and indication' pattern.

A small number of eligibility criteria referred directly to treatment failure; the subject had therapy with the particular medication, but it was unsuccessful in achieving the desired therapeutic effect. In addition, in the analysis of those criteria that were deemed to not be directly related to the Medication Profile but referenced medication in some way, the majority concerned allergy/hypersensitivity or an adverse event. If these are considered together as 'reason(s) to stop' a therapy, this amounts to significant number of the eligibility criteria. Reason for discontinuation information is rarely recorded explicitly in any clinical record system, but these results suggest that it would be of use if it were.

Other

The very small number of eligibility criteria that are concerned a potential subject's ability to self-administer particular formulations of a study agent do not currently have any data that would support identifying such subjects computably. The small proportion of criteria does not offer significant evidence to support this as a new requirement for addition to the Medication Profile.

Ethical and medico-legal implications

This analysis of eligibility criteria requirements for the Medication Profile has focussed on the medication specific data elements that the Profile would need to contain to support the systems mediated detection of suitable subjects for protocol feasibility testing and patient recruitment. However, for these data to be actually used in such testing or going forward as part of a clinical trial data set, it would be necessary to comply with all the appropriate ethical and medico-legal requirements, including those of Good Clinical Practice (GCP)[227]. These include the requirement that the authorship and time stamping of all data is preserved, and that all changes are made in a version controlled manner permitting full traceability and the potential for rollback to a prior version of the data, a comprehensive audit trail and a long-term commitment to data retention. Many of these GCP medico-legal requirements are identical or very similar to the medico-legal requirements for electronic health record data, such as published in ISO EN 18308:2011 'Requirements for an electronic health record architecture'[228].

Limitations of this study

The main limitation of this study that it used information from phase III trial protocols provided by the pharmaceutical industry specifically for research. Despite this, the number of criteria studied was similar to that investigated in the few other studies in this area. Repeating this investigation using a different set of protocols would be beneficial, as would a similar type of investigation using other study phases and study types. This should include observational (phase IV) studies for medications, and studies into other types of medical intervention (procedures, device use).

Recommendations for further work

Since a proportion of eligibility criteria refer to groups of medicines with specific non-therapeutic actions, such as Q-T interval prolongation or CYP modulation, it would be useful if work were undertaken to establish clearly which medications should be considered members of these groups, based on evidence of clinical effect rather than theoretical possibility. These standard lists could then be used in all studies, in both design and execution, and would have value in the wider context of clinical decision support.

Further investigation could be undertaken into whether it is indeed valuable to encourage study protocol authors to employ a 'diagnosis with medication qualifier' structure in the statement of an eligibility criterion as opposed to using a 'medication

for this indication' structure, particularly if one pattern was significantly more effective in protocol feasibility studies and patient recruitment tooling. Given the known lack of recording of indication information, the former pattern appears the more useful, yet the latter pattern appears to have use that is more extensive in eligibility criteria. Optimisation of the eligibility criteria given in a study protocol would be expected to optimise recruitment of subjects to that study, so this would be a useful area for further work.

Conclusion

Information from a potential subject's Medication Profile makes a significant contribution to the overall set of queries based on study eligibility criteria, which are used in protocol feasibility studies and patient recruitment tooling. Information on both current medication use and past medication use where shown to be equally useful, when use of a past study agent is included as a type of past medication, which supports the requirement to have longitudinal information in a Medication Profile as well as current medication information.

In terms of the detail of what is recorded in the Medication Profile in addition to the identification of the medicinal products themselves, the most useful element is the timing of the course of therapy – when it commenced and if/when it has ceased. Other dosage information, including route of administration and dose quantity was found to have limited use. In conjunction with the start and stop timing, direct recording of information about the indication to start a therapy, and reasons for its cessation were found to be of benefit in this context. Neither is currently recorded in routine practice.

The analysis demonstrated the requirement to be able to query a Medication Profile to ascertain whether any of the medications that a patient has received is an investigational agent (i.e. a medication that does not possess a marketing authorisation and therefore is administered as part of formal clinical research).

It was clear that, due to the way eligibility criteria are currently written, a medicines knowledgebase is required to expand some grouping concepts from the criteria into individual medication concepts such that the Medication Profile can be queried directly.

The results of this analysis give several recommendations, beyond the provision of requirements for the content of a Medication Profile. These recommendations are primarily aimed at authors of eligibility criteria, but also to authors of medicines knowledgebases and to the providers of electronic health record systems.

Medication Profile information in EHR systems should be structured and designed such that their recording of medication information and in particular the granularity of the data elements within that support all of the relevant use cases for that information: high quality direct care delivery and also secondary uses, including clinical research.

Standardised sets of the medications that are acknowledged to cause important clinical effects such as prolongation of the QT interval and CYP modulation should be developed. These should be agreed for use in both patient care and clinical research, and should be available for use in knowledgebase systems. In the interim, when an eligibility criterion refers to such an effect, it should provide the set of medications that the author(s) deem to be causative, to avoid different investigators using different sets.

Part 2: Pharmacovigilance

Introduction

Adverse drug reactions have an enormous human and economic cost. This is in terms of the suffering caused to individuals and their families, in direct costs to the healthcare system of treating the adverse events, in the loss of revenues if/when a medicinal product must be prematurely withdrawn from the market and in terms of any litigation arising from inadequate safety information for the sponsoring pharmaceutical company.

Clinical trials, despite having a clear responsibility to demonstrate safety[229], no matter how carefully they are undertaken or how much data they collect, will always have limitations in terms of the safety information they provide[230]. This is not least because the primary purpose of any pre-authorisation trial is to actively and explicitly demonstrate efficacy, not to assess harm[231,232], whereas safety is demonstrated passively and implicitly. This is seen in the contrast of the two submission documents included in an eCTD[233] (electronic Common Technical Document) submission to the FDA based on pooled cross study data: the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE). The first looks to try to find 'the needle in the haystack'[35] through critical assessment of the safety data itself and by analysis of additional data that might be a pointer to safety issues such as trial drop-outs etc. whereas the second looks to actively demonstrate the benefits of the product and particularly that these benefits outweigh any risks[234].

The adverse effects of a medicine can be hard to detect and this may be made harder still in the context of time-limited clinical trials. This is because some adverse events take time to manifest themselves (late reactions) and may even occur after the medication course has finished (delayed reactions) [235] and the trial has been completed. In addition, age[236,237] and morbidity[238,239] can have a considerable effect on the pharmacokinetics of many medications, which may then have a consequential effect to their adverse event profile in those sub-populations. Yet most phase II and phase III clinical trials are both age limited and co-morbidity limited. One area that is assessed is the effect on safety of concomitant medications taken by study subjects[240]. Therefore, for any subject in a clinical study who has an adverse event, having information on the concomitant medications they are taking is a requirement. This information is gathered in the trial for each study subject and is reported in the Concomitant Medications domain of the Study Data Tabulation Model[31].

Since understanding serious adverse events is a critical component of the overall medication safety landscape and because of the detection difficulties in clinical trials, continuing to gather safety information beyond the formal clinical trials phases is

vital. This means that the role of the spontaneous adverse event reporting systems that provide post marketing surveillance of medicines operating throughout the world is invaluable, indeed essential, in detection of adverse events[241]. Capturing information about spontaneous adverse events is a major, possibly the major, element in shaping the necessary understanding of the overall safety of a medicinal product. Spontaneous adverse event reporting must therefore be a global initiative to gather enough data to have a realistic chance of success.

Spontaneous adverse event reporting is usually managed by what the WHO refers to in it its Partners in Pharmacovigilance as the collating agencies[157], the National Pharmacovigilance Centres, who, alongside the WHO's own teams, provide the main co-ordination for post-marketing surveillance and whose core activity is the collection of suspected adverse drug reaction information.   These agencies form a major part of the partnership, which includes the different organisations and disciplines that must work together in the science of pharmacovigilance to safeguard the public in their use of medicines.   National medicines regulatory agencies are also core members of the partnership and need close collaboration with the national centres[242] and indeed in some cases may incorporate the national centre within their structures[243].

The cornerstone of spontaneous adverse event reporting systems and therefore of post marketing surveillance is the collection and analysis of adverse drug reaction information from healthcare practitioners and increasingly, from patients themselves. The raw data collection is undertaken through the adverse event forms that the reporter completes and submits to the collating agency. The older systems started using paper-based forms submitted by mail or fax and most have now moved to also offer web-based forms submitted directly on line. The data from the forms is entered into the collating agency's database. These databases grow over time, the FDA's AERS database receives approximately a thousand reports per day, and is the primary resource for adverse event analysis and detection[244], although that detection is an extremely complex and difficult process[35].

The adverse event reporting forms are therefore of great significance since it is these that provide the raw material for the adverse event assessment.   However, there has been little critical assessment of the requested data elements on spontaneous adverse event reporting forms, although it is clearly acknowledged that reports with little clinical data are of limited value because the relationship between a drug and a suspected adverse event cannot be assessed[245].

Getz et al[246] undertook an assessment of the completeness and basic accuracy of the information present in a set of FDA MedWatch forms. This assessment noted that the patient information was generally more complete than the data on the suspect product, with dosage information (for the suspect product) being complete in less than a third of reports. Further analysis showed that information that was provided was often erroneous; a quarter of the names given for the suspect product were inaccurate, with spelling, even of common medicines, being a key issue. Getz et al concluded that the low levels of completeness of suspect product information were 'troublesome', since this information is essential to identifying root causes in adverse events. This analysis concentrated only on patient and suspect medication data elements; no assessment of information on the concomitant medications was undertaken.

One known issue with spontaneous adverse event reporting forms is the amount of time taken to complete[247]; it is estimated that the FDA's 3500 MedWatch form takes a healthcare professional an average of 36 minutes to complete manually[248]. There are been some initiatives to obtain the information for the forms directly from an electronic health record. Probably the most widely known of these is the proof of concept undertaken by the ASTER pilot[249]. This pilot used the electronic health record to supply data directly into an adverse event report when requested by the user, and in addition used information from the electronic health record to trigger a query to the user that an adverse event may have occurred and therefore to request that a report be submitted.

The patient's Medication Profile is a valuable source information for the information required for pharmacovigilance, so it should be the most robust and reliable source for the data elements needed. Therefore, by undertaking an analysis of the requirements of reporting forms, both for spontaneous adverse events in post marketing surveillance and for clinical trials, the requirements that the Medication Profile must meet to be that authoritative information source will be elucidated.

Methodology

The aim of the investigation was to analyse a set of spontaneous adverse event reporting forms from various national medicines regulatory agencies to document the data elements about medicines, both suspect and concomitant, that are requested from reporters in order to assess adverse events. These data elements become information requirements for the Medication Profile, so that, ideally, these items of information can be drawn directly into an adverse event report by a reporter.

Post marketing surveillance forms are created by national pharmacovigilance reporting centres who are often part of the national regulatory agencies, so each country therefore uses its own standard form(s) for data collection. Although they vary in the scope of products for which they are to be used, these forms collect a broadly similar set of data even though they are not conforming to any international standard. In order to ascertain exactly the data items that are most usually collected on such forms so as to take these forward as data requirements for the Medication Profile, a purposeful sample was undertaken of forms used within Europe, North America and Australasia. There was not scope in this research to undertake an exhaustive international survey of these forms, which is not considered an important limitation given their similarity. The forms were those in current use during the period of this study, which was October to December 2014. The analysis studied 13 spontaneous adverse event reporting forms that are available electronically for use by reporters from patient care; and one local one available in hard copy; these forms were from seven countries.

The forms in languages other than English where translated. The Dutch form was translated by a Dutch pharmacist working for the royal Dutch pharmacists' association, Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, (KNMP)[164]. The French and Spanish forms were translated by a graduate specialising in these languages with significant familiarity with medication concepts. Since medication concepts keep their close association to their Latin base (e.g. 'posologie' in French to describe dosage instructions, which translates to posology in English), the accuracy of the translation could be confirmed by the researcher, with her own understanding of modern languages and medication concepts.

In the pharmaceutical industry in regulated clinical research, there are just two standard forms in use; these are the international reporting forms known as the CIOMS[250] form and the ICH E2B(R3)[251]. In addition, the data elements (variables) collected to describe study medication(s) (the exposure domain EX) and concomitant medications (the CM domain) in CDISC's Study Data Tabulation Model (SDTM) were included for study. This is the only available specification for data elements to be used in the submission of raw clinical trial data, and it provides the data that would be used to support investigation of an adverse event occurring during a clinical study.

Each form was examined in turn and the data elements it requested for both the suspect medication(s) and any concomitant medications were noted. The extraction of data elements was crosschecked by the author by undertaking a separate second pass through each form. The research supervisor independently checked the

extraction for a sample of the forms. The parent for the medication data elements was usually a description of the medication itself (e.g. a section entitled 'product name'). Due to the variation in granularity of the data elements themselves (for example, two forms collected batch number as part of the product name section, whilst the others collected batch number as a separate data item) an iterative approach was used to develop a meaningful description of the Results in tabular form.

Results

Sixteen forms were examined to ascertain the data elements required to describe the suspect medication(s) and concomitant medications involved in adverse reactions. 13 forms were spontaneous adverse event reporting forms for use by reporters from patient care, 2 were forms for use by the pharmaceutical industry and one is used to report subject information from clinical studies. The details of the 16 forms is shown below in Table 12.

Table 12: Description of the ADR report forms examined

Form Short Name	Form Full Name	Country	Owner	Reference
Medwatch 3500	Medwatch Voluntary 3500	United States of America	Food and Drugs Administration (FDA)	http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf
Medwatch 3500A	Medwatch Mandatory 3500A	United States of America	Food and Drugs Administration (FDA)	http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
Medwatch 3500B	Medwatch Voluntary for Consumers 3500B	United States of America	Food and Drugs Administration (FDA)	http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149236.htm
Yellow Card: paper	Report of Suspected Adverse Drug Reactions (paper)	United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	https://yellowcard.mhra.gov.uk/ https://www.medicinescomplete.com/mc/bnf/current/
Yellow Card: online	Report of Suspected Adverse Drug Reactions (online)	United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	https://yellowcard.mhra.gov.uk/

Table 12 (cont.): Description of the ADR report forms examined

Form Short Name	Form Full Name	Country	Owner	Reference
Blue Card	Report of Suspected Adverse Reaction to medicines or vaccines	Australia	Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/sites/default/files/blue-card-adverse-reaction-reporting-form-151102.pdf
ANSM	Déclaration d'effet indésirable susceptible d'être dû à un médicament	France	Agence nationale de sécurité du médicament et des produits de santé (ANSM)	http://ansm.sante.fr/var/ansm_site/storage/original/application/dd527d3fd8e9727b05476386c555fbcd.pdf
IMB ADR	Adverse Reaction Report Form	Ireland	Irish Medicines Board (now Healthcare Products Regulatory Agency) (IMB/HPRA)	https://www.hpra.ie/homepage/veterinary/safety-information/adverse-reaction-reporting
Lareb ADR	Meldformulier Zorgverlener	The Netherlands	Lareb	https://www.lareb.nl/Meld-bijwerking/Meldformulier

Table 12 (cont.): Description of the ADR report forms examined

Form Short Name	Form Full Name	Country	Owner	Reference
SEFV-H A	SEFV-H (Madrid) [A] Notificar sospechas de reacciones adversas a medicamentos	Spain	Sistema Español de Faramcovigilancia de Medicamentos de Uso Humano (SEFV)	https://www.notificaram.es/FNotificacionPS.aspx
SEFV-H B	SEFV-H-Madrid) [B] Notificar sospechas de reacciones adversas a medicamentos	Spain	Sistema Español de Faramcovigilancia de Medicamentos de Uso Humano (SEFV)	https://www.notificaram.es/FNotificacion.aspx
VAERS	Vaccine Adverse Event Reporting System Form	United States of America	Food and Drugs Administration (FDA) and Centers for Disease Control and Prevention (CDC)	https://vaers.hhs.gov/esub/step1

Table 12 (cont.): Description of the ADR report forms examined

Form Short Name	Form Full Name	Country	Owner	Reference
AEFI	Adverse Events following Immunisation Form	Australia	Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/form/national-adverse-events-following-immunisation-aefi-reporting-form
CIOMS 1	Suspect Adverse Reaction Report Form (CIOMS Form 1)	Global	Council for International Organizations of Medical Sciences (CIOMS)	http://cioms.ch/index.php/cioms-form-i
E2B(R3)	Data Elements for the Transmission of Individual Case Safety Reports	Global	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)	http://estri.ich.org/e2br3/index.htm
SDTM forms	Study Data Tabulation Model for Exposure to Study Drug (EX) and Concomitant Medication (CM)	Global	Clinical Data Interchange Standards Consortium (CDISC)	https://www.cdisc.org/standards/foundational/sdtm

Scope, Event type and Reporter type

The 13 spontaneous adverse event reporting forms for use by reporters from patient care varied considerably in their scope, usage and paradigm of reported event type, whereas forms for use by the pharmaceutical industry in regulated clinical research showed less variation. The following two tables show the scope (the types of products whose adverse events can be reported on the form) and the types of events that should be reported with the types of reporters that may use the form.

Table 13: Description of the scope (type of products) covered by each ADR report form

Form Short Name	Prescription medicines	Biologic products	Vaccines	Over-the-counter medication	Nutrition products	Cosmetic products	Food products
Medwatch 3500	✓	✓	✓	✓	✓	✓	✓
Medwatch 3500A	✓	✓	✓	✓	x	x	x
Medwatch 3500B	✓	✓	✓	✓	✓	x	x
Yellow Card: paper	✓	✓	✓	✓	✓	x	x
Yellow Card: online	✓	✓	✓	✓	x	x	x

Table 13 (cont.): Description of the scope (type of products) covered by each ADR report form

Form Short Name	Prescription medicines	Biologic products	Vaccines	Over-the-counter medication	Nutrition products	Cosmetic products	Food products
Blue Card	✓	✓	✓	✓	✓	x	x
ANSM	✓	✓	✓	✓	x	x	x
IMB ADR	✓	✓	✓	✓	x	x	x
Lareb ADR	✓	✓	✓	✓	x	x	x
SEFV-H A	✓	✓	✓	✓	x	x	x
SEFV-H B	✓	✓	✓	✓	x	x	x
VAERS	x	x	✓	x	x	x	x

Table 13 (cont.): Description of the scope (type of products) covered by each ADR report form

Form Short Name	Prescription medicines	Biologic products	Vaccines	Over-the-counter medication	Nutrition products	Cosmetic products	Food products
AEFI	x	x	✓	x	x	x	x
CIOMS	✓	✓	✓	✓	x	x	x
E2B(R3)	✓	✓	✓	✓	x	x	x
SDTM forms	✓	✓	✓	✓	x	x	x

The biggest difference across the 13 spontaneous adverse event reporting forms is that two forms are for reporting vaccine events only, whereas all the others and indeed including the industry-focussed forms, cover medicinal products and vaccines (or they do not differentiate between these two types of product (the SEFV-H, CIOMS and E2B forms).

Three agencies (FDA, MHRA and TGA) responsible for adverse event forms listed the types of medicinal products that could have events reported and explicitly included over-the-counter medication (both the MHRA and the TGA gave a definition of these as 'purchased without a prescription') and complimentary therapies (which the Australian TGA helpfully defined as 'erbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals'). The FDA's MedWatch form also covers events relating to foods and cosmetic products. All the other forms were limited to events for medicines only, with both the IMB and Lareb forms specifically including vaccines as medicinal products.

Table 14: Description of the reporter types and event types for each ADR report form

Form Short Name	Reporter Type				Event Type			
	Healthcare professionals	Patients & Consumers	Pharmaceutical Companies	Other	Adverse Event	Product Problem	Medication Error	Product Switch Problem
Medwatch 3500	✓	✓	x	x	✓	✓	✓	✓
Medwatch 3500A	x	x	✓	User facilities Distributors Importers	✓	✓	x	x

Table 14 (cont.): Description of the reporter types and event types for each ADR report form

Form Short Name	Reporter Type				Event Type			
	Healthcare professionals	Patients & Consumers	Pharmaceutical Companies	Other	Adverse Event	Product Problem	Medication Error	Product Switch Problem
Medwatch 3500B	x	✓	x	x	✓	✓	✓	✓
Yellow Card: paper	✓	✓	x	x	✓	x	x	x
Yellow Card: online	✓	x	x	x	✓	x	x	x
Blue Card	✓	x	x	x	✓	x	x	x
ANSM	✓	x	x	x	✓	x	x	x

Table 14 (cont.): Description of the reporter types and event types for each ADR report form

Form Short Name	Reporter Type				Event Type			
	Healthcare professionals	Patients & Consumers	Pharmaceutical Companies	Other	Adverse Event	Product Problem	Medication Error	Product Switch Problem
IMB ADR	✓	x	x	x	✓	x	x	x
Lareb ADR	✓	x	x	x	✓	x	x	x
SEFV-H A	x	✓	x	x	✓	x	✓	x
SEFV-H B	✓	x	x	x	✓	x	✓	x
VAERS	✓	✓	✓	Vaccine administrators	✓	✓	✓	x
AEFI	✓	✓	x	x	✓	x	x	x

Table 14 (cont.): Description of the reporter types and event types for each ADR report form

Form Short Name	Reporter Type				Event Type			
	Healthcare professionals	Patients & Consumers	Pharmaceutical Companies	Other	Adverse Event	Product Problem	Medication Error	Product Switch Problem
CIOMS 1	x	x	✓	Investigators	✓	x	x	x
E2B(R3)	x	x	✓	Investigators	✓	x	✓	x
SDTM	x	x	x	Investigators	✓	x	x	x

Some agencies provide a set of spontaneous adverse event reporting forms, aimed at their different reporter communities. The FDA provides three separate forms; the MedWatch 3500 may be used by healthcare professionals and consumers/patients, the MedWatch 3500A is to be used by all industry reporters (manufacturers/distributers etc.) and the MedWatch 3500B is aimed solely at consumers. The MHRA's Yellow Card paper version may be used by healthcare professionals and members of the public, whereas the on-line version should be used by healthcare professionals only. SEFV-H provides two forms – one for

healthcare professionals only and one for patients only. Both the specifically vaccines-focussed adverse event forms accept reports from both healthcare professionals and members of the public. All the other agencies provide only one form, which is for the use of healthcare professionals. The TGA advises members of the public to seek advice from a healthcare professional if they feel they have experienced an adverse event, but very recently a consumer focussed form has been placed on-line[252]. The CIOMS and E2B forms are industry only, which includes any healthcare professionals in their role as investigators conducting clinical trials on behalf of the clinical research industry.

Whilst all of the report forms cover product adverse events, the FDA forms have the broadest event coverage, including product problems (defects etc.), medication errors and product switching problem (adverse event because of being given an alternative manufactured product for the same medication). Two of forms (MHRA Yellow Card: paper and TGA Blue Card) specifically stated that product problems should be reported using a separate system. The SEFV-H and E2B forms explicitly included medication errors in their event types.

Medication Data Elements

Each of the 16 ADR report forms were examined in detail and the medication data elements required by each form, both for the suspect medication (Table 15) and for the concomitant medications (Table 16) were recorded.

Table 15: Presence of the detailed medication data elements for each report form: Suspect medication

Form	Product description		Dosage information			Therapy dates			Indication	Batch or Lot number	Other
	Name	Code	Dose quantity	Dose frequency	Route	Start date	Stop date	Duration			
Medwatch 3500	Trade/brand name OR Generic name + manufacturer Strength	✓	✓	✓	✓	✓	✓	✓	✓	✓	Expiry date
Medwatch 3500A	Trade/Brand Name OR Generic name + manufacturer OR Foreign trade name + manufacturer	✓	✓	✓	✓	✓	✓	✓	✓	✓	Expiry date
Medwatch 3500B	Name(s) of the product Name of company that makes product	✓	✓	✓	✓	✓	✓	x	✓	✓	NA

Table 15 (cont.): Presence of the detailed medication data elements for each report form: Suspect medication

| Form | Product description | | Dosage information | | Therapy dates | | | Indication | Batch or Lot number | Other |
	Name	Code	Dose quantity	Dose frequency	Route	Start date	Stop date	Duration			
Yellow Card: paper	Name of Drug/Vaccine (Brand if known)	x	✓ free text (daily dose)		✓	✓	✓	x	✓	✓	NA
Yellow Card: online	Name of Drug/Vaccine (from drop down)	x	✓ free text (daily dose)		✓	✓	✓	x	✓	✓	NA
Blue Card	Medicine/vaccine (please use trade names)	✓	✓ Dosage (dose number for vaccines e.g. 1st DTP)		x	✓	✓	x	✓	✓	NA
ANSM	Medicine name	x	✓ free text (daily dose)		✓	✓	✓	x	✓	✓	NA
IMB ADR	Name of Drug/Vaccine (brand name where possible)	x	✓ free text (daily dose)		✓	✓	✓	✓	✓	✓	NA

Table 15 (cont.): Presence of the detailed medication data elements for each report form: Suspect medication

	Product description		Dosage information			Therapy dates			Indication	Batch or Lot number	Other
	Name	Code	Dose quantity	Dose frequency	Route	Start date	Stop date	Duration			
Lareb ADR	Name of product (from drop down)	x	✓	✓	✓	✓	✓	x	✓	x	NA
SEFV-H A	Name of product (from drop down)	✓	✓	✓	✓	✓	✓	x	✓	✓	Expiry
SEFV-H B	Name of product (from drop down)	x	✓	✓	✓	✓	✓	x	✓	✓	Expiry
VAERS	Vaccine (type) + Manufacturer	x	Number of previous doses		✓	Date of vaccination			x	✓	Site of administration
AEFI	Name (brand)	x	Dose number		✓	Date of vaccination			x	✓	Site of administration
CIOMS Form 1	Drug name (include generic name); Manufacturer	x	✓ free text (daily dose)		✓	✓	✓	x	✓	✓	NA
E2B(R3)	Medicine (generic & proprietary)	x	✓	✓	✓	✓	✓	✓	✓	✓	Active ingredient
SDTM EX	Name + Dose form	x	✓	✓	✓	✓	✓	✓	x	✓	Site of administration

In the FDA forms where medication errors are specifically included as reportable events, there is a note that in the case of overdose, the overdose amount should be reported rather than the prescribed dose quantity for the suspect medication.

Table 16: Presence of the detailed medication data elements for each report form; Concomitant medication

Form	Product description		Dosage information			Therapy dates			Indication	Batch or Lot number	Other
	Name	**Code**	**Dose quantity**	**Dose frequency**	**Route**	**Start date**	**Stop date**	**Duration**			
Medwatch 3500	Free text name	x	x	x	x	✓	✓	x	x	x	NA
Medwatch 3500A	Free text name	x	x	x	x	✓	✓	x	x	x	NA
Medwatch 3500B	Free text name	x	x	x	x	x	x	x	x	x	NA
Yellow Card: paper	Name of Drug/Vaccine (Brand if known)	x	✓ free text (daily dose)			✓	✓	x	✓	✓	NA

Table 16 (cont.): Presence of the detailed medication data elements for each report form; Concomitant medication

| Form | Product description | | Dosage information | | | Therapy dates | | | Indication | Batch or Lot number | Other |
	Name	Code	Dose quantity	Dose frequency	Route	Start date	Stop date	Duration			
Yellow Card: online	Name only (from drop down)	x	x	x	x	x	x	x	x	x	Source:
Blue Card	Name	x	Dosage		x	✓	✓	x	✓	x	NA
ANSM	Product name	x	✓ free text (daily dose)		✓	✓	✓	x	✓	x	NA
IMB ADR	Drug name	x	✓ free text (daily		✓	✓	✓	✓	✓	x	NA
Lareb ADR	Name: can include strength and form	x	✓	✓	✓	✓	✓	x	✓	✓	Expiry
SEFV-H A	Name	x	✓	✓	✓	✓	✓	x	✓	✓	Expiry

Table 16 (cont.): Presence of the detailed medication data elements for each report form; Concomitant medication

Form	Product description		Dosage information			Therapy dates			Indication	Batch or Lot number	Other
	Name	Code	Dose quantity	Dose frequency	Route	Start date	Stop date	Duration			
SEFV-H B	*No requirement for information*										
VAERS	Vaccine (type) Manufacturer Other medications (free text)	x	Number of previous doses		✓	Date of vaccination			x	✓	Site of administration
AEFI	*Allergies and previous vaccination reaction information only*										
CIOMS Form 1	Name	x	x	x	x	✓	✓	x	x	x	NA
E2B(R3)	Name	✓	✓	✓	✓	✓	✓	✓	✓	x	NA
SDTM CM	Verbatim name and standardised name	X	✓	✓	✓	✓	✓	✓	x	✓	Site of administration

Product Description – Suspect and Concomitant

All forms required some identification of the medicinal products (and/vaccines) involved in the event.   In several forms, there was a difference in the level of detail required for the description of the suspect product from that of any concomitant products.   The brand/trade name for the suspect product was specifically requested in the FDA forms, Yellow Card, Blue Card and IMB ADR forms whereas concomitant medications just requested a name.   In both the industry forms, brand and generic names are equally requested.

Almost all forms collect information about concomitant medication, but it should be noted that one of the forms (SEFV-H B) did not collect concomitant medication information at all, and the FDA MedWatch for Consumers form collects it only in free text in the 'patient/person information' section rather than in a medication information section.

The FDA forms, the SEFV-H A form and the TGA form request the user to provide a code for the medication as does the SDTM CM domain form, which expect a code and product name from the WHO Drug Dictionary Extended (WHO DDE)[253].   The ANSM form requests a tracing number if the suspect product is a blood product (only). The on-line forms from the MHRA, Lareb and SEFV-H allow the user to select the suspect product from a drop down list, which implies that there may be coding scheme underlying that; only the MHRA form also allows concomitant medication selection using a drop down, although the Lareb form, once a name has been entered in free text for the concomitant medication supports description of the form and strength using drop down value sets.

Only the Lareb form does not request batch number information for the suspect product; batch number information is not requested for concomitant medications on all forms except the MHRA paper Yellow Card.

The Lareb form is unique in that it supports the uploading of a patient's medication list; this is possible because in the Dutch healthcare culture there is a centralised process to manage patients' medication information, provided under the auspices of their national healthcare organisation NICTIZ[15].

Dosage Information

Dose quantity (the amount of medication taken in a single administration event), dose frequency (the number of times in a given – usually 24 hour – period that an administration event takes place) and the route of administration form the dosage information collected on adverse event forms and for clinical trial submissions, with this latter also collecting total daily dose information even though that can be

calculated from the dose quantity and dose frequency. Although each of these data elements has a definition (given above and used throughout this work), no definition is provided on the forms themselves. Indeed several of the forms (from the MHRA, TGA, ANSM and IMB ADR) do not request dose quantity and dose frequency as separate data elements but ask for 'dosage' as free text, with the route of administration as a separate data element. The vaccine event forms request dose number or previous dose information rather than dose quantity and dose frequency, and also ask for site of administration as well as the route. The FDA forms did not specifically request dosage information for concomitant medications but the other forms used the same pattern of information for both suspect and concomitant medications.

Start/Stop Dates

All of the forms request start and stop dates for all medication, both suspect and concomitant, except the SEFV-H form that has no concomitant medication information at all and the FDA Consumer MedWatch form that collected concomitant medication information as text with the person/patient information. In contrast, only the IMB ADR form requested duration of therapy and this was in addition to the start and stop dates. The FDA forms allow the reporter to give duration of therapy (or an estimate of such) if start and stop dates are not available.

Indication

All of the forms request indication (or reason for use) for the suspect medication, with the exception of the vaccine specific forms, where of course the indication is implicit: prophylaxis of the disease caused by the antigen(s) administered. Similarly in the SDTM Concomitant Medication domain form, no indication would be required as this would be stated in the protocol for the study itself. Also in the SDTM Concomitant Medication domain form, the verbatim name is the name of the medicine as it is provided by the reporter, exactly, including any spelling errors, whereas the standardised name is the name of the medication as it is held in a medicinal product terminology used in clinical research, such as the WHO DDE[253]. Several of the forms also requested indication for concomitant medications.

Concomitant medication description

The description of concomitant information that each form employed is given where that was provided on the form itself or in the completion instructions accompanying the form in Table 17.

Table 17: Definition of concomitant medication from the report forms

Form	Concomitant medication description
Medwatch 3500	Medicines used at the time of the event
Medwatch 3500A	Medicines used at the time of the event
Medwatch 3500B	All **current** prescription medications, All OTC medications any vitamins, minerals, supplements herbal remedies, and medical devices being used
Yellow Card: paper	Other drugs (including self-medication and complementary remedies) **over last 3 months** including medicines obtained from the internet
Yellow Card: online	Additional medicines in the last three months (inc. prescription, OTC or herbal)
Blue Card	Other medicine(s)/vaccine(s) taken at the time of (over the period of) the reaction
ANSM	*None given*
IMB ADR	Any other drugs used over this period? (None/Unknown)
Lareb ADR	*None given*

Table 17 (cont.): Definition of concomitant medication from the report forms

Form	Concomitant medication description
SEFV-H A	Other medicines in last 3 months
SEFV-H B	No requirement for information
VAERS	Any other vaccinations within 4 weeks prior to the date List any prescription or non-prescription medications the patient was taking when the vaccine(s) was given.
AEFI	Allergies and previous vaccination reaction information only
CIOMS 1	*None given*
IMB ADR	Any other drugs used over this period? (None/Unknown)

No formal definition of what is required as concomitant medication is available. The FDA provides guidance of other products 'used at the time of the event'; the MHRA and one of the SEFV-H forms requests 'additional medicines in the last three months (inc. prescription, OTC or herbal)'; the TGA asks for other medicines 'taken at the time of (over the period of) the reaction'and the IMB asks for the names of medicines taken 'over this period' which is presumably the period of the adverse event. For the VAERS form, concomitant medication has two components: 'any other vaccinations within 4 weeks prior to the date (presumably of the event)' and 'any prescription or non-prescription medications the patient was taking when the vaccine(s) was given'.

Discussion

The Forms

The set of 16 forms examined were somewhat heterogeneous in terms of their scope (the products they covered), the reporters who should use the form and the medication event types that they covered. Indeed others have found a similar heterogeneity when seeking to do analysis of other paradigms in pharmacovigilance and have found it a hindrance to true comparative analysis[254]. Each of these paradigms is discussed below.

Product Scope

Vaccines only

Two of the 16 forms have a very limited scope, collecting information about vaccine adverse events only. There are several reasons why information about adverse events to vaccines may be collected and therefore evaluated separately. In some healthcare cultures, most notably the United States, vaccines are licensed by a separate part of the national regulatory agency, the Center for Biologics Evaluation and Research (CBER)[255], and placed into a separate adverse event reporting system: VAERS, the Vaccine Adverse Event Reporting System[256]. This is managed jointly by CBER and the CDC, the Centers for Disease Control and Prevention[257]. VAERS therefore has its own VAERS form, which was used in this analysis. In Australia, the Therapeutic Goods Administration licenses vaccines in the same way as other medicines but collects adverse events separately for their adverse event database[258] using the AEFI form.

Vaccines are generally given to healthy people and have public health as well as individual health considerations. The understanding and risk/benefit analysis that should accompany all adverse event investigations must consider not just the individual but also the wider community. This can be seen both in the actual change in vaccination schedule for MMR (measles, mumps and rubella vaccination) to include boys as well as girls[259] and in the change of attitude of the public to this, as the public's perception of the risks to individuals and the benefits to the general population shifts[260]. Although many vaccines are administered by healthcare professionals, the setting for the administration may range from a healthcare establishment through to a school, a military establishment and indeed, to temporary clinics in public buildings set up to deal with a specific public health event.

Vaccines are often given in combination, either several antigens administered in a single product (for example the diphtheria, tetanus, pertussis, poliomyelitis and

Haemophilus type b vaccine given at 2, 3 and 6 months to all babies in the United Kingdom) or at a single administration session (for example the BCG and hepatitis B vaccine products given to at risk neonates at birth). Alternatively, a single administration session having both combination vaccines and single vaccines (for example at 2 and 3 months babies in the UK receive meningococcal group C conjugate vaccine and rotavirus vaccine in addition to the diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus type b vaccine) may be used. Consequently, it can be extremely hard to see the effect of an individual antigen or formulation of an antigen and assign responsibility for an adverse event.

Other products

All the other forms had a wider scope, focusing on medicinal products and including vaccines and over the counter medicines. Each agency will have good reasons to have separate forms for adverse events for different product types, often related to the regulations under which they operate. From the perspective of the data elements required, the main consideration is to have consistency in the data element use and definition, even if that definition is worded differently for a patient/consumer focussed audience. Otherwise, it becomes extremely difficult to collate data together for analysis[261], which defeats the reason for the data collection. However, to achieve that consistency of use and definition across a wide product range is difficult; for example vaccines have a single point administration time, not a start/stop date, they have a dosing schedule rather than a dose quantity/frequency, and food and cosmetic products do not have dosage information at all.

A sensible compromise might be to have separate forms for vaccines and medicinal products for those healthcare cultures that find that explicit division useful and to have a standard mapping between the defined medication data elements from each form type, but also to have a completely standard pattern for collection of the data elements for concomitant medications in both cases.

Rather than attempting to cover such a diverse scope, collecting adverse events for non-medicinal product types (foods and cosmetics) should use a separate form, because they do not have the same information available (e.g. dose quantity), so it is unfair to ask any reporter to provide information that is not available, the data quality will be poor.

Reporter Usage

In the early years of pharmacovigilance following such triggers as the thalidomide tragedy, spontaneous adverse event reports were accepted by the national collating centres from only from medical practitioners. But recent years as the science of

pharmacovigilance has matured, there has been a growing understanding of the issue of underreporting of adverse events. To combat this, the range of types of individuals who may report adverse events has expanded, initially to include other healthcare professionals (primarily pharmacists and nurses) and then also to include patients themselves. In several countries, notably France, Italy and Spain, pharmacist reporting of adverse events to medications is mandatory.

Reporting by healthcare professionals other than medical practitioners in part reflects the growing role of non-medical prescribers (be they supplementary or independent) and the responsibility that a prescriber has in reporting adverse events to medications they have personally prescribed. As reporting by other healthcare professionals has expanded, so has the appreciation of those reports[262], which is in itself encouragement for further reporting when appropriate. By including patients as reporters of adverse reactions, as well as increasing the number of reports obtained and generally adding value to the pharmacovigilance process[263,264], a unique view of post marketing surveillance of over-the-counter medicinal products can gained[254].

Some national collating centres supply a single form for all reporters – all types of healthcare professionals and consumers, whereas others, most notably the FDA, have different forms, with the wording of the consumer focussed form using language that is much more inclusive ('how much of the medicine was taken each day' as opposed to 'daily dosage').

From the perspective of the medication data element requirements, the heterogeneity of reporter type is little direct import. However, in order to have consistency in reporter use of the medication data elements, these should be clearly defined and provided in a style that the reporter can unambiguously understand. Having separately worded forms for consumers to use is therefore likely to be beneficial, but they should keep the same pattern of data elements.

Event Type

Just as the types of reporter of adverse events as grown in recent years, so have the types of events that can be reported.

The concept of pharmacovigilance and the management of medication adverse events has recently been broadened to include adverse events that are not related to the pharmacology or pharmaceutics of the medicinal product but which are caused by external factors related to the medicinal product, for example issues with the packaging or labelling of the product. An example of this is the case where an

adverse event occurs due to incorrect dose quantity being administered; on analysis it might be found that the description of the strength of the medicine on the packaging lacks the necessary clarity[265].

In terms of the medication data elements required, if the analysis database to be used is for all safety events for medications, then having a single form with well-defined medication data elements is acceptable. The advantage of this is that the reporter does not necessarily have to make any decision as to what type of event they are reporting and may provide the raw data directly. The disadvantage is that some of the wording of the data element description is more appropriate to the standard adverse event than a medication error, most particularly the division between suspect and concomitant medication (see more below).

Medication Data Elements

The medication data elements have been assembled into two sections for discussion; the definition and description of the suspect or concomitant medications, followed by the dosage instructions information for those medications.

None of the forms gives any guidance as to what to provide if a particular item of data is not available (whether to add a 'not applicable' or a 'not known' comment). The use of such flavours of null[147] can be very helpful in analysis, which is the prime use case for collecting adverse event information. It does add a little to the time for completion and therefore this additional reporter burden must be balanced against the value of the increased data quality.

Product description

One of the major issues in the big analysis databases is lack of standardisation of product names[261] and it is this has been recognised as such a concern that it has led to the development of the ISO Identification of Medicinal Products (IDMP) suite of standards and particularly ISO 11615 – the identifiers for Medicinal Products[144]. Although the core standards are now available, their implementation is still in progress, but the E2B R3 form does already specifically reference this system for product identification (the MPID, PCID and Substance identifier).   However, even with that in place, the forms themselves demonstrate a lack of standardisation in the terms they use to request the medication, being as unspecific as asking for the name of the medicine, with the exception of one of the FDA forms and the SDTM form, all the others were without any mention of whether that name should include the dose form and strength if available or not.

Encouraging the use of electronic data capture and providing lists of medicines with appropriate levels of granularity of description and encouraging all reporters to use the most granular to provide all the information they have available should help to improve this element of the data, including reducing spelling issues in free text entry. Supporting coded information directly, which only 5 forms did for the suspect medication, would also improve this. Only the E2B form supported coded information for concomitant medications (as it moves towards IDMP implementation) and it did not support coded information for the suspect medication as in blinded studies, this information would not be known.

The Lareb form was unique in supporting the acquisition of the correct description of the suspect and concomitant medication directly from the patient's Medication Profile, although the dosage information required separate data entry. This demonstrates the initial stages of one of the aims of this work, to be able to acquire all the relevant medication information for an adverse event report direct from a patient's Medication Profile.

Dosage Information

Dosage information, if it is provided, is useful in event analysis to check that the product was being administered within its authorised schedule and also to compute disproportionality signal scores against different dose ranges for a medication[261][261]. Information to populate these three data elements could be sourced directly from the patient's Medication Profile for both the suspect and concomitant products and as such is a requirement for the overall content of that Profile; although, based on this investigation and the use that the information is put to in analysis, the presence of these data elements is not as critical as some of the others.

Start/Stop Dates

Start and stop dates are used in basic initial event analysis; if the dates of exposure for the suspect medication are not contemporaneous with the date of the event, then a causative relationship between the suspect product and the event is unlikely[266]. That start and stop dates are requested on almost all forms indicate that they are very important, second only to the description of the products themselves and as such are key requirements that the Medication Profile should be able to support.

Since duration of therapy can always be calculated from start and stop dates, it should not in and of itself be a data element requirement for the Medication Profile to fulfil in addition to the start and stop dates, not least because duplication of information is an error risk.

Indication

Knowing the therapeutic use for the product in each event allows analysts to ascertain whether it was being administered according to its licensed indications, which is important in evaluation of the significance of the event, especially for the suspect medication. It is also important when looking beyond traditional pharmacovigilance toward risk management planning and minimisation strategies as it gives a measure of compliance with the license and whether there are gaps in post-authorisation usage[230].

One of the major criticisms of the ASTER pilot made by Brajovic et al[245] was that, despite using the patient record as a source for adverse event report information, none of the submitted reports provided indication information, highlighting how important indication information is deemed to be in pharmacovigilance.

The indication for a medication, and particularly for the suspect medication is clearly an important and desirable data element for adverse event reporting and is therefore a key information requirement for the Medication Profile to supply.

Suspect and Concomitant Medication Definition

Because spontaneous adverse event reports come from situations where a patient or healthcare professional *suspect* that a particular unwanted and usually unpleasant event that a patient experiences is related to the administration of a certain medicinal product, that product is always known as the suspect product. Information about other medicinal products that the patient is taking may also be provided, but these are not the suspect product and are therefore described as the concomitant products, those taken in parallel with the suspect product.

Concomitant medication information is particularly important to support the complex disproportionality and regression analysis required to detect new drug-drug interactions[261] so having an agreed global definition with guidance for reporters is something that should be developed. Having an agreed global definition for concomitant medication would then facilitate being able to extract this data directly and accurately from the patient's Medication Profile.

Limitations of this study

Responsibility for pharmacovigilance may be national or it may be regional with no pattern associated; federally managed countries such as the United States of America and Australia have national pharmacovigilance schemes, whereas Spain has a regional scheme. This makes any estimate of the total number of adverse event forms that exist globally very difficult and no figure was found. This study

examined only a small number of adverse event report forms (13) from 7 different countries and the agencies responsible for their pharmacovigilance, plus the two globally used forms for regulatory reporting, and the standard forms used for medication information in clinical studies. In order to further validate these results, a larger set of forms could be examined. However, the value of examination of a wider set of forms to this work would only be if additional data elements were introduced that would then need support from the Medication Profile, or if the priority of others were altered (for example if new forms were found to require site of administration information for all medicine events, not just for vaccine adverse events).

Recommendations for further work

Development of a clear specification as to the medication information required in all adverse event report forms should be undertaken, focussing on gaining agreement on the most useful data elements such as treatment start/stop dates and indication, so that the forms could explicitly encourage reporters to provide these wherever possible. Supporting information such as dose quantity and dose frequency should be requested as separate data elements since total daily dosage can be calculated from this. If only total daily dose is available, provision should be made to gather that explicitly. Redundant information (such as duration of treatment) should be removed from forms so as not to cause reporting burden or confusion. Implementation guidance for such a global specification should explicitly state how 'no information' should be managed for any particular data element. Having this clear global specification would facilitate the sharing and amalgamation of adverse event reporting, which is so important in order to find the signals of adverse reactions that occur at very low levels in the population.

The development of a global definition for concomitant medications should be undertaken to be used in spontaneous adverse event reporting. This should describe the scope of what a concomitant medication covers (for example: prescribed medications, over the counter medicines being taken, and whether or not herbal and nutritional supplements should be included). It should also describe the period during which the medication is considered to be concomitant to the adverse event (for example: all medications taken in the (4 week) month prior to the adverse event occurring). For reporting adverse events in clinical research studies, the protocol will provide some guidance to the investigator, but work should be undertaken to standardise this as much as possible so that data from a range of clinical studies can be properly aggregated for safety analysis.

Conclusion

Despite an acknowledged desire to have a single canonical adverse event reporting database supported by standardised forms completed in near-real time[261], this remains an aspiration rather than a reality. There continues to be a lack of standardisation in the data collection instruments (different scopes, different reporters, different product types, different data element formats) such that the scalability of automatic extraction of information for adverse event reporting and pharmacovigilance continues to be challenging.

However, by having this understanding of the data elements that are required, and a sense of the priority of them, it is possible to place these as requirements against the Medication Profile itself. The Medication Profile can then be a robust and reliable – and indeed automatic – source of the necessary data when and if such reporting is required. It could also directly provide the necessary instantiation of the data elements required for concomitant medication information in clinical trials, reducing the reporting burden, increasing accuracy and thereby increasing the intelligence available to contribute to the medication safety landscape.

Chapter 6: Consolidated Results Summary

This chapter presents both the summary and the superset of the requirements for a Medication Profile gathered in the preceding chapters from the four high level use cases of recording of information to support patient care and safe use of medication facilitated by medication decision support, and supporting feasibility checking and patient recruitment in clinical research and pharmacovigilance.

The Results Summary is presented in tabular form, in the three sections of types of requirement: the medication use (current or past), the description of the medication (naming, categorical and clinical information) and the description of dosage instructions for use of the medication.

Each of tables 18-30 in the Summary has a column for each of the 4 high level use cases and a row for the requirement; the following abbreviations are used for the use cases:

- Patient recruitment and protocol feasibility checking: PR & PFC
- Pharmacovigilance: PV
- Patient care: Pt Care
- Medication decision support: MDS

The intersecting cell indicates whether that use case has a requirement for that information, and uses an informative colour coding:

- red is used where the results indicated all or almost all of the situations examined in the requirements gathering required the information,
- green is used where at least half of the situations required the information and
- blue is used where at least one but less than half of the situations required the information

Current and past medication information

Current medication information is medication that the patient is using or has had administered to them **now** (which for pharmacovigilance is 'the time of the event') or has used 'recently'. Past medication is medication that the patient has used or has had administered to them at any point in the past and that is not 'current'. Table 18 summarises the requirements for this information from the four use cases.

Table 18: Summary of information requirements for current and past medication information for the Medication Profile from the four use cases

	PR & PFC	PV	Pt care	MDS
Current medication	YES	YES	YES	YES
Past medication	YES		YES	YES

Medication identification

There are various ways to identify a medication, directly and indirectly using additional factual information (e.g. authorisation status) or additional clinical information (e.g. therapeutic use). These latter two types of information are more descriptive and obtained from knowledge beyond an identification terminology, whilst the requirements have been documented in the use cases, they do not go forward as requirements to be met by the Medication Profile itself. Table 19 therefore summarises only the requirements for terminological medication identification for a Medication Profile information from the four use cases.

Table 19: Summary of medication identification requirements for the Medication Profile from the four use cases

	PR & PFC	PV	Pt care	MDS
Medication name	YES	YES	YES	YES
Generic name		YES	YES	YES
Brand name		YES	YES	
Manufacturer		YES		
Medication code		YES	YES	YES
Medication batch number		YES		
Medication expiry date		YES		

Dosage instructions information

Table 20 summaries the requirements for the detail of dosage instructions (how the medication is being or was administered to the patient) for a Medication Profile information from the four use cases. The requirements for the dosage instructions data elements were the most diverse. To further draw out the relative importance of each data element, a notional weighting was assigned, based on a 'YES' being worth '3', a 'YES' being worth '2', and a 'YES' being worth '1'.

Table 20: Summary of dosage instructions information requirements for the Medication Profile from the four use cases

	PR & PFC	PV	Pt care	MDS	Weighting
Dose instructions clause			YES		1
Dose quantity	YES	YES	YES	YES	5
Total daily dose		YES		YES	2
Route of administration	YES	YES	YES	YES	9
Site of administration		YES	YES		3
Method of administration			YES		1
Timing information	YES	YES	YES	YES	9
Dose frequency		YES	YES	YES	5
Course of therapy Start/Stop (dates)		YES	YES	YES	7
Discontinuation or future stop (dates)			YES		1
Course of therapy duration		YES	YES	YES	4
Indication	YES	YES	YES	YES	11
Rate of administration			YES	YES	2
Dosage upper bound			YES		1
Non-administration reason			YES		1
Additional instructions			YES		1
Quantity prescribed or dispensed			YES		1

Summary discussion

These tables provide a summary and superset of all the information that could be present in a Medication Profile to support the four high level use cases described in detail in the preceding chapters. In those chapters, the information requirements were gathered from a detailed investigation of a sample of relevant specifications, chosen based on experience in the field to be representative, or in the case of medication decision support, described many years of experience in specification development. However, this sample is in no sense a robust and randomised sample, therefore the results from them cannot be considered to be quantitative. But the

tables do present a qualitative assessment of the importance of individual data items in the overall information model for a Medication Profile, and therefore they give a useful signal as to how much effort should be made to define, capture and maintain a particular data item within the Profile.

For all use cases, information about current medication is paramount; information about past medication (history) is important for three out of four use cases – more than enough to indicate that a full Medication Profile should contain it.

For three out of four use cases, the medication name is essential; the exception being the feasibility checking and patient recruitment use case where description of medication can be by 'proxy', particularly by therapeutic class rather than individual product. A generic description is preferable to a brand description, although for pharmacovigilance a branded description is desirable, as is manufacturer information. A machine-readable (coded) description is of particular value to decision support, but is also useful for pharmacovigilance and patient care. The feasibility checking and patient recruitment use case does not require this, not least because medications are more often referred to by their classification than described as individual products and also because within clinical research at present there is no good terminology to provide such coded information, so not unnaturally, the requirement cannot be instantiated. Only the pharmacovigilance use case had requirements for batch number and expiry information. No examination was made of any fraud prevention or counterfeit detection use cases since these relate to supply chain management at levels above individual patient medication consumption; had these been within scope, no doubt information about the batch number of medicinal products would have been seen as important.

The requirements for the dosage instructions data elements were the most diverse. The weighting highlights that indication information is the most valuable data element to the four use cases, followed by route of administration information and timing information – principally the start (and stop if appropriate) dates. This latter overlaps with the 'current' and 'past' medication definition in the first table and provides the link between the static nature of the data element requirements and the dynamic nature of a Medication Profile that persists over time and must be populated and accurately maintained with these data items. This dynamic paradigm and the rules that govern it are further described in the dynamic models of the Medication Profile Model chapter. However, as previously noted, other than this, there is a notable absence of requirements for true dynamic (behaviour of objects) model requirements.

Chapter 7: Identifying the Scope of the Medication Profile

Introduction

It might be a natural to assume that 'medicines' would form the core of a Medication Profile, but on the premise that assumption can be misleading, the examination of exactly what is meant by the 'medications' that are recorded in a Medication Profile is an important part of the development of the requirements for an ideal Medication Profile. As was clearly seen in the Literature Review, there is no universal agreement as to the types of products that should be properly included in the scope. A further issue that adds to the confusion is that the term 'prescribing' is frequently used to describe the process of a healthcare professional making an order for supply and use of a product for a patient, where the product could be a 'medicine, a medical device, a dressing, or another type of remedy'[267].

The phrase 'medicines are not ordinary items of commerce' is often used[268] to highlight that medicines form a special class of objects; indeed in the UK there is an entire statute that makes provisions with respect to medicinal products and related matters, the Medicines Act 1968, which describes the arrangements for the licensing, sale and supply of medicines to the population. This is enacted in conjunction with the various articles and directives in European law, and it is here that the current formal definition of a medicine may be found: 'Any substance or combination of substances being presented as having properties for treating or preventing disease in human beings; Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.'[269]

This definition has been further developed as part of the international initiative for the Identification of Medicinal Products (IDMP) in ISO 11615[144], where a Medicinal Product is defined as 'Any substance or combination of substances that may be administered to human beings (or animals) for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions'.

The Notes in ISO 11615 state that its provisions apply to proprietary (registered) medicinal products for human use intended to be placed on the market, and to industrially manufactured medicinal products, the marketing of which has been

authorised by a Medicines Regulatory Agency. The Notes then describe other types of medicinal products: a) those prepared according to prescription, i.e. prepared in a pharmacy from a prescription intended for a specific patient; b) medicinal products prepared in accordance with an official formula, i.e. prepared in a pharmacy in accordance with the instructions in a pharmacopoeia and intended to be given direct to the patient by the pharmacy; c) medicinal products intended for research and development trials; and d) intermediate products intended for subsequent processing by an authorised manufacturer.

The legislation, and the standards that support it, can provide a framework within which various types of things that *could* be considered 'medicines' can be evaluated for their inclusion in a Medication Profile. This chapter therefore to examines each of these various types of things in terms of what they are exactly and how that intrinsic nature relates to whether they should (or should not) be included in a **Medication** Profile. Information about products that are not intrinsically *medicines* may well still be relevant for various use cases in supporting patient care and clinical research but that information should reside elsewhere in the patient record structure, not in the Medication Profile. This explicit scope statement then avoids ambiguity and the issues around completeness of information that are frequently seen reported in the literature[102,117 -119].

Methodology

Unfortunately, there is no formal standard to provide a full set of the categories of things that could be considered 'medicines'. However, the author has had considerable experience in this area, and this section has been written based on knowledge and experience gathered in roles over the preceding 20 years, especially in international medicines terminology, as described in detail in the General Methodology. The categories that have been used in this examination are therefore well known and well used within the domain[270].

To fulfil the objective of the provision of a clear scope statement for 'medication' that should be included in the Medication Profile, each of these categories was examined in turn. A definition for the content of each category is given, based where possible on the legislative framework, followed by a description of their use, and particularly the documentation of that use, in clinical care. This then forms the evidence from which to make the assessment for their inclusion or otherwise in the Medication Profile.

Note that all of the following is written on the premise of the culture and practice of Western, so-called allopathic medicine; alternative cultures and practices of

medicine, such as Chinese medicine or anthroposophical medicine have not been considered here.

Results

Licensed Medicines

Definition: Licensed (or authorised) medicines are medicines that have a marketing authorisation from the regulatory authority appropriate for the realm or jurisdiction (nation state) in which the medicines are marketed. Licensed medicines are evaluated by a regulatory authority to ensure that they provide benefit and are acceptably safe and that their manufacture is in accordance with quality standards[271].

Clinicians are encouraged to prescribe licensed medicines for patients whenever possible, and to ensure that the use is within the terms of the license[267]. Similarly pharmacists should dispense a licenced medication whenever possible[272].

Biologic product medicines (including immunologic products)

Definition: Biologic product medicines are medicines that are made by or derived from a biological source, usually using biotechnology processes, such as recombinant DNA technology. Biosimilar medicines are a sub type of biologic products.

In most realms or jurisdictions, the regulatory authority responsible for granting marketing authorisations deals with all types of medicinal products, be they of chemical or biological substance composition, and regardless of their use (diagnosis, treatment, prevention of disease). However, some jurisdictions, and most notably the United States of America, have separate authorities depending on product type: the Food and Drug Administration has various quite separate divisions[273] (Centers), most particularly: the Center for Drug Evaluation and Research(CDER)[274], the Center for Biologics Evaluation and Research (CBER)[255], the Center for Devices and Radiological Health (CDRH)[275]. This division, and the fact that the Centers for Disease Control and Prevention[257] manage most of the information about vaccination and vaccination programmes, mean that there can be, particularly in North America, a sense that 'a medication' does not include products based on biologically sourced substances as active ingredients, unless otherwise explicitly specified. This divided medication world view is reflected in the top level partition of the international medical terminology, SNOMED® CT[276], which currently has a

'pharmaceutical and biologic product hierarchy' [SCTID = 373873005] rather than simply a 'medicinal product hierarchy'.

Immunisation products are often not prescribed and dispensed following normal patterns, for example they are often administered in a clinic environment with only an administration record produced. This means that there can be separate recording entries for that administration information (for example, a separate section in the Continuity of Care Document for Immunisations, see Patient Care sub-chapter 4(1)). In some healthcare cultures, recording of vaccine administration may only occur in a specific vaccination registry system.

Human derived therapeutic products

Products from pooled resources
Definition: Human derived products from pooled resources are medicinal products manufactured from donations of human blood collected together and processed. These products include the haemostatic products such as clotting factors and other substances involved in the clotting cascade, and immunoglobulins and albumin solutions.

These products are evaluated by a regulatory authority for quality, safety and efficacy and as such are licensed medicines. They are prescribed, dispensed and administered using the standard patterns of the medication process and recording in systems reflects this.

Individual donated items
Definition: Individually donated items are items of human origin that can be directly associated to a single donation event, be that autologous or unrelated. Examples include whole blood and its components derived from a single whole blood donation such as platelets or red blood cells.

There is no authorisation process for these items in any regulatory sense. Both the collection process and the administration process for these items is undertaken and documented in an EHR as a type of clinical procedure. This means that the product collected/administered is described as an integral part of that procedure, not separate to it. The requirements[277] to describe the collection, management and administration of these items and therefore that systems used to manage this are completely different from those used for medicinal products and there is a separate international terminology to support it (ISBT128)[278].

Definition: Other human tissue products are products derived from individual human donations, used therapeutically, either autologously or to an unrelated individual. They in include dura (mater) grafts, skin fibroblasts and bone tissue.

The use of all human derived products is undertaken and documented in an EHR as a procedure, with the product collected/administered described as part of that procedure using ISBT128, the global standard for the terminology, identification, coding and labelling of products of human origin (including cell, tissue, human milk, and organ products, including for transplantation).

Orphan designation medicines

Definition: Orphan designation medicines are medicines intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating, but that is a rare condition (the prevalence of the condition in the EU must not be more than 5 in 10,000)[279].

The authorisation process for these products is a little different, and includes such benefits to sponsors as protection from competition once on the market. However, they are licensed medicinal products and they are subject to the normal activities of the medication process and are recorded as such.

Previously licensed medicines

Definition: Previously licensed medicines are whose authorisation for sale or supply has ended, either by voluntary discontinuation (lapsing) or withdrawal, or by compulsory withdrawal of the license.

These products were once authorised, and as such could be included within the overall 'licenced medicines' category, but in the lifecycle of a licensed medicine they have moved, either voluntarily or compulsorily to no longer having a license.

Over the Counter medicines

Definition: Over the counter (OTC) medicines are a particular subset of licensed medicines, characterised by their sale or supply being aimed directly at the purchaser/consumer of the medicine, rather than being used under the direct supervision of a healthcare professional.

OTC medicines may be prescribed and dispensed following the standard patterns of the medication process; they may also be sold and as such recording of their

administration to individuals is less accurate, often only occurring when the results of a medication reconciliation activity are recorded.

Unlicensed and investigational medicines

Definition: Unlicensed medicines are those that do not have an active authorisation for their sale or supply that is valid within the jurisdiction of their use.

In most healthcare jurisdictions, if an unlicensed medicine is used to treat a patient, the normal professional indemnities are revoked; and the responsibility that falls on healthcare professionals when prescribing an unlicensed medicine may be greater than when prescribing a licensed medicine within the terms of its license[280].

Extemporaneous (magistral) medicinal products

Definition: Extemporaneous medicinal products are medicines that are prepared by a pharmacist without a product licence, in the UK under section 10 of the Medicines Act 1968[281], in Europe as described in the European Parliament Directive 2001/83/EC[269].

This definition includes parenteral preparations that made by diluting a medicinal product into a larger volume prior to administration (for example in a CIVAS, a Central Intravenous Additive Service), even when this is in accordance with the Summary of Product Characteristics (SPC) (this does not include the act of reconstitution itself) and also includes fulfilling an order to supply where the administration of the product requires that it is crushed or opened and mixed with a specified agent other than water, e.g. a suspending agent[282]. For the purposes of this categorisation, pharmacopoeial standard preparations, also known as 'officinal formula' (such as British Pharmacopoeia (BP)[283] formulations) would be included.

The use of extemporaneously prepared medicines follows the standard patterns of the medication process, although there may be extra information recorded (e.g. batch numbers of ingredients used in the preparation).

Investigational medicinal products

Definition: An investigational medicinal product is defined as 'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form'[144].

This definition, focussing as it does on the product being studied against a hypothesis in a clinical trial, includes medicinal products where the study relates to clinical uses outside of a current authorisation. It also includes products used in observational studies relating to risk management, to delineate additional information about the medicinal product's risks, benefits, and optimal use (phase IV and phase V studies[284]).

The use of investigational medicinal products is usually recorded in a specialist clinical study data capture system by the investigator and is likely to include active adherence checking. This information may or may not also be recorded through standard care systems.

Homoeopathic and herbal medicines

Definition: Homoeopathic medicinal products are 'any medicinal product prepared from substances called homoeopathic stocks in accordance with a homoeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homoeopathic medicinal product may contain a number of principles'[269].

Some homoeopathic products regulated under either the simplified registration scheme or the national rules scheme; both schemes require data on product quality and some information about safety[285]. Others may be made available in a similar manner to an extemporaneous preparation.

Definition: Herbal (drug) products are defined by the European Pharmacopoeia as preparations that 'are obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal drugs, tinctures extracts, essential oils, expressed juices and processed exudates.'[286]

Herbal products typically contain a mix of compounds and it is often difficult to identify those that are therapeutically relevant.

Homoeopathic and herbal medicines are sometimes subject to the standard patterns of the medication process, but are more commonly used outside of that. Information on their use may be recorded as a result of medication reconciliation.

Other Types of Products

Nanotechnology Products

Definition: Nanotechnology products are those in which the design, characterization, production and application of structures, devices and systems are achieved by controlling shape and size at nanometre scale.

Nanomedicine itself is defined as the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale[287]. The majority of current commercial applications of nanotechnology in medicinal products are geared towards drug delivery to enable new modes of action, as well as better targeting and bioavailability of existing medicinal substances, such as nanostructures that allow transport across biological barriers and multifunctional chemical structures for drug delivery and targeting of disease.

Currently, there are no regulations specific to medicines (or medical devices) using nanotechnology, but it is a developing area and new products are possible in the coming years.

Nutritional products: Foods and food supplements

Definition: The definition of a food or foodstuff is 'any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans…Food shall not include…medicinal products within the meaning of Council Directive 65/65/EEC [now Directive 2001/83/EC.]'[269].

This definition states that foods are not medicinal products, and can be distinguished from medicinal products on the grounds of being identified as products which a person would regard as something to be eaten, drunk or chewed as part of his/her diet.

Definition: A food supplement or nutritional supplement is defined as '[a] foodstuff or foodstuffs, the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form'[269].

Food supplements are concentrated sources of nutrients or other substances with a nutritional or physiological effect, there whose purpose is to supplement the normal diet. Although they are usually supplied and marketed in a 'dose form' i.e. as tablets, capsules, liquids in measured doses etc. which can make them appear to be like

medicinal products, they are clearly not medicinal products as per the definition of a food above.

There are also a set of dietary foods for special medical purposes; these are 'foods used in patients with specific intolerance conditions (e.g. lactose free foods) or foods for patients with gluten sensitive enteropathies, such as coeliac disease ('gluten-free foods'), and low protein foods for patients suffering from inherited metabolic disorders, renal or liver failure requiring a low-protein diet'[288].

Nutritional products that make and can support medicinal claims or can show that they modify physiological functions by acting pharmacologically, immunologically or metabolically, and/or are marketed and used with a view to having such an effect, for example for athletes and persons engaged in significant exercise or for extreme weight loss, will fall within the definition of a medicinal product and require formal authorisation for sale or supply.

Food products may be ordered and/or supplied for a patient's use by a healthcare professional in the course of their provision of care; this may need to be recorded in some way within electronic health records, both for general reference and to facilitate re-supply if required. It may also be recorded by specialist dietetics systems.

Medical devices

Definition: A medical device is defined as 'any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: 1) diagnosis, prevention, monitoring, treatment or alleviation of disease; 2) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; 3) investigation, replacement or modification of the anatomy or of a physiological process; 4) control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. In the case of a medical device, the principal intended action is typically fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions).'[289]

As well as medical device products whose principal therapeutic action is typically fulfilled by physical means as defined above, there are products that incorporate a medicinal substance to the patient as part of their therapeutic process or that administer a medicinal product. A product of this type may be regulated as either a medical device or as a medicinal product, depending on the principal intended

function of the product and the method by which this action is achieved. There are three main types of medical device which incorporate or are used to administer a medicinal product:

1. Devices which are used to administer medicinal products: for example, a syringe marketed empty, medicine spoons, droppers etc. This category also includes devices which can be refilled with further doses of medication contained within the same pack as the medicine. All of these products are covered by the Medical Devices Regulations.

2. Devices for administering medicinal products where the device and the medicinal product form a single integral product designed to be used exclusively in the given combination and which are not re-usable or re-fillable: for example: a syringe marketed pre-filled, or a metered dosage inhaler. These products are covered by medicines legislation, although in addition to this, the relevant essential requirements in Annex 1 of the Medical Devices Directive 93/42/EEC apply with respect to safety and performance related features of the device (e.g. a syringe forming part of such a product).

3. Devices incorporating, as an integral part (i.e. a single component product (e.g. such as coated or incorporated within) rather than a pack containing the two components (i.e. a drug and a device)) a substance, which, if used separately, may be considered to be a medicinal product and which is such that the substance is liable to act upon the body with action ancillary to that of the device: for example: a heparin coated catheter, or a thrombolytic eluting stent, an antibiotic-containing bone cement. These products are subject to the Medical Devices Regulations. In addition, the safety, quality and usefulness of the medicinal substance must be verified by analogy with the methods required in Directive 2001/83/EC concerning the testing of proprietary medicinal products.

In a comparable manner to food products, medical devices may be ordered and/or supplied for a patient's use by a healthcare professional in the course of their provision of care. Similarly, their order and supply may need to be recorded in some way within electronic health records, both for general reference and to facilitate re-supply if required. Some device products will be recorded in an EHR as part of a record of a procedure, particularly an implantation procedure.

Leeches and Maggots

Leeches (*Hirudo medicinalis*) and maggots (*Lucilia sericata* or *Protophormia terraenovae*) if supplied commercially are sometimes thought of as being 'products' when intended for medicinal use; that is, in skin graft salvage and in biodebridement respectively. However at present they not subject to licensing as medicinal products or as medical devices. When they are used in patient care, leeches and maggots are likely to be described and recorded as part of the procedure that uses them.

Cosmetics and Toiletries

Cosmetics (products applied to the body, especially the face to improve its appearance[290]) and toiletries (articles used in washing and taking care of one's body, such as soap, shampoo and toothpaste[290]) are not defined as medicinal products, even when their use is recommended to a patient by a healthcare professional (e.g. a sunscreen for a patient with a sun sensitivity due to medication such as amiodarone).

Just as with food products, some cosmetic and toiletry products may be ordered and/or supplied for a patient's use by a healthcare professional in the course of their provision of care and their order and supply may need to be recorded in some way within electronic health records, both for general reference and to facilitate re-supply if required.

Discussion

Licensed Medicines

Most of the medicines in use in clinical practice should be licensed medicines, so it is self-evident that all licensed medicines that have been or are being used in the treatment of a patient should be described in a Medication Profile. However, because there are several situations that militate against that statement as being self-evident; it was therefore important to identify each of those situations so that all the relevant categories of products can be explicitly described for inclusion in the Medication Profile.

Biologic product medicines (including immunologic products)

Although all biologic products are considered medicinal products, the sometimes separated view of their regulation by distinct sub-agencies and, for vaccines, the different pattern of their use and recording within the medication process, mean that their presence within the scope of a Medication Profile needs to be described

explicitly to ensure that they are included. The process of use of vaccine products is such that a separate section within the Medication Profile could be considered.

Human derived therapeutic products

Individually donated items, both blood and its components and tissue products are not considered to be medicinal products in a regulatory sense although there is a substantial level of control placed on such products, due in a large part to various unfortunate incidents causing patient harm[291]. There is significant difference in both description of and use and recording of individually donated items in systems. It is therefore unwise to attempt to duplicate any of this information in a patient's Medication Profile. Furthermore, there is no sense in any of the literature that would support these items being included with any sort of recording of medication information.

Products from pooled resources, although related, are different in that they are licensed medicines, used within the normal medication process; they are included in the scope for the Medication Profile.   But since they can be confused with individually donated items, it is useful to state their inclusion explicitly.

Orphan designation medicines

Orphan products are licensed medicines used within the normal medication process and should be explicitly included in a Medication Profile.

Previously licensed medicines

The supply of medicines is becoming increasingly globalised and consequently definitive information on licensing and availability of medicines, although managed on a jurisdictional basis, is becoming less absolute in a global sense. A medicine that is discontinued in one jurisdiction may well still be licensed and available in another, and as such still have limited availability in the original jurisdiction (as a 'special' or unlicensed medicine). Since a Medication Profile is a longitudinal record of a patient's medication use, it should contain information about medications that were licensed at a previous point in time, because either they provide historic information (the product was licensed when it was being actively used by the patient) or because they are being used currently in a 'specials' capacity.

Over the Counter medicines

There is a general worldwide trend in promoting self-medication, described by the World Health Organisation as 'the use of medicinal products by the consumer to treat self-recognised disorders or symptoms, or the intermittent or continued use of a

medication prescribed by a physician for chronic or recurring diseases or symptoms'[292], to improve the access to treatment while minimising health care costs. This trend is evidenced in the increasing deregulation of medicines (the so called 'POM to P switches') whereby medicinal products initially licensed as for supply by prescription only, once more safety data becomes available, have also become available with an OTC license, often in a lower strength or smaller pack size (for example H2 antagonists such as ranitidine, proton pump inhibitors such as omeprazole).   This trend emphasises that the boundary between prescription medicines and OTC medicines is blurred, which in itself supports the premise that use of all OTC medicines should be explicitly included in a Medication Profile whenever possible.   Further evidence is available from studies that have focussed on the safety or otherwise OTC medication use[293],[294] medications and particularly their potential for causing adverse effects due to interactions, and that in some patient groups, almost as many OTC medications are used as prescribed medications[295].

Licenced medicinal products used in other systems: Anaesthetics and diagnostic agents, dental products

In the above discussion, the pattern of use of the product has been important in determining its inclusion or otherwise in a Medication Profile. Anaesthetic products, especially gaseous/volatile products administered by inhalation but also those administered parenterally are all licensed medicines, but they have the potential to be omitted from the scope of a Medication Profile because they are almost exclusively administered and recorded in a specialist setting using specialist systems (even if those systems are paper-based, such as a specific anaesthetic record sheet).   The same is true for contrast media for all forms of imaging, and nuclear medicine products, whose use is usually in diagnosis rather than treatment (although some nuclear medicine products are now also being used in treatment, especially of solid tumours). It is important therefore that such products are explicitly included in the scope of a Medication Profile, and information on their use documented in specialist systems is shared with a Medication Profile system.

Similarly, dental practitioners use a range of medicinal products, many of which are developed specifically for dental use.   These include: medicated mouth ulcer preparations, antibacterial mouthwashes and gels, periodontal antibacterial gels, ointments and fibres and fluoride tablets. As medicinal products, information on the use of these products by an individual should be explicitly included in a Medication Profile for that patient, including their dosage instructions. Medical devices used in dental procedures such as sealants for fissures and root canal pits, pulp capping material and materials for dry socket preparation and root canal dressings (even

though these usually contain antibiotics and/or antiseptics) should not be recorded in the Medication Profile; they will be recorded as items used within a procedure.

Unlicensed and investigational medicines

Just as within the broad category of licensed medicines there are various subtypes, so within unlicensed medicines there are a set of subtypes to be discussed, so as to be explicit as to their inclusion or otherwise within a Medication Profile. Medicines that have been previously licensed in a jurisdiction but whose license has been discontinued or withdrawn become 'unlicensed medicines' if and when they are then used in patient care in that jurisdiction. The inclusion of such medicines in the Medication Profile is discussed above.

Extemporaneous (magistral) medicinal products

Although there may be some challenges in describing and communicating information for extemporaneous preparations since they fall outside normal medicinal product terminologies, they are medicinal products and their use should be explicitly included in a Medication Profile.

Investigational medicinal products

Medicinal products in Phase I ('first in human') through to Phase III (large scale efficacy and benefit/risk) studies must be administered strictly in accordance with the protocol that governs the study, which must be approved by the regulatory authority(ies) for all the countries in which the study will be conducted. Although many such studies are designed using the double blind design, in which neither the subject nor the investigator knows whether the subject is receiving the investigational product or a placebo/comparator product, this information is available in the randomisation and trial supply management system used to support such a study, and will be made available after formal database lock for the study.

Although there may be some challenges in accessing and describing the use of investigational products, these are medicinal products and their use should be explicitly included in a Medication Profile. During a study, a placeholder description could be placed in the Medication Profile, which is replaced with explicit information after the final data lock point.

Homoeopathic and herbal medicines

Although this scoping is written on the premise of the culture and practice of Western medicine, homoeopathic and herbal medicines sit on the boundary of that culture

and practice and therefore must be discussed in order for that boundary to be delineated.

Due to the potential potency of some homoeopathic and herbal medicines, shown for example by the interaction between *Hypericum perforatum* and the coumarins, or milk thistle and simeprevir, if information is available on a patient's use of homoeopathic and herbal medicines it should be included in a patient's Medication Profile; such information should not be actively excluded.

Other Types of Products

Nanotechnology products

It is likely that as products in this area are developed, they will be formally studied following an approved protocol, which makes them very similar to standard investigational medicinal products. And as such, the use of these products should be explicitly included in the patient's Medication Profile.

Nutritional products: Foods and food supplements

These products can be clearly differentiated from medicinal products by their (lack of) regulatory authorisation and by the recording or otherwise of their use. Their lack of therapeutic significance suggests that their use should be explicitly considered beyond the scope for inclusion in a patient's Medication Profile.

Medical devices

Medical devices are a diverse category of products that are important to the care of patients that would at first sight appear to be similar to medicinal products but which are in fact quite separate. This is despite there being are some products that were originally authorised and made available as medicinal products that have been re-classified and re-authorised as medical devices; for example: carmellose eye drop solutions.

Since medical devices are not medicinal products, even though some may incorporate medicinal substances within them, they are explicitly considered beyond the scope of what should be included in a patient's Medication Profile.

Leeches and maggots

Neither leeches nor maggots are considered as medicinal products, and the record of their use is within a procedure. There is therefore no requirement for their use to be included in the patient's Medication Profile.

Cosmetics and toiletries

Even though these products may be prescribed and dispensed in some healthcare cultures, they are not medicinal products, and therefore they can be explicitly considered beyond the scope of the products what should be included in a patient's Medication Profile.

Limitations of this study

The main limitation of this analysis is also the reason for it: the lack of published and/or formally agreed information on the categories of things that should be considered within scope for a Medication Profile. The assessment made by this analysis should therefore be thoroughly examined and tested in the domain, both for the validity of the categories themselves and for the inclusion and exclusion decisions.

This analysis explicitly excluded products used in alternative cultures and practices of medicine; products from these traditions could be examined in using similar principles.

Recommendations for further work

For those products whose use should be included within a Medication Profile but whose recording is normally undertaken in discrete specialist systems (e.g. dental medicines, anaesthetics, investigational medicinal products), the business process(es) for sharing that information with the Medication Profile should be investigated.

Currently, based on this analysis, devices that have a medication substance integral to them are excluded from being recorded in a Medication Profile, based on their authorisation. The validity or otherwise of this should be formally investigated against the use cases for the Medication Profile.

The practice of healthcare, and particularly the development of therapeutic products, is by no means static, and therefore as and when new types of products emerge, the inclusion or otherwise of these within the scope of the Medication Profile will need reviewing.

Conclusion

In order to support the use cases of provision of high quality care to individual patients and also for secondary use of that information in clinical research to promote better and safer medication development, a Medication Profile should contain

information about a patient's use of **all** licensed medicinal products of any type, including those not prescribed (i.e. purchased over the counter for self-medication), and **all** unlicensed medicinal products. Whenever possible, information about use of homoeopathic and herbal medicines should also be included in the Profile.

But although the premise used in this research is that all licensed medicinal product types, includes biological products and therefore particularly those biological products used in vaccination, the management and presentation of some of this information – particularly for vaccination – will be explored further in the Evaluation of the model for the Medication Profile.

Information about use of medical devices, nutritional products and cosmetics and toiletries used in a healthcare context is excluded from the Medication Profile per se. It is recognised that recording information about these products for reference and for possible re-supply is of considerable value to both the patient and the healthcare practitioner, but the Medication Profile is deemed not to be the place to manage that.

Information about the use of whole blood or its major components, although vital for patient care and clinical research, is recorded separately in EHR systems and should explicitly not be included in a Medication Profile.

Chapter 8: The Medication Profile Model

Context of the Model

In the context of the Medication Profile, it is clear from the literature search and from the requirements gathering that although there has been considerable discussion of the concept of a Medication Profile and its use, there has been no full and formal description of the domain in a formal modelling notation covering both the static and dynamic elements. Therefore it has proved impossible to date to create a system to manage a Medication Profile such that it that can provide the necessary information to meet the requirements of healthcare and clinical research. It is clear that without this formal domain information model of with the static and the dynamic views, there is no consistency in the way in which systems provide and populate a Medication Profile, so none of the use cases can be met dependably.

The following sections of this chapter therefore seek to address this by providing a complete domain information model of the Medication Profile that can be used to support a Medication Profile system, on its own or as part of a larger electronic health record, in order to provide a Medication Profile that contains high quality, consistent, trustworthy information that can be presented to the use cases efficiently and clearly.

It is not possible to provide exact traceability from the various features in the model and its sub-models to the Requirements gathered in the previous chapters, particularly since there was so little available for the dynamic models. There has been some consolidation, but generally the requirements for the attributes in the static model are referenced, and the derived attributes that have been added to the model to support the functional use cases have been explicitly justified. The principles used for the construction of the dynamic models are discussed in detail in the relevant sections.

UML, Model Paradigms and the Medication Profile

UML is the Universal Modelling Language initially developed by Booch, Rumbaugh and Jacobson in the 1990s, and now managed by the Object Management Group[296] (an international technology standards body). It is an international standard through ISO (ISO/IEC 19505-1:2012 Information technology -- Object Management Group Unified Modelling Language (OMG UML))[297.] The purpose of UML is to visualise, specify and document the artefacts in a system, usually a software system (also called 'the domain').[298.] Because of the limits of the human ability to understand complexity, it is important to divide and conquer, to reduce the complexity into its

different parts. This is achieved by working in two paradigms, the paradigm of the types of models and the paradigm of the granularity of the models themselves.

The first paradigm expresses itself in the various diagrammatic styles – model types – that are a grammar and syntax that can be understood by both humans and machines, to describe the static and dynamic components of the system. This paradigm embodies the first and last of the four principles of UML: 'the choice of which models to create has a profound influence on how a problem is described and how a solution is shaped; and 'no single model is sufficient'[298].

The static model components are the entities that exist in the system, described using classes, attributes and relationships, and sometimes also the operations that can be performed on these components. The static models are often called the 'structural views'. The dynamic model components describe the behaviour of the system, and the entities in the system as they transition through states or interact or collaborate together. In addition, in recent years, business process modelling has been added to UML, allowing description of the behaviour of users with a system

The second paradigm is that of using layers within one or more of the types of diagrams, where detail (or granularity) increases or decreases as the viewer moves down or up through the layers. This is the manifestation of the second principle of UML, that 'every model may be expressed at different levels of precision'[298]. By keeping the layers closely related to each other (using a 'drill down' approach) the overall pattern of the information in the model type is maintained.

But even with clear principles and good tooling support, authoring the models is an art as much as it is a science, and it is important to remember that 'the model in its entirety' consists of a set of diagrams (sub-models) of various different types and appropriate levels of granularity, whose aim is to provide a comprehensive and a cohesive description of the domain of interest.

Static (Structural) Models

The static UML models show the class of (the thing that represents) a Medication Profile and a representation of the things (data elements) that are required to be in the Medication Profile in order to meet the business use cases. These are therefore the data elements that have been gathered and defined in the preceding chapters as being those that are relevant for the four core use cases for Medication Profile information and summarised in the immediately preceding chapter.

The static model is presented as two layers. The first is a high level conceptual model. This describes the data elements at their most abstract, so the more granular sub-elements of the Medication Profile are not identified individually, but are shown only as classes representing groups of similar elements.

The second layer, which is in effect truly an intermediate layer between the abstract model and implementable models (see the Discussion section), is a more logical model, where the overall pattern of classes is the same, but the supporting classes have attributes to represent individual data elements and is where the definition of these attributes should be provided.

The domain model presented here is focused entirely and specifically on the Medication part of the Medication Profile; there is no attempt made to further describe the Patient/Subject to whom the Profile applies and in the logical level model, the Patient/Subject is no longer shown.

High level conceptual model

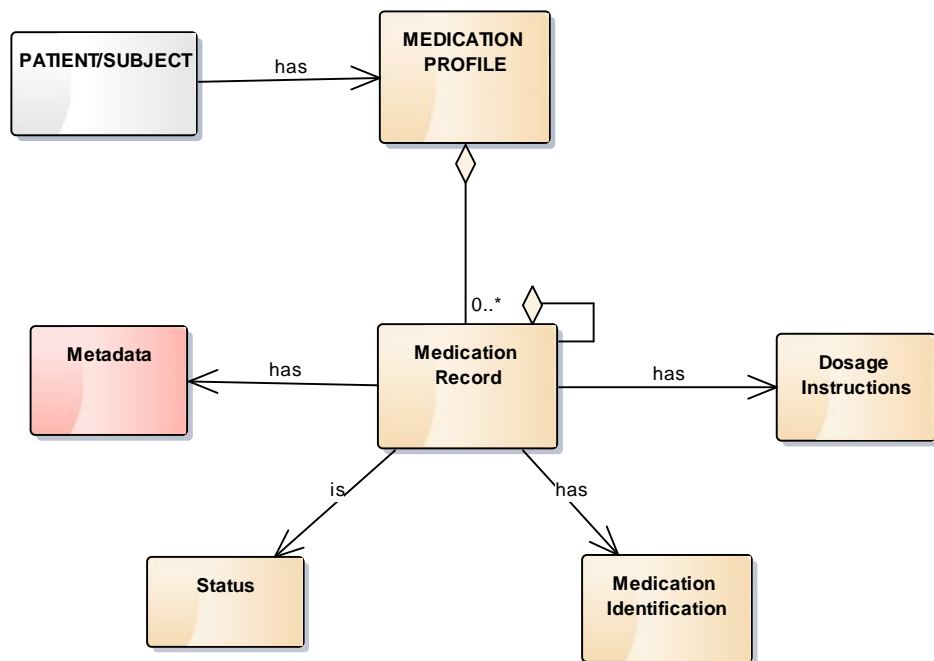*Figure 10: High level conceptual model of the classes and relationships of the Medication Profile*

At a conceptual level, this model, drawn in Figure 10, shows the Medication Profile belonging to a Patient/Subject being totally composed of Medication Records, which themselves can be composed of Medication Records, through the recursive relationship. A Medication Record is the documentation of a course of therapy for a

single medication (therapeutic moiety). This focus reflects the scope of this work. But it does not explicitly exclude other classes of record information, such as allergy information, being added to a Medication Profile should others consider that essential.

A Medication Profile is composed of zero to many Medication Records; a Medication Profile should exist for a patient even if no medication has ever been given to that patient; the requirement was for a cradle to grave longitudinal record, and information that no medication has ever been given is valuable information.

A Medication Record has information about the identification of a medication – the medicinal product that the record relates to, and the additional information from Dosage instructions and the Status (Current or Past) of the use of the medication described in the record.

A Medication Record also has metadata, information that accompanies the core data and describes additional non-core context; for example the provenance: the 'who' and 'where' of any item of data. Requirements for the definition and use of general provenance metadata for records in healthcare is well advanced and documented[228] and therefore is not further discussed in here, although, like Patient/Subject, it is shown on the high level conceptual model. But specifically, this must include the information source(s), the medication activities and processes, specifically prescription, dispense, administration and statement as sources.
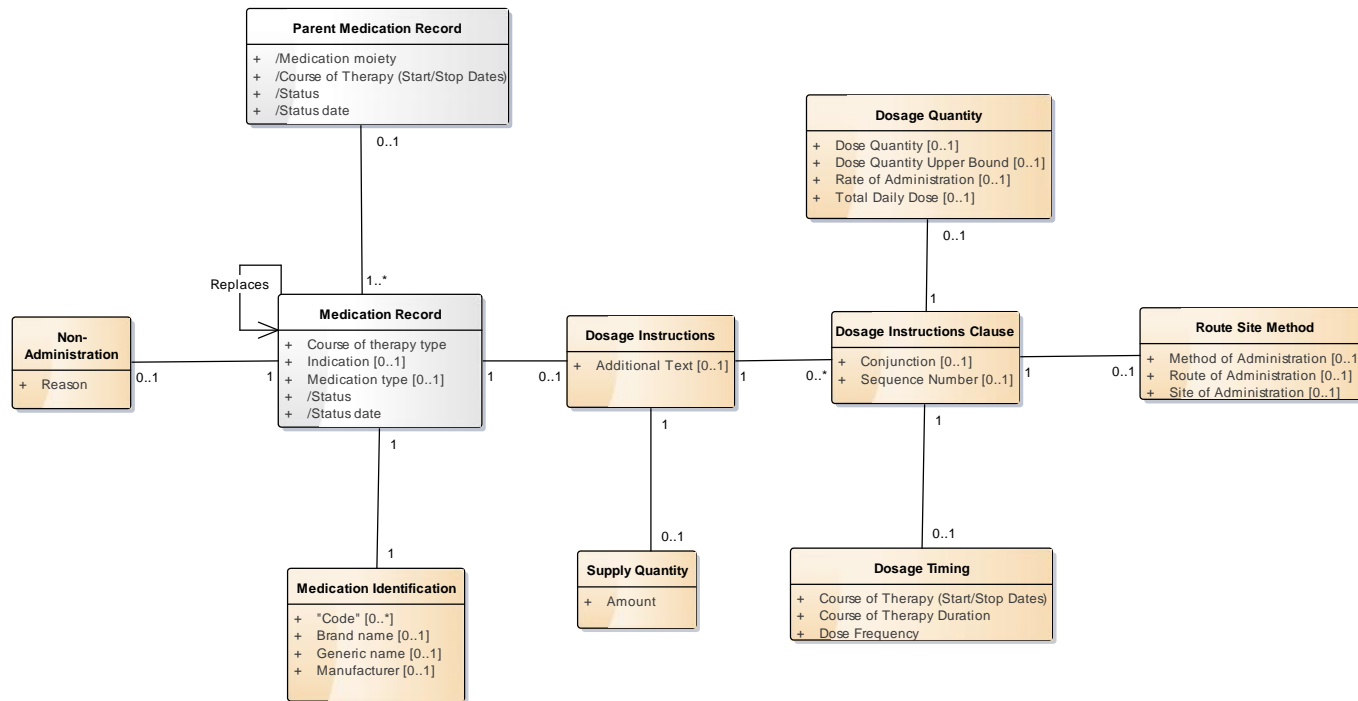
Logical level model

Figure 11: Logical model of the classes, attributes and relationships of the Medication Profile

The following sections describe each of the classes and attributes in the logical model shown in Figure 11 in detail.

Parent Medication Record

Parent Medication Record
+ /Medication moiety
+ /Course of Therapy (Start/Stop Dates)
+ /Status
+ /Status date

Figure 12: Parent medication record class (detail)

The Parent Medication Record class represents the overarching record (documentation of a course of therapy for a single medication moiety) that is populated when a continuous course of therapy (see below) has changes during its lifecycle. This class is a class generated explicitly for management of the Medication Profile to meet its use cases, and such all its attributes are derived, as opposed to being populated from information obtained directly from medication processes.

The Parent Medication Record exists to meet the use case of providing an overall 'course of therapy duration' for a particular medication. This is one of the key differentiators of a properly managed Medication Profile as compared to a list of medications used sorted uniquely and presented in an approximate chronological order.

In the logical model, the Parent Medication Record and the Medication Record are the result of a single 'unrolling' of the recursion shown on the Medication Record class in the conceptual model.

Medication moiety

This attribute is the description of the medication of the continuous course of therapy, described at its abstract level (i.e. without presentation – dose form or strength – information). This is analogous to a 'virtual therapeutic moiety'[192] or similar classes in medicinal product dictionaries. It is information that should be derived from the medication identification information using a structured medication terminology.

Course of therapy start/stop dates

This describes the timing information for the overall continuous course of therapy, if and when it has had changes applied to it. The course of therapy start/stop dates

are calculated from the course of therapy start/stop dates of the individual medication record.

Status and status date

This describes whether the overall continuous course of therapy is currently occurring or occurred in the past and has concluded.
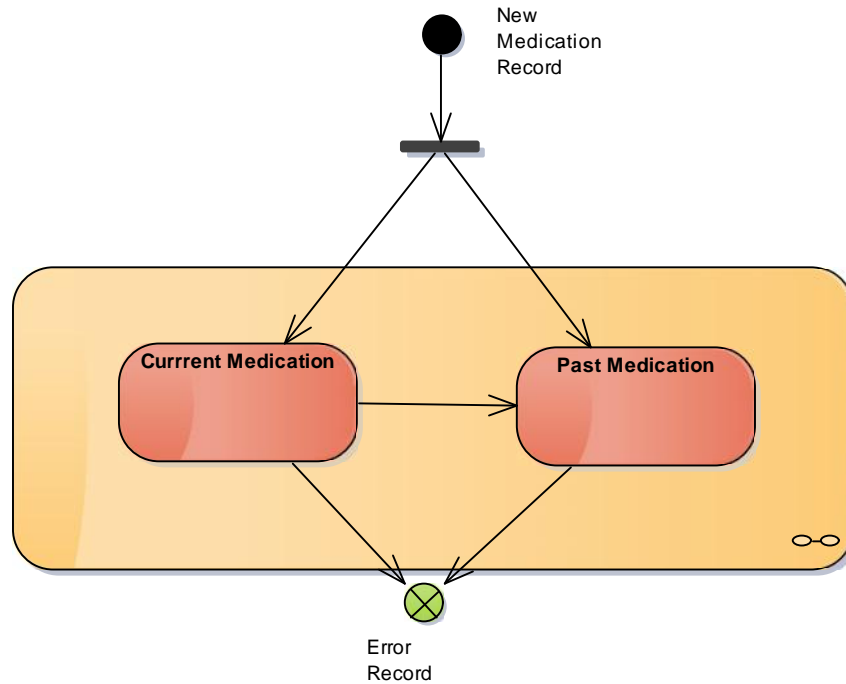
Figure 13: State diagram for a Medication Record status

There are two standard states – 'current' and 'past' – as gathered from the Requirements. The triggers for moving from one to the other are discussed below in the 'Processing information into the Medication Profile' section. Medication records may at some point found to be in error and therefore an error state must be permitted; this should be used following the same principles as for other records erroneously placed in an EHR system.

Status date: any status can only be truly understood in the context of the point of time that it relates to, so a status must have a status date to make it relevant at any single point in time.

Medication Record

Figure 14: Medication Record class (detail)

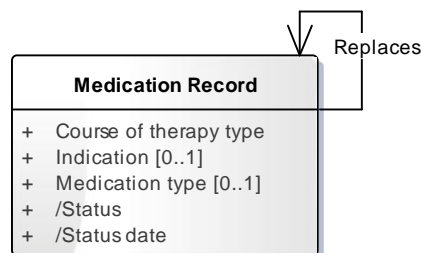The medication record is the documentation of a course of therapy for a single presentation of medication in a single course of therapy.

When a continuous course of therapy has a clinically significant change (e.g. change in dose quantity/frequency or change in strength of the medicinal product), then a new medication record is created that replaces the previous one, and both are related to a Parent Medication Record.

Course of therapy type
The course of therapy type describes the overall pattern of the medication administration to the patient,– as either a single short term course or as a continuous process.

Indication
The indication is the reason why the medication is administered to the patient to effect a cure or management of or prophylaxis of a disease or symptom or condition.

Indication has been grouped with the dosage instructions in the Requirements, but in a logical model would relate directly to the medication itself, and therefore is shown as such. In an ideal world, each medication would have an indication (which may have multiple parts, for example 'to relieve nausea and vomiting').

Medication Type
The medication type supports categorisation of the medication by means of classification, and can be used to identify particular kinds of medication at the Medication Record level rather than at the Medication Identification level.

In the Requirements, there was a need to be able to identify immunological products (vaccines) explicitly, for pharmacovigilance and for patient care purposes, and this could be done by use of the medication type.

This would also allow a subset of the Medication Profile to focus particularly on vaccinations. This is not a use case found explicitly in the literature but one that is expressed implicitly, for example by the fact that in the specifications examined in Chapter 4(1), immunisation information is called forth separately from other medication information. In addition, the requirement for separate vaccine information in the Medication Profile has been expressed to the author in discussion by national health organisations such as Canada Health Infoway.

This attribute could also be used to identify a medication administered as a study drug in a clinical study; identifying such medications was particularly important in the protocol feasibility and patient recruitment use cases.

Status and status date

This describes whether the medication that is the subject of the Medication Record is currently being used by the patient 'now' (as in – this point of time) or whether its use occurred in the past and has concluded.

As described in the state model above, there are only two status envisaged from the Requirements: 'current' and 'past. There is no transition back from 'past' to 'current'; re-use of the same medication after a record has moved to 'past' status will require a new record to be created, as a new course of therapy has been initiated, possibly with a new set of dosage instructions and new indication, depending on the clinical context.

Non-administration
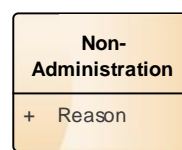
Figure 15: Non-administration class (detail)

Non-administration reason provides information to explain why a medication that has been prescribed has not actually administered or used by the patient; the Patient Care use case had a requirement for this information, however how it would be communicated by currently available business processes is not clear. The attribute has therefore been added to the static information model, but there is no information in the dynamic model section as to how this attribute should be populated.

Medication Identification

Medication Identification
+ "Code" [0..*]
+ Brand name [0..1]
+ Generic name [0..1]
+ Manufacturer [0..1]

Figure 16: Medication identification class (detail)

Each medication that is the subject of a Medication Record in the Medication Profile must be identified, using some or all of the following attributes; the rules for which combination of each would be managed at implementation to ensure a full description was available.

Code

The machine-readable identification of a particular medicinal product obtained from one or more code systems or medicinal product terminologies. There are a variety of code systems or medicinal product terminologies available and different healthcare cultures may specify which terminologies are appropriate for use in that enterprise. Some cultures use a single standard system (such as the NHS in the UK use the NHS dm+d[192] or the Dutch healthcare culture that use the G-Standaard[299]); some cultures use a range of terminological systems and so identifying the medication using more than one of those may be appropriate (e.g. the USA uses a several proprietary terminologies from commercial providers and have the metathesaurus of RxNorm[112] bringing them together).

Brand name

The proprietary name for a medicinal product assigned to it by its manufacturer. Brand name information is particularly important for the pharmacovigilance use case, the exact identification of the medication by use of the brand name is desirable, and brand naming is appropriate for certain types of medicinal products (e.g. those with a narrow therapeutic index or bioavailability issues or those whose administration is associated with particular supporting devices, such as insulin injections).

Generic name

This is the non-proprietary name for the medicinal product and usually consists of the international non-proprietary name with the appropriate dose form and strength information. Identification of a medicinal product by its generic name is preferable for many use cases; however this is not always desirable (see above).

Manufacturer

The organisation that is responsible for making the medicinal available for use. This information is desirable information for the pharmacovigilance use case. A medication as administered to a patient can have only one manufacturer.

Dosage instructions
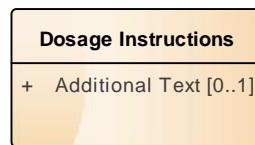
Figure 17: Dosage instructions class (detail)

The dosage instructions describe the how, how much, where and how often the medicinal product should be or was administered.

Additional Text

This attribute holds any additional text that is relevant to the administration of the medicinal product and that does not fit in any of the dosage instructions detailed classes and attributes.

Supply Quantity
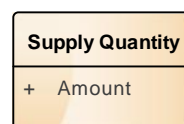
Figure 18: Supply quantity class (detail)

Each medication may have an amount that is to be or has been supplied to a patient for administration. This information was mentioned in only one of the situations examined in the requirements gathering exercise (the CCR) and was just an amount on its own; however, logically in a Medication Profile, both the date of that supply information and some metadata whether it is a requested supply (from a prescription) or a performed supply (from a dispensing) is also necessary to truly put the Supply Quantity information into its correct context.

Amount

This is the amount of medicinal product that is to be or was supplied to a patient in a medication process (prescribe or dispense). The amount should be present as a quantity (countable or measurable) and a unit.

Dosage instructions clause

Figure 19: Dosage instructions clause class (detail)

A dose instructions clause is a single statement that stands on its own to describe a single set of dosage instruction information; it will contain a number of component parts (the quantity, route site and method and timing information). A single dose instructions clause may form the complete dose instruction, or two or more dose instruction clauses may be concatenated together to give the complete dose instruction, using sequence number to ensure that the clauses are brought together in the correct order.

A dose instructions clause was mentioned in only one of the situations examined in the requirements gathering exercise (the CCR, which had both a sequence number and an indication of conjunction) but logically it would exist in a model of dosage instructions.

Conjunction

A dose instructions clause that has a relationship to another Dose instructions clause may have a Conjunction ('or', 'then' or 'and') and, if it is part of a sequence ('then') it will have an indication of where in that sequence it occurs.

Sequence Number

This is an integer that is used to indicate the order of clauses when more than one Dose instructions clause are used together.

The components that can go into a Dose instructions clause are:

Dosage Quantity

Dosage Quantity

+ Dose Quantity [0..1]
+ Total Daily Dose [0..1]
+ Dose Quantity Upper Bound [0..1]
+ Rate of Administration [0..1]

Figure 20: Dosage quantity class (detail)

Each of the four attributes here relate to the amount of the medication administered to a patient. Their definitions are as given in the requirements gathering, but are repeated here for convenience:

Dose quantity
This describes the amount of the described medication that is to be (or was) administered to the patient at a single point in time (i.e. a single dosage administration act).

Total Daily Dose
This describes the amount of the described medication that is to be (or was) administered to the patient in a 24 hour period of time.

Dose Quantity Upper Bound
This describes a limit for the amount of medication that can be administered during a particular timing period.

Rate of Administration
This describes information about the 'delivery speed' with which a specified amount of a medication should be administered to a patient per unit of time.

Route Site Method

Route Site Method

+ Route of Administration [0..1]
+ Site of Administration [0..1]
+ Method of Administration [0..1]

Figure 21: Route Site Method class (detail)

This class and its three attributes describe the 'where' and the 'how' the prescribed medication was or is to be administered to the patient. As above, their definitions are as given in the requirements gathering, but are repeated here for convenience:

Route of Administration

This describes which way that the administered medication should take to get into the body or into contact with the body.

Site of Administration

This describes the specific area of the body where the medication is to be administered.

Method of Administration

This describes how the medication should be administered - the particular way of carrying out or accomplishing the substance administration.

Dosage Timing

Dosage Timing
+   Course of Therapy (Start/Stop Dates)
+   Course of Therapy Duration
+   Dose Frequency

Figure 22: Dosage timing class (detail)

This class and its attributes describe the 'when' the medication was or is to be administered to the patient, and therefore also forms the foundation for the derived information about the status of the medication.

Course of therapy (Start/Stop Dates)

This describes the timing information for when the medication was or is being used by the patient as a treatment whole, and hence is based on dates, rather than the individual dose by dose frequency timing which is described in the attribute below. The course of therapy information is synonymous with a regimen timing concept sometimes described in specifications. Note that this attribute is specific to the Medication Record; a similar attribute exists on the Parent Medication Record, but is derived.

Course of therapy duration

This describes how long the course of therapy of that medication is to be or was, in terms of amount of time (days, months, years) rather than actual point in time dates.

Dose frequency

This describes when the medication (expressed as the dose quantity) is to be (or was) administered to the patient using a measured time pattern (twice per 24 hours, once per 2 weeks, every 6 hours).

Dynamic (Behavioural) Models

The static model describes what the Medication Profile should contain in terms of information at a point in time. It does not give any indication of where that information could or should be sourced from and if any transformation of source information is required, or how that transformation should be undertaken. Nor does it give any indication of how that information should be managed over time. It indicates if the content of an attribute can be derived from other information (which may be elsewhere) rather than being populated by instance data.

A Medication Profile is not an ordered list of records of medication activities, it is a cohesive whole that provides the information to meet the use case requirements in a reliable and timely manner. For example, no clinician has the time to wait for 90 seconds (or more) while a Medication Profile downloads from a central point only to find it contains a hundred identical records of daily methadone dispensing from the past 3 months listed in date order. And no decision support system or protocol feasibility testing system wishes to wade through this set of a hundred identical records of daily methadone dispensing, with the attendant risk of generating an equal number of impractical duplicate therapy alerts. As the Requirements of the previous chapters have shown, the users, both human and system, wish to know that the patient is currently taking methadone and the dosage details of that.

In order to provide a sensibly populated Medication Profile with high quality, consistent, trustworthy information that can be presented to fulfil the use cases efficiently and clearly, all of these things must be taken into consideration. To be truly successful in meeting its use cases, the population of the Medication Profile must be managed with a high quality process that supports consistent curation over time; the Medication Profile is a longitudinal record of care. There should be completeness of information visible to all care givers and all use cases; discontinuation of medication should be clear; non-dispense or non-administration information should be clear.

And taking into account that the majority of information from the provision of healthcare to patient has to be managed in a federated environment, the challenge to provide a single integrated view of information from a variety of sources with the possibility of duplication of information and even conflicting items of information, urgently needs to be addressed.

Yet these aspects have surprisingly not been taken into account within any of the specifications examined and consequently nothing approaching an ideal Medication Profile exists in any system or culture; systems continue to develop in an ad hoc manner with little or no interoperability between them, compromising patient safety and reducing dramatically the ease with which information can be used for secondary purposes such as clinical research.

The objective of the dynamic models is therefore to address this using a threefold approach:

> ➢ to describe the business processes that are the source of and provide flows of information in the real world and to regularise these so that their information can be reflected into the Medication Profile as accurately as possible

> ➢ to describe how information from these flows can be related together, and how the information that they provide can be processed and used in the Medication Profile to meet the use cases

> ➢ to describe the status (lifecycle) of the core classes of information in the Medication Profile (the Medication Record), and how the basic state transitions through that lifecycle should be managed transparently

Activities in the Medication process: sources and flows of information for a Medication Profile

As discussed in the Scope chapter, the concept that 'medicines are not ordinary items of commerce'[268] is often used to highlight that medicines form a special class of objects, and as such their use is managed through a the medication process, with its specialist set of activities as defined and discussed in the Patient Care chapter: prescribing, dispensing and medication administration. In addition to information from these directly medication related activities, as in most of healthcare, there is process of making and recording a statement about a medication process, usually communicated in the form of a summary administration-type process.

These activities and the systems that support them are the sources of the information that will flow into the Medication Profile. Any system wishing to provide a Medication Profile must accept information from the three medication activities and from medication statements, and transform it into a cohesive whole, to populate the Profile. Unless this transformation is performed consistently, against a documented set of rules, different results will be generated by different systems and the Medication Profile will cease to be a consistent whole, able to reliably support its various use cases. This transformation also has implications for how different care sectors and in particular primary and secondary care, can blend their medication information together.

All the specifications for medication information which were studied in detail in the Patient Care chapter detailed **what** information should be stored and **what** information should be shared; none of them made any comment about **how** to undertake the transforms to blend different sets of information together to give an overall harmonious cradle to grave view of a patient's medication.

Medication process activities

All the activities described below occur in patient care, whereas the scope of the requirements for the Medication Profile cover both patient care and clinical research. Clinical research **uses** the Medication Profile, but it does not have any unique activities that would contribute information to the Medication Profile. For example, even within a clinical study, administration of the investigational product should be documented as part of the normal patient care process, then that information re-used (basically, copied) into the appropriate case report form(s) (dealing with the exposure to the investigational product) and reported in the Exposure domain of Study Data Tabulation Model specification or similar. Each of the activities is described in turn below.

Prescription

The prescription activity initiates the overall Medication process. As discussed in the Patient Care sub-chapter, it is the prescribing activity where the selection of the medication itself and its dosage instructions is made. A prescription has two roles: it signals the prescriber's intent that the patient should have the prescribed medication administered and (in most healthcare cultures) it provides the legal authorisation for the supply of that medication to allow that administration to take place.

Dispensing

The dispense activity supplies the medication such that it can be administered. If the medication has been counter prescribed, the selection of the medication and its supply has occurred in one activity, and in the patterns below should be considered as a dispense event because it concludes with that supply activity.

Administration

The administration activity gets the medication *into* or *onto* the patient in order for it to exert its therapeutic effect(s). The administration activity is recorded in only a small proportion of all medication use, in care environments such as secondary and tertiary care facilities or nursing care homes, or on specific occasions in primary care (vaccination, administration of a steroid injection etc.). The vast majority of administration occurs unrecorded and is managed by the patient themselves or their carer(s).

In medication administration systems, each administration event is usually recorded as a single entity (e.g. an antibiotic administered with a frequency of 'every 8 hours' will have three administration event records in any one 24 hour period) in both secondary (hospital) and primary (nursing home) care. But the information (the data elements) that is required by the Medication Profile is 'the dose timing'; there is no requirement in the use cases for 'dose by dose information'. This places a requirement on the type of administration information to be shared with the Medication Profile and when it is shared: administration information shared with the Medication Profile should be a summary of a set of administration events, described as the dose frequency and course of therapy start and end dates. The requirements for the generation and sharing of that administration summary will differ depending on whether the medication activity is a single event (as in a vaccination), whether it is a simple course of therapy or whether it is a continuous course of therapy.

Medication Statement

A medication statement describes the activity whereby an individual or a system provides an account or a report of a medication activity made by someone at a specific point in time: for example 'I used salbutamol to treat my asthma when I was a child' or 'this patient was on azathioprine for several months to control a rheumatoid flare'. Information generated from a formal medication reconciliation process would also be communicated to the Medication Profile using a medication statement or series of statements. Note that a medication statement may be made in the context of another type of communication or report, for example in a referral letter or a discharge form. This is a sub-type of a more generalised 'clinical statement' for which there continues to be much debate but no formal definition[300]. When included

as part of another communication, the receiving system needs to have the capability to separate out the medication statement information and forward it to the Medication Profile system for processing.

Negative Information

Only rarely is negative information captured in health records, and even more rarely is it shared between systems.

Information that a medication is 'not prescribed' would be very rare; a possible scenario might be if a medication was recommended for use by one clinician, but another clinician decides not to use it, for example after a specialist consultation a patient is offered a particular treatment but declines it and therefore no prescription is necessary. Information about a prescription being 'not dispensed' is also rarely captured, even though this scenario does occur for many reasons: from clinical reasons of the prescription being clinically inappropriate due to interaction, incorrect dosage, etc. through to patient-centred reasons such as being unable to afford the cost of the medication or simply the patient not wishing to receive the medication. In systems that record administration of medicines, a medication 'not administered' is likely to be recorded (indeed, ethically such non-administration information is usually required); however that may or not be made available for sharing with other systems.

Relating information from the Medication Process together

Simple, fully complete Medication Process
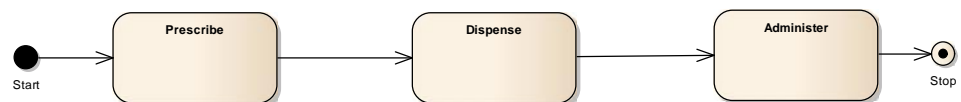
Figure 23: Simple, fully complete Medication Process

This is the simplest and most complete sub-pattern where all activities occur in a linear pattern. A medication is prescribed, dispensed and administered and each activity is recorded and shared. This complete pattern is only likely to occur in a small number of situations – for example in a care environment – because medication administration recording systems tend to be limited to such contexts. An example would be of a patient in a hospice, prescribed an antibiotic for an infection by a primary care physician, which is then dispensed by a community pharmacy but is administered by nursing staff in the hospice and recorded as such. However, with the increasing development and use of mobile applications for use in healthcare, including a significant number aimed at supporting medication adherence[301], it is

possible that in the future much more administration information will be available, including from primary care.

The prescription process is usually recorded on the general practice system in primary care or in the prescribing module of an electronic system in secondary care and could be shared from there, especially in a healthcare culture that utilises electronic sharing of prescription information. The dispensing process is recorded in the pharmacy system and could be shared from that, especially in a healthcare culture that utilises electronic sharing of dispensing information for payment purposes. The administration is recorded (for example as part of the hospice patient care system) and could be shared from that. Because administration systems are required to provide summary information, to support the above, the system needs the functionality to 1) be clear as to if and when a final administration event occurs, 2) to summarise the individual administrations into a single cohesive whole either at its end or at a convenient point and then 3) to communicate this to the Medication Profile.

Prescription and dispense activities
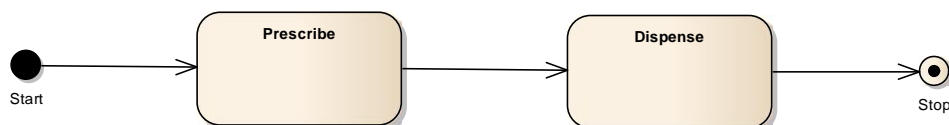
Figure 24: Simple prescribe and dispense only process

This is a less complete but much more common pattern. A medication is prescribed and dispensed and these two activities are recorded. No system information is available about the administration of the medication; it is assumed that the patient or carer administers the medication correctly as directed by the dosage instructions. It is the most common pattern seen in primary care.

Prescription and administer

Figure 25: Simple prescribe and administer process

This is another less complete but relatively common pattern. Records exist and are shared for the prescription and administration of a single medication. This pattern is common in secondary care, in cultures where electronic systems are widely used on

the wards and medication is supplied for use in patients generally (as 'ward stock' for example) rather than dispensed (and charged to) individual patients, for a range of clinical scenarios, including those already described above (for example, treatment of an infection).

Dispense and administer

Figure 26: Simple dispense and administer process

This pattern is likely to be very rare, as it would be exception for a medication to be dispensed and have the administration recorded and not to have the prescription recorded. A possible example might be a medication purchased through over the counter sales, although currently this business process is rarely recorded and shared, for a patient in a formal care facility where all medication administration was recorded. It may also occur with protocol based medication dispensing used in emergency/unplanned care scenarios.

Using the patterns

Although the above patterns describe the logical order for the provision and receipt of medication information (prescribe, then dispense, then administration) to the Medication Profile system, there is no guarantee that a) a system will receive information in that order or b) that information for all three of those processes will be presented. This latter is particularly true for administration information, which is available only in limited circumstances. Therefore any system wishing to manage a Medication Profile and make it available for use must be capable of accepting any medication information from any process and reconcile it to pre-existing information or allow it to initiate a new item of information.

The following sections describe the logical processing and the rules for that processing that a system must undertake to allow it to deal with each and any type of medication information input and to successfully use that in the population of the Medication Profile to provide a cohesive single view of the patient's medication activity in a consistent manner, not merely to regurgitate a list of activities that have occurred.

This means that the Medication Profile system must compute how the received information needs to be processed into the Profile using one of the classic

'Create/Update/Delete' operations – or the Medication Profile specialist equivalents of these – which have 'Archive' rather than 'Delete' as information should never be deleted from a Medication Profile. Any 'corrections' should be made through an 'update' and no longer current information is archived with a status of being past medication. Note that in all of these processes, it is assumed the matching of the information to a single patient has occurred successfully, using processes specifically designed for that task.

Populating the Medication Profile

The following activities can be used to take information from the medication processes populate the data elements within the Medication Profile.
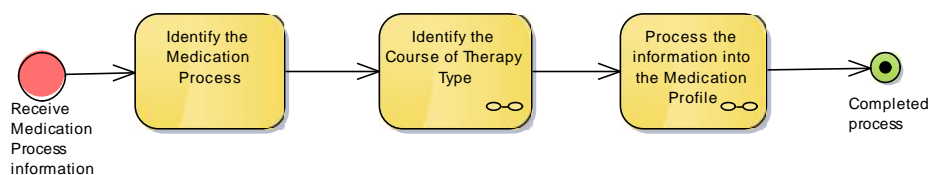
Figure 27: Activity diagram for processing information into the Medication Profile[f]

The first thing for any Medication Profile system to identify is which of the four medication activities the information it is receiving relates to; only once this has been identified is it possible to understand how to further process the information into the Medication Profile.

The specifications for communicating medication information were examined in the Patient Care sub-chapter for their contribution to the requirements for the data elements needed in the Medication Profile. All bar one of the specifications were explicit in having the requirement to identify which activity/process was being communicated. Communications flow between systems using HL7 V2 or V3 messages, or CDA document communications, or in some realms and cultures, specific proprietary messaging formats such as those provided by NCPDP[138138] in the US. In each of those communications it is critical to identify whether a medication message relates to a prescription, a dispensing, and an administration/series of administrations or to a statement about administration. For example: a pharmacy system must correctly understand that the communication it is receiving is a

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[f] The "infinity symbol" [ ] denotes that there are sub-activities present within a main activity – part of model drill granularity and drill down

prescription, since it is this that provides the authority for the dispensing of the medication for the patient; a reimbursement system must correctly understand that the communication it is receiving is a notification of a dispensing, in order to be able to make the correct payment for that supply.

This type of medication activity information is therefore a requirement from the Medication Profile itself to the systems that provide information into it. The Medication Profile system is a communication subscribing system, i.e. it subscribes to all medication related communications flowing in a federated enterprise (a 'notification receiver' in HL7 V3 terms or a 'subscriber' in a basic publication-subscription service) and should receive this business information routinely as a by-product of the general communication flow.

Identify the course of therapy type

Having identified which type of medication activity the communication is describing, the second step is to ascertain where the information from that activity fits in an overall pattern of information present in the Medication Profile. This fit will be different for each of the types of medication activity and will be determined by the information already present in the Profile. It therefore involves making reference to an understanding of how medications are used in 'courses of therapy'. It is this that differentiates an ordered list of medication activities from a proper Medication Profile, which sets activity information in its correct place to provide cohesive information about current medication and medication history (past medication).

It is in the data elements that form part of the dosage instructions that the concept of a course of therapy can be determined both for the Parent Medication Record and the Medication Record itself: when did the patient start taking the medication, and if appropriate and when did they stop (or discontinue) taking it. The start date and end date data elements provide that information and therefore it is these data elements that are critical in supporting the calculation of whether, at any one point in time, a medication is 'current' or 'past' - although, as discussed elsewhere, there is little if any definition of what that actually means in terms of measurable elapsed time. And unfortunately, as discussed above, for any one individual medication activity, its place in an overall course of therapy is not usually explicitly described in any healthcare culture; it has to be evaluated using logical rules, which are described below. For example: the date of any one individual prescription may or may not be the start date for a course of therapy. There are possibly some exceptions to this statement, for example a chemotherapy protocol where each part of the overall protocol is explicitly documented; but even then, relating the medication events from those disparate parts together in a Medication Profile system would require those

relationships to be explicitly documented (e.g. this is administration 2 of 5 against prescription ABC, which is part of protocol XYZ) and that is almost never done within the actual prescribing and administration recording systems.

There is currently no accepted standard for nor any documentation on describing the types of course of therapy for medication so the following is offered, initially as a discussion of the principles, followed by definition of the types with examples. In the practice of healthcare, conditions and symptoms are often differentiated using the terms 'acute' and 'chronic'. An acute condition or symptom is one that may be of rapid onset, brief not prolonged, and sometimes loosely used to mean severe[302] whereas a chronic condition or symptom is one that is lasting a long time, and sometimes meaning also low intensity[302]. Concentrating on the time period part of definition of these two terms, rather than the intensity part, they give a divide based on a qualitative assessment of duration: acute means not prolonged whereas chronic does mean prolonged. This differentiation, although not the terms themselves (so as to remove any link to the concept of intensity which would be unwarranted in this context) can be taken forward and used in conjunction with other differentiators to describe the different types of course of medication therapy that a Medication Profile will encounter.

As stated above, prolonged – or in some senses continuous and not prolonged (i.e. short) are qualitative assessments, and unfortunately, computer systems cannot make qualitative judgements; systems need to use quantitative assessments. To assign a quantitative value to 'not prolonged', so that everything of greater duration would be considered 'prolonged' would involve a significant effort in selecting a set of indicative conditions and their therapy and researching the literature to ascertain the length of time that each is considered to have an acute presentation and treatment period, then from that set of information to make an assessment of an actual time period that can be considered to represent not prolonged or short. That is beyond the scope of this work at present, and therefore, to demonstrate the principle, an arbitrary but hopefully clinically sensible qualitative period of 30 days has been selected, roughly corresponding to the lunar cycle, and is therefore a time period common to all cultures. This is further discussed in the section below on 'Managing medication activity information to identify courses of therapy type'.

Unfortunately, that neat divide into prolonged or continuous and not prolonged or single is complicated by the fact that medications may also be given in an episodic fashion, where several separate short courses are repeated to give a series that has a duration considerably longer than the duration that would have occurred if the medication had been administered continuously.

Single course of therapy

This pattern describes when a medication is used for a short period of time (a month or less) as a single instance and independent of any other pattern. Examples of this include an antimicrobial preparations used to eradicate an infection, or an analgesic or anti-inflammatory medication for symptomatic and short term management of an injury. This contrasts with and is differentiated from a chronic course of medication which is one that is prolonged, where the duration of continuous use of the medication is greater than one month (greater than or equal to 30 days).

Continuous course of therapy

This pattern describes when a medication is used chronically, for a prolonged period (several months and maybe many years) and usually uninterruptedly, and as such consists of the pattern that covers the majority of medication use for the management of chronic conditions such as hypertension, angina pectoris, diabetes mellitus etc.

The continuous course of therapy usually involves some element of a repeating activity, either by having a formal repeat prescribing or repeat dispensing process, or by the constant repetition of a basic single prescribe-dispense process. Note that the method of managing the latter as a repeated course of therapy will also apply to the linkage between the conclusion of one time-limited repeat prescribing or repeat dispensing process into the next one (see further below).

Repeat Prescribing

The repeat prescribing process is one where a number of individual and identical prescription orders are authorised at a single point in time (a 'set') and each can be used sequentially until they have all been fulfilled or the time limit for the overall set of prescriptions has expired. Each dispensing is made as a fulfilment of a single sibling prescription[g] as shown in Figure 28 below.

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[g] In the English NHS, this process is somewhat oddly described as a repeat dispensing process, when it is actually a repeat prescription process, including terms such as repeatable prescription and batch [of prescriptions] held by a pharmacy
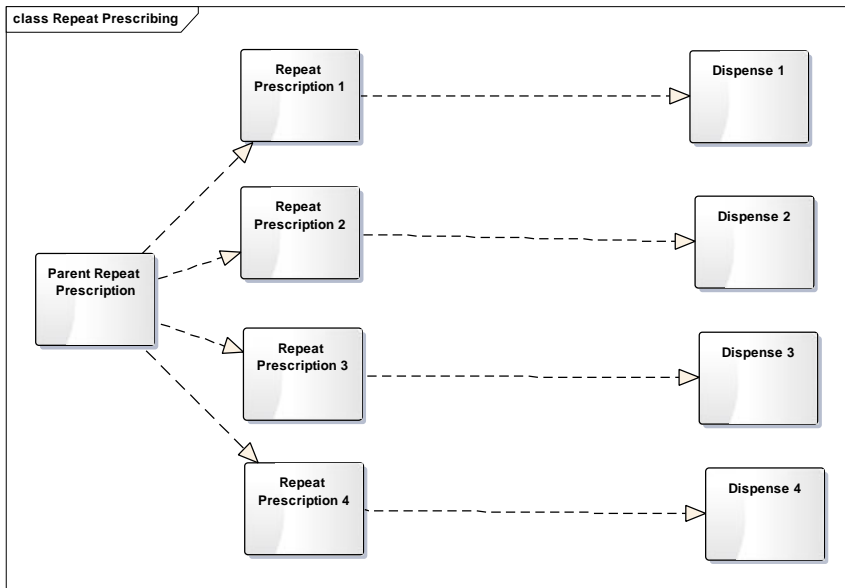
Figure 28: Diagram describing the relationship between a Parent Repeat Prescription and its Dispenses

Use of identifiers such as UUID[h] should support traceability between the Parent Repeat Prescription and all its sibling Repeat Prescription instances, and for the Dispense for each Repeat Prescription.   These identifiers can also be used to support the requirement that some healthcare cultures have, to put limits on the time interval that must exist between each dispensing.

Repeat Dispensing

The repeat dispensing process is one that is supported by a single prescription that, when issued, also instructs how many times it can be used to support a dispensing of the medication for example 'Repeat 3x' would support four dispensing events: the initial one and three repeats, as shown in Figure 29. An example of this would be a standard private prescription in the United Kingdom.   Use of identifiers such as UUIDs maintain traceability between the Repeat Prescription and the Dispenses that it supports.

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[h] UUID – universally unique identifier

class Repeat Dispensing

Dispense 1

Dispense 2

Repeat Prescription

-     Repeat value = "3 Repeats"

Dispense 3
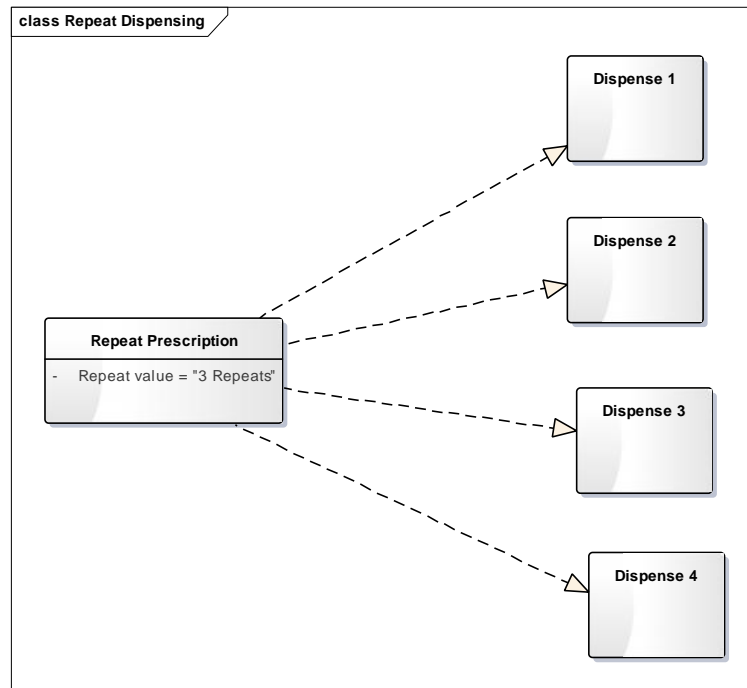
Dispense 4

Figure 29: Diagram describing the relationship between a single Repeatable Prescription and its Dispenses

Changed course of therapy

Because the data element requirements elicited from the use cases in the previous chapters include the data elements that make up the dosage instructions for a medication, a single continuous course of therapy should be defined as one where both the medication and the dosage instructions remain the same. Therefore if there is a change to a data element present in the dosage instructions, this must be managed as a change in the course of therapy. For example, if a patient changed from taking 'furosemide 40mg orally once per day' to taking 'furosemide 40mg orally twice per day', this would constitute a change in the course of therapy, a new Medication Record in the Medication Profile part of the overall Parent Medication Record.

This same principle could be applied to a change in the presentation of the medication itself, since those data elements (medication name, dose form and strength) are also data elements that form key parts of the requirements for the static data. A change in presentation can indicate a significantly different and possibly unrelated therapy (for example therapy using prednisolone eye drops will occur in a clinically very different scenario from that using prednisolone suppositories) so this would not be represented as a change to a continuous course of therapy, it would be a new course of therapy. But there are some scenarios where a change in presentation could also be the implementation of a straightforward dosage change

(for example 'enalapril 5mg tablets, to be taken once a day' to ''enalapril 10mg tablets, to be taken once a day') and this could and probably should be managed as a change to a continuous course of therapy.

To manage this accurately, there a complex set of rules would need to be developed, primarily based around route of administration (or route of administration imputed from the dose form) and which may even need to be medication specific. At this point any change in the presentation of the medication will be taken as a changed course of therapy rather than a new course of therapy, since this most closely fulfils the eligibility criteria based use cases, with the requirement to know, for example, 'has the patient being taking medication X for more than 6 months and less than 2 years?'.

Cyclic (episodic) course of therapy

This pattern describes when a medication is used in phases, in a set of successive short courses (cycles) given at stated intervals which together form a complete course of therapy. The most common example of this is cytotoxic medications used in oncology, but the pattern can also be used to describe vaccination schedules. This pattern could also be used to describe medication to treat seasonal conditions (such as seasonal rhinitis (hay fever)), with the complete course being a continuous course with an annual cycle flowing through that.

The pattern is complex because the course of therapy information recurses. The inner part of the recursion describes each of the shorter courses: the single cycles which may consist of a single administration, or may be as long as a month or more of repeated administrations. The outer part describes the complete course of therapy: its overall duration and the frequency of the repeats within that overall duration.

Although it should be possible to identify cyclic courses of therapy and manage these in the Medication Profile, with the information currently available in healthcare enterprises it would be very difficult to do so accurately, and therefore the logic to do this has not been described here. As a pragmatic but admittedly imperfect solution in current conditions, it is suggested that each cycle is managed as a course of therapy in its own right.

Managing medication process information to identify course of therapy type

The following sections examine in turn how to manage information from each of the four different medication activities into cohesive course of therapy information.

In all of the sections, a time period has been used to differentiate between a communication regarding the continuation of an existing (and therefore continuous) course of therapy and an instance of a new course of therapy. As can be seen from the Requirements chapters, there is very little guidance as to what can be considered a sensible amount of time to actually differentiate this. For pharmacovigilance, only the VAERS form gave any explicit guidance (which was 4 weeks); all the other forms used phrases such as 'concomitant', 'at the same time as [the reaction]' and 'current'. In the eligibility criteria, there were only 4 criteria that had explicit time periods for prior medication, and each of these were different (28 days, 30 days, 12 weeks, 3 months). In the Patient Care chapters, apart from the arbitrary 90 day requirement for drug interaction checking, none of the specifications or care modules had any explicit guidance for timing of current or past courses of therapy, or the differentiation between these. Therefore, in the absence of any consistent guidance, a time period of 30 days has been selected. This closely reflects the lower end of the few explicit figures given and as such can be considered most conservative.

Alternatively, this time period could be determined by the guidance within a particular healthcare culture (for example, if prescriptions are only valid for fulfilment within 28 days of their issue, as is the case for prescriptions for opiates and similar medications in the United Kingdom[303]) and could vary between the different processes. For example, a time period of 90 days *could* be used in the logic for processing dispense communications on the grounds that this is long enough to cover situations that are known to occur with seasonally applicable medication; for example a prescription issued for hay fever treatment in this spring that is not presented for dispensing until the pollen count for the particular allergens for that patient has reached a level to induce symptoms, which might be high summer for patients mostly affected by grass pollens. A dispense event notified to the Medication Profile more than 90 days after its instantiating prescription event would therefore be managed in the Profile as representing a different course of therapy from its instantiating prescription event. This might not always be a completely accurate reflection of the real situation, but any clinician viewing the Profile would make their judgement as to the actual situation and act appropriately. Any system using the information in the Profile would process both the prescription and the dispense event separately and therefore would have a double positive in terms of alerts for decision support or matches for recruitment, which is a safer alternative than a negative.

For practical purposes, a continuous course of therapy represents treatment for a chronic condition, and a patient would be expected, indeed encouraged, to obtain further supplies of medication before existing supplies had run out; this is part of good treatment compliance and medicines management.

There are two possible ways to ascertain course of therapy (as indicated by the drill-down shown in Figure 27) these are shown below in Figure 30: one using identifiers (e.g. UUIDs) to relate processes together to give course of therapy type information, the other using the medication name.
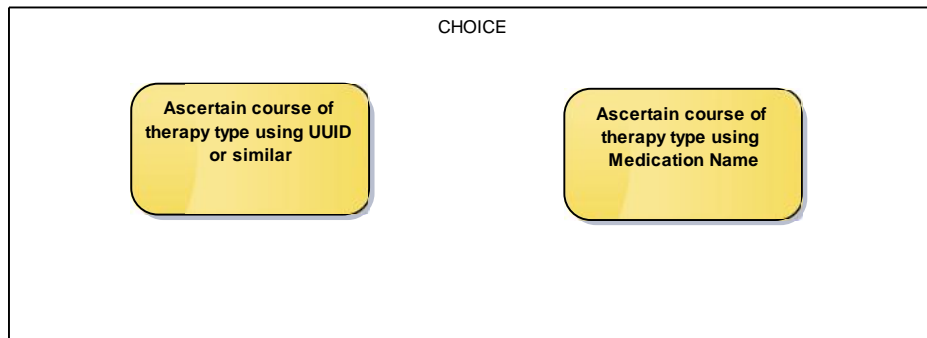
Figure 30: Alternative sub-activity for ascertaining course of therapy type

Processing prescription information

For a prescription, the dynamic model describes that this is the start of 'a medication process' in some way; it will authorise

- The start of a new single course of therapy

- The start of a new continuous course of therapy

- The start of the next portion of a continuation of a continuous course of therapy

- The start of a cyclic course of therapy

- The start of the next cycle of a continuation of a course within a cycle of therapy
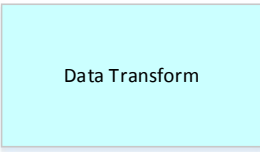
When processing single prescriptions without any explicit course of therapy information, it is impossible to distinguish between the start of a new continuous course of therapy and the start of a new single course of therapy; in the flows that follow these will both be termed a new course of therapy. Later on in the process it is possible to differentiate these using rules and logic. Note also that the latter two options are not explored in detail in this section, for the reasons already described above in the cyclic course of therapy section.

In order to correctly process any prescription information that it receives, a Medication Profile system must use rules to elicit – to the extent to which that is possible – which of these the prescription represents. Within the current practice of healthcare and particularly medication information and its communication, there has been to date no expression of a requirement for a prescription to describe the course of therapy type that it supports, other than in the context of repeat prescribing or repeat dispensing. But even in those contexts, there is no indication of whether a set of repeats is initiating a new therapy or continuing an existing course. This limits what can be done by and for the Medication Profile purely by logic when examining a prescription in isolation.

In the absence of any such specific course of therapy information, the Medication Profile has two other areas in which to apply logic; the first is a reasonably accurate area in that it uses and matches artefacts designed for machine processing (UUIDs), whereas the second relies on matching the information that is available, the medication and the accompanying dosage instructions.

In all the figures below that describe the logical flow and rules for processing information, the convention shown in Table 21 is used.

Table 21: Symbols used in the flow diagrams describing the logic used to process information into the Medication Profile

Question/Decision	Indicates a question or decision that the information must be processed through
Data Transform	Indicates a data transformation should occur
New Course of Therapy process	Indicates the next process that should occur is a new course of therapy process
Changed Course of Therapy process	Indicates the next process that should occur is a changed course of therapy process
Change with a Continuous Course of Therapy	Indicates the next process that should occur is change to information in an existing continuous course of therapy process
Update to an existing record in the MP	Indicates the next process that should occur is an update to an existing Medication Record in the Medication Profile
Confirms existing record within the MP	Indicates the next process that should occur is confirmation of the information in an existing Medication Record in the Medication Profile

Using UUIDs

As described above, in a Repeat Prescribing scenario, UUIDs can be used to match 'child' repeat prescription communication with their parent and also allows identification of the parent itself; this allows identification of either a continuous course of therapy (a new parent repeat prescription) or a continuation of a continuous course of therapy).

The flow diagram in Figure 31 shows the logic that the Medication Profile must apply when receiving a prescription containing a UUID.
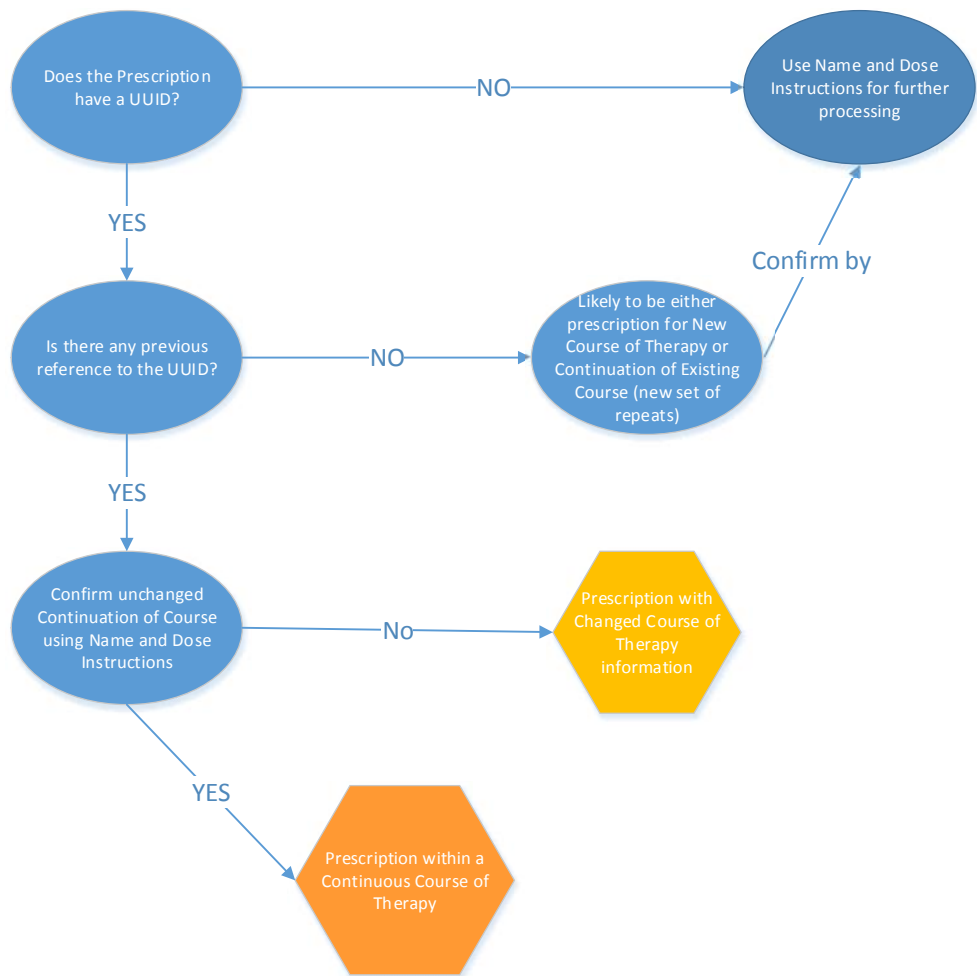
Figure 31: Flow diagram of logic used to ascertain course of therapy for a prescription using UUID

Using the medication name and dosage instructions

In a healthcare culture that does not support the use of UUIDs to relate prescriptions and their dispenses together, to meet its use cases in that environment, a Medication Profile must employ logic based on the information that is available, the description of medication itself and the accompanying dosage instructions, to ascertain what an

individual prescription represents in terms of the course of therapy.   This matching process is complicated by the fact that medications are named in various ways and at various different levels of abstraction. The flow chart shown in Figure 32 seeks to address this; there is a transformation process between a brand name and a generic name; some healthcare cultures allow generic substitution or interchangeability of branded products based local rules and guidance. By having this transformation in the process, a prescription with its medication written as a brand but dispensed as a generic, or dispensed using a different brand name can be related together correctly and accurately. It would also be possible, if the information is available, to use the medication code as an alternative to or in conjunction with the medication name although this is not shown in the flow due to special constraints. Either or both of name and code should be used in conjunction with a knowledgebase that contains equivalence relationships between branded and generically named products.
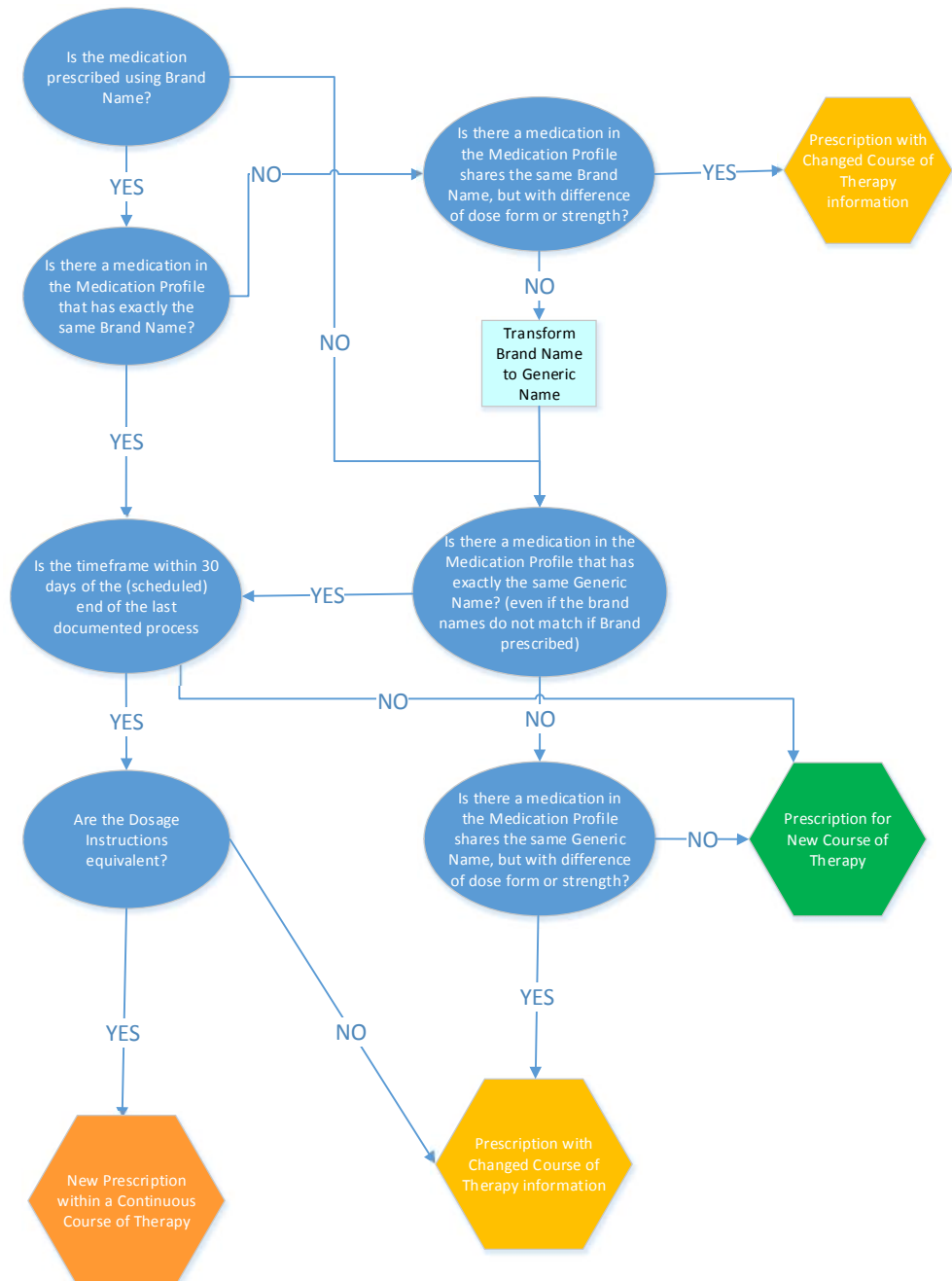
Figure 32: Flow diagram of logic used to ascertain course of therapy for a prescription using medication name and dosage instructions

Processing dispensing information

Dispensing events provide information on the supply of the medication against a prescription; information from that prescription may or may not be already present in the Medication Profile and this is the first thing that the Profile must determine. Once that has been elucidated, for a dispense that provides information that is not supported by a prescription, then the type of course of therapy that the dispense supports must be ascertained.

Dispensing: supporting an existing prescription or providing new medication information

The Medication Profile has to apply logic to differentiate these two different scenarios and again there are two options: using UUIDs or matching the information that is available using the medication name; each is shown below in Figure 33 and Figure 34 respectively.

Using UUIDs
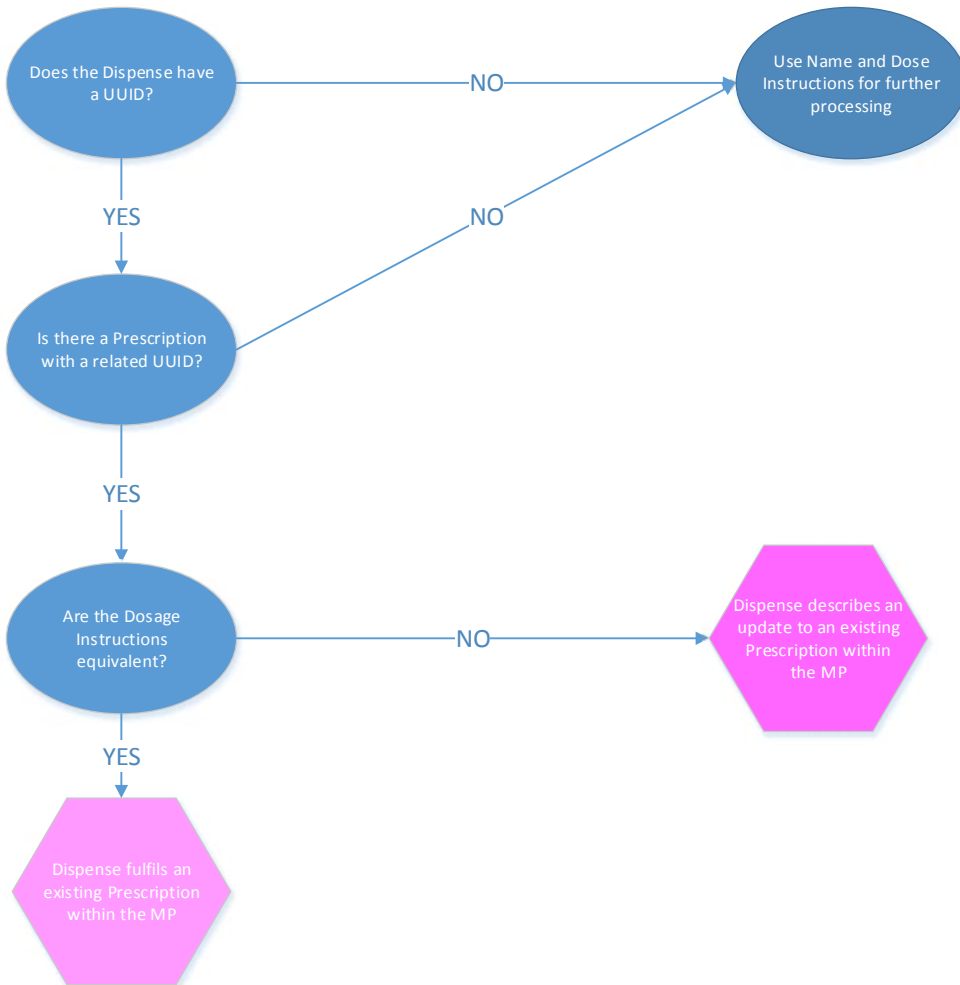
Figure 33: Flow diagram of logic to ascertain whether a Dispense supports an existing Prescription using UUID

Using the medication name
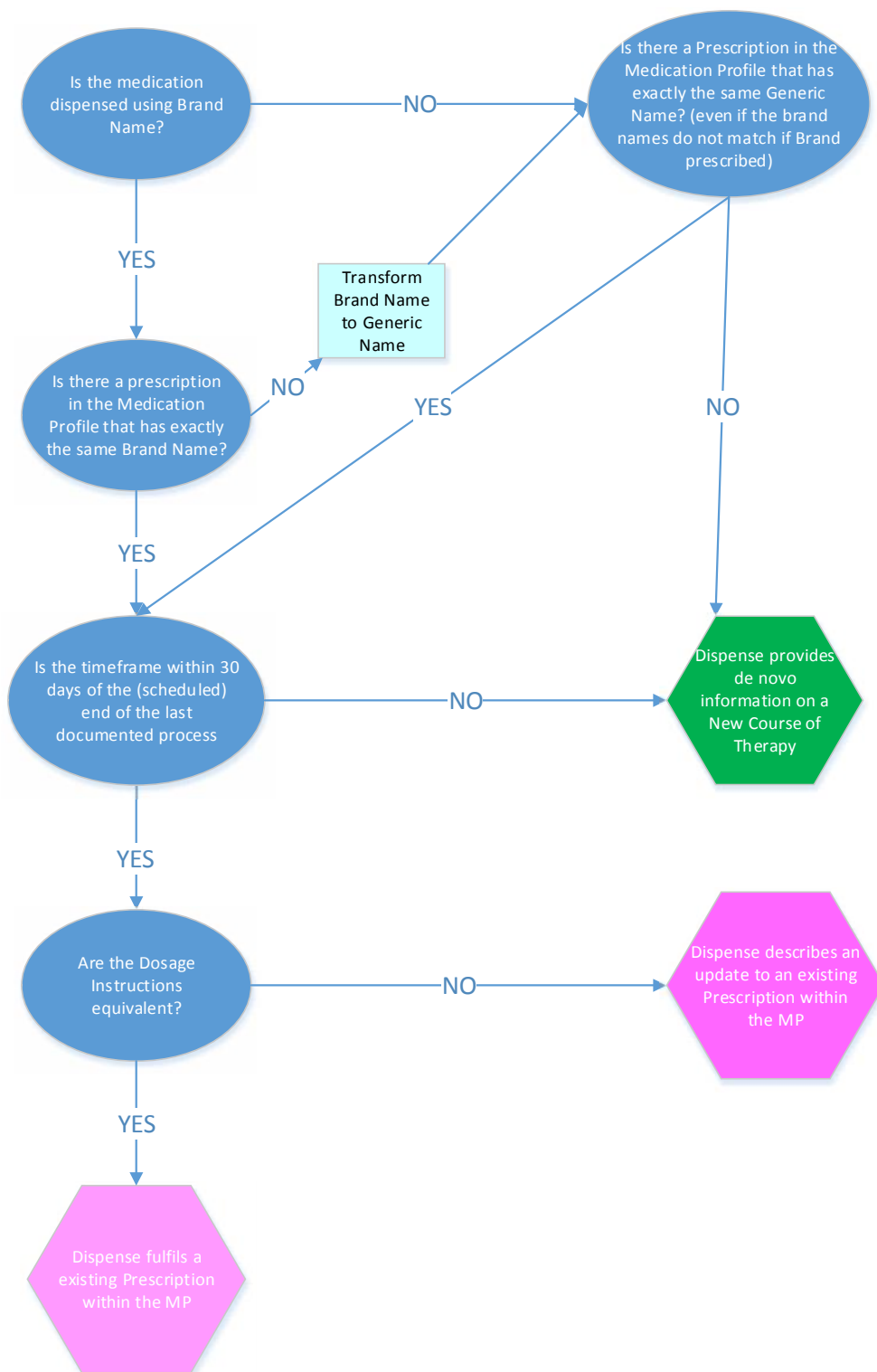
Figure 34: Flow diagram of logic used to ascertain whether a Dispense supports an existing Prescription using medication name

Dispensing (no prescription): de novo course of therapy

If there is no supporting prescription already present in the Medication Profile, then the type of course of therapy that the dispense supports should be clarified using the logic shown in Figure 35 below.
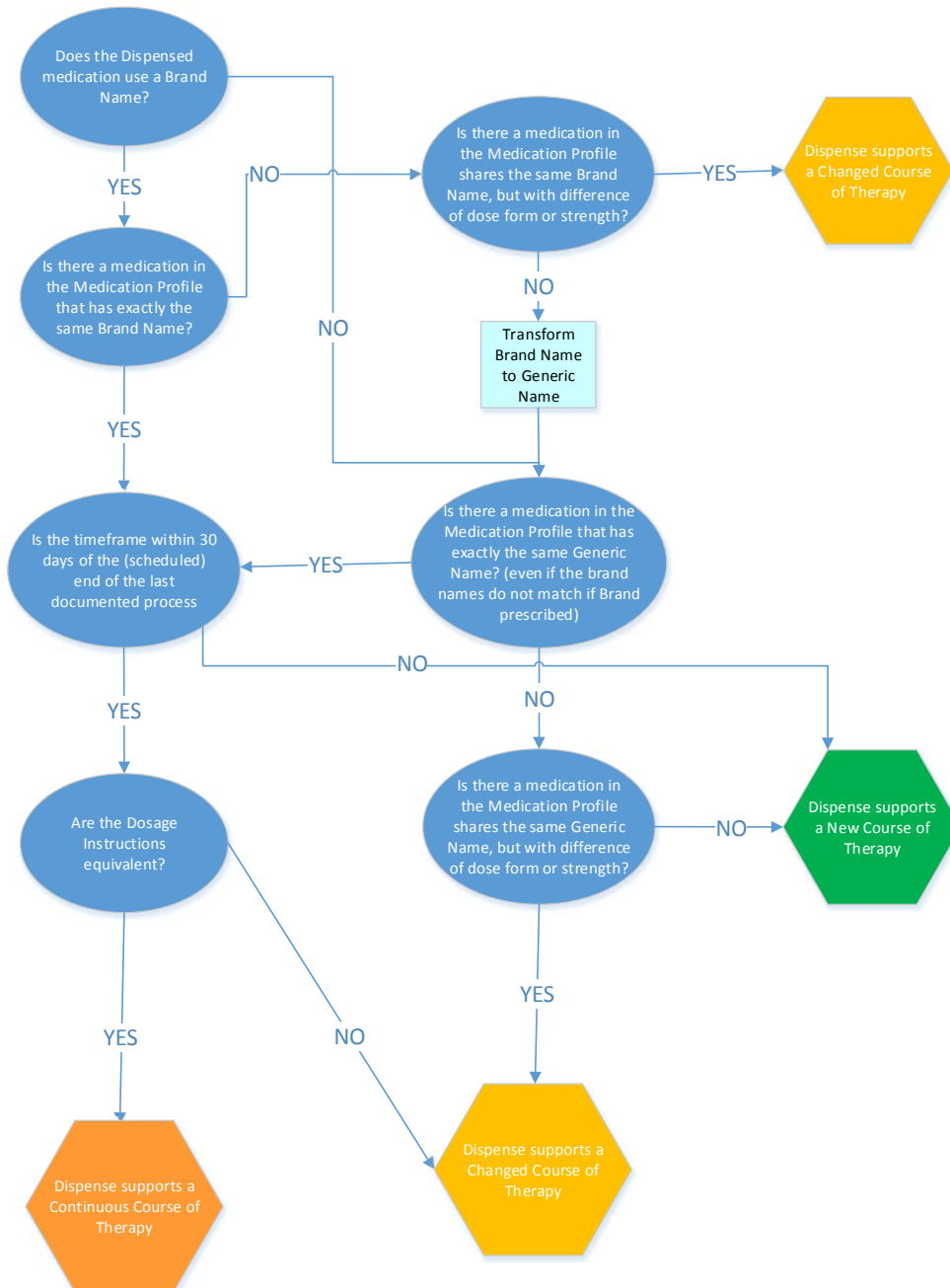
Figure 35: Flow diagram of logic used to ascertain the course of therapy for Dispense only information

Processing administration information

Administration events provide information on the final activity in the medication process. There may be one or both of the supporting prescription and dispensing

information already available in the Medication Profile, such that the administration information is the final piece; or there may be *only* administration information, in which case the type of course of therapy that the administration supports must be ascertained.

Administration: supporting existing Prescription and/or Dispense or providing new medication information

As with dispense information, the Medication Profile has to apply logic to differentiate these different scenarios and again there are two options; using UUIDs or matching the information that is available, the medication name. The logic is somewhat similar, but it is described in detail below in Figures 36 and 37 to be explicit for implications for further processing.

Using UUIDs
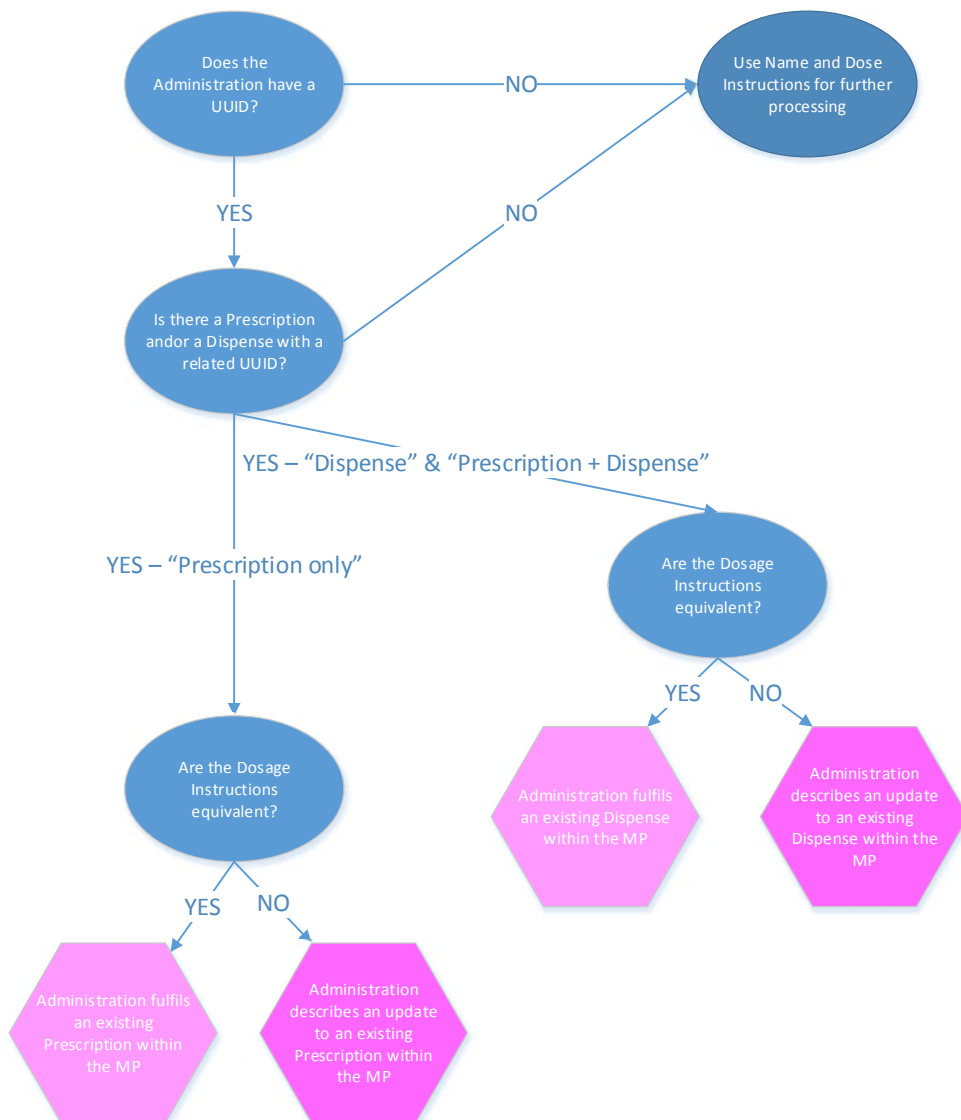
Figure 36: Flow diagram of logic used to ascertain whether Administration information supports an existing Prescription and/or Dispense using UUID

Using the medication name
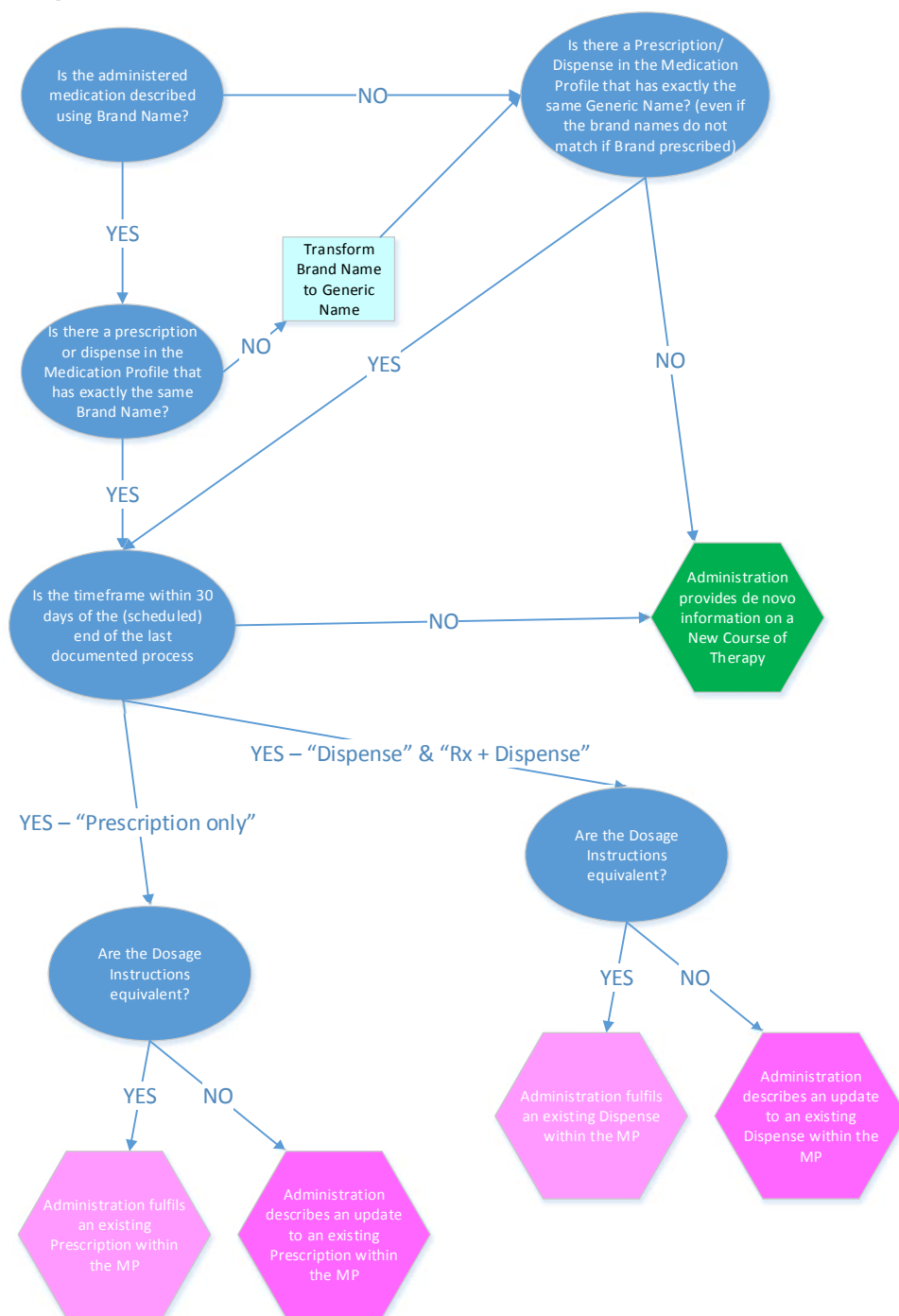
Figure 37: Flow diagram of logic used to ascertain whether Administration information supports an existing Prescription or Dispense using medication name

Administration (no prescription or dispense): de novo course of therapy

If there is no supporting prescription or dispense information already present in the Medication Profile, then the type of course of therapy that the administration information supports should be clarified using the logic shown in Figure 38.
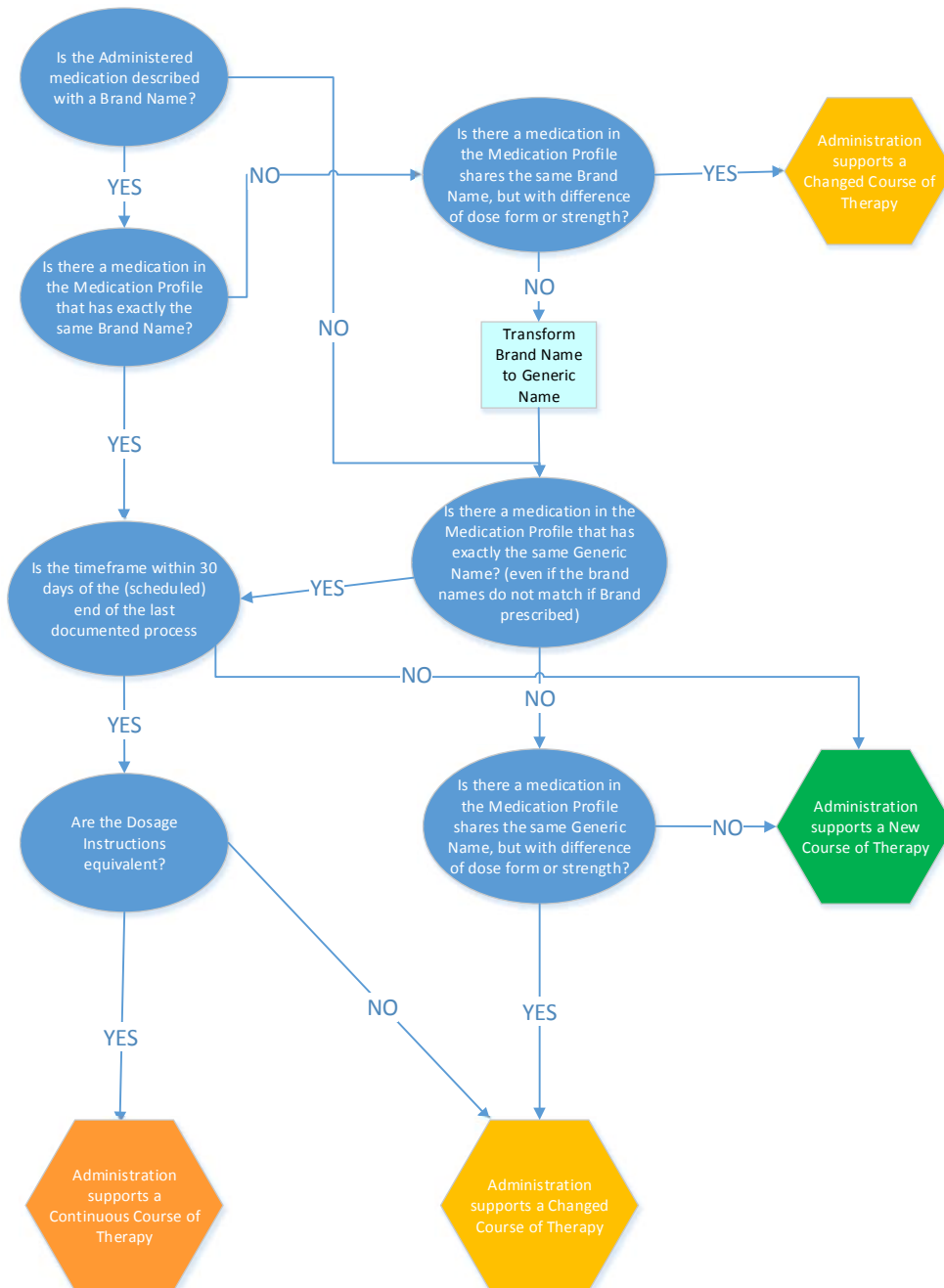
Figure 38: Flow diagram of logic used to ascertain the course of therapy for Administration only information

Processing statement information

Medication statements, in system terms, are a sub-type of medication administration communications since they describe an administration process, but not in the usual context of the prescribe-dispense-administration activity model.

As such, information from medication statements may be processed into the Medication Profile using the flow for 'administration only' information shown in Figure 38 (above), since they may provide information about a new course of therapy

medication (i.e. one that is not already present in the Profile) or they may provide new information about a medication already present in the Profile, or they may confirm information already present in the Profile. However, based on any course of therapy start and stop dates, it may be that a new record that is created goes straight to the 'past' status and into the archive part of the Medication Profile, and also, based on those start and stop dates, if the course of therapy was longer than 30 days, with the type as 'continuous' rather than as 'simple'.

A medication statement needs to provide its content to the Medication Profile using the attributes described in the static model, and this in turn places requirements on how medication statements are recorded in systems. Medication statements also need to have their metadata: who made the statement, when it was made and in what context it was made, available for reference, so that a user of the Medication Profile can see the clinical context of the statement, in the same way that they could see the context of prescription, dispense or administration information. This may mean that the Medication Profile has to have links to other parts of an EHR, and this in turn may mean that the Profile ceases to be self-contained.

Medication statements can be made in the negative, for example, 'the patient asserts that they have never taken nifedipine'. Handling negated information continues to prove difficult in all electronic health record contexts, and the Medication Profile is no exception in that. For this reason, negated medication statements have not been explicitly addressed at this point, and further work should be undertaken in this area, as soon as the more general issue of handling negated data in health records is resolved.

Processing the information to populate the Medication Profile

In each of the process flow diagrams above, the conclusion positions are that the activity information supports one of

> ➢ a new course of therapy
> ➢ a continuing course of therapy
> ➢ a changed course of therapy

Having ascertained this, the final activity is to process the information into the Medication Profile, either creating a new record or making an update to an existing record. As shown above in Figure 27, this activity has sub-activities, which are shown in detail below in Figure 39.
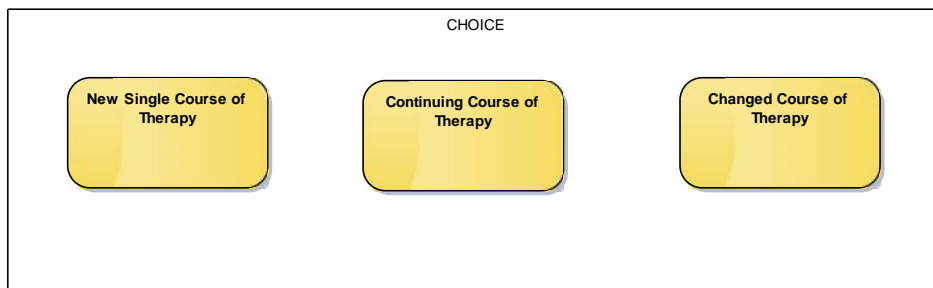
Figure 39: Alternative sub-activities for processing the types of course of therapy information into the Medication Profile

The actions that the Medication Profile should perform for each of these are discussed below. In all these, it is assumed that the Medication Profile system can semantically process the dosage instructions information. If dosage instructions are provided only as unstructured text and with no parsing facility, the only option is to process based on medication name.

New single course of therapy (a 'create' record)

Figure 40: New course of therapy

On receipt of information about a new course of therapy, the Medication Profile creates a record (an entry in the Profile) for this Medication, with all the available attributes (indication, dose quantity, route, site and method, and the dose frequency and duration attributes of dosage timing) being filled with information from the process. At this point, it is impossible for the Medication Profile system to ascertain the type of course of therapy, so it must be typed as a **single** course of therapy type.

For the course of therapy timing (Start/Stop date), the following rules would be applied as shown in Table 22 below. Administration information may be provided in summary at the end of the administration process (the most likely scenario) or in near to real time; for the latter, no change would be made to the Medication Profile in formation based on provision of intermediate information.

Table 22: Rules for processing course of therapy timing information into the Medication Profile for a new course of therapy

	Prescription	**Dispense (only)**	**Administration Summary (only)**	**Administration (near to real time)**
Course of therapy start date	Date of prescription	Date of dispense	Date of first administration	Date of first administration
Course of therapy duration	Calculated from supply quantity or supply period	Calculated from supply quantity or supply period	Not stated	Not stated
Course of therapy end date	Not stated	Not stated	Date of last administration	Not stated, until last administration

The timing of the receipt of the information about new course of therapy, coupled with the dosage timing information, will also necessarily affect how the Medication Profile will calculate the derived value for Status (and StatusDate). Receipt of information from any process at or very near to the date at which that process occurred and within the duration of the applicability of the process will mean that the status will be set to 'current'. Receipt of information from any process greater than 30 days after the projected end of the process will mean that the status will be set to 'past'. For example, a prescription dated 1 November 2012 for a 7 day course of the antibiotic amoxicillin, received by the Medication Profile system on 2 November 2012 would be processed with the status of 'current' since the receipt of the information is within the 7 days' duration of the process activity. An administration summary dated 26 February 2014 for a 3 day administration of dobutamine given in hospital after major surgery and communicated to the Medication Profile system 31 March 2014 would be processed with the status of 'past' since the receipt of the information is outside the duration of the process activity and more than 30 days have elapsed since the end of the reported medication process.

The metadata that must be recorded and made accessible to a user (human or system) of the Medication Profile content is the type of process that provided this information (prescribe, dispense, administration or statement).

Archival Process

After a period of time, initially suggested to be 30 days after the projected end of the duration of a new course of therapy, where no further process information has been received, the record/entry in the Medication Profile needs to be managed such that its status changes from 'Current' to an inactive 'Past' status. There is no business process to effect this change of status; it must be managed by the Medication Profile itself.

Continuing course of therapy (an 'update' record)
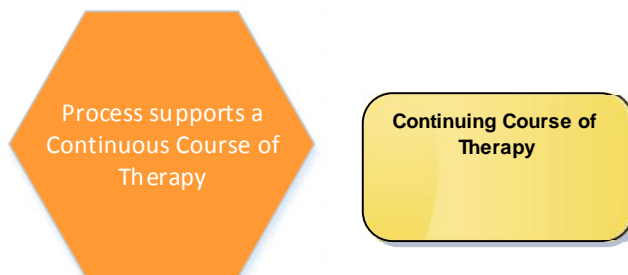
Figure 41: Continuing course of therapy

On receipt of information that supports a continuous course of therapy, the Medication Profile updates a record (an entry in the Profile) for this Medication. This update depends on the initial information itself.

If the record/entry in the Medication Profile already has the course of therapy type of 'continuous', then no further action/processing on this component is required.

If the record/entry in the Medication Profile is noted as a single course of therapy type, which must be the initial default for any new entry, on receipt of a communication that moves the Medication to a continuous course, there must be an update made in the Profile to change the course type to 'continuous'.

For a continuous course, there should be no change to any of the descriptive information (indication, dose quantity, route, site and method, and the dose frequency part of dosage timing). The course of therapy start date is unaffected but the information *may* affect the calculation of end date/duration, which may itself affect the archival process (whereby a Medication status changes to 'past'). If the process is communicating an extension to a continuous course (e.g. is a new prescription or is a new dispense with no prior prescription), then the course of therapy duration

should be extended by the amount of time calculated from supply quantity or supply period.

The supporting metadata for the Medication Profile should be updated to indicate that the record has further process information supporting it. Over time, for a continuing course of therapy, this list of metadata has the potential to be of significant size (for example, for the prescription and dispense data for monthly supply of medication to treat a chronic condition over a number of years this will give approximately 24 entries per year per medication). Managing this is an implementation issue that is out of scope for this modelling of the clinical content of the Medication Profile, but it is important because managing and if necessary displaying this metadata sensibly can support the veracity and reliability of the information the Medication Profile provides.

Archival Process

After a period of time, initially suggested to be 30 days after the projected end of the duration of a continuous course of therapy, where no further process information has been received, the record/entry in the Medication Profile needs to be managed such that its status changes from 'current' to an inactive 'past' status. There is no business process to effect this change of status; it must be managed by the Medication Profile itself. The course of therapy end date should also be entered, either by using an explicitly provided end date (e.g. from an administration record) or by using a date that is calculated as the projected end of the course, based on the duration. If the end date is calculated, this should be indicated as such to the user.

Note: if the archived continuous course of therapy is the final child record of a parent containing record, the status of the parent containing record should also be moved from changes from 'current' to an inactive 'past' status and an end date added using the same logic as described above.

Fulfilment of a pre-existing process
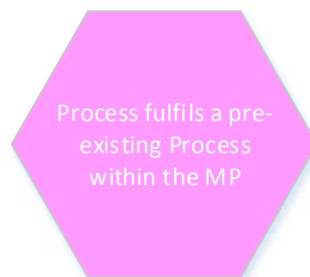
Figure 42: Fulfilment of a pre-existing process

This activity is supplementary to the processing of a new course of therapy type or a continuous course of therapy type, where the information received from a medication activity communication provides confirmation of the fulfilment of a pre-existing activity (the dispense information confirms the fulfilment of a prescription, or the administration confirms the fulfilment of a prescription and/or a dispensing), and there is no update in any of the supporting information. There is therefore no information to be changed/updated for that Medication Record in the Medication Profile, with the exception of if the process is an administration, in which case the course of therapy stop date *may* require updating using the logic described above in the new course of therapy section, or possibly if there is further detail as to the actual brand/manufacturer of the actual medicinal product dispensed. Display of brand/manufacturer information obtained from a dispense communication should be optional and an implementation decision, although the information should be stored for use if required particularly for pharmacovigilance use cases.

The course of therapy type will remain as described by the logic from the initial process information (prescription or dispense) as the fulfilment of a pre-existing activity may relate to medication being given in either a new single course or in a continuous course. The supporting metadata for the Medication Profile should be updated to indicate that the record has further activity information supporting it.

Changed course of therapy and update to a pre-existing process (an 'update') record
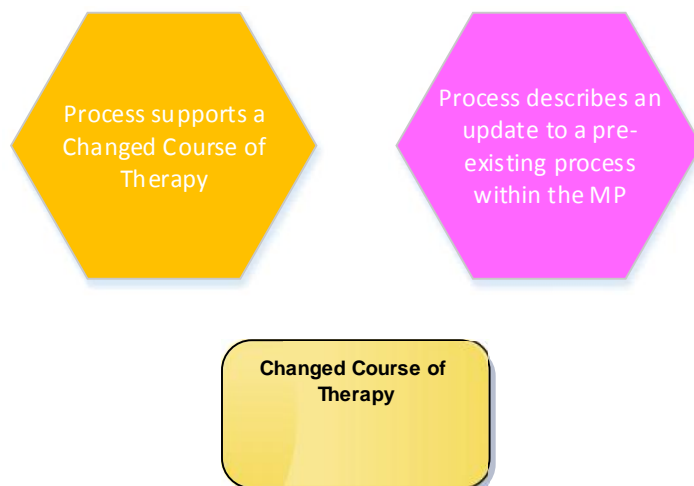
Figure 43: Changed or updated course of therapy

This is a complex situation requiring further logic and processing from the Medication Profile to be correctly managed and thereby to provide the data to support the use cases.

Additional information

If the information received provides additional new information or a greater level of detail for the indication or dosage instructions (for example the dispense information contains detailed dosage instructions whereas the prescription had no instructions or only 'use as directed'), then then the new information should be added and used if required in further processing (e.g. to calculate archival and change to 'past' status in due course). The Medication Profile system should indicate to users, particularly human users, by the use of some sort of graphical interface indicator (such as highlighting) that the information presented has been updated, and should allow the user to see the previous information (e.g. by a double-click drill down). The rationale to support the update is that both the dispensing and the administration process move closer to the actual clinical use of the medication by the patient and should therefore be the most accurate reflection of what actually happened/is happening. For example: a prescription for 'amoxicillin 500mg capsules' was actually administered as for 'amoxicillin 250mg/5ml oral solution' with the dose quantity adjusted appropriately because the elderly patient could not swallow the large capsules. This situation is rare in UK primary care, where the dispensing (and administration) normally follow exactly the item as ordered, but is more common in other healthcare cultures.

This logic applies to both course of therapy types although the changes expected to continuous courses are likely to be small. However, there may be a practical situation in the repeat prescribing and dispensing pattern where this simple single update *may* prove difficult, if the prescription always states the dosage instructions as 'use as directed' and the dispense always has the detail of 'inhale two puffs morning and evening'. There are various alternatives for resolving this, using both systems and process, but this degree of practical implementation complexity is out of scope for the basic modelling of the clinical content of the Medication Profile; it would be a significant topic for further practical investigation.

Changed medication presentation

A change in the presentation of the medication itself (different dose form or strength) has the potential to significantly alter the clinical effect of the medication in the patient. This is because such a change will either increase or decrease the total amount of medication present in the patient's body or by change the pattern of distribution of the medication in the body. The Medication Profile must process these changes differently depending on the course of therapy type.

For a single course of therapy, the information should be updated with the new information, with the previous information available for view. For a continuous course of therapy, several actions are necessary.

1. The new information should be used in full to create a new child Medication Record in the Medication Profile. The course of therapy start date for the new related record follows the pattern given in the new single course of therapy section

2. The now replaced record should have its course of therapy end date entered, using the same date as for the course of therapy start date in 1) above

3. A containing Parent Medication Record should be created or updated, that may or may not be initially visible to the human user. The course of therapy start date should be the course of therapy start date from the first child record in the container

Managing negative information

If the Medication Profile system receives non-administration information it should be processed in a similar way to normal information, i.e. ascertain if a Medication Record already exists for that medication. If it does, the non-administration information should be appended to that, and the reason for the non-administration added to the record as an attribute.

If the non-administration information is such that the course of therapy has ended, then the system should process this, adding the stop date, and marking the Medication Record to be archived into a 'past' state after the appropriate time period (30 days).

Model examples

This section gives examples of the application of the dynamic model process, the activities and rules described above, used to populate the data elements of the static model in exemplar scenarios. There is an example for each of the main areas of processing, using data from activities as would be encountered in day to day healthcare without specifying a particular context of culture and practice.

Example 1: Simple Course of Therapy, Prescription and Dispense, with UUIDs

Prescription [ABC123GH456] for Stephen Smith, dated 02 October 2015, received by the Medication Profile System 03 October 2015 for '21 Amoxicillin 250mg capsules [323509004], one to be taken every 8 hours'

Identify the process: 'Prescription'

Identify the course of therapy:

Is there a UUID? Yes

Does the UUID match anything already present in the Medication Profile? No; confirm using brand and generic name check; still no match. Therefore: start of a new course of therapy

Action: Process into the Medication Profile as a new single course of therapy, with status 'current' (as is current dates)

Table 23: Initial population of Medication Record attributes for Example 1

Data Element	Example	Comments
Course of therapy:	Single	
Indication:	*no information*	
Medication type:	*no information*	
Status:	'Current'	(based on date of prescription = 02 Oct 2015, received into system 03 Oct 2015)
Status date:	03Oct15	

Non-administration reason: Not applicable

Table 24: Initial population of Medication Identification attributes for Example 1

Data Element	Example	Comments
Medication code(s):	323509004	
Brand name:	*no information*	
Medication type:	*no information*	
Generic name:	'Amoxicillin 250mg capsules'	
Manufacturer:	*no information*	

Table 25: Initial population of Dosage Instructions attributes for Example 1

Data Element	Example	Comments
Additional text:	*no information*	
Supply quantity:	21	
Dosage instructions clause:	'single'	conjunction and sequence number not applicable
Dose quantity:	'1'	(250mg capsule)
Dose quantity upper bound:	*no information*	
Rate of administration:	*no information*	
Total daily dose:	*no information*	
Method of administration:	*no information*	
Route of administration:	*no information*	could be implied to be 'oral'
Site of administration:	*no information*	
Course of therapy start date:	02 October 2015	date of prescription
Course of therapy stop date:	09 October 2015	Implied from supply quantity and dose frequency
Course of therapy duration:	7 days	
Dose frequency:	'every 8 hours'	

Dispense [123XYZ987MN] in response to prescription [ABC123GH456] for Stephen Smith, dated 02 October 2015, received by the Medication Profile System 03 October 2015 supplied as '21 Amoxicillin 250mg capsules (Fred's Pharmaceuticals) [644811000001234], one to be taken every 8 hours'

Identify the process: 'Dispense'

Identify the course of therapy:

Is there a UUID? Yes.

Does the UUID match anything already present in the Medication Profile? Yes; is in fulfilment of a prescription already processed into the Medication Profile

Do the Dosage Instructions match? Yes; therefore this Dispense is fulfils an existing prescription

Action: Update to the metadata for this record in the Medication Profile plus update to Medication identification information; this may or may not be displayed in any implementation of the Medication Profile.

Table 26: Updated population of Medication Identification attributes for Example 1

Data Element	Example	Comments
Medication code(s):	323509004	644811000001234
Brand name:	*no information*	
Medication type:	*no information*	
Generic name:	'Amoxicillin 250mg capsules'	
Manufacturer:	*no information*	Fred's Pharmaceuticals

Archive: To 'past' medication

The prescription is for 7 days' supply, which calculates a stop date of 09 Oct 2015 (both the prescription and the dispense were dated for 2 Oct 2015), so 30 days from this course of therapy stop date (8 Nov 2015), if no further information is obtained (e.g. another prescription for amoxicillin, which would be clinically very unlikely) the record status should be changed to 'past'.

Example 2: Continuous Course of Therapy, Prescription, no UUIDs

Prescription for Jane Jones, dated 10 September 2015, received by the Medication Profile System 12 September 2015 for '56 Metformin 500mg tablets [325278007], one to be taken three times a day'

Identify the process: 'Prescription'

Identify the course of therapy:

Is there a UUID? No

Does the medicinal product match anything already present in the Medication Profile (based on brand or generic name and/or code match)?

Figure 44: Initial display of Medication Profile for Example 2

Yes; there is a match; therefore there is a continuation of an existing course of therapy.

Most recent events in the 'Further details' were a prescription and dispense both dated 14th July for 56 Metformin 500mg tablets [325278007]

Are the presentation and dosage instructions the same? Yes 'Metformin 500mg tablets' and 'One to be taken three times a day'

Action: Process into the Medication Profile as a continuation of a Continuous course of therapy; no update required to dosage instructions, status stays as 'current'; the information for the prescription is stored to be used as part of the 'Further details' if required.

Example 3: Changed Course of Therapy

Prescription for Toby Chang, dated 6 July 2015, received by the Medication Profile System 8 July 2015 for 'Beclomethasone 250microgram/dose inhaler, two puffs to be inhaled twice a day'

Identify the process: 'Prescription'

Identify the course of therapy:

Is there a UUID? No

Does the medicinal product match anything already present in the Medication Profile (based on brand or generic name and/or code match)?

Figure 45: Initial display of Medication Profile for Example 3

No; there is no direct match. However, using knowledge accessed in a medicinal product terminology, the Medication Profile can deduce that the prescribed medication is a different presentation of an existing medication present in the 'Current Medication' part of the Medication Profile. This is therefore a changed course of therapy.

Action: Process into the Medication Profile as a new record in the Medication Profile, with a type of continuous course and a status of 'current' and 'replacing' (by updating) the existing record.

In addition, the Medication Profile will:

1) Create a new parent record for beclomethasone:

Table 27: Initial population of Parent Medication Record attributes for Example 3

Data Element	Example	Comments
Medication moiety:	Beclomethasone	
Course of therapy: Start date Stop date	3 February 2014	
Status	Current	
Status date	Today's date	

2) Move the existing record to an archive, with a replaced relationship to the new record, and with the addition of the course of therapy stop date based on the projected supply duration for the last process applicable to the record, which in this case was the last dispensing of a Beclomethasone 100microgram/dose inhaler, on 2 May 2015. [200 dose inhaler, 4 doses per day – 50 day's supply; projected to last until 21 June 2015. The record would be moved to archive (as 'past medication') on 21 July 2015.

Example 4: Medication Statement

Medication Statement, made as part of a referral letter, that Nadia Goldberg (aged 43) took chlorphenamine to control severe hay fever for several years in her teens and early twenties – 1978 to 1993.

Identify the process: 'Statement'

Identify the course of therapy:

   Is there a UUID? No

   Does the medicinal product match anything already present in the Medication Profile (based on brand or generic name and/or code match)? No; so a new record in the Medication Profile

Action: Process into the Medication Profile as a new record, with type continuous course of therapy, and status of 'past' (due to the start and stop dates being many years ago). Ensure that the metadata of the statement (where it was made (in this case in a referral letter), who authored the statement (in this case the same person as authored the letter), and when the statement was made and to whom) is recorded in the Medication Profile metadata section.

Medication Record: (direct into archive)

Table 28: Initial population of Medication Record attributes for Example 4

Data Element	Example	Comments
Medication (moiety):	Chlorphenamine	
Course of therapy: Start date Stop date	 1986 1991	
Status	Past (Archive)	
Status date	Today's date	

Discussion

Static (Structural) Models

Levels of model

Only two levels of static information models have been defined in this chapter. Several further levels could be defined, through the platform independent and platform specific models of the Model Driven Architecture[304] (MDA) moving towards a model that could be physically implemented in a particular database technology (a platform specific physical model).

The addition of a datatype for each attribute, using those defined in Health informatics - Harmonized data types for information interchange (ISO 21090:2011)[147] would move the static model further through the MDA levels, to the level most usually seen in health informatics in the domains of reference, such as the HL7 Reference Information Model[305] and HL7/NCI/FDA/CDISC BRIDG model[306]. This level starts to go beyond the conceptual towards implementation but without necessarily being platform specific.   For example, in the Medication Identification class, the code and the name of a medication/medicinal product are given as separate attributes, and the two most common types of medication name (brand name, generic name) are shown explicitly as these are explicit requirements for some of the use cases. However, if this information was to be managed using the

Concept Descriptor datatype of ISO 21090, the code and displayName would be included in a single attribute. Similarly, in the model as currently defined, the manufacturer of a medicinal product has been modelled as a specific separate attribute, again reflecting its place as a separate data element requirement. But in many medicinal product terminologies this would be included as part of the brand name concept and would be available through reference from the code representing the branded product.

There are other attributes defined within the static model that could be further refined and elaborated to greater depth and detail; for example indication for a medication could be described with more granularity by the symptom or disease being addressed and the aim or prospective effect of the treatment (prophylaxis, cure, alleviation etc.) being given as separate attributes. This level of static model representation is available in other models and standards, but was beyond the requirements for this model.

The static model for the Medication Profile has been limited to the two conceptual levels, to reflect a close tie to the use cases and requirements described in the preceding chapters. As such is at a similar level of abstraction to some more recent standards in the domain, such as Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated medicinal product information (EN ISO 11615:2012)[144].

Recursion and Unrolling

Moving from the conceptual level of model to the logical level, the recursion on the Medication Record is unrolled to give a Parent Medication Record and a child Medication Record class, which itself can have a recursive replaces relationship. This is required to describe an overall course of therapy for moiety, a requirement which is present in both clinical research and patient care. When this logical model is implemented in real systems, this would need further detailed investigation and modelling to support the presentation of the information for the various use cases. This would be particularly pertinent to the view model (or presentation model or GUI model), where a system presents the Medication Profile to a human user. In this, the view is likely to be primarily on the set of current Medication Records, but for any record that has a Parent, a reference to that, and most particularly the start date of that, may need to be made.

Medication Type

Medication type is present as an attribute in the Medication Record class supporting classification of the medication, particularly to fulfil the use case of being able to identify vaccines as a specific sub type of medicinal product or to identify investigational medications. The knowledge that a particular medicinal product is a vaccine or investigational product could be obtained from a medicines knowledgebase, but this requires the Medication Profile to have access to such a knowledgebase, whereas having this information directly present allows the Profile to be self-contained to fulfil this use case. Many healthcare cultures have explicit messages for vaccine administration and these would be processed directly these into a vaccination view of the Medication Profile.

Medication process metadata

A description of the type of medication activities that are contributing information to the Medication Records in the Medication Profile are not explicitly identified in the static model currently. This type of activity information is deemed to be metadata rather than primary data, which reflects the requirements gathered in the use cases.

Negative information

There is no negation indicator present in the static information model. No specific requirements for negative medication information were found that would justify its inclusion. The semantics of negated information in electronic health information are well known to be problematic and no widely accepted approach to the issues currently exist[i]. The only actual requirement for information with negative connotation was the facility to record a non-administration reason if an ordered medication was not administered according to the prescribed schedule, which is present as an explicit class in the static model.

This lack of negative requirements is probably due to a closed world assumption that is implicit in this area. Most EHR systems are developed from databases and database technology generally works on the closed world assumption; specifications for EHRs and EHR communications will therefore adopt this prevailing philosophy. And for the world of medications, which are highly regulated both in their development and their use, this closed world assumption is a reasonable assumption to hold because there is good availability and considerable control of the information.

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[i] The author has participated in many discussions of this topic in a variety of fora, including in meetings of international standards development organisations, over many years.

The closed world assumption supports the related concept of negation as failure whereby every predicate that cannot be proved to be true is deemed to be believed to be false. So, if there is no record that 'Patient X took ibuprofen' then 'Patient X has not taken ibuprofen'.

Dynamic (Behavioural) Models

Machine-readable Dosage Instructions

In all of the logic described in the dynamic models to determine course of therapy type and timing for status information (current/past), there is an absolute requirement for the Medication Profile system to read and understand the dosage instructions information. Dosage instruction information is generally easy to provide as machine-readable information; the traditional Latin script and abbreviations of dosage instructions take the clinician most of the way towards structured and coded information as part of routine practice, so implementing this in all medication process systems should be routine. There are also a small number of intelligent parsing systems for dosage instructions available[307], so even if information is presented to the Medication Profile only as human readable text, the Profile system could interpret this and use it to provide the information needed for the rules to determine course of therapy type and timing for status information.

Using UUIDs

In the dynamic model, there are two sets of rules for processing; those that involve the use of UUIDs and those that do not. The logic required for processing medication information that has UUIDs is considerably less complex. If all medication communications were to have UUIDs and these were used in conjunction with a descriptor for the course of therapy as described above, it would be possible for a system to clearly ascertain the role that an individual prescription communication is playing within the overall set of patterns for Course of Therapy, even complex courses such as a cyclic course. For example, to identify a continuation of a cyclic course of therapy, if there was a prescription communication of the cyclic course of therapy (e.g. 'Doxorubicin 60mg/m2 given IV as a single dose once every 21 days for 6 cycles') and each of the single prescriptions – the third cycle described here 'Doxorubicin 100mg IV on 20150803' - could be easily identified and managed within the Medication Profile.

Some secondary care systems do have the facility to record and share this type of information, at least for cyclic courses of therapy, but almost all systems and healthcare cultures do not. Making this small addition to the standard patterns of

communication information for prescriptions would significantly improve the accuracy of the information that a Medication Profile could provide in order to meet its use cases.

Counter prescribing

Currently very few if any systems either record or share information about counter prescribed medication. With the growth of patient managed medical information systems on smart phones etc. this area of medication information should be developed and patients should be encouraged to participate in this. As modelled currently, the Medication Profile would treat a counter prescribed medication in the same way as for a dispensed medication.

Communicating medication administration to the Medication Profile

The requirements for the Medication Profile are for the dose timing information; there is no requirement found in the analysis of the use cases for dose by dose administration information. This in itself provides an implicit requirement from the Medication Profile to the information that is shared with it; for this information to be provided in a format that gives a summary of a set of administration events, described as the dose frequency and course of therapy start and end dates. Within the requirements from the use cases, and therefore within the dynamic model, there is no recommendation as to when that summary information should be provided: options include daily, weekly, monthly, at the end of the course of therapy or at the end of a care event such as a stay in hospital.

There are two paradigms to consider in finding the optimal time for sharing administration summary information: the course of therapy being described and the set of activities occurring. Taking the latter first, it is unusual in the medication process that an administration record would be the only record available for the use of a medication by a patient, and therefore administration information is usually supporting and confirming information that has already been processed into the Medication Profile. The need to have administration summary information quickly (e.g. a summary of each day's administrations, starting from day one and continuing) in order to have a current medication recorded in the Profile is not great, and processing administration information on a daily basis could quickly and unnecessarily fill the metadata of the Medication Profile (although not the core data, which would continue to have one consolidated record). There is one major exception to this: vaccination. Due to the protocol and schedule driven nature of the vaccination, and that the majority are administered under the auspices of schemes such as the Patient Group Directions[308] or similar provisions in other jurisdictions, no

prescription or dispensing process takes place in advance of the administration, and the administration is the only process that is recorded and available for communication to the Medication Profile.

It is at this point that the other of the two paradigms should be discussed: the course of therapy being described. Most vaccinations are single events and as such correspond to single simple courses of therapy. Therefore, communicating the single administration is the same as communicating the administration summary for a single short course.

For other types of medication administration, communicating the administration summary for a single short course is also considered an appropriate point. For continuous courses of therapy where prescription and possibly also dispense information is available, the communication could be at monthly intervals, corresponding to the pattern used for the course of therapy definition itself.

Medication statements

Medication statements, whether they are made as part of a medication focussed activity such as medication reconciliation or whether they are part of a more general care communication such as a discharge summary or referral letter, should contribute content to the Medication Profile. This in turn places requirements on how medication statements are recorded in systems. Firstly, they should be clearly identifiable so that they are available for processing, and secondly they should use a similar pattern of descriptive attributes as the medication processes: medication identification and dosage instructions, even if only partial information can be provided.

Recommendations for further work

Static model

Further exploration of the various options for the view model could be undertaken, with the use of wireframes etc. to present options for evaluation. As discussed elsewhere, currently there are no documented requirements for such a model, even in projects that have looked specifically at GUI design for healthcare systems such as the NHS Common User Interface project[309]. Such exploration may also provide additional requirements into both the static and dynamic models for the Medication Profile.

Once accurate and informative Medication Profile information becomes routinely available to clinicians in healthcare, the boundary between primary data and

metadata could be further explored to see if it would increase the usefulness of the Medication Profile.

Testing of the validity of the closed world assumption for the Medication Profile should be undertaken, particularly in conjunction with those use cases that interrogate the Medication Profile for such negative information (e.g. patient recruitment – an inclusion criterion of 'patient has never taken oral steroids'). Similarly, further work to gather requirements for negated medication information, for example 'medication X was not prescribed' and/or negative statements such as 'the patient asserts that they have never taken nifedipine' – should be undertaken. This will be particularly relevant for negated statements arising from medication reconciliation, where the clinician undertaking the reconciliation may wish to negate a set of information already present in the Medication Profile.

A related topic for further investigation is the availability of information regarding reasons for non-administration of a medication; this appears as a requirement in the use cases, but sources for such data are not currently evident.

Dynamic model

The dynamic models have proposed a course of therapy type, which can be determined from the dosage instructions for the medication. The proposal detailed here should be further evaluated and validated, as should the drawing of the boundary between the simple course of therapy and the continuing course of therapy, and when medication is deemed to be 'current', or 'past' and archived. If these are confirmed to be useful concepts, in order to support the creation of useful and accurate Medication Profile information, it is suggested that course of therapy type information including continuation information, should become a routine addition to prescription information.

In a situation where course of therapy type remains unstated and therefore requires calculation, there should be further evaluation of the rules to determine whether a change in presentation for a medication is truly a changed course of therapy, using medication moiety and route of administration, or possibly dose form as a proxy for route of administration. It may even be that some systems would wish to develop course of therapy rules based for on the medication itself. These would be based on the premise that certain medications are always used in a course of therapy (e.g. hormone replacement such as insulin) and certain medications are almost never used in a course of therapy (e.g. some antibiotics). It is suggested that this would be a very useful area for exploration in further research and testing.

Management of repeating differences in granularity of information provided from a prescription and its associated dispensing activity within the continuous course of therapy, would be a valuable area for further research and development.

The dynamic models presented above have adopted a simplistic approach to identifying and managing cyclic courses of therapy in the Medication Profile. This is another area that would be valuable to investigate further, to ascertain whether it is possible to obtain enough information from the medication activities to correctly and usefully describe cycles of medication therapy in the Medication Profile.

If and when counter prescribed medication information is collected and shared, the current assumption that the Medication Profile should treat a counter prescribed medication in the same way as for a dispensed medication should be further tested to confirm that it is correct.

The suggestions are when to communicate summary administration information are currently untested and further research and evaluation in this area, to confirm that this guidance does provide sufficient timely information into the Medication Profile to meet the use cases should be undertaken.

Some healthcare cultures have specified discontinue medication messages: in particular the Netherlands[310] and Canada[311]; these are not currently widespread, but if their use increases, further research into how best to process these into the Medication Profile should be undertaken.

In the dynamic models, medication statements are processed using the same pattern as for administrations, reflecting the practice of healthcare in that medication statements are made using administration patterns and reflecting that their information is usually confirmatory rather than novel. However, further investigating the processing of medication statements from various sources and contexts into a Medication Profile to confirm this pattern would be a useful area of further research. This further work could also investigate the value or otherwise of linking medication statement information in the Medication Profile to source documentation, especially if this resides elsewhere within an EHR system.

Chapter 9: An Evaluation of the Domain Information Model for a Medication Profile

Introduction

Development of a domain information model and indeed of all information technology artefacts, is iterative, with review and evaluation being part of that iterative process. It is important that the review relates back to the use cases, although those use cases may be extended and/or supplemented as new requirements emerge from new processes to be supported, or new ways of managing data evolve.

Various approaches can be used for the evaluation of a domain information model. One of these is direct review of the model itself, which requires expert knowledge both of the domain and of the principles of domain modelling, and is therefore somewhat theoretical, as a model in itself is a reference artefact only. Another more powerful approach is to generate implementation artefacts from the model; this method makes the content of the model accessible for user evaluation (both to the expert, and to the ordinary user) in the service of the real world scenarios (use cases) that the model aims to support. This approach can be performed in a variety of ways:

- The development of a new full stand-alone Medication Profile system, constructed and implemented within an enterprise, using the structures (static part) and populated according to the processes and rules (dynamic part) of the model
- The development of a Medication Profile system within an existing medication management system within an enterprise, adapting its existing functionality to implement the structures of the domain model and populating those structures according to the processes and rules of the model, either as additional functionality or in parallel to current process

Both of these approaches are expensive in both time and resource, and require an enterprise able to undertake the initiative. The second approach carries the additional risk of disruption to the existing work of the enterprise. Neither would therefore be considered until after a successful proof of concept had been performed. Therefore, the most appropriate approach for this research, in terms of resource efficiency yet still facilitating review by a range of users, was the development of a paper-based evaluation. This provided mock-ups of the functionality that would be available to users as if the Medication Profile system had been developed and implemented using the structures and processes of the Medication Profile domain model, and as such fulfils the criteria for an early proof of concept.

Methodology

Preparation of the evaluation material

The paper-based evaluation examined five exemplar scenarios where medication information is used to support performance of a clinical or clinical research activity. Following standard good software development practice, where the use cases for the requirements logically flow into the forming the formal test cases[312] the testing scenarios were developed from each of the areas from which requirements for the Medication Profile had been elicited. Three scenarios focus on patient care; two of these, the emergency medication supply scenario, which uses the Medication Profile as a proxy medical history and the decision support scenario, support a prescribing activity, which as discussed in Chapter 4, is the foundational activity in the overall medication process; the third focuses on medication history supporting an administration activity, specifically relating to Immunisation information. Two scenarios focus on the areas in clinical research that provided requirements; a patient recruitment scenario to assess a patient's suitability to be included in as a subject in a clinical study and a pharmacovigilance scenario, reporting a suspected adverse reaction.

Each scenario was presented with its own clinical story, described in text. Stories, or storyboards as they are often called, are part of the standard methodology for undertaking testing and are written to set the context for the data under examination[313]. Having set the context, sets of medication information were presented in diagrammatic form, simulating the presentation to a user in a basic graphical user interface of a clinical application. This used basic presentation (slides) technology, as is normally undertaken in initial user centred system design. The medication information was presented as it would be, having been transformed into the structures and using the processes and rules described in the Medication Profile model. A small set of questions about the medication information were posed following each scenario, to guide the evaluators' consideration of the accuracy, relevance and comprehensiveness or otherwise of the medication information as it supported the scenario, following standard practice in user acceptance testing of a system[314]. Any additional comments were also explicitly sought.

Emergency medication supply scenario

In this scenario, the main research question to be explored was whether the Medication Profile, if correctly structured and populated, could provide enough information about an individual's use of medicinal products to enable a clinician who does not know the individual to make a decision on a course of action which itself results in the supply and use of medication to that individual. This reflects the use case that, whilst the Medication Profile *should* exist as a core part of a full electronic

health record within an enterprise, it is well recognised that until that full health record situation is reached, any available medication information is pragmatically used as a proxy for a health record in an unplanned care situation, as described in the chapter on patient pare requirements.   This scenario also contained a question about the display of 'current medication' information in the context of an example Medication Profile, to elicit the evaluators' thoughts on this somewhat vexed concept.

Patient recruitment scenario

One of the aims of this research is to model the structures of the Medication Profile and populate them by defined processes not only to support the care of the individual patient but also to meet secondary uses of medication data, particularly those from clinical research. The research question underpinning this scenario therefore looks to investigate to what extent Medication Profile information is helpful in identifying potential subjects for recruitment into a clinical study.

Immunisation record scenario

This scenario explores the scope of the Medication Profile in relation to a group of medicinal products, vaccines, whose use is not usually through the normal medication process of prescribing, dispensing and administration, as they are frequently administered through specific clinics, as this scenario identifies. It was also seeking to explore how much information should be provided for these medicines, especially in terms of representation of dosage information, and how information that is essentially 'repeated' could or should be presented.

Pharmacovigilance scenario

This scenario evaluates the extent to which the Medication Profile, when structured and populated according to the Model described in this research, is able to fulfil the secondary clinical research use case of the provision of information for pharmacovigilance, and specifically for reporting of medication information a suspected adverse event report. An explicit secondary research question was to explore the provision of information about the indication(s) for the medication(s) involved in a suspected adverse event. This scenario was also specifically set in a secondary/acute care context to explore the similarities or differences of Medication Profile information this care environment.

Decision support scenario

One of the requirements placed on the Medication Profile is that it can provide information to decision support systems as inputs for their algorithms, to guide clinicians in delivering safer medication care. The research question in this scenario

looked to explore this, in that the medication activity described in the scenario was interrupted by a decision support alert (notification of a drug interaction).   There was a secondary question to explicitly investigate how 'as required' medications should be managed and displayed by the Medication Profile, although several evaluators had already raised this as a theme independently in a previous scenario. The setting for this scenario was in a healthcare culture where different clinicians have responsibility for different types of care provision and there is no single clinician responsible for care co-ordination.

Pilot of the evaluation material

An initial quality assurance process and piloting of the evaluation material was undertaken with two volunteers. Both were known to the author but neither had had any previous connection with this research. One was an extremely experienced informatics pharmacist who as guided the digital development of his nation's premier medicines information product and the second an internationally recognised healthcare system architect and analyst who specialises in medication information. Both volunteers piloted completion of the questionnaires, also examining the scenarios, the diagrammatic information and the questions for ease of comprehension, to minimise the possibility of ambiguity in the text or questions and to check for any errors such as a medication misspelling. No significant changes were required after this testing and therefore the responses to the questions from the two volunteers was included in the main set of results.

Conduct of the evaluation

A package (provided in Appendix 2) with the five scenarios, their diagrams and their questions, and accompanied by a personalised covering letter and a synopsis of the thesis as a whole was sent to a set of evaluators. Evaluators were given a timescale in which to complete the evaluation (3 weeks from receipt) and also requested, if at all possible, to give notice if they either would be able to complete the evaluation but needed a longer timescale or were sure that they would be unable to complete it (and therefore would not be included in any further correspondence on it). For those evaluators who had either not indicated 'no further participation' or who had not returned a completed evaluation, further contact was made after approximately 3 weeks from the initial contact. Evaluators were also given the facility to contact the investigator with any queries although no respondents exercised that option.

Since this was a qualitative evaluation, using purposive sampling to obtain a set of evaluators is acceptable[315], not least because this is an area where there is a limited number of people who have expertise in the area being researched.   The set of evaluators was not aiming to be representative, but was aiming to have as much

diversity as possible. Evaluators were drawn from the researcher's contacts, both professional and personal, who it was felt would be able and willing answer the questions and therefore give an evaluation of the effectiveness of the Medication Profile Model in providing the information to meet the use cases. The candidate list of invitees was reviewed and supplemented by both thesis supervisors, in order to ensure that all relevant stakeholder categories were included with experts having suitable career backgrounds. The set of people sent the evaluations encompassed a range of professional disciplines: healthcare professionals (physicians, pharmacists, nurses) at different stages of maturity of their careers, and covered those working in primary care and in secondary care, those working in academia, and also a small number of software engineers experienced in working in health informatics and the design and development of systems to support medication focused processes. From the healthcare professionals, the scope of experience covered those working in health informatics, in clinical research (from both sides: the conduct of research and the regulation of research) and those continuing to work in direct care provision. Several of the evaluators either currently or in the past have worked for vendors of medication decision support systems, either as knowledge engineers or as software engineers and several are or have been active in international standards development organisations. The evaluators came from a range of healthcare cultures: the United Kingdom, with its National Health Service and unified health information environment; and a variety of countries in Europe, North America and Australasia and therefore covered cultures with no unified health information environment at all and a spectrum of positions in between. Not all evaluators were or are working in English speaking environments.

Because this evaluation was qualitative in nature, there was no requirement to quantify or therefore to reach statistically significant numbers of different types of evaluators, nor a requirement to achieve a minimum number of responses, in total or from the different types. However, a minimum target of 20 responses from the original set of 43 evaluators was targeted, with the intention that if that objective were not achieved, an extended pool of potential evaluators would be sought. This sample sizing was selected in order to explore and appraise the evaluators' perceptions of and preferences for the data presented from the Medication Profile in each of the clinical scenarios in some depth, as in a phenomenological study, where small sample sizes are appropriate[316].

Before the evaluation was undertaken, the Principal Supervisor (DK) who was also the Head of Department checked the UCL Research Ethics Committee's criteria for exemption from the requirement for approval, published at http://ethics.grad.ucl.ac.uk/exemptions.php:

'In accordance with the following criteria, Department Heads have final judgement as to whether a particular activity should be exempt from the requirement for approval by the UCL Ethics Committee.'

In his assessment, the following exemption was deemed to apply.

'Research involving the use of non-sensitive, completely anonymous educational tests, survey and interview procedures when the participants are not defined as "vulnerable" and participation will not induce undue psychological stress or anxiety.'

Evaluation assessment

The responses were analysed using a thematic analysis technique[317], whereby the dataset is assessed for the patterns (themes) present, in the context of the research question(s) itself. The 6 steps of thematic analysis were undertaken. The initial step of data familiarisation normally occurs through a process such as transcription. All the responses from the individual evaluation documents were collated together into a single dataset, allowing each to be read and be familiarised with. The next step, which is termed 'coding', was to systematically review each scenario, highlighting relevant features in the data. Steps 3-5 are essentially a recursive process of taking the highlighted features and examining the patterns of those features into one or more themes. In thematic analysis, the prevalence and therefore the weight given to the presence of a theme within the data is not measured in any way; the 'keyness' of a theme is assessed in the light of the overall research question, not in terms of any proportionality of how much attention the theme received within the dataset. Finally, in step 6, the analysis is reported by describing the compelling themes from the dataset in relation to the research question.

To support the analysis process, a commercial qualitative analysis package was not used, since the researcher was able to use an SQL database directly, whereby each evaluator's verbatim response to each question was identified, stored and codified. Although there was no facility to quality assure each coding event, the researcher is a certified terminologist and coding professional and one supervisor (DK) examined samples of the responses and their coding to confirm the theme extraction. An example of an evaluation response and its coding is given in Appendix 3.

Although thematic analysis is clear that the themes should not and must not correspond to questions asked[317], each evaluation scenario was analysed as a data item within the overall dataset (the full set of evaluators' responses and comments); this allows the analysis to be properly rooted in the research question asked. Evaluators occasionally commented on the clinical content itself, e.g. whether the

best choices of medication had been made in these fictitious patients. These comments were not highlighted because they were not relevant to the evaluation being undertaken.

A concept map visualising the different themes and their interrelationships is provided in addition to the narrative description of the themes for each scenario. The core themes are shown **in bold** directly connected to the Profile. Sub themes are shown in a smaller font, connected to the relevant core theme. Themes that represent a caution, a risk or an element of information that requires some sense of negation are represented in red.

The recursive nature of thematic analysis[317] was also followed in that, as well as presenting the themes for each scenario, an overall set of themes from the dataset was given to tell the overarching story that the evaluators gave as they provided a qualitative assessment of the validity of the information that could be provided from a Medication Profile, if it was constructed using the structures and populated according to the processes and rules described in the Medication Profile Model. This overall set of themes was also visualised using a concept map.

Results

Including the two initial volunteer scrutineers, 43 people were contacted to undertake the evaluation, and of these responses were received from 28 (a 65% response rate), as shown in Table 29. Two respondents returned paper copies of their evaluation; everyone else responded electronically, although one in text in an e-mail rather than using the facility within the package itself.

Table 29: Describing evaluators' professional expertise

Profession	Initial request sent	Number of respondents	Number of respondents with Health Informatics expertise
Pharmacist	19	14	10
Nurse	3	2	1
Physician	11	7	6
Clinical Research	6	2	1
Software engineer	4	3	3

Table 30: Describing evaluators' geographical location

Geographical Location	Number of respondents
United Kingdom	10
Europe (excluding UK)	6
Australasia	3
North America	9

Themes of results

In the following discussion of the results, quotes from evaluators can be pseudo-identified using the following information.

Table 31: Evaluators' identification information

Identifier	Profession	Geographical Location
A	Physician	UK
B	Software engineer	UK
C	Pharmacist	UK
D	Pharmacist	Europe
E	Pharmacist	UK
F	Physician	Australasia
G	Software engineer	North America
H	Pharmacist	North America
I	Pharmacist	Australasia
J	Physician	Europe
K	Physician	Europe
L	Physician	Europe
M	Pharmacist	UK
N	Physician	North America
O	Pharmacist	UK
P	Physician	North America
Q	Pharmacist	North America
R	Physician	Australasia
S	Pharmacist	North America
T	Pharmacist	UK
U	Pharmacist	Europe
V	Software engineer	UK
W	Nurse	North America
X	Clinical research	North America
Y	Pharmacist	UK

Emergency medication supply scenario

The main research question explored in this scenario is whether the Medication Profile can provide enough information about medication use to enable a clinician who does not know the individual to make a decision on a course of action which itself results in the supply and use of medication to that individual. There was also a question about the display of 'current medication' information in the context of an example Medication Profile.

The main response from the evaluators was that the Medication Profile information was useful and helpful, as in the comment:

'Yes this has been helpful for her to know what he has required previously and helps build a picture of his previous exacerbations.' [A]

But certainly not all evaluators felt there was 'sufficient' information in the scenario as presented. However, the overall sense was that the full Medication Profile implemented in a system would be able to provide sufficient information to support the emergency supply:

'There is not enough information in the medication history alone. Additional information from other parts of the [medication] *record is also required. Why did the medications change? What were the triggers for the change?'* [B]

In terms of additional information within the Medication Profile, the scenario did present evaluators with course of therapy details for one of the medications and several evaluators stated they would have wanted to see this for other medications listed on the main screen before being able to provide emergency supply medication, which in a working system would naturally be available to them:

'However, I would have wanted to review the salmeterol "further details" before proceeding'. [C]

Several evaluators wanted to see explicit indication information, particularly since the medication in focus in this scenario could be used for different indication, although in this particular case that would be unlikely:

'For conditions like asthma and diabetes the medication is defining but inferring the underlying condition from the medication profile is not something to be recommended. Each medication should be associated with an indication' [C]

A small number of evaluators also explicitly requested information about reason for therapy change and particularly the reason if a medication is stopped.

A secondary theme arising from the evaluation of this scenario was a sense of how to use Medication Profile information to assess a patient's compliance with their medication, although that had not been explicit in any of the evaluation questions. One of clinical conditions in focus in the scenario was asthma, where compliance with prescribed medication is important to maintain good control and the reason for the emergency consultation was that the patient was not in good asthmatic control. In the requirements gathering chapters of this research, medication compliance assessment had not been explicitly studied, so any unique requirements for the Medication Profile have not been explicitly documented. But for this use case in this scenario, a significant number of evaluators expressed a requirement to drill down through the Medication Profile, to see the raw prescription and dispensing activity information that produced the Medication Profile information, to use this to assess compliance. Only then did they feel they would be able to make the emergency supply:

'Frequency of repeat prescription and fulfilment dates would help build the picture. We don't actually know how much medication was used as we don't have the dispense history available.' [B]

One evaluator was confident that such information would be available to them in a real situation:

'It would be nice to see something indicating how frequently the salbutamol was being prescribed as the dose is not specific and this would give an indication of severity of asthma. Presumably this information would have been available via the "more detail" tab.' [E]

Others were more specific that they would like the Medication Profile to actively support compliance, pointing out that, of itself, the prescribing and dispensing information does not indicate actual use of the medicinal product:

'Prescription and/or dispense does not indicate administration! The long gaps between scripts would suggest this patient has not been using sufficient medication to be an asthma preventative and depending on the meaning of the dates may not have had some of the scripts dispensed' [F]

'Given that this is a system that does have dispensing information…..explicitly tell the viewer that this prescription had never been dispensed against'. [G]

Two respondents specifically requested presentation of the 'Medication Possession Ratio' explicitly as part of the Medication Profile:

'Computing a compliance score such as a Medication Possession Ratio (MPR)
may be useful as a "dashboard" next to each medication prescription to allow rapid
identification of potential compliance issues' [H]

And one of these two requested display of compliance information by graphical means:

'It would probably be more helpful to display Dispense medication histories in a
more cognitively useful manner such as using a simple timeline to show breaks in
medication compliance' [H]

For the Medication Profile to support this would require supply quantity (pack size) information to be captured and processed, and the display of this data item was explicitly mentioned by a small number of evaluators.

In their responses to the current medications question, evaluators also raised the theme of the scope of the Medication Profile and in particular the availability of and rules for inclusion of information about over the counter medication use. Several respondents felt that a Medication Profile cannot be complete without the inclusion of this information:

'No [the display is not correct]. *There may be herbal or OTC medications or*
medications that have not been recorded.' [B]

There was also a suggestion that patients should be actively asked about OTC and herbal medication use for then that information to be explicitly and directly recorded in the Medication Profile.

The final theme from this scenario was the need to make any calculation of information presented in the Medication Profile clear to the user, although very few comments on how to do that were made, other than this one:

'I think the best solution for that is at least to show on the profile which profile it is:
the intention of the doctor, just the dispense data, or the profile with the real usage
by the patient. That makes clear how to weigh (?? Right wording??) these data and
*what you do **not** know when you see the data.'* [D]

In the comments relating directly to the display or otherwise of 'current medication', it was clear that there was no collective understanding of that concept, although there was a wide sense of agreement that medications whose use is to be 'as required' should be included in a current medications section. One evaluator wrote:

'An absolute answer [to the question about display of Current Medications] depends on the formal definition of Current Medications and on the presumption of how ubiquitous the clinical professions' understanding of that definition is'[I]

A small number of evaluators suggested that, whatever the definition of current medication, when a particular patient had did not have any of these that should be explicitly stated:

'It would be better for it to state "No current Medications" as otherwise a failure of data retrieval may not be recognised.'[F]

The concept map for the emergency medication scenario is shown in Figure 46 below. For the completeness theme, the related subthemes were: the requirement for having explicit indication information and having information about reasons for changed regimens; for the scope of the Medication Profile to include all medication, including medicines not prescribed (purchased over the counter); and to be able to drill down into the detail of the medication information to see individual prescribing and dispensing activities. Supporting the main theme of clarity, the subthemes were to be able to access the rules and calculations that provided the summary Profile information (particularly in relation to compliance scores, hence the cross-link to the relevant completeness subtheme) and the definition of the concepts used in the Profile, particularly for current medication. The need for explicit negation information affects both major themes and therefore links to both.
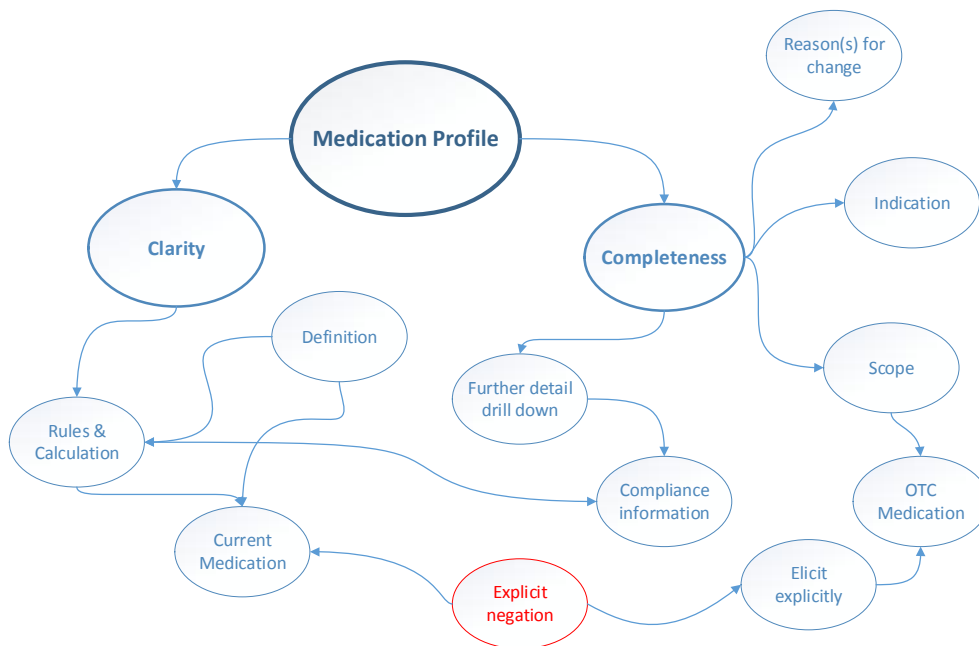
Figure 46: Concept map of themes in the evaluation of the emergency medication scenario

Patient recruitment scenario

The overall sense from the evaluators was that there was sufficient information given in the Medication Profile for the query as presented to have correctly identified the patient as a potential subject. Although as one evaluator pointed out, to confirm this:

'It still needs elaborate mental processes (and time and focused attention) for the physician to figure out the story behind these numbers/data' [J]

This 'elaborate process' and the risk that it is unlikely to either be undertaken at all or undertaken consistently is one of the main reasons why using a query/algorithm directly onto Medication Profile data should be much more effective than the most common currently used method, in which research staff look directly at patient records either on paper or on screen, and make those judgements and deductions based on raw activity data. For this scenario, the predominant theme of the comments was the need for a clear presentation of all the relevant information, in particular covering the whole of the relevant time period – which was longer than that covered by the information provided in the scenario. This opens a possibility that the content of a Medication Profile might need to be presented in different formats to support different use cases, particularly for clinical research when confirming long term use of medication is often important. However, suggestions for more useful presentation styles from the evaluators could also be appropriate for other use cases:

'the separation in 2 separate screens for history and current profile is not user friendly and does not give an easy picture of the situation and may lead to errors. It would be much better to have a time line showing – per therapeutic area – when a drug was started, when potentially dosage was changes and when the drug was stopped. This allows seeing the complete medication profile in a much easier way' [K]

'I think providing a timeline rather than tabular data would be a better way to present the information' [B]

Some sort of timeline type of display per medication might also address a theme from several evaluators, which concerned whether it would possible to easily see if there were any significant gaps in what might otherwise be considered a continuous course of therapy.

One suggestion given in this scenario but nowhere else, and particularly to improve the clarity of information presentation focussing on longitudinal medication use, was to explicitly provide a 'last information date' for the set of information provided for each medication (available from the metadata). Other suggestions that also appear as comments to other scenarios include the reason for stopping for any course of therapy, and to have provision for inclusion of over the counter medicines. And one evaluator noted in this scenario, as others did in other scenarios, that:

'regular dispensing is not definitive proof of compliance' [M]

The concept map for the patient recruitment scenario is shown in Figure 47. In this scenario, the core theme of clarity was the most commented upon, particularly in respect to the course of therapy subtheme, and using different presentation methods to highlight those medications that are part of a continuous course from those used acutely. This presentation subtheme itself was related to the possibility of longitudinal display of information (with drill down facility, linking it across to the completeness theme) and which could include a last information date. The need for access to rules and calculations, especially when using algorithms to select patients for recruitment was also highlighted. The core theme of completeness in this scenario had only one supporting subtheme; the requirement to be able to drill down for further information, particularly compliance information.
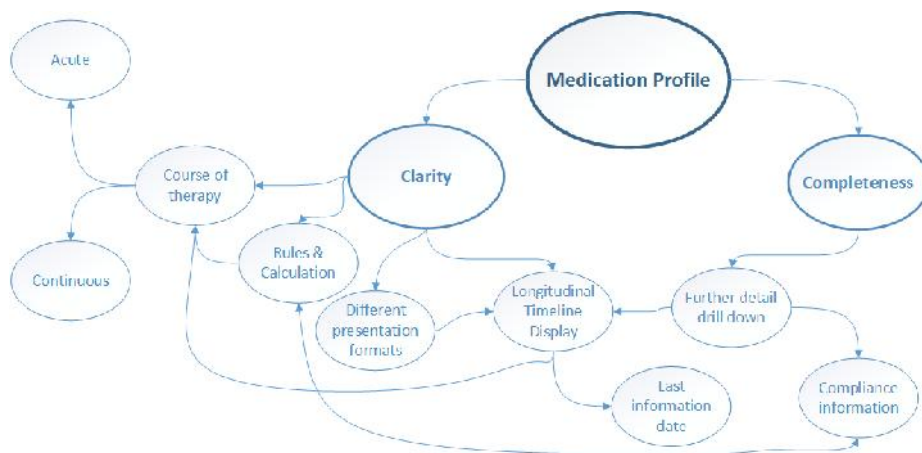
Figure 47: Concept map of themes in the evaluation of the patient recruitment scenario

Immunisation record scenario

The overarching theme from the evaluators' responses was that immunisation information is important in health records for individual patients and that it should be covered within the overall concept of a Medication Profile. However, some

evaluators – and particularly those from North America – commented that for example:

'The most typical practice in the US would be to have a separate immunization (US spelling) section that would not be part of the medication record (profile)' [N]

Several of the non-North American evaluators were positive that for immunisation information, there is a good justification for a separate section within the Medication Profile. Reasons to support this view were quite consistent across the evaluators and can be described in three subthemes. Firstly, the use of medicinal products to provide immunisation (i.e. vaccines) does not follow the usual 'prescribe, dispense, administer' medication process. Often only administration is recorded and this may well be in a completely separate and possibly atypical system external to the normal healthcare enterprise, such as a national immunisation repository or a travel clinical system. One comment summarises this well:

'Yes it is essential to have accurate immunisation history, and one that will be reliably updated if the vaccines are received in different places (changed GP surgeries, travel clinics) and very useful to have these clearly laid out in their own section for easy reference' [A]

Administration occurs infrequently and at particular points in a lifetime and personal remembrance of that information can be particularly difficult:

'many people forget or are 'hazy' about recall' [O]

Secondly, the information about immunisation is usually relevant for a protracted period, possibly even an entire lifetime, not for a limited period close to the time of the medicinal product administration; as pointed out thus:

'*Vaccines are effective for years and so if included in main med history would be less easy to identify amongst other short and longer term meds that may be in patient medication history'* [E]

Another evaluator highlighted the risk that such information might get effectively lost over time unless it is managed specially:

> *'Even though Immunizations are medications, having a
> separate section for them pulls out relevant data that is not
> easily done by the user if immunizations were lumped in with
> other medications. As well, there might be archiving strategies
> in place for historical medications that would lead to
> immunizations not being readily available, i.e. maintaining 24-
> 36 months of medication history readily and requiring a service
> call to a data warehousing facility to access older information
> would lead to immunization information not being on many
> patients' profiles'* [G]

And finally, and particularly persuasively, having a special immunisation section in the Medication Profile would enable this section to have data structured to describe immunisation status rather than be required to follow the structure of the main Medication Profile which exists to support the standard medication process of prescription, dispense and administration of a medicinal product. Several evaluators felt that having a separate section would provide the opportunity and freedom to present information in a different and possibly more useful way, based on describing the conditions or organisms for which there is immunity and the status of that immunity, and on completion of courses and correct administration of booster doses, rather than being constrained by the data structures required for non-immunisation medicinal products. Several comments were particularly pertinent to this, one of which is:

> *'To this point, it may also be useful to see the age at
> vaccination and elapsed time since the vaccine was given to
> alleviate having to do the math. If vaccines have boosters or
> need re-administration then missed boosters and repeat
> vaccines should be highlighted, as should missed doses in a
> course. In fact a grid based around "condition immunised for"
> and status would probably be a more helpful way of providing
> the information…... The important thing is to track the
> immunisation status of the patient without the Doctor having to
> 'work it out' in his head from the presented information'* [B]

However, it was clear that the rules for processing information into such a structure would need to be defined and widely accepted, and that these rules would need to be clear about now to deal with missing or incomplete data:

> '*So I think there must be good consensus among the hcp's what's primary and what's booster before you can use these terms*' [D]

But one evaluator, although supportive of a separate section for vaccination information, pointed out that there is a risk in this:

> '*Where is the end? Then there is the risk that the dermatologists want to have a separate section for the cutaneous preparations, the physicians for the medicines used in the clinic (because he do not want to see that), and in the end all the information is scattered. What's the criterium to create separate sections? That should be clear beforehand. - In case you create different sections, there is a risk that a doctor overlooks a section and do not see all the information that is important to see*' [D]

That comment leads into the last major theme in this section, that however information is presented for immunisation, it needs to be clear and complete, with nothing important hidden away, and minimising the risk of being misleading. As such, most evaluators felt that the full 'medication process information' such as what (actual product and batch number), when and how (full dosage information) must be available somewhere within the Medication Profile, for completeness and to support adverse event reporting; for example:

> '*Knowing the dosage given means knowing, rather than assuming*' [P]

Two points of interest that were made in this dataset by individual evaluators concerned use cases that have not been found in the requirements gathering exercise and that are relevant to immunisation information. One described functionality to support recording and sharing of future administration information (administrations that will be required at some distant point in the future to provide full protection or that will be required to maintain full protection (booster doses)); no requirement for future administration information, other than normal prescribing process which expects fulfilment of the order usually within hours or days of its issuing, has previously been documented. The other described the need for complete vaccine product administration information to support supplies forecasting, although this latter could be considered a pharmacoepidemiology use case or a pharmacoeconomics use case, both of which are out of scope of this research.

The concept map for the immunisation scenario is shown below in Figure 48. In this scenario, the core theme of clarity is supported by the subthemes of the requirement for different presentation formats, including the separation of the immunisation record, with its own subthemes of immunisation status information (as opposed to medication use information) and planned administration information. The completeness theme is supported by the scope subtheme, which includes a link to planned administration, since this would be an extension of the scope of a Medication Profile. The separation of immunisation information introduces the risk of fragmentation of information, which clearly affects completeness and as such is shown as a risk both to clarity and completeness.
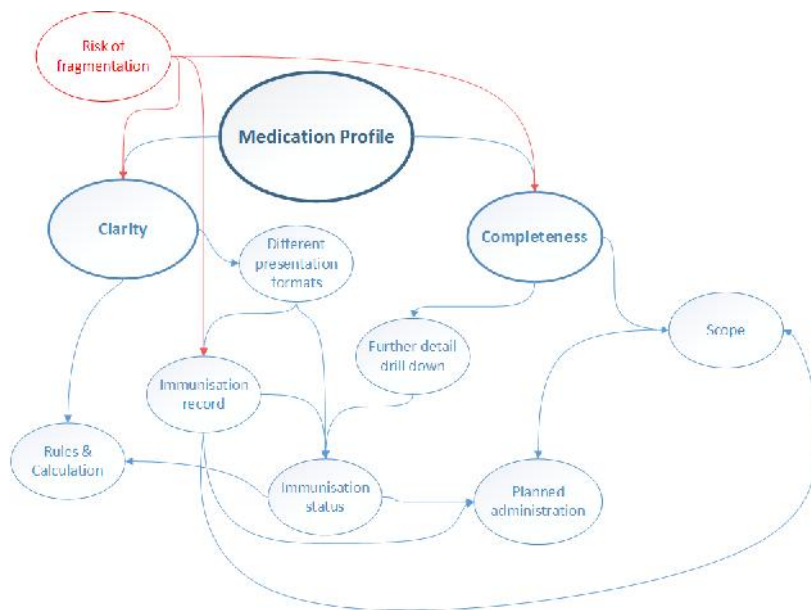
Figure 48: Concept map of themes in the evaluation of the immunisation record scenario

Pharmacovigilance scenario

The most striking theme visible from the responses to this scenario was the evaluators' own understanding of the information requirements of the suspected adverse event report form, as it was displayed in the scenario. The mock-up form used the same data elements, terms and layout as the United Kingdom's Yellow Card form, issued by the MHRA and as found as tear-off cards in the back of the British National Formulary, and as studied in detail in Chapter 5(2). It had been assumed that all of the evaluators from the United Kingdom would be very familiar with its data requirements and that non-UK evaluators should find the form self-explanatory. However, when asked to evaluate whether completion of the specific medication related sections of the form presented in the scenario accurately reflected the information in the patient's medication history, approximately a third of the evaluators, including some from the UK, noted that the medication given to treat

the adverse reaction had not been included. Treatment of an adverse reaction, including any medication which is necessarily given during and sometimes after the adverse event has occurred, should be described the Treatment section, a different part of the form, not least because it cannot be included in any causative analysis for the event. The fact that a proportion of evaluators thought that this treatment information should have been included in the 'Other drugs in the last three months' section emphasises that offering an initial rules-based population of information from the Medication Profile directly into safety reporting forms has value in providing consistency in the interpretation of the form itself, on top of any additional value in reducing transcription errors or missing information.

The second major theme centred on the presentation of information about a cancelled or withheld medication. Since this scenario was set in acute care, the Medication Profile information presented was close to real time and there was much comment from the evaluators as to what should therefore appear as current medication in these circumstances. Most evaluators felt that the medication given as single doses, and single immediate ('stat') doses such as those for emergency treatment of the hypersensitivity reaction, should not be presented in the current medication section, even though they had been administered very recently and the course was shown as complete.

> *'The history* [Medication Profile] *contains everything has been administrated on chronic basis as well as on emergency basis, from a start date to an end date or at one moment in history'*
> and *'"perhaps stat doses should be in a different colour to demonstrate the difference between short courses and one only doses.'* [L]

Others commented that the prophylactic antibiotic medication should not have been listed in the 'current medication' section, even though it had been prescribed, because that prescription had been cancelled as the surgery did not take place. The display showed the cancelled prescription in red, but evaluators did not feel this was enough and there could be a risk that it would be administered incorrectly.

> *'I think the pre-op antibiotic order would be cancelled and should not appear on the course of therapy details. This was not a case of failure to administer'* [R]

Following a theme found in another scenario, one evaluator commented on the need for the Medication Profile to manage information about the medication that has been and is being used by a patient, as compared to a separate and distinct piece of

information about medication that it is planned for the patient to use at some point in the future:

> *'The profile contains all medicinal products that has to be taken*
> */ administered on ongoing basis from start to end date, the end*
> *date being a date in the future at the moment of registration'* [L]

This was re-enforced by the following comment:

> *'I have problems with this Cefuroxime registration. It has no*
> *added value. It only "spoils the screen". Exception might be in*
> *case a "planning" was recorded that needs to be "cancelled"'* [L]

This comment also circles back to the subtheme of how to safely manage and display information about cancellation of an order.   Another evaluator commented:

> *'It is not because something is prescribed that it should be in*
> *the medication profile if not actually administered (even with red*
> *colour. this is confusing – useless information as it does not say*
> *why it was not administered)'* [K]

A small number of evaluators commented on the need to distinguish between 'cancelled' and 'not administered':

> *'There is a difference between "not administered" and*
> *"cancelled". Cancelled seems more appropriate here'* [L]

This is particularly pertinent in a near real time secondary care environment, and several evaluators commented on the need to show the status of a medication more clearly

> *'I think that having a status on the medication and also a link to*
> *allergy/adverse reaction would provide better information'* [S]

Some evaluators noted, as has also occurred in other scenarios, that there should be provision to record over the counter medications, and one evaluator pointed out that for assessing a suspected adverse reaction, it would be helpful to look a lot further back into the patient's past medication history to see if medications similar to the suspect medication had been administered in the past.

Since this scenario focused on a hypersensitivity reaction, several evaluators commented that they expected to specifically see allergy/hypersensitivity information

recorded directly in the Medication Profile, to hope to avoid any risk of the allergen being administered to the patient again.

For the subsidiary research question in this scenario, regarding the provision of indication information, the responses were split. More evaluators were in favour than against, some very definitely:

'Absolutely! And in general indication should be provided with any drug in the medication profile to help the physician to assess overall clinical picture' [K]

The evaluator described benefits they felt existed beyond those anticipated in the scenario itself:

'Inclusion of an indication or reason for prescribing would support the process of complete documentation of all patient conditions e.g. post-operatively a script for a cephalosporin could be related to post-operative UTI which would not otherwise be documented other than in the progress notes and not in a secondary diagnosis data field' [R]

One evaluator gave their thoughts as to how obtaining indication information could be facilitated, either specifically for an adverse event form or more generally:

'That may be possible if the "prescribed for" field is filled from a coded list and the codes are from (or can be mapped to) an agreed (preferably international) terminology' [F]

Others were less enthusiastic but still positive:

'Yes, but don't feel that this benefit is likely to be the major benefit from this practice or sufficient justification on its own for making this a standard for medication ordering' [R]

But a small number of evaluators, including two pharmacists, were definitively negative, and thereby expressing somewhat contradictory views to comments from other evaluators in other scenarios, on the value of indication information:

'No. Indication or "diagnosis" may not always be confirmed at the point medication may be initially started. For many

treatments that can be used for multiple indications there may

be misclassification which could have other consequences' [O]

But one evaluator felt that this one topic was significant enough to warrant further investigation in its own right:

'Many clinicians would argue that the cognitive and workflow

load created by requiring an indication (and the subsequent

effort to add conditions to the problem list etc.) is not justified or

possible within existing work practices and software design -

this is probably needs to be the subject of further investigation

as to effort and benefit' [R]

The concept map for the pharmacovigilance scenario is shown below in Figure 49. The core theme of completeness was again supported by the subthemes of needing indication information, OTC medication information (as a subtheme of scope) and reason for change information. In addition in this scenario, the inclusion of allergy information as part of the Medication Profile was raised. Linking across from the completeness theme to the core clarity theme, there is again the subtheme of availability of drill down information, drilling through any calculated longitudinal display. Within the core clarity theme, this scenario introduced the subtheme of the status of each medication, which itself is related to the previous mentioned planned medication, current medication, and particularly highlighted in this scenario, cancelled medication.
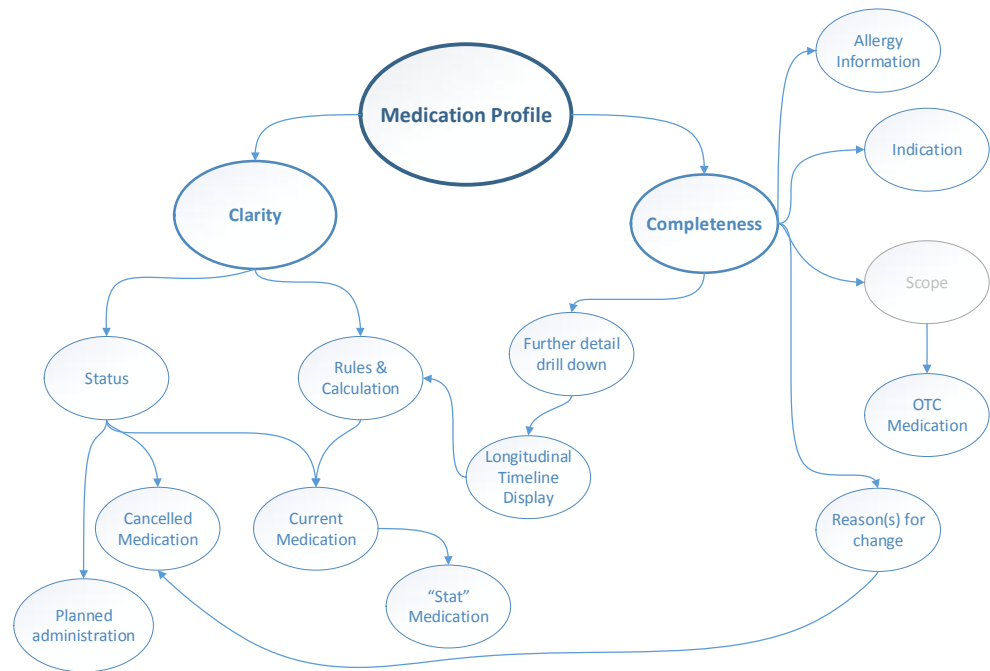
Figure 49: Concept map of themes in the evaluation of the pharmacovigilance scenario

Decision support scenario

Evaluators' opinions were evenly split between the negative and positive in their view as to whether the Medication Profile was providing enough information to support a prescribing decision, particularly after a decision support alert has been raised:

'I don't think that there is any information in the Medication Profile to support Dr. Hoffman's decision. We do not know the diagnosis or the antibiotic susceptibility' [Q]

'Yes I do. Luisa has been told to reduce the dose of zolmitriptan should she get a migraine attack while on the ciprofloxacin.' [U]

One evaluator was detailed in their comment, although ambivalent as to their view of whether the Medication Profile did enough to in terms of decision support for safe care:

'There's no medication history available and the decision support system appears to be the typical context-insensitive alerting system. So it will tend to over-alert. In this case, because of the lack of dispense data, the alert is useful in that it should trigger further investigation by the physician' [H]

A theme recurring in this scenario was to have allergy information provided as part of the Medication Profile, and alongside this request for allergy information, one evaluator returned to the theme of the Medication Profile not being the only source of information needed in the clinical situation of the scenario:

'she cannot get sufficient information from the medication profile alone to make the prescribing of a new medication safe. She would require information about the patient's allergies and intolerances, as well as information about any co-morbidities' [C]

Although there was a specific question about 'as required' medications, it was clear that several evaluators were concerned about this as part of the main assessment of the scenario itself, and wanting more information about the amount of actual use of the 'as required' medication. There were several reasons given for the desire for more detailed information: firstly as a way of assessing clinical condition, for example:

'Also it would be good to know how often she has taken the Zolmitriptan as a measure of the severity of her migraines' [F]

Secondly as a measure of how relevant the decision support alert was in this individual situation:

'knowing when the prn was likely to have last been used would help assess the suitability of the ciprofloxacin' [V]

And thirdly, in this distributed care setting to try to get an overview of the patient's condition:

'Usage patterns for "take as required" medications would be very helpful especially in a situation where a patient is getting somewhat fragmented care' [H]

When asked specifically about how to manage 'as required' medication information in the Medication Profile, evaluators were divided, almost equally, in whether their preference was to see them as a separately with their different pattern of use made explicit, or whether to see them as no different from any other medication in the Medication Profile:

'Clearly a separate section' [J]

*'A new section would be more obvious at a quick glance. The
more specific the better'* W

and in contrast:

*'We believe it is best to list them all in one place. Having to
look in two different places to get the full story on a patient
would not be desirable'* X

That comment leads back to one of the main themes: although evaluators were split
about the best method of displaying all the information, many expressed wanting to
avoid any danger of available information being hidden:

*'Anecdote on using "flags" or separation – currently in the Drug
Information System I am working on, we separate out
continuous, short term and "Other" (aka OTCs, etc). We are
finding that users are only looking at continuous and short term
without recognizing that there may be meds categorized in the
other section. I would put in the same section, but flag
differently'* S

A sub-theme expressed by a small number of evaluators on how to best achieve
presentation of information about 'as required' medications was to consider using
different models of presentation in different care environments. The most detailed
comment to that effect was:

*'Different profile for primary and for secondary care, I think. In
primary care systems seen, p.r.n medication included as part
of 'current' and 'repeat' templates, which is useful (when
checking patient's medication history) In secondary care, in
systems worked with, p.r.n medications are separated from
'regular' and 'stat' medications, which again is useful in this
particular clinical environment'* Y

*A theme re-emerged has been expressed elsewhere but here
was expressed with particular respect to 'as required'
medications is the need for clear and shared definition of the
concepts themselves:*

'Creating a separate section that defines "prn-ness" within its data definition provides no greater certainty of the record being correct if the clinical professions do not manage the standard of population of that' [I]

And finally, and specifically in response to the explicit research question concerned with 'as required' medication, was the recurrence of the request for wider, supporting information to be available to enable estimation of the degree of requirement for use of the 'as required' medication:

'but there should be an ability to show how often and how recently they have been taken. A prn medication that has been taken daily for the last 2 weeks needs to be flagged as different from a prn medication that is taken once a year and last time more than 6 months ago' [F]

This sense of data to support estimation of the degree of requirement for use of the 'as required' medication was made more simply the request here:

'Adding the date of last use or of last dispensing could be helpful' [L]

The concept map for the decision support scenario is shown in Figure 50. In this scenario, the core clarity theme was underpinned by the status subtheme that arose in the previous scenario, but in this case particularly in the context of medication given as required, and the subtheme of different presentation formats by the differing requirements in various care contexts (primary and secondary care). The completeness theme was supported by the scope subtheme, and particularly again OTC medication, and by the drill down for compliance information (linking back to the as required medication subtheme). Inclusion of allergy information was also a repeated subtheme.

1°/2° Care display

Different presentation formats

Medication Profile

Clarity

Nothing hidden

Completeness

Allergy Information

Status

Rules & Calculation

Further detail drill down

Scope

"PRN" Medication

Last information date

Compliance information

OTC Medication
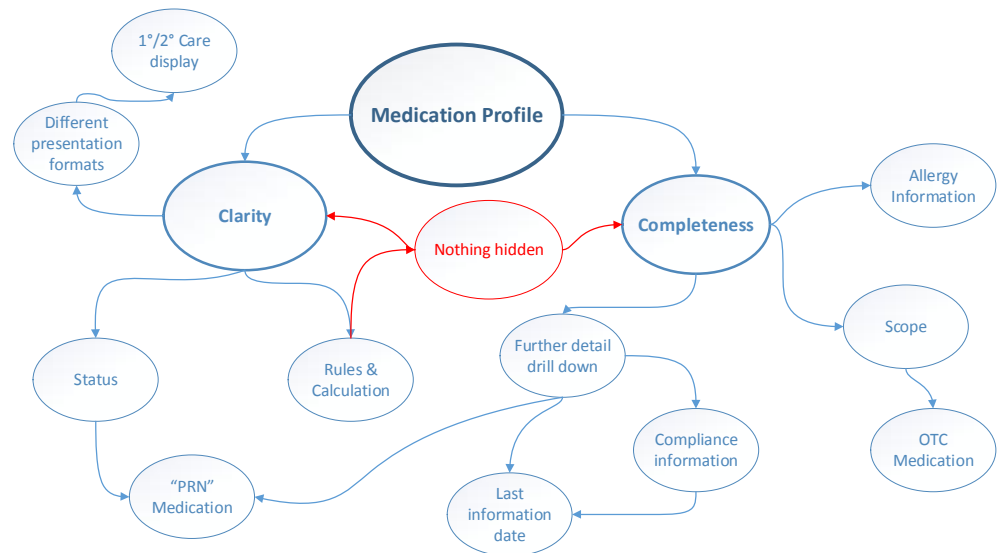
Figure 50: Concept map of themes in the evaluation of the decision support scenario

General comments

This section returned explicitly to two research questions that were explored in the scenarios: that of the definition of current in 'current medication' should be 30 days; and of the value or otherwise of differentiating between a continuous course of therapy and an acute course of therapy in the Medication Profile. It also provided opportunity for evaluators to provide any additional thoughts, observations and comments on the Medication Profile as demonstrated in the scenarios that they had not made elsewhere in the Evaluation.

Current medication

On the first of those questions, evaluators were generally positive, with this comment being typical:

> *'That is a reasonable approach. The 30 day window is certainly arbitrary, but is likely close to optimum. A shorter window might pose some risk of missing potential issues and interactions (for example, with fluoxetine). A longer window would have to potential to clutter the profile with clinically irrelevant data'* [N]

However, there were two comments, with one given here, both from non-clinicians, connecting 'currency' with a sense of the pharmacokinetic half-life of medication:

> *'Yes. In my experience, using past 30 days is reasonable. If one had a source of drug half-life information (the length of time that a drug is considered to possibly be active in a patient for purposes of interactions), then you could perhaps change the definition of "Recently Active" to be the half-life of the drug"* [G]

Comments from other evaluators went beyond the simple 'is this time period reasonable' to an orthogonal approach to for current medication:

> *'I think (for display purposes) it would be more intuitive for "current medication" to include only those currently prescribed (or obtained OTC) and then all completed treatments can be grouped together within "medication history". Provided the latter are ordered in reverse-chronological order (with the most recently completed course at the top of the list) it should still be reasonably easy to identify completed treatment courses that may still be having a physiological impact'* [C]

However, one evaluator did address the root issue of how to draw what might be considered an arbitrary line based on a time period, and how different medications would affect that, and therefore proposed that the time period should actually not exist at all, but be clearly marked as cessation of therapy:

> *'I would not recommend to define a certain period after stopping the medicine during which you still say it is "current". Firstly because 30 days is arbitrary, and does everybody know the assumption that the medication is still considered to be current during 30 days? And secondly, this period differs per drug. It is not needed to have a period of 30 days after an antibiotic treatment of 5 days. Who decides when such a period is needed or not? I prefer clear definitions: just put it "current" only when the end date is not in the past'* [D]

The recurring theme of clear definition and ubiquitous understanding was also underlined in this context:

> *'No approach will be perfect I think that the important thing is that the clinicians using your medication profile understand the definition that you are using and the limitations of such a definition'* [Q]

The theme of clear definition and minimising the risk of presenting information that is in any way misleadingly was highlighted with reference to the need to be very clear about those medications that have been used recently but whose course has concluded, either normally or exceptionally:

'Probably but need a very explicit differentiation of completed courses from currently prescribed meds, as completed courses aren't technically 'current' and completed/stopped courses may otherwise be in danger of being restarted erroneously' [T]

The theme of using status to indicate active and stopped medication in some way was also present in this context:

'All medications which are currently active should be mentioned. That may mean that also recently stopped medications should be mentioned.' [J]

Two other themes recurred in responses to the current medication question; firstly that of the need to be able to see more from the Medication Profile when necessary:

'The last year of therapy should be readily available e.g. by scrolling' [F]

Secondly, the issue of how to manage 'as required' medications, which revisited and re-enforced the opinions expressed in the specific question from those that wished to see 'as required' medications in a 'current medication' section.

In particular, two comments described how, for 'as required' medications, a 30 day timeframe may not be appropriate, and therefore highlight this dosage instructions pattern as being one that really does merit special consideration:

'Yes. It's never going to be simple to define a time period appropriate for currently relevant therapy but for most meds 30 days is sufficient although when required meds are more difficult as the interval between prescription and usage may be much greater. Maybe 30 days for current regular but longer for prn meds? [E]

The concept map for the exploration of how to handle current medication is shown in Figure 51. This shows clearly how the evaluators' main concern was with clarity of information – its definition, status and how it was calculated for display, particularly

for as required medication and cancelled medication. The completeness theme was less prominent, with the requirement for drill down beyond a longitudinal display or similar being the only subtheme.
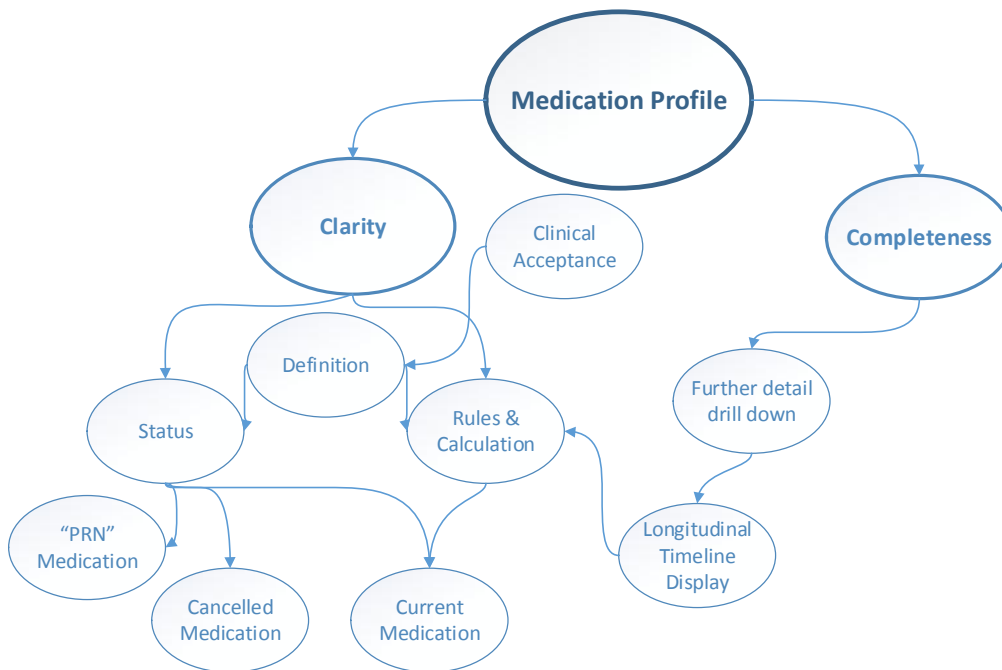
Figure 51: Concept map of themes for current medication in the general comments

Acute and continuous courses of therapy
Most of the evaluators expressed a view that this differentiation between acute and continuous use of medication was valuable for the information in the Medication Profile:

> *'Yes I'd say it's essential otherwise short courses could be mistakenly continued'* [T]

The theme of clear definition of these concepts was emphasised, along with a question as to whether this differentiation is something that can be implemented by algorithm or whether it is something that should be explicitly indicated by a clinician:

> *'I do think that it is useful, but again, you need a clear definition that clinicians understand and a determination of whether a system can determine if a medication is acute (based on your definition) or whether a clinician needs to enter that data'* [Q]

One commentator listed clearly the three differentiations they perceive should exist within the Medication Profile:

'Chronic therapy (with or without a planned stop date) acute
therapy (with foreseen duration), and "if needed", should be
differentiated' [J]

Another evaluator commented on how the differentiation could be implemented, and remarked on the need to keep a patient's 'medication story' (a concept that no one else had brought out in any other context) within the Profile:

'Yes. Though I prefer the approach you have adopted here of
using a visual key to deliver than meaning rather than a
structural key resulting in the separation of current and
historical medications into sub-sections that will break the flow
of the 'medication story' that can be derived from the profile' [I]

Just one or two evaluators were not keen on having this type of differentiation, as expressed by this comment:

'It doesn't seem that differentiation needs to be explicitly
represented, other than in the start and end dates of the
medications. That is a clear enough means of differentiating
between the two cases' [N]

The concept map for the exploration of how to handle course of therapy is shown in Figure 52. Similar to the previous question, this also shows clearly how the evaluators' main concern was with clarity of the information, its definition and calculation, and the status of the medication. The completeness theme was again particularly focused on the requirement to be able to drill down to see detail beyond the initial presentation of Profile information.
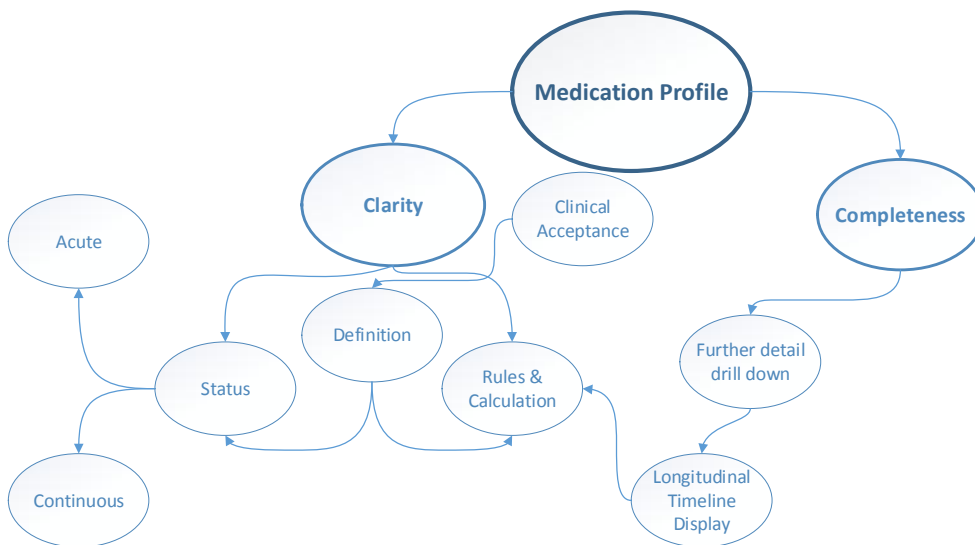
Figure 52: Concept map of themes for course of therapy in the general comments

Other comments

Only a few evaluators took the opportunity to make additional comments. The substance of the comments reflected an expansion of themes expressed already through the scenarios:

- the need for clear definition and clear presentation of information and the requirement for functionality to drill down for more detailed information:

> *'Main one is that I really think it is important to give treating staff, information in a simple/graphical way rather than a lot of text and tables. What is also important is to understand what is truly needed/helpful and what is noise (e.g. detailed on the doses of the same vaccine). The detailed information should be available on request not by default'* [K]

- the possible need for information to be displayed in different care scenarios

> *'Which elements need to be displayed up front (without further user clicks/scrolls etc) may be care setting dependent e.g. primary care vs hospital'* [F]

- that allergy information should also be available

> *'Allergies need to be displayed wherever possible as part of the medication profile as this helps inform as to why certain medications may or may not be in the profile'* [F]

- and the same evaluator felt that indication information is useful but may be hard to obtain

> *'Reason for prescription is very valuable but difficult to capture without interrupting workflow'* [F]

One new theme also appeared; that the different healthcare disciplines possibly approach medication information differently, and what if any affect this has on requirements for a Medication Profile:

> *'A complete healthcare record including present and past prescriptions helps paint a profile of any acute or chronic conditions the patient might have. In past experiences, the pharmacist is much more apt to look at concomitant medications and see possible adverse drug interactions than are physicians. Physicians must take the time to read the record before prescribing new medications. Again, past experience is that the physician may move too quickly while the pharmacist is more attuned to the patient's medication history. Just a personal observation based on my own situation and those of aging relatives'* [X]

And finally, two comments that focus on the overall requirement for the concept of a defined, modelled and dynamic (process based) Medication Profile that truly supports clinicians providing care for patients on a daily basis:

> *'I believe that we focus too much on providing a medication profile as a dump of data, which is difficult for clinicians for clinicians to review and fully understand. I think that we need to focus more effort on simplified views of the profile with the ability to "drill down" and get more details. I would characterize it as providing information instead of data'* [Q]

> *'That systems recognise that a medication history is a clinical process and that the prescribe [+] dispense data can be used to assist with the population of this'* [R]

Discussion

Themes from the Evaluation

The analysis of the results yielded a set of themes, most of which were recurring throughout all the scenarios. The only themes that were specific to a single scenario were those concerned with immunisation information and were specific to the immunisation scenario.

The concept map below (Figure 53) shows all the themes and sub-themes from all the scenarios and general questions and comment section, related together around the two core themes for evaluation of a Medication Profile: clarity and completeness.
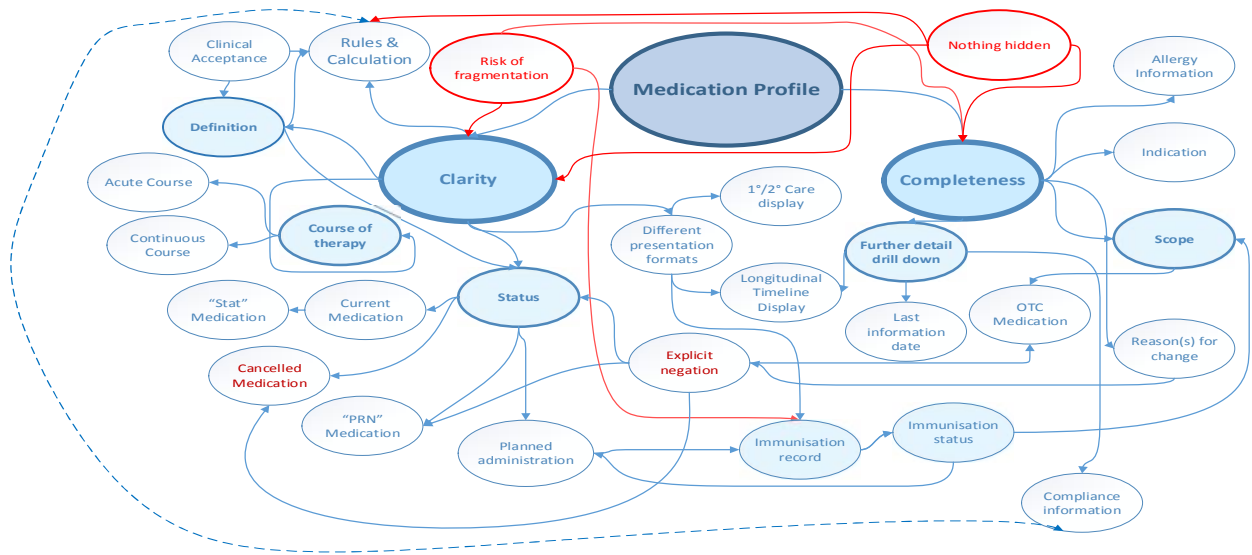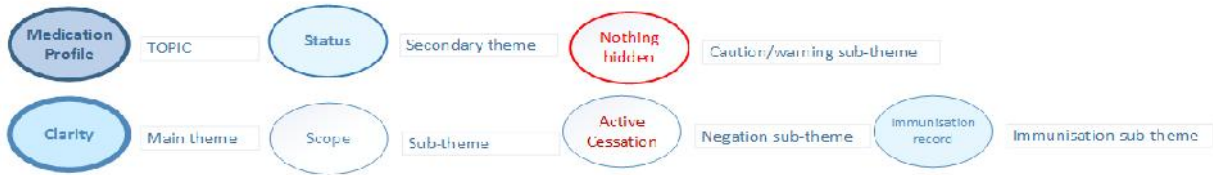
Figure 53: Concept map of the overall themes of the evaluation

Completeness

One of the two key themes expressed by the evaluators was the requirement for the Medication Profile to be 'complete'. This theme relates most closely to the structural part of the model for the Medication Profile, evaluating whether all the necessary data elements are present.   The concept of completeness is somewhat difficult to fully evaluate, as completeness can only be defined and tested in the context of a set of use cases[314], and as such one of the core research questions of the evaluation was asking evaluators to assess whether sufficient information was presented. The scenarios were presented with various sets of information, some of which were representations of likely initial views and some of which were representations of the sort of further information that a Medication Profile application could provide and which could be presented to the user (human or system) on request – the so-called drill down functionality. There was a general positive sense that the Medication Profile as presented would provide sufficient information to support its use cases.

Several aspects of completeness were picked out as sub-themes; one of these concerned the scope of product coverage for the Medication Profile, and in particular the availability of information about the use of over the counter and herbal medicines. These are within the scope of the Medication Profile (see Chapter 7) and information on their use would be available in the Medication Profile; however there were no examples of this in the scenarios, so this was a valid concern from the evaluators. One evaluator suggested an additional data requirement that is not covered in the current model, and which was not found in any of the specifications or use cases is that of functionality (implemented for examples as a flag or statement) that explicitly states, when appropriate, that the patient is not taking any other (over the counter) medication. This additional data item could be added to the model as an attribute of the Medication Record class, whilst acknowledging the complexity of stating negative information, particularly in the closed world view. But a practical challenge, at least currently, would be population of the attribute: this information is not captured in any currently known system other than ad hoc in text or in a paper record. But, if it was captured, it would be straightforward to incorporate into the Medication Profile by processing as a specific type of medication statement and applying the Medication Profile rules for those.

An additional functional requirement suggested by an evaluator was the inclusion of a 'last information date' relating to information as presented. This requirement could be satisfied in an application, using 'metadata already present in the content of the Medication Profile, and as such is would not require a change to the model, it is a requirement on the display of the content of the Profile to the user.

Another sub-theme under the overall theme of completeness of the Medication Profile included the inclusion of allergy information. This is a specific exclusion of the Medication Profile as defined by this research, but is obviously a critical component of evaluators' thinking in regard to medication information. It is clear therefore that any system wanting to support the medication process must also have allergy information available to it and must present it in tandem with Medication Profile information.

The inclusion of indication information in the Medication Profile was a specific research question posed by the evaluation, since it is a data item that is included in the patient care specifications and was found to be one of the most useful items of data for the clinical research use cases. It is included in the model, but it is not currently captured by most medication systems so could not be easily populated and is not accounted for in the rules-based processing. Evaluators were generally but not unanimously in favour of the Medication Profile containing indication information, not least because it is hard to obtain, but their reasons for its inclusion were to provide clarity when assessing medications used for a variety of indications and for completeness in understanding the patient's care as a whole. Some were so positive as to provide suggestions as to how collection of this information could be facilitated in systems, especially for adverse event reporting (where it is important to ascertain whether a suspect product was being used within the scope of its authorisation). This topic is obviously one that challenges, since one evaluator directly suggested further formal investigation of the benefit/cost of indication information, which would no doubt be useful for those evaluators who, whilst positive, expressed doubt on that particular benefit/cost ratio, or for those few evaluators who did not feel there was any benefit from indication information.

Linked to indication information in that it provides rationale for medication related actions other than commencing a therapy, is the data on 'reason(s) for change in therapy' (where change includes cessation). The structural model for the Medication Profile does have a 'non-administration reason' attribute which was included based on a small number of requirements and which was therefore not explicitly tested in the evaluation scenarios. This evaluation suggests that the definition of this attribute could be broadened to a more general 'reason for change in therapy' usage. Although this would likely be desirable information to inform clinical decision making, there are no well accepted documentation standards in clinical applications and/or EHR systems for how this information should captured today (there was nothing in the specifications studied in Chapter 4) and the rationale for prescribing changes is not always well documented. It is therefore likely to be even more challenging to

populate this data than indication data in practice, if it were included in the Medication Profile specification.

In discussion of the themes around completeness, it is important to review the evaluation comments on the specific research question of the inclusion of immunisation information in the Medication Profile.   The regional difference in evaluators' thoughts was marked; those from the North American healthcare culture, where immunisation products are licensed separately from other medicinal products and adverse events tracked using separate forms etc. were more of the view that whilst immunisation information should be present in an overarching electronic health record, it would not necessarily be seen as part of the Medication Profile. This view is further reflected in the separate Immunisation section of documents such as the Community of Care Record specification reviewed extensively in Chapter 4(1) of this research. This separation of opinion highlights very clearly the need to define 'completeness' in the light of its use cases; for many evaluators from other healthcare cultures, immunisation was very positively part of the Medication Profile, although, for the many reasons given in the Results above, a special case within. This was not least because by being a special case, some data element requirements could be specifically tailored for this use case: both to exclude those structures supporting dosage instructions which are not relevant and to include other data elements specific to vaccination courses only (for example, the 'immunisation status' of the patient, based on the antigen(s) received and the completeness of the course, including booster administrations, rather than on the medicinal products administered) and the calculation rules to support these.

The final completeness subtheme focussed on the provision of information about the patient's adherence to their therapy. Whilst quantitative measurement of adherence can be calculated from the data and metadata that underpins the Medication Profile, a couple of evaluators suggested the explicit inclusion of the Medication Possession Ratio[318] as a data element. No requirement for this data element had been found in the use cases as developed in this research, probably because Medication Possession Ratios of various types are all calculations (as evidenced by their 'ratio' nature).   The fact that this information is calculated from raw data leads to the second major theme of the evaluation: that information from the Medication Profile must be presented to users with clarity.

Clarity

The other key theme expressed by the evaluators was the requirement for the Medication Profile to have clarity in the information that it presents.   This theme relates most closely to the processes and the rules that are applied to the data that

these processes can supply into the Medication Profile and as such evaluate the dynamic part of the Medication Profile model.   One of the subthemes from the evaluators was that these rules and calculations need to be properly validated in a wide community, so that their acceptance by the wider clinical community – the whole clinical community - can be assured. It is not sufficient, and could be construed to be dangerous, to leave the development and application of such rules to individual suppliers of medication process systems, where there can be no guarantee of consistency. Clinicians using a variety of systems could make incorrect assumptions on information presented in similar ways but generated by different calculations, leading to incorrect care of patients.   Similarly, the definitions of the data elements themselves should be validated such that they have acceptance across the whole clinical community.   And given the international nature of the market for clinical systems supporting medication processes, this validation must be at an international level, beyond the limitations of the partial specifications existing at present and discussed in Chapter 4(1).

The area that appeared to concern evaluators the most, and which strikes at the heart of the motivation for this thesis, is clarity in – and ubiquitous clinical professional acceptance of - the definition, calculation and implementation of the 'status' of a medication in a patient's Medication Profile.   The Medication Profile as designed in this research presents information about the nature of the use of a medication on two different axes, only one of which was termed 'status'. The first axis is not one that is currently recognised or used in systems or specifications and is concerned with the nature of the medication as a therapy and its pattern of use: whether it is/was a continuous/long term course of therapy of a condition or symptom, or whether it is/was an acute course of therapy for management of a short term condition or symptom.   Evaluators were asked specifically about this and most of them were comfortable with this distinction and felt it added value to the presentation of medication information.   However, there may need to be further investigation as to how to recognise any significant gaps in what might otherwise be considered a continuous course of therapy, and what to do in that situation.

The second axis is the more widely recognised distinction between 'current medication' and 'past medication' (i.e. that which has been used historically) and additionally as some evaluators suggested, particularly in regard to immunisation information but also more generally, the concept of 'planned medication'. A couple of evaluators felt that 'the Medication Profile' should only include current or active medication information and that all information about past medication use should be in a history section 'somewhere else' in the electronic health record. Unfortunately, that view would defeat the request for completeness for the use cases, which do

require information about past medication use. Most evaluators felt that an arbitrary limit on currency was acceptable, as long as it was explicitly stated what that limit was. Only non-clinician evaluators expressed concern about how that arbitrary limit would relate to pharmacokinetic considerations, presumably with a consideration of how to query for information for drug interaction checking in their thoughts. A couple of evaluators felt that status and therefore this distinction per se was not a useful concept, and that alternatives, such as a timeline display or therapy cessation dates (which are present in the Medication Profile) and display ordered by date, could remove the need for this concept. Whilst there is merit in this suggestion in that it avoids the need for an agreed definition of the concepts across the clinical professions, it neglects the practical issue that in a distributed enterprise, the query to a Medication Profile applications would still need an initial time limit for information return because to return the total set of information for a patient is likely to rapidly become unsustainable due to system response times. Bearing in mind the requirement for completeness, it would appear that, based on this evaluation, the best proposition is to have a clearly defined, agreed, accepted and stated time limit for 'current medication' (even if it is arbitrary - such as 30 days) and the ability to drill down for further information quickly and easily to see beyond this limit; whether or how the necessary clinical professional agreement for this can be achieved is another matter.

There were two further sub themes related to clarity of information, and particularly that information presented as 'current medication': that of 'as required' medication and medication administered as a single immediate (urgent) administration (often termed a 'stat' administration, based on the Latin abbreviation of 'statim' meaning 'immediate' used in dosage instructions). Evaluators commented that although stat administrations need to be available in the Medication Profile, it is important that they are not accidentally repeated and therefore should be presented differently, possibly not in the 'current medication' section even if they had been administered in the last 30 days, and the same comment was also made about completed courses (usually acute courses of therapy).   Although these comments relate more to the presentation of information from the Medication Profile than to the actual information itself (either in terms of data elements or population of them), they possibly also indicate a system requirement for restricting the functionality of any medication process application using that information. For example, an application could display stat administrations and completed acute courses in the current medication display, but (if a prescribing application) not allow further use (prescribing) of those medications without an explicitly entered reason.

One issue that relates to clarity is the difference between the display of medication activity information and the display of Medication Profile information. The Medication Profile dynamic model recommends that information from medication activities that occur during an episode in secondary care be processed into the Medication Profile from their distinct applications either at specific points during that episode of care and/or at the end of the episode. There was a sense that some evaluators were looking at the display of Medication Profile information as if it was synonymous with a medication chart or prescription chart at the patient's bedside, because of their comments about the need to avoid accidentally administering cancelled medications or re-administering the one-off stat medications (for example). This is understandable since the Medication Profile information presented in the scenario was simple and tabular and therefore looks similar to a basic secondary care medication chart that some evaluators would be familiar with on a daily basis. This leads into another of the sub-themes from the evaluators in relation to clarity: that of different presentation formats for Medication Profile information. In a sense the comments could be considered out of scope of the evaluation of the Medication Profile model itself, but as humans we not unnaturally comment on the presentation and not just the content of information, particularly when that presentation can have an effect on the interpretation of the information itself. They are therefore akin to user requirements for clinical applications that would utilise the Medication Profile as their data source. The scenarios used a very basic presentation of information since it was the model that was the focus of the evaluation, and it is expected that real applications would use much more sophisticated user interface techniques, including timelines etc. and good application development should use a range of methods to engage users in interface design. However, the evaluation theme on presentation did offer some useful insights, including having different displays for different usage contexts – particularly primary and secondary care – and particularly having different presentation for immunisation information. This latter would further support the suggestion of having some different data elements for an immunisation section in the Medication Profile, as discussed above. No evaluator suggested different presentations for different types of healthcare professional, but that might be because each focussed on their own area only and did not think more widely; there was only one comment in the entire evaluation that actively put comments regarding professional groups and their relationship to the Medication Profile in conjunction with each other.

The last set of sub-themes concerned with clarity of information are those that concern specific negation of information: the first of these was to clearly indicate cancelled medications, those whose course is terminated prior to their initially intended end, which would also overlap with the suggested 'reason for change' data

element.   The second of these was to express specifically when no information was available; for example to specifically state 'no current medications' when the processes and rules have been applied to the available information at a particular point, and a query for current medications has returned nothing appropriate.

Finally, there were two sub-themes from the evaluators that were cautions, rather than comments.   One caution was expressed in regard to having different presentation formats, especially for different types of medication information and the necessity to avoid the risk of fragmentation of information and therefore to lose both its clarity and its completeness. So whilst there seem to be sound reasons for having a specific subsection within the Medication Profile to handle immunisation information, this should not encourage the sense that any other type of medication information should be handled separately. For example, in the patient recruitment use case, many oncology studies will wish to query about past history of use of cytotoxic medications; this should not be taken as a requirement to have a separate section within the Medication Profile for cytotoxic medications, since there are no other characteristics about these medications other than their therapeutic class that sets them apart (they have dosage instructions, and courses of therapy just like all other medications even though these may be complex).   The second caution, which is also linked to both clarity and completeness, is to avoid hiding any information through presentation issues or through the application of rules etc. that are not well defined and well accepted. This again hits at the heart of this research: to have a Medication Profile that is structured and populated against robustly defined rules and processes to properly support the use cases placed upon it.

Limitations of this study

Most evaluators were comfortable with the paradigm of representation of initial views of data from the Medication Profile and then representation of some of the further information that a Medication Profile application could provide and which could be presented to the user (human or system) on request – the so-called drill down functionality.   But the static representation of what would be a dynamic situation in a real system is an obvious limitation of the evaluation, particularly since evaluators were unable to explore dynamically how additional information populated from the Medication Profile would meet their assessment of completeness.   Despite these limitations, there was a general positive sense that the Medication Profile as presented would provide sufficient information to support its use cases.

The display of medication information in this evaluation was tabular. Other more graphical methods using timelines could have been used, although these are more complex to produce by hand. Different display methods may have elicited more or

different comments from the evaluators, but since the evaluation was aimed at examining the validity of the information that could be provided from a Medication Profile, not the display of that information, the limitation of the tabular display was not felt to be significant.

The ideal evaluation

The ideal evaluation for both the static and dynamic parts of the model for a Medication Profile would be somewhat complex, time consuming and expensive. It would involve the construction of a Medication Profile application developed using the structures, processes and logic rules defined in the Medication Profile model (Chapter 8) of this thesis, set in the context of a wider healthcare enterprise. This Medication Profile application would then be used over a number of years (minimum of 5 years) and its content would be populated from a range of different clinical systems (minimum of 3) that deal with medication information in the enterprise, in both primary and secondary care, and covering all the activities that occur in the medication process: prescribing, dispensing, administration and making statements. These systems would also query and receive information from the Medication Profile application to support their processes. The system would need to ensure that it included a whole range of patients, covering a variety of ages and a wide range of states of health and healthcare needs, and therefore a different set of frequency of interaction with healthcare. Other care provision systems that require medication information could also query the Medication Profile application to receive information required to support the care processes that they facilitate (e.g. in unscheduled care).

During this time of use various evaluations would take place, including assessment of the ease of construction of a software application (and particularly whether there was information being received that could not be properly processed) and accuracy, validity, acceptability and timeliness of the information provided in response to the queries received for various use cases. No doubt during that time, refinements of the structures, processes and rules would be required to produce a working system that really did meet the use cases, which is of course why system development now uses not just the Rational Unified Process, with significant initial investment in analysis and design, but also Agile[319] methodologies that allow requirements and solutions evolve through collaboration between end users, designers and system engineers.

Unfortunately, no enterprise level implementation of electronic health records or shared patient summaries has, to date contemplated, never mind actually embarked upon such a coordinated approach to development and evaluation for *any* specification for an interoperable healthcare information resource such as a

longitudinal individual patient Medication Profile. Therefore all such specifications, such as those evaluated in detail in Chapter 4(1), and the model from this thesis, remain largely un-validated by any robust methodology.

However, the responses received from the evaluators, as exhibited in the depth of thought and interest in their comments, shared through the quotes in the Results above, demonstrates that the community – clinicians, informaticians and software engineers – do see the Medication Profile as a critical area in healthcare, and that there is a problem, and it is worth trying to solve it. The evaluation also gave a positive endorsement of one of the core tenets of this thesis, that the Medication Profile can and should support requirements for **both** patient care **and** clinical research, as translational research becomes a reality. Although not asked directly, no evaluator gave any sense that they felt that any of the scenarios were inappropriate or unworkable with or for medication information.

Recommendations for further work

One clear recommendation for further work must be to investigate how to achieve ubiquitous acceptance of the robust definitions for the medication data elements and particularly the definition of current medication provided by this research in the wider community.

Further investigation of the suggested specific data elements for presentation of immunisation information as a separate section within the Medication Profile and the dynamic model for their population would seem a constructive area for further work.

Indication for use is clearly a vital data element within the Medication Profile, no source of such information is available from any of the medication processes in any healthcare culture currently. The benefits and costs of providing indication information, should be urgently investigated.

Validation of the concept of 'course of therapy' and its use within a Medication Profile should be undertaken, initially focusing on the two types proposed here (acute and continuous), and then moving on into the complexity of seasonal and episodic courses.

Although the presentation of Medication Profile information to users could be considered out of scope of the evaluation of the Medication Profile model itself, it is clearly an area that is of great importance in maintaining the clarity and completeness of the information provided, and this, although implementation focussed, should be further explored using the development techniques specifically available for this such as user centred design[320].

Conclusion

The general consensus from the evaluations received against the research questions asked was that the Medication Profile, as structured and populated based on the Medication Profile model, does support its use cases. The model for the Medication Profile can therefore be described as complete, although there were a small number of minor modifications that could be made, such as the change to support a wider 'reason for change' information attribute. The inclusion of indication information is perceived as very important, despite there currently being no source to provide that information. In terms of clarity, the overall sense was positive, but to truly claim to be fit for purpose, the definitions and calculation rules would need confirmation of acceptance in the wider clinical and research communities.

The specific research question about inclusion of immunisation information, the general consensus was that it is a very valuable part of the Medication Profile but that it does also merit a special section for itself.

Chapter 10: Overall Discussion and Recommendations

Original hypothesis, aims and objectives

The original hypothesis for this thesis was that, despite there being a pervasive understanding that high quality comprehensive and cohesive medication information is a vital component of electronic health records, for use in the safe provision of care to individuals and for secondary use clinical research to promote better and safer medication development for the future, no evidence based formal definition of what that medication information should be exists. Nor is there any sense of how that set of information, the Medication Profile, could be maintained over time using available information from medication activities. The aim of the thesis was therefore to formally document the requirements for a Medication Profile from a set of use cases from patient care and clinical research, and having blended these together, to produce a formal domain information model of the Medication Profile to meet both sets of requirements in an integrated manner. The model would have its scope defined, its data elements identified (static model) and a process for populating those data elements consistently and meaningfully over time, based on the business process that occurs (the dynamic models), such that a comprehensive and cohesive cradle to grave longitudinal record of medication use by an individual can be maintained. The information provided by the Medication Profile delivers the solid foundation from which to conduct the safe and high quality performance of the processes of patient care and clinical research, mediated by the application of filters and queries to supply the data relevant for each of the different use cases of patient care and clinical research. Having produced that model, the intention was to subject it to evaluation by a range of reviewers from both patient care and clinical research.

A secondary objective was, by dint of producing a formal *modelled* specification for the Medication Profile, to achieve the melding together of the academic discipline of a thesis, with the practical and formal discipline of the informatics/systems development process. This process uses modelling with various diagramming styles as well as text to define data elements and formally describe processes and also uses requirements as the basis for testing and user evaluation. The aim of this melding was to produce something that is truly evidence-based but directly and practically implementable in the development of the healthcare systems of tomorrow.

It has been possible to gather a set of requirements for the Medication Profile from both patient care and clinical research and to blend these together into a cohesive whole. There have been no conspicuously conflicting requirements, only slight differences in emphasis between the various requirements scenarios. Requirements

for data elements have been the clearest, excepting the glaring lack of shared understanding as to what 'current medication' actually means; and therefore construction of a static model for the Medication Profile to support the superset of those data element requirements was possible and has been completed. Requirements for the scope of the Medication Profile was a little more challenging as there was less clarity and some cultural and practice differences, particularly in pharmacovigilance, which considering this use case needs global data to be most effective is perhaps all the more perplexing. As with all boundaries, clearly defining exclusion is as important as defining inclusion, and therefore the scope definition in this thesis is considered to be of significant value overall. True requirements for the dynamic model, to manage the population of the data elements over time, were almost non-existent in the formal sense. Therefore, in the presentation of a dynamic model, this thesis has developed new knowledge, and as such this area should be subjected to considerable further evaluation and refinement over time. However, by formally presenting dynamic models and rules, there is a firm foundation from which to further evaluate and refine, which has never been present before. This explicit definition and understanding the limits of that definition was one that was picked out specifically by the evaluation as valuable.

The melding together of the academic discipline of a thesis with the formal discipline of the informatics/systems development process to produce a domain information model for a patient's Medication Profile to meet the requirements of patient care and clinical research has been successfully achieved and has been well received in evaluation. It provides a foundational set of artefacts from which to develop the real systems that healthcare acknowledges it needs to achieve safe medication practice and continuing safe and effective development of new medications.

Discussion of research studies

Each chapter of this work has a detailed discussion section for that particular topic; this section provides a summary and reflection of the research as a whole, focussing on the key themes from the various components of the research.

The Literature review

The Literature Review showed that healthcare generally clearly acknowledges the need for consolidated and reconciled medication information derived from multiple sources to exist for each patient, in order to underpin their ongoing safe and high quality care. This information is sometimes even referred to as the 'gold standard' medication record or medication profile. However, the review also confirmed the premise that despite this acknowledgement and all the studies that document when

and who should provide such information, the scope, the detailed content and the detailed maintenance processes for that content are very rarely defined and are almost never justified. The urgent requirement for this work, to examine the use cases, gather the requirements and then formally to define a Medication Profile by defining the scope, the content and a methodology for the population of that content was therefore confirmed.

The Requirements for the Medication Profile

From patient care

By examining a number of national and supranational health record specifications, this thesis was able to conduct what was in effect a systematic review of the content of the specifications, and therefore to promote the evidence base of their requirements from a lower level corresponding to their authorship being by volunteer expert opinion, to a more robust level commensurate with that systematic review.

In the health record specifications examined, and indeed in all the literature, for patient care it is vital to have information about the actual medicinal products that the patient is using; at a minimum this is the medicinal product name (either brand name or generic name, or sometimes by both, especially if bioequivalence issues exist) and including the dose form and strength of the product. If coded identification of the medicinal product is available, use of this is encouraged. The clear identification of each medication is also vital for any of the various types of decision support safety checking that can be provided electronically to operate, and for interpretation and action of any alerts provided. It is also essential for any ongoing management of the patient, especially at points of transfer of care for ongoing course of therapy management and in shared care.   In addition, and principally for adherence management, information about the package of medicinal product, in terms of the amount of medication supplied and any accompanying compliance aids, is useful.   Part of the fulfilment of these requirements relies on the availability of a high quality medicinal product terminology and the other part on the use of that within the Medication Profile.

For any one set of medication information, its place within the medication process was important (prescribed, dispensed or administered) and in all the health record specifications examined this was the only area in which any sense of a dynamic model for medication information was described.   No specification gave any description of how medication information should be maintained longitudinally over time, using information from various sources, to give the comprehensive cradle to grave record. All that is ever described is some sort of list of 'current' and 'past'

medications, with these terms remaining undefined, although with an implicit sense that the former relates to the medications that a patient can reasonably be assumed to be using at the point of time that is 'now'. This is a glaring absence, since to provide high quality healthcare to a patient requires all the healthcare professionals to be on the same page, to have the same comprehensive set of information available and to understand it in the same way.

The requirements for the different detailed data elements that make up the dosage instructions for a medication were varied across the health record specifications examined, with dose quantity and route of administration being important in all specifications, although this latter can be implicit from some dose forms (e.g. the oral dose forms). Timing information, particularly dose frequency but also start and stop date information were described, but there was no explicit requirement for partial date information, even though it is well known that this frequently is all that is available. Indication information was explicitly required. For medication safety and particularly for decision support, route of administration is important for dose checking and drug interaction checking

From clinical research

Almost all of the literature that studies the concept of a patient's Medication Profile does so from the perspective of the care of that individual patient; no literature, other than that written as a result of this thesis, has examined the requirements from the perspective of clinical research. Yet clinical research uses the same medication concepts and this is very significant information. When describing inclusion and exclusion criteria for studies, just under a fifth of all the eligibility criteria examined for this thesis referred to medication use. In pharmacovigilance, as well as identifying the suspect medical product itself, all reports require information about all other concomitant medication use.

When describing inclusion and exclusion criteria for studies, the actual medication was of little importance, in contrast to all the other use cases. Inclusion and exclusion criteria most often describe medication using grouping concepts; chemical grouping, therapeutic use grouping, or even adverse effect grouping, rather than naming specific mediations. Whereas for pharmacovigilance, each individual medicinal product (and for some jurisdictions, use of products that are not considered medications and which are considered out of scope of a Medication Profile, such as foods or cosmetics, if they are suspected of causing an adverse reaction) should be explicitly described in full. This should be either by brand name or generic name, or both, or including the dose form and strength of the product and any machine-readable code if known.

Just as in patient care, the terms 'current medication' and 'past medication' are widely used but never formally defined in clinical research, meaning that their application by individual investigators or by querying systems is unlikely to be consistent, which for eligibility criteria risks compromise to the study and its final results and conclusions right at its outset, and underlining yet further the need for formal definition. For pharmacovigilance, this lack of consistency could cause important concomitant medications not being reported, so that effects such as emerging new drug interactions may be missed. An explicit formal time-bounded specification for 'current medication' is therefore clearly required; no compelling evidence of what this should be was found, but the candidates were of the order of 4 weeks or 3 months prior to the now point in time (be that the time of a suspected adverse event or the application of the eligibility criteria).

The detailed data element requirements from clinical research were less than those from patient care, with dosage instructions information being of less significance, although timing information, as in the start and stop dates for a course of therapy was important, as it is these that will differentiate between what is 'current medication' and what is 'past medication' at any one point in time. Indication information (reason for use) was a clear requirement for both eligibility criteria and pharmacovigilance. In eligibility criteria, it could be expressed using two different patterns: the diagnosis + medication qualifier pattern or the medication + indication pattern. Although diagnosis is usually recorded in a healthcare record, it is not a data element for the Medication Profile, so to query against that pattern is more complex: it requires querying of two different record types and relating these through timing (whether in a system or in paper records). The use of the medication + indication pattern in eligibility criteria should therefore be encouraged alongside encouragement for population of the indication data element in a Medication Profile.

The scope of the Medication Profile

It was clear that there is currently no universal agreement as to the types of products that should be properly included in the scope of a Medication Profile, and that this is an issue for patient care, and to a lesser extent to clinical research. By examination of the various types of products that are possible candidates for inclusion against the use cases for the Medication Profile it has been possible to define a scope, thereby removing the ambiguity that the lack of universal agreement on scope would otherwise maintain.   The examination was such that it aimed to transcend the influence of any particular healthcare culture, especially regulatory culture, because patients themselves are less and less likely to receive care within a single culture

and because systems too are now so large and resource intensive to build and maintain that they must be suitable for use in a variety of cultures and practices.

The scope of the Medication Profile as defined in this thesis is such that it should contain information about a patient's use of all licensed medicinal products of any type, including those not prescribed (i.e. purchased over the counter for self-medication), and all unlicensed medicinal products. Whenever it is available, information about use of homoeopathic and herbal medicines should also be included in the Profile.   Information about the administration of blood products and the use of medical devices, nutritional products, dental products and cosmetics and toiletries used in a healthcare context is excluded from the Medication Profile per se and should be held elsewhere in healthcare information systems not in the Medication Profile. The scope for the Medication Profile will however need reviewing as new products emerge and/or new healthcare practices develop.

Note that here scope is specifically constrained to the types of products to be included rather than the data elements themselves; some might argue (for example) that other areas, such as recording allergy information, should be in scope; that is not the type of scope discussed here.

The Medication Profile model and its evaluation

A domain information model for the Medication Profile was constructed. The static model (data elements) was defined based on the consolidated requirements gathered from the use cases, but due to a general lack of detailed requirements for the dynamic modelling, this latter was developed by documenting the usual business process and deriving a set of logic rules to process data from various activities in the process to meet the objective of populating a comprehensive and cohesive longitudinal record of medication use. The static models were constructed in formal UML using layering, whereas the dynamic models, reflecting the premise that modelling is both an art and a science, use both standard business process models and more freeform non-standard diagrams to describe decision trees.

The models were deliberately kept at a conceptual level to such an extent that attributes were not assigned formal healthcare datatypes; this is because as soon as those sorts of assignments are made, a degree of implementation configuration is imposed which the requirements themselves do not justify.   Similarly, due to no clear requirements for it, the overall model did not include any facility to manage the acknowledged problematic areas of negated information and is developed explicitly on the closed world paradigm. As well as presenting the model, some exemplar population of different parts of the model using the processes and showing the

application of the model dynamic processes and logic was provided, in order to bring some reality to an otherwise theoretical modelling process.

Because a full systems and technology based evaluation of the model for a Medication Profile was not a viable option, by building on the exemplar population of the model using various clinical scenarios reflecting the requirements, a paper-based qualitative evaluation was undertaken to evaluate the validity of the information that could be provided from the Medication Profile, constructed from the conceptual model. The two key themes arising from the evaluation were the desire for clarity and completeness in the information content of the Model. These reflect strongly and positively on the validity of the original aims for the thesis itself and the model at the heart of it: to provide 'high quality comprehensive and cohesive medication information'. It also reflects on the continuing lack of these core values in the medication information, and the requirements for that information, currently present in specifications and working systems used in practice.

In terms of completeness, the Medication Profile model is explicit as to its scope, which, although there were no examples of these products in the test scenarios would include over the counter medications and herbal products, as mentioned in evaluation. Some may wish to argue for a wider scope (e.g. inclusion of allergy information, or inclusion of food supplement products) but having a clear statement of what complete means for this Medication Profile is in itself part of its clarity.   It was evident that despite medication for immunisation being seen as a different type of medication, evaluators were clear that information on immunisation was in scope of the Medication Profile, although the presentation of that information could be implemented separately, still supported by the overall model.

There was no sense in the evaluation that the model for the Medication Profile was incomplete, and it was deemed to provide sufficient information for its use cases. Indication information, as a specific data item present in the gathered requirements for all use cases but rarely captured in existing systems, was specifically investigated. Evaluators were generally supportive that this information should be included to make the Medication Profile sufficiently complete.   The one data item that the static model does not currently have but which would be a modest alteration to make would be to support 'reason for change' information. This should be held against the Medication Record class, and as such would be most simply effected by broadening the definition of the Non-Administration Reason class to the a Reason for Change class.

It is difficult to divorce the concept of the clarity information in itself from its presentation in an implementation, and a paper-based evaluation is very limited in what can be offered in terms of presentation. However, by having a formal defined model underpinning any implementation, there should be clarity as to what any item of information actually represents and how it has been derived, if it has. In a real system a user could access those definitions using drill downs, tool-tips or other user interface technologies which support both clarity and completeness. Even if a user does not particularly like a formal definition (e.g. current medications are those that the patient is or has been taking within the last 30 days) at least it is clearly and explicitly articulated and the dynamic model and logic used to calculate those medications that fall into that definition is also explicitly available. Evaluators were generally supportive of the clarity that comes from the explicit definition of a formal model, as well as commenting that it forms a basis from which to move forward to get wider professional agreement.

Strengths and limitations

A core strength of this work has been the formal requirements gathering from two distinct subdomains within healthcare that traditionally are somewhat divorced from each other; patient care and clinical research. Medication information is a topic for which there is a pervasive sense of it being fully defined, yet this research has shown that this is clearly not the case, for either of the two subdomains. By gathering requirements from a range of perspectives and specifications, it is suggested that the evidence level for the requirements moves from the individual item level towards systematic review, which has value for the wider domain as well as supporting the modelling activity. However, by gathering requirements from specific areas, this by definition excludes others. In patient care, patient adherence (compliance) was a specific area that was not explicitly studied for requirements but it was a use case that some evaluators raised. Two areas that are secondary users of medication information and from which requirements should be further investigated in the future are pharmacoepidemiology and pharmacoeconomics. Similarly, other areas within clinical research itself may require further investigation in the future for requirements onto the Medication Profile.

This research has taken the gathered requirements and used them to underpin a fully defined domain information model for the medication information in a Medication Profile to meet the use cases. It has provided formal and explicit definition for those things that previously have been either undefined or had implicit and therefore possibly ambiguous definition. By undertaking this definition using formal conceptual modelling techniques, the definitions themselves provide value to the

domain by increasing the precision and understanding of these important concepts, whether or not they are actually implemented in systems.

Because of the notable lack of requirements for the dynamic model, other than a sense that the Medication Profile must be able to harmonise data from many and various sources and support 'current' and 'past' medication information, the dynamic side of the Medication Profile model has been developed de novo, and introduces the concept of a 'course of therapy' to as a structure to support the presentation of information from the various sources and medication process in a cohesive manner. It also presents a methodology for the population of the course of therapy information based on explicitly elaborated rules reflecting the possible sources of information from the overall medication process. This therefore provides, for the first time, a formal and firm foundation from which to build onward to meet the objective of a high quality comprehensive and cohesive medication information that is maintainable and useful both for patient care and clinical research.

There is an area that could be considered a strategic weakness of this work in that the model as presented has had only an initial validation, and in order to be considered in any sense authoritative the Medication Profile model would need considerably more robust testing, particularly for the dynamic model logic. The initial validation showed that the foundations are solid to support the use cases, but some modification to peripheral parts of the static part of the model such as reason for change should be undertaken prior to more robust evaluation within larger systems. The dynamic model should also be tested with a much larger set of information, using a wide range of medicinal products, including over the counter medications, managed over a significant period of time, with varying amounts of supporting data provided (e.g. from the dose instructions) as is found in the real world. In addition, the fundamental assumption of the closed world paradigm and the lack of any evidence of requirements to manage negative or negated information should also be more widely validated against all the use cases in both subdomains, particularly since this was not tested at all in the evaluation. There was also no attempt in this thesis to explore if situations might arise where conflicting information was presented to the Medication Profile for processing, and therefore no investigation as to how this might be resolved.

There are therefore considerable opportunities to take the firm foundations established in this work forward to deliver a Medication Profile that will truly provide the high quality comprehensive and cohesive medication information for use in the provision of care to individuals and also to support secondary use of medication

information in clinical research to promote better and safer medication development for the future.

Further research

In patient care, medication adherence (compliance) was not specifically studied for its requirements; these should be investigated and if not already supported by the model for the Medication Profile, the necessary data elements, metadata or process/logic should be added.

Two areas of secondary uses of medication information that were explicitly not studied in this thesis, pharmacoepidemiology and pharmacoeconomics, should be formally investigated for their requirements and if that investigation reveals additional data element or process requirements, these too should be added into the Medication Profile model. It is unlikely that there would be conflicting requirements found, because intrinsically these disciplines are secondary users of information and are therefore reliant on the main medication processes for that information.

The Medication Profile domain information model should be significantly more robustly tested. The static model development should include the additional data elements to support reason for change information. The concept of the course of therapy as defined in the Medication Profile domain model should be more widely validated, and particularly in terms of the level(s) of recursion to be supported, the rules that implement that recursion and the display of this to users through the use of the Parent Medication Record and Medication Record. The practical implementation of such recursion is closely tied to the dynamic model rules and the reason for change information; the further investigation of these could initially be undertaken by development of more detailed scenarios to illustrate this prior to a larger systems level evaluation. The metadata from the activities that the logic uses should also be more thoroughly evaluated, as should how episodic course of therapy could best be incorporated.

The fundamental assumption of this work of using a closed world paradigm, based on there being few if any requirements for negative information, should be further explored. This fundamental assumption may need to be challenged, especially if after a deeper investigation of the medication reconciliation requirements a need for negated information is established for the Medication Profile. There should also be further investigation of patterns of situations where conflicting information could be presented to the Medication Profile, and the options for resolving that, both programmatically and by human intervention, should be explored.

The Medication Profile model evaluation included one scenario that specifically focussed on how a particular subtype of medicinal product information could be managed within it, that of vaccination information. Various reasons for treating vaccination information as a special case were expounded, and the evaluators had a number of suggestions about how vaccination information should be managed, including the possibility of having an antigen based record rather than a medication based record. This subdomain merits its own detailed investigation, in terms of both the static data elements (antigen rather than product, immunity status rather than dosage instructions) and the dynamic model (course completion status rather than course of therapy) and also the possibility of display of prospective future administration information.

Future work

Testing of the dynamic model in processing information from the variety of medication processes performed in all contexts of care (primary, secondary and tertiary) should be undertaken, and particularly to confirm that medication statement information and especially that arising from a medication reconciliation process, can be seamlessly and effectively integrated into the Medication Profile model. The use of UUIDs to further facilitate reconciliation of information from various sources and various stages in the medication process should also be investigated, as should explicit description of course of therapy in the medication process. The availability and use of machine-readable dosage instructions to support management of course of therapy information should also be investigated more deeply, looking at both simple and complex scenarios.

As stated in the Modelling chapter, the static information model was presented at only a conceptual and intermediate logical level. Further development of lower levels of model, towards a more implementable solution using the ISO 21090 healthcare datatypes and the various national and international medicinal product terminologies should be explored, and particularly whether there these introduce any detrimental effects on the ability of the model to support the various use cases (for example, whether the use of pre-co-ordinated medicinal product and manufacturer information is an issue in any way).

As part of a larger and more robust testing process, two areas of information that according to the requirements and use cases are clearly needed within the Medication Profile but which are known to currently be rarely available, should be further investigated. These are: the inclusion of over the counter medication use, where the examination should focus on the dynamic model to support the

identification of the sources of this information and the processing of that information into the Medication Profile; and the inclusion of indication information, which is rarely captured in systems. For this latter, it would be important to investigate any options for facilitating the gathering of this data element with as little disruption to current practice or process as possible.

Finally, although this work has provided a very robust and formally defined domain information model for a high quality comprehensive and cohesive Medication Profile, it is clear from all of the research that, because of the current state of ambiguity for many of these things that persists in clinical practice, there needs to be widespread and inter-professional agreement and acceptance of definitions (particularly for 'current medication' and 'past medication (history)' and the place of 'as required' medication within them) and business rules of the information concepts and for the information processing. Due to the global nature of healthcare and particularly to the global nature of clinical research, it would be valuable if that inter-professional agreement could be reached at a global level, through international standardisation processes and implemented in systems across the globe. If further work could be undertaken towards gaining that global inter-professional agreement, and this was then implemented uniformly in medication systems which were able to provide a Medication Profile for individual patients based on that, the goal of providing safe, high quality healthcare to individual patients whilst also providing information to support clinical research to promote better and safer medication development for the future could become a reality.

Appendix 1: Report of the initial literature search

The following is the literature search that was initially undertaken as a proof of concept for the thesis. This focussed on an investigation of the use and understanding of the term "medication profile". This initial single keyword search found that the term was used extensively, very often in very clinically focussed studies of a disease area, to generically describe "information about a patient's medication"[50-53] – but almost never was any formal definition of what the term actually meant is given either explicitly or implicitly. Some gave a little information; in a study by van Bruggen *et al*[321] on clinical inertia in diabetes care, one of the measurements was "treatment intensification" which was assessed using a "complete medication profile of all participating patients" by gathering the electronic records from all the pharmacies in the study area and using these to obtain "accurate medication histories" of all patients using those medications in the focus of the study (based on ATC code), which were then matched with the research data. The criteria used in the matching were not given. Interestingly in a study by the same authors, this time focussing on patient non-adherence to diabetic medication[322], used the same process to obtain "the complete medication profile" of its subjects and used this to calculate adherence indices.

"Medication profile" as a synonym for "current medication"

It was clear that some authors use the term "medication profile" to implicitly refer to a patient's "current medication"– the medications actually being taken by the patient at the time. This definition can reasonably be implied to the study by Guill *et al*[323] because the inclusion criteria for the study was for the subject to have "8 or more active medications"; in the study by Sobieraj[324] the results used an endpoint of a new prescription being made "on the medication profile" and in the study by Naso[325] the pharmacists involved were expected to "conduct a prospective review of the individual patient's medication profile" to determine if a prescription for a particular class of therapeutic agent already existed as a safety measure against inappropriate therapeutic duplication. In the large-scale (10,000 patient) genetic database created for cardiovascular studies reported by Agah et al[326] "medication profile" is one of the main additional sets of data sorted in the database; however all that is described is that the profile is "a complete list of medications (exact formulation)" for every patient enrolled (no other data such as dosage instructions appears to be collected), and, by implication since the data collection tool includes a list of "100 common vitamins and herbals", the scope is not be limited to prescription medications. Since the Medications Module in the appendix notes that the list contains the medications

patients were on at the time of enrolment, by implication one must assume that "medication profile" here means "current medications".

In many situations, although no formal definition or description of what is meant by the concept of a "medication profile" is provided, some information about its form and content (and exclusions) can be gleaned implicitly from details given. In a study on using fax as a method for sharing medication information[327], it is clear that allergy information was excluded from the profile as it is mentioned as a separate characteristic; there is a sense that a medication profile would be longitudinal, as "current medication" is also given as a separate concept that would be used to "update the medication profile". Becket *et al*[328] studied "medication profile appropriateness" as an endpoint to compare pharmacist medication reconciliation against the institution's normal practice. For a medication profile to be deemed as "appropriate," it required all discrepancies from the medication reconciliation to have been resolved and all medication use to be appropriate as documented by the reviewing pharmacist. Therefore the interpretation of "medication profile" in this context would be the patient's current medication, an interpretation both challenged and supported by other work in this area, discussed in detail below in the section on Medication Information at the Point of Transfer of Care, which looks at medication information and the medication reconciliation process in detail.

Undefined use of "Medication profile"

In a survey of psychiatrists' expectations of clinical pharmacists[329] "maintenance of a medication profile" was one of the survey criteria. However, it gave very little indication as to what was meant by this; the most that can be gleaned is from one of the participant's quotes "I expect clinical pharmacists to maintain a complete medication profile on my patients (i.e. medication history, allergy history)". Similarly a study investigating the role of community pharmacists in improving asthma care[330] used the "medication profile" to mean a patient's dispensed medication history, but it described "the daily dose of medications" to be a separate clinical entity from that profile; by implication therefore the concept of medication profile in this study was just the list of a patient's medications with no other supporting information about dosage, duration or authorisation of use. McAuley[331], investigating epilepsy patients' view of the role of their community pharmacist noted that 61% of patients wished that their community pharmacist could maintain a "complete and current medication profile". This was in the context of the statement that epilepsy patients are expected to be administering medication for most of their lives, and as such must imply that a "medication profile" in this context must be a longitudinal record. Stuijt *et al*[332] used a "medication profile" as a basis from which to measure appropriateness of

prescribing for elderly patients in a residential home. This medication profile combined the patient's medical records with his or her complete prescription record (current and previous [last 3 years] medication history) and pharmaceutical record (electronic journal entries ("dispensings") for the patient over the same period) and took approximately 45 minutes of pharmacist time per patient to prepare. As such, the concept of medication profile here is broader than just medication, in that it was looking to see how clinical problems can be revealed as (probable) drug related problems and make alterations in prescribing as a consequence.

Even in studies where medication management was the focus – as in the study by Jing et al[333] looking at medication adherence the description of the "medication profile" was not explicitly given, however some sense as to what the authors meant can be gathered from the information sent to the primary care physician of non-adherent patients, which included the "medication names, dosage, dispensing date(s), quantity dispensed, days' supply and name of prescriber".

Other authors[334],[335] clearly saw the "medication profile" purely as a source of information for study rather than something for clinical use – for example to when investigating polypharmacy in elderly patients suffering from falls. In the second of these two papers by Kojima et al, at least give some indication as to what was meant by "medication profile" was given in the specific mention of "therapeutic drugs" and information on "prescribed drugs obtained from the chart").

Medication profile and safety events

Other papers emphasised the importance of the "medication profile", particularly those focussing on drug interactions – but again without any definition as to exactly what it might contain. For example, in describing the potential for and implications of lidocaine drug interactions, a paper by Bill et al[336] highlighted that "medications that a patient may consider innocuous have the potential to greatly increase surgical risk" and noted importance of obtaining a complete preoperative history that includes all medications. However, it made no reference as to the source of that information, other than to advise that a "complete preoperative history that includes all medications" should be obtained.

A study of drug interactions for warfarin and the newer anticoagulants[337], uses the concept of "medication profile" but again gives no definition, whereas an analysis of drug interactions in cardiac and cardiothoracic intensive case uses the same concept, but by implication this is deemed to mean all current medications that the patient receives whilst on the unit[338].

The "medication profile" was a term used in studies and reports concerning adverse events – as in a "non-confounding medication profile"[339] and to describe "the set of things being currently administered" when the adverse event occurred[340] and to identify those medications that had or had not been modified and therefore would be (un)likely to be responsible for the adverse event[341].

Definitions for "Medication profile"

However, there were just a few articles where the medication profile took centre stage and a significant amount of detail was provided. A study by Vawdrey et al into the impact of adopting medication reconciliation referenced an "Outpatient Medication Profile" (OMP) which was maintained in their EHR system as a "coded, longitudinal medication list"[86]. This was made available to clinicians through the facility's commercial EHR system and in community-based clinics. Active prescriptions could also be entered into this Profile. There is little detail as to the structure or content of the Profile other than that it contained "coded data elements" and optionally, "form, dose, route, frequency and start and end times". Being a longitudinal record, it was available for use when a patient subsequently revisited the facility, at which point it was updated as part of the reconciliation process and this updated Profile was then used to support admission prescribing. Although the focus of this study was improving compliance with the medication reconciliation process to meet Joint Commission requirements, it made several observations that are pertinent to this thesis. It showed that that tools such as the OMP as implemented are dependent on human intervention for their accuracy and therefore for their value; at the start of the study the average number of medications in the OMP for a patient was less than 2, whereas after one year of active effort to improve compliance with the reconciliation process, the average number was 4.7. The study also noted the benefit of a longitudinal medication record, in that over a two year period, the average number of modifications made to the record on admission decreased from more than three to approximately one; the record as refined and maintained over time more accurately reflected what the patient was actually taking. Two other points can be drawn: the study notes that clinicians complained about the amount of time taken to perform the reconciliation; an accurate medication profile that did not require significant human intervention and effort to maintain would alleviate this. Indeed the study recommended that "synchronising data with external pharmacies and personal health records to enhance the accuracy and completeness of home medication lists" would be beneficial and it admitted that "no 'gold standard' home medication list" exists and that there is often uncertainty about the medications a patient is taking". The specification for an integrated Medication Profile for a patient

would aim to address these recommendations directly and provide the framework for that "gold standard" to exist.

Hornick *et al*[342] developed a Visual Medication Profile (VMP) to aid communication between patient and physician and to improve patient compliance with their treatment regimen, for optimisation of medication regimen for elderly patients. This was a web-based tool that visualised each of a patient's medications in pictorial tabular form and interpreted the dose schedule into columns for when to take the medication. It was designed by an interdisciplinary team that included patients and used data from a pharmacy database, a patient database and pill photograph database. It was found to be helpful in several areas, in particular for the healthcare professionals who expressed issues with an ongoing mismatch between a patient's self-report of their current medications and their medication record.

A second larger study of the medication reconciliation process by Varkey *et al*[343] looked at both admission and discharge medication and documented the medication name, dosage, route, and frequency of administration for all medications. On admission, the information source was patients, family members and the medications brought in; no reference to external sources other than these was sought. The discharge medication list in the hospital summary document was compared against the original patient's home medications list, inpatient medication profile, and prescriptions detailed in the hospital EHR to investigate any medication discrepancies. The discharge medication list included medications to be continued after discharge, new medications added to the patient's regimen, and any medications that were to be discontinued. Changes to preadmission medications, new medications ordered upon hospital discharge, and discontinued medications were to be specifically noted on the discharge sheet. The study noted a reduction in discrepancies as it progressed, including a gradual decrease in the severity of the discrepancies. The effort involved in undertaking the reconciliation was significant, although it also reduced as the study progressed. This study distinguished between an "inpatient medication profile" which was defined as "active medication orders on the day of hospital discharge" and "the patient's regimen" which appears to be a more comprehensive term for the overall picture of a patient's medication. It also highlighted that it viewed information about changes to that regimen, and in particular separately documenting discontinued medications, as important components of the overall profile.

Finally, one study whose focus was to investigate the use of potassium and phosphorus repletion, rather than in any sense having a medication profile focus, actually did provide a full description of its concept of a "medication profile"[344], which

was: "a description of the product ordered, including drug formulation, dose, route, frequency and rate of administration, the day and time of the initial order, and the stop date for administration, if applicable".

Initial Conclusion

From this initial brief review of the literature, it was indeed clear that, despite being a widely used term in the clinical community generally and in medication process focused study in particular, no formal definition of a "medication profile" exists in the literature. This initial review and its sense of there being a lot of generic and implicit information but not very much explicit information, helped to inform the fully structured and broader examination of the literature, whose intent was to explore the broader sense of "medication information", so as to evaluate what information does exist and what could or should be used in support of a formal definition of a "Gold Standard Medication Profile" for this thesis. It would also hopefully confirm the value of such a fully defined concept to the provision of high quality healthcare. This initial review also gathered further evidence for the position that the present published specifications are inadequate for the task in hand: which is how to construct a high quality longitudinal Medication Profile to serve the use cases for it from patient care and clinical research.

Appendix 2: Evaluation package

The Medication Profile
For use in Patient Care and Clinical Research
Julie M James

Centre for Health Informatics and Multi-professional Education (CHIME), University College London

Supervisors: Professor Dipak Kalra; Professor Jane Portlock

Evaluation Storyboards

In the following pages, you will find five separate storyboards, describing five different patients in different care or research scenarios; each one focuses on a different use case for information from the patient's Medication Profile.

In each case, there are one or more representations of information in the patient's Medication Profile that have been generated according to the models and patterns developed through my research. The display shows only a name and date of birth; it is assumed that "patient matching" has been performed to EHR best practice.

Please read through the storyboard and the Medication Profile and provide your answers to the questions and give comments for each one. Please note that the representation is exemplar only, but that there is some meaning in the colour of the typescript:

> - black text indicates continuous course of therapy
> - purple text indicates a short course of therapy (<30 days' continuous treatment)
> - red text indicates therapy prescribed but known not to have been administered

There are also some general questions at the end of the scenarios.

I estimate completing this evaluation will take about 60-90 minutes hour of your time.

Thank you so much for your assistance and support.

Julie

Please return the completed document to me, preferably electronically, at Julie_james@bluewaveinformatics.co.uk or alternatively by post to 20 West Garth Road, Exeter, EX4 5AH, UK.

There is a short abstract describing my thesis appended to the back of this document for your interest.

Clinical Care – Emergency Medication Supply Use Case

Winston Gordon is a 13-year-old boy on an activity holiday with his local youth group in the early summer of 2015. During that time he picks up a viral infection, but he carries on with the activities despite a mild fever, sore throat and slightly runny nose. As a child, Winston has suffered from asthma, but like many teenagers, he's not keen to acknowledge this too much; he didn't put it on his form for the activity holiday and he hasn't brought any medication (inhalers etc.) with him. In fact, he hasn't used his inhalers regularly since he started senior school and really no longer thinks of himself as "asthmatic". He has one old "reliever" inhaler at home that he occasionally uses if he thinks he's wheezy.

Probably due to a combination of the virus and all the activity, Winston's asthma reappears and after a day or so of trying to hide it and ignore it he really needs help. After phoning his parents to get their permission, one of the activity holiday leaders who has been mentoring Winston takes Winston to the local Walk-in Centre.

Dr Sarah McMasters sees Winston, talks to him and the accompanying adult about his recent symptoms and past history and listens to his breathing and his chest and takes a peak flow reading. Sarah then searches on-line to get an overview of Winston's Medication Profile. She is presented with the following:

Winston Gordon   **MEDICATION PROFILE**   DoB: 17 February 2002

Current Medication

Medication	Dosage Instructions	Start date:

Medication History

Medication	Dosage Instructions	Course of therapy dates:	
Beclomethasone 100micrograms per dose dry powder inhaler	Inhale one puff twice a day	Sept 2006 – 31 March 2013	Further details
Salbutamol 200micrograms per dose dry powder inhaler	Use up to 4 times per day	Sept 2006 – 31 March 2013	Further details
Salmeterol 50micrograms per dose dry powder inhaler	Inhale one puff twice a day	Nov 2009 – 31 March 2013	Further details
Amoxicillin 250mg/5mL oral solution	5mL to be taken every 8 hours for 7 days	14-21 January 2011	Further details
Prednisolone 5mg soluble tablets	20mg to be taken daily for 4 days	14-18 January 2011	Further details

Click here for more history

In the system that Dr McMasters is using, the symbol with the yellow colour denotes that the course of therapy has changed during the dates displayed in the Medication Profile History section. So, by requesting these further details for the Beclomethasone course of therapy, Sarah is then presented with the following information:

Winston Gordon   **MEDICATION PROFILE**   DoB: 17 February 2002
Course of Therapy Details

Beclomethasone   More detail

Medication	Dosage Instructions	Course of therapy dates:
Beclomethasone 100micrograms per dose dry powder inhaler	Inhale one puff twice a day	14 Nov 2012 – 31 Mar 2013
Beclomethasone 100micrograms per dose dry powder inhaler	Inhale two puffs twice a day	29 Mar 2011 14 Nov 2012
Beclomethasone 250micrograms per dose dry powder inhaler	Inhale one puffs twice a day	14 Jan 2011 – 29 Mar 2011
Beclomethasone 100micrograms per dose dry powder inhaler	Inhale two puffs twice a day	31 Mar 2009– 14 Jan 2011
Beclomethasone 100micrograms per dose dry powder inhaler	Inhale one puff twice a day	31 Oct 2007 – 31 Mar 2009
Beclomethasone 50micrograms per dose dry powder inhaler	Inhale one puff twice a day	30 Sept 2006 31 Oct 2007

The red date in Sarah's system indicates that the Medication Profile has derived this date; the last prescription for this medication was issued to Winston on 28 February 2013 but no dispensing information was ever received for processing by the Profile.

This confirms Winston's admission that he hasn't regularly used any asthma medication since he started secondary school.

Based on the history, examination and information from the Medication Profile, Sarah McMasters is sure this is Winston's asthma getting the better of him, and she is able to prescribe medications that he is familiar with (salbutamol and beclomethasone in a dry powder inhaler formulation) to get the situation under control again.

For Reviewers

Do you think there is enough information in the Medication Profile to support Dr McMaster's conclusions about Winston's asthma in the past?

Is it correct to display no current medications for Winston in the Medication Profile?

Clinical Research - Patient Recruitment Use Case

Harry Peters is a 72-year-old gentleman who has suffered from reasonably well-controlled primary hypertension for some years. He was initially treated with bendroflumethiazide, but in 2010 this was augmented with ramipril.

In 2011, at a routine check-up, Harry was found to have a raised blood-glucose level. Harry is not overweight and exercises regularly (and has done since he was diagnosed with hypertension); carbohydrate restriction did not give enough of a reduction in the glucose level, so Harry was started on Metformin, which has kept his blood glucose at a satisfactory level since then

In 2013, in a review of his treatment and to bring this in line with recent guidelines, the thiazide diuretic was stopped and long-acting nifedipine introduced.

Harry's GP, Dr Anthony Chung, is participating in a retrospective observational clinical study being managed by Good Health University Hospital (GHUH). The study is investigating the effects of ACE inhibitors on reducing cardiovascular outcomes (e.g. myocardial infarctions, cerebrovascular accidents) in patients receiving this class of medication for treatment of primary hypertension.

There is a secondary study investigation, looking for incidence of type 2 diabetes mellitus arising in this population[10].

In order to identify subjects who would be eligible for recruitment to this study, GHUH has sent participating centres a structured query to execute against their patient database. This query searches for all patients who have received an ACE inhibitor medication (ATC C09A or C09B) for more than 2 years of continuous therapy in the last 10 years. The query lists all the medications in the relevant classes explicitly; it does not expect the patient database to determine this itself.

A second query is then performed against the cohort of patients found by the first query, to identify patients who commenced taking one or more medications from ATC class A10BA (Biguanides) or A10BB (Sulfonylureas), and for whom the start of that therapy was concurrent with the ACE inhibitor therapy.

Dr Chung has run the queries sent by GHUH and is reviewing the results against the Medication Profiles of the various patients that have been selected by the query as potential subjects for the study. Harry Peters is one of seven patients (out of the 2760 that Dr Chung has in the practice) that are possible subjects for both the

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[10] For a similar study, see NCT 01152567

primary and secondary parts of the study, so Dr Chung looks at the detail of Harry Peters' Medication Profile and confirms that Harry is indeed a potential subject.

He puts Harry's name on the list of patients to receive an invitation to find out more about participating in the study.

Harry Peters   **MEDICATION PROFILE**   DoB: 17 September 1943

Current Medication

Medication	Dosage Instructions	Start date:	
Ramipril 5mg tablets	One to be taken daily	24 February 2010	Further details
Metformin 500mg tablets	One to be taken twice daily	2 May 2011	Further details
Adalat LA 20mg MR tablets	One to be taken daily	7 November 2013	Further details

Medication History

Medication	Dosage instructions	Course of therapy dates:	
Amoxicillin 250mg capsules	One to be taken every 8 hours for 5 days	16-21 January 2015	Further details
Bendroflumethiazide 2.5mg tablets	One to be taken daily	June 2007 - 7 November 2013	Further details
Miconazole 1% topical cream	To be applied to the toes twice a day	18 March 2012 – 18 April 2012	Further details

All of the information in Harry's Medication Profile has come from prescription and dispensing medication processes in primary care and Harry has been consistent in having prescriptions dispensed (fulfilled) within a couple of days of their issue, so that it has been easy to tie together prescription and dispensing information.

When Dr Chung requested "Further details" for the Ramipril course of therapy, he was presented with:

MEDICATION PROFILE
Course of Therapy Details

Harry Peters

DoB: 17 September 1943

Ramipril 5mg tablets
One to be taken daily

Most recent 6 months' detail:

More history

Process	Performed date	Medication	Dosage Instructions	Supply amount
Dispense	29 Sept 2015	Ramipril 5mg tablets (GoodPharm plc)	One to be taken daily	2 x 28 tablets
Rx	27 Sept 2015	Ramipril 5mg tablets	One to be taken daily	2 x 28 tablets
Dispense	25 July 2015	Ramipril 5mg tablets (PharmaMake plc)	One to be taken daily	2 x 28 tablets
Rx	23 July 2015	Ramipril 5mg tablets	One to be taken daily	2 x 28 tablets
Dispense	22 May 2015	Ramipril 5mg tablets (GoodPharm plc)	One to be taken daily	2 x 28 tablets
Rx	21 May 2015	Ramipril 5mg tablets	One to be taken daily	2 x 28 tablets

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For Reviewers

Do you agree that, based on the medication process information in the story above, the display of the Medication Profile information is accurate?

Please give reasons for your answer

Similar screens were available for the Metformin and Adalat LA courses of therapy, confirming to Dr Chung that Harry Peters conscientiously has his prescriptions dispensed and is therefore likely to be conscientious about taking his medicines, and may indeed be a good subject for the study.

The queries from GHUH identified Harry Peters as a potential subject for the study because:

A current course of therapy for ramipril (an ACE inhibitor in the ATC class C09A) was identifiable and the start of the course of therapy was identifiable (24 February 2010) allowing the duration to be calculated (5 years 7 months)

This fulfils the criterion "patients who have received an ACE inhibitor medication (ATC C09A or C09B) for more than 2 years of continuous therapy in the last 10 years"

A current course of therapy for metformin (a biguanide in the ATC class A10BA) was identifiable and the start of the course of therapy was identifiable (2 May 2011) and could be compared with the dates for the course of therapy for the ramipril (24 February 2010 to present)

This fulfils the criterion that "the start of that therapy was concurrent with the ACE inhibitor therapy"

For Reviewers

Do you agree that, based on the story above, Harry Peters is a potential subject for the study being conducted by GHUH?

Please give reasons for your answer

Clinical Care – Immunisation Use Case

Amrita Cheema is an 18-year-old girl about to embark on "gap year travel" before she goes to university to study Politics with Spanish. Her aim is to travel extensively in continental South America, but most probably not to those countries bordering the Caribbean (e.g. Colombia and Venezuela).

Amrita is making an initial visit to a specialist travel clinic to sort out vaccinations etc. several months in advance of her departure, and is discussing the situation with Nurse Peter Furman. Peter uses the website from the National Travel Health Network and Centre (NaTHNaC) [http://travelhealthpro.org.uk/country-information/] to check the vaccination requirements and malaria prophylaxis requirements for Brazil, Uruguay, Paraguay, Chile, Bolivia, Argentina and Peru.

In summary, for all of the countries, MMR and Dip/Tet/Polio are recommended. In addition, for most countries hep A, hep B and typhoid are recommended. Yellow fever vaccination is recommended for certain parts of several countries and for a couple rabies and TB vaccination would be recommended for high-risk personnel. Amrita agrees with Peter that she doesn't fall into that high-risk category, but will have a think about her likely itinerary and the need for yellow fever vaccination, but all the others she should have.

Like most teenagers, Amrita is pretty hazy about which vaccinations she has actually received, although she clearly remembers having the HPV vaccination (as this was only given to girls) and "a set of vaccinations" just before taking her GCSEs. Peter therefore accesses Amrita's Medication Profile to find out what her vaccination status is.

Amrita has suffered from atopic eczema since she was a baby, so the initial view of her Medication Profile shows the following:

MEDICATION PROFILE — Amrita Cheema — DoB: 19 June 1997

Current Medication

Medication	Dosage Instructions	Start date:

Medication History

Medication	Dosage Instructions	Course of therapy dates.	
Hydrocortisone 1% Topical Cream	Apply twice a day to affected areas	14 May 2009 30 June 2015	Further details
Clobetasone 0.05% Topical Cream	Apply twice a day to affected areas	14 May 2009 30 June 2015	Further details
E45 Topical Cream	Apply to affected areas as needed	14 May 2009 30 June 2015	Further details
E45 Emollient Bath Liquid	Use as required	14 May 2009 – 31 October 2012	Further details

Click here for more history.

Peter notes this, as it may be relevant for vaccine reactions, but wants to move to a specific screen for the Immunisation History:

MEDICATION PROFILE — Amrita Cheema — DoB: 19 June 1997

Immunisation Record – Displayed in date order

Medication	Dosage Instructions	Administration date:	
(Adsorbed)Diphtheria/Tetanus/Polio Vaccine	Booster: 0.5mL IM	06 April 2012	Further details
Meningococcal Group C Conjugate Vaccine	Booster: 0.5mL IM	06 April 2012	Further details
Human Papillomavirus Vaccine	3rd dose: 0.5mL IM	18 May2009	Further details
Human Papillomavirus Vaccine	2nd dose: 0.5mL IM	21 December 2008	Further details
Human Papillomavirus Vaccine	1st dose: 0.5mL IM	07 November 2008	Further details
(Adsorbed)Diphtheria/Pertussis/Tetanus/Polio Vaccine	Booster: 0.5mL IM	13 November 2001	Further details
Measles/Mumps/Rubella Vaccine	Booster: 0.5mL IM	13 November 2001	Further details
Measles/Mumps/Rubella Vaccine	Primary: 0.5mL IM	28 July 1998	Further details
(Adsorbed)Diphtheria/Pertussis/Tetanus/Polio Vaccine	Primary 3rd dose: 0.5mL IM	22 October 1997	Further details
Haemophilus influenza type B Vaccine	Primary 3rd dose: 0.5mL IM	22 October 1997	Further details
Meningococcal Group C Conjugate Vaccine	Primary 3rd dose: 0.5mL IM	22 October 1997	Further details

Click here for more history.   Click here for display in vaccine order.

From this, Peter can see Amrita is fully up to date with her childhood immunisation schedule and therefore is covered for diphtheria, tetanus, polio, measles, mumps and rubella. This means that specifically for her travel, she needs to add in hepatitis

A and B (which can be achieved using a single product with the two antigens) on a three-dose schedule and typhoid vaccine.

For Reviewers

Do you think it is useful to have a specific Immunisation section within a Medication Profile?

Is it acceptable to provide the "Dosage instructions" with reference to the type of vaccination given (primary or booster)?

Clinical Research - Pharmacovigilance Use Case

June Stevens is a 56-year-old lady who has been admitted this autumn (2015) to Good Health University Hospital (GHUH) for a knee replacement; her knee joint has been steadily deteriorating and causing increasing pain since an accident 5 years ago. June has been using regular analgesia for the knee pain for some time.

On admission, June's Medication Profile is as shown below:

June Stevens   **MEDICATION PROFILE**   DoB: 14 March 1959

Current Medication – Continuing Course

Medication	Dosage Instructions	Start date:	End date:	
Paracetamol 500mg tablets	Two to be taken up to four times daily for pain relief	19 August 2010	ongoing	Further details
Naproxen 500mg tablets	One to be taken twice daily	14 September 2012	ongoing	Further details
Omeprazole 20mg capsules	One to be taken daily	6 November 2012	ongoing	Further details

Medication History

Medication	Dosage Instructions	Course of therapy dates:	
Chloramphenical 0.5% Eye Drop Solution	One drop into both eyes every 6 hours for 5 days	26-31 August 2015	Further details
Erythromycin 250mg tablets	One to be taken every 6 hours for 5 days	2-7 February 2013	Further details
Diclofenac 3% topical gel	Applied twice daily	August 2010 – September 2012	Further details

June has two children, and during both pregnancies she experienced some issues with thromboembolism, and therefore for the orthopaedic surgery she requires pharmacologic prophylaxis; in GHUH the medication of choice is enoxaparin given subcutaneously 12 hours prior to surgery and then for 5-7 days post-surgery, depending on the patient's mobility.

Unfortunately, within about half an hour of receiving the pre-operative administration of enoxaparin, June feels quite unwell; her tongue feels swollen and she is becoming breathless, despite resting in the chair by her bed. The duty doctor, Dr John Carter, is called and diagnoses a hypersensitivity reaction, manifesting with angioedema. June is immediately given oxygen, 500micrograms of adrenaline IM, 100mg hydrocortisone (as sodium succinate) IV and 10 mg chlorphenamine IV. Thankfully this stabilises June's condition and within 3 hours the angioedema has resolved. However, her surgery is postponed.

In addition to the information as presented in the screen shot above, June's Medication Profile now has the following information:

June Stevens — MEDICATION PROFILE — DoB: 14 March 1959

Current Medication – Simple Course

Medication	Dosage Instructions	Start date:	End date:	
Enoxaparin	40mg SC; 12 hr before surgery daily for 5-7 days post surgery	06 Oct 15	06 Oct 15	Further details
Adrenaline	500micrograms IM; Stat	06 Oct 15	06 Oct 15	Further details
Hydrocortisone	100mg IV; Stat	06 Oct 15	06 Oct 15	Further details
Chlorphenamine	10mg IV; Stat	06 Oct 15	06 Oct 15	Further details
Cefuroxime	1.5g IV; 30mins prior to surgery	06 Oct 15	06 Oct 15	Further details
Cefuroxime	750mg IV; q8h for 24 hours, starting 8 hours post surgery	06 Oct 15	07 Oct 15	Further details

The "Further details" for the Cefuroxime courses give the following information (shown for both – although each would be viewed separately):

June Stevens — MEDICATION PROFILE — Course of Therapy Details — DoB: 14 March 1959

Cefuroxime – not administered: 6 Oct 15

Process	Date	Medication	Dosage Instructions	Administration Status	Reason
Rx	5 Oct 2015	Cefuroxime	1.5g IV; 30mins prior to surgery	Not administered	Surgery postponed

Cefuroxime – not administered: 6 Oct 15

Process	Date	Medication	Dosage Instructions	Administration Status	Reason
Rx	5 Oct 2015	Cefuroxime	750mg IV; q8h for 24 hours, starting 8 hours post surgery	Not administered	Surgery postponed

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For Reviewers

Do you agree that, based on the Storyboard above, the display of the Medication Profile information is accurate?

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Please give reasons for your answer if possible

At the ward round/review the next day, the team decide June has experienced a rare but serious hypersensitivity reaction to the enoxaparin and record this in her electronic health record

The EHR system at GHUH encourages all clinical staff to engage in adverse reaction reporting, and has an application that supports this. It monitors EHRs for various indicators of an adverse reaction, and if it detects a likely scenario, it actively asks the clinician managing the patient if an ADR report should be filed, and if so, it provides as much pre-filled information as possible to the clinician, including from the Medication Profile of the patient. Dr Carter accepts the request to complete an ADR report for June and reviews the pre-filled information.

For the Medication sections, the following is presented, drawn from the Medication Profile:

GHUH

Note: this shows only the medicinal product information

Report of a Suspected Adverse Drug Reaction

SUSPECT DRUG/VACCINE

Drug/Vaccine	Batch	Route	Dosage	Date Started	Date Stopped	Prescribed for
Enoxaparin		SC	12 hr before surgery	06 Oct 15	06 Oct 15	....

OTHER DRUGS *(3 months prior)*

Drug/Vaccine	Batch	Route	Dosage	Date Started	Date Stopped	Prescribed for
Paracetamol 500mg tablets		Oral	Two to be taken up to four times daily for pain relief	19 Aug 10	....	....
Naproxen 500mg tablets		Oral	One to be taken twice daily	14 Sep 12	....	....
Omeprazole 20mg capsules		Oral	One to be taken daily	6 Nov 12	....	....
Chloramphenicol 0.5% Eye Drop Solution		Ophthalmic	One drop into both eyes every 6 hours for 5 days	26 Aug 15	31 Aug 15	....

For Reviewers

Do you agree that, based on the story above, that the pre-populated Medication information in the Adverse Drug Reaction report generated by the application and presented to Dr Carter is accurate?

Please give reasons for your answer if possible

Dr Carter decides to edit the form, particularly to add the indication ("Prescribed for") for the enoxaparin, since indication information is currently not given with prescriptions, but may be recorded elsewhere in the patient's notes.

In addition, Dr Carter is able to select the four items from June's Medication Profile to add to the "Treatment" section of the Suspect ADR Form – the adrenaline, hydrocortisone, chlorphenamine and oxygen. Rather than having to transcribe the information, by selecting those items and using "drag and drop" functionality, the Suspected ADR Form gets the full information from the Medication Profile directly.

GHUH

Report of a Suspected Adverse Drug Reaction

Note: this shows only the medicinal product information

Details of any Treatments given for the Suspected Adverse Reaction:

Drug/Vaccine	Batch	Route	Dosage	Date Started	Date Stopped	Prescribed for
Adrenaline		IM	500microgram stat	12.05hr 06 Oct 15	12.06 hr 06 Oct 15	anaphylaxis
Hydrocortisone		IV	100mg stat	12.07hr 06 Oct 15	12.08 hr 06 Oct 15	anaphylaxis
Chlorphenamine		IV	10mg stat	12.08hr 06 Oct 15	12.09 hr 06 Oct 15	anaphylaxis
Oxygen		Resp		12.05hr 06 Oct 15	14.00 hr 06 Oct 15	anaphylaxis

For Reviewers

Do you think that if "indication" information were routinely present for medications, even more information could have been populated "automatically" into the Suspect ADR Form?

Clinical Care – Decision Support Use Case

Luisa Schmitt is a 29-year-old lady living and working in mainland Europe, where the healthcare culture does not have a single "gatekeeper" medical practitioner (a general practitioner or family doctor); the patient is cared for by a set of specialist practitioners depending on the patient's healthcare needs. Since being a teenager, Luisa has unfortunately been susceptible to severe migraines. She has had various treatments over the years but now manages her condition by lifestyle management, prophylactic propranolol and the use of zolmitriptan for symptomatic treatment of any migraine that occurs.

In February 2015, Luisa suffers a severe urinary tract infection and visits her gynaecologist, Dr. Hoffman, seeking treatment. Luisa's symptoms are such that Dr Hoffman wishes to commence antibiotic treatment straight away and intends to prescribe ciprofloxacin. She uses her clinical system to issue the prescription. Dr. Hoffman is aware that Luisa has suffered from migraines since her teenage years, as it was a consideration when selecting a suitable method of contraception for Luisa, but she is not aware of the exact therapy that Luisa has. The clinical system has a medication decision support module, which references Luisa's Medication Profile, and therefore as soon as the ciprofloxacin has been selected, an alert is displayed to Dr Hoffman, reminding her of the probable interaction between zolmitriptan and ciprofloxacin, due to the enzyme inhibition effect of the ciprofloxacin. A dosage reduction for the zolmitriptan is recommended.

Dr. Hoffman decides to review the detail of Luisa's Medication Profile and receives the following information:

Based on the information present in the alert, on viewing Luisa's Medication Profile and on further discussion with Luisa on prevalence and likelihood of a migraine

occurring during or soon after this proposed course of therapy, Dr. Hoffman decides to continue with the prescription of ciprofloxacin, but counsels Luisa that if a migraine occurs, she should use only 2.5mg of zolmitriptan for symptomatic relief rather than her normal 5mg dose.

Dr. Hoffman is also concerned that Luisa may experience a bout of vaginal candidiasis as a result of the use of the broad spectrum antibiotic and the imbalance in internal flora that this can cause. Having already been alerted to the possibilities of drug interactions occurring with Luisa's anti-migraine treatment, she checks on the use of itraconazole, and finds that could also be a problem; she therefore advises Luisa to use local clotrimazole as a first line of therapy if thrush does develop.

For Reviewers

Do you think there is enough information in the Medication Profile to support Dr Hoffman's decision to prescribe ciprofloxacin for Luisa?

For medications that are used "as required", do you think it is acceptable to describe them as "Current Medications" and as a "Continuous course of therapy" or do you think they should be described in a separate section?

General Questions

There is no agreed definition for "Current Medication". Do you feel that for **display purposes**, showing those medications the patient is currently prescribed or whose course has completed within 30 days is reasonable?

Do you feel that differentiating between a continuous course of therapy and a simple or "acute" course of therapy is useful for the Medication Profile?

Are there any specific comments not covered in the scenarios or in the questions above that you would like to make?

Thank you very much for completing this evaluation.

The Medication Profile

Julie M James

Centre for Health Informatics and Multi-professional Education (CHIME)

University College London

Supervisors: Professor Dipak Kalra; Professor Jane Portlock

Abstract

Use of medicines is the commonest intervention used in the care of patients. Information about the use of medicines by an individual over their lifetime, managed as a coherent whole but presented as appropriate to particular contexts, is central to providing good quality care.

Considerable investment continues to be made in specifying and implementing the information structures underpinning electronic health systems to provide clinicians with patient information to support their care provision, yet medication errors continue to occur at rates that are not reducing.

At the same time, the quantity of healthcare information — which includes medication information – is increasing, and there is growing interest in "secondary uses" of such data, one of the largest of which is to support clinical research. Unfortunately, for both primary and secondary uses, the requirements for the actual data elements that are needed for medication information are poorly specified, despite a variety of major national and international initiatives. The process for populating those data elements with high quality, consistent, trustworthy information that can be presented efficiently and clearly in order to service those use cases is even more poorly specified.

By gathering requirements from processes within clinical research and within patient care *alongside* each other rather than separately, it is possible to generate an integrated data element view of how a patient's medication use over their lifetime should be described and presented to support high quality patient care and clinical research; this is termed the patient's Medication Profile.

Examination of the care processes that can provide the data to populate that integrated view elicits the method and rules for the realisation of the Medication Profile.

Layered formal information models are used to support the description of the data elements of the Medication Profile (the static model) and the description of the processes and rules to instantiate that model with data (the dynamic model).

These models are then evaluated against test scenarios to assess their success in describing and presenting a patient's Medication Profile to support both clinical care and clinical research.

Appendix 3: Evaluation coding example

Emergency Medication Supply Use Case

Question: Do you think there is enough information in the Medication Profile to support Dr McMaster's conclusions about Winston's asthma in the past?

Verbatim:

I think that based on this information, you can conclude that Winston has asthma at the time he used these medicines: these medicines are ==used for== asthma and for COPD, but regarding his age it is reasonable to conclude he has asthma. So I think for the conclusion about his disease in the past this information is rather ==sufficient==. Although you preferably do not want to derive that from medication, but based on an ==indication== (e.g. ICPC or SNOMED code) in the EHR.

Coded as: "sufficient information provided" and "indication would be helpful" based on highlighted words or phrases in the verbatim

Question: Is it correct to display no current medications for Winston in the Medication Profile?

Verbatim:

Questionable. An absolute answer depends on the formal definition of Current Medications and on the presumption of how ubiquitous the clinical professions' understanding of that definition is i.e. is the understanding of such definitions an absolute requirement for being deemed competent to practice in an eHealth enabled health care system?

If the system is able ==to reliably and repeatably infer Winston's concordance== based on a health system wide reconciliation of prescribing and dispensing dates then displaying "Patient's behavioural current medications" can be considered correct. If the system cannot reliably and repeatably infer that concordance then the only view that can be inferred is "Caring clinicians' perceived current medications". Perhaps both interpretations ==require explicit definition as separate parts of the data element==.

Coded as: "agreed definition of 'current' needed" and "how to record/display/infer compliance" based on highlighted words or phrases in the verbatim

Appendix 4: The NHS Dose Syntax

Introduction

What is the "Dose Syntax"?

Whenever a medicine is used (prescribed, dispensed or administered) to provide healthcare for a patient or group of patients, or reference to a medicine is made in the care of patients, it is likely that there will information about the dosage of the medicine.

This dosage information, which has been described as the **"Dose Instruction"** is defined as "the full set of information that supports the correct administration of a medication to a patient in order for it to have its therapeutic effect". Within this set of information, there are a variety of different concepts represented, such as the amount of medication to be administered, the frequency with which it is to be administered etc.

In this era of distributed healthcare, with many different individuals and teams of clinicians being involved in the care of a patient, it is vital that, as well as being able to clearly and unambiguously describe the medicines themselves, there is a requirement to clearly and unambiguously describe the Dose Instructions that accompany the medicine in its use. This is a requirement both for human communication, and for electronic (machine-to-machine) communication and information storage and retrieval.

In order to facilitate this communication, an Analysis of Dose Instructions was undertaken, covering all domains (primary, secondary, tertiary care) in which medications are used, including the core clinical specialties that have particular dosage information requirements (chemotherapy, child health, anaesthesiology, etc.). The objective was to identify, define and describe the various concepts that are used in Dose Instructions, to facilitate the clear and unambiguous description of how a medicine is/was/should be administered, for all stages of the medication process (prescribing, dispensing and administration).

The Dose Syntax Model

cd Simplified Class Model (informal data types)

Name: Simplified Class Model (informal data types)
Package: Logical View
Version: 7
Author: Hugh Glover

DoseInstructions

Objectives and Goals
+ text() : string
+ value() : coded vocab

Dose Quantity
+ value and units() : value (range)
+ value and units per() : value (range)

Additional Instruction
+ text() : string
+ value() : coded vocab

+contains 1..*

Dose Quantiy Upper Bound
+ duration and units() : time (range)
+ quantity and units() : value (range)

DoseInstructionClause
+ sequence() : sequenceNumber
+ conjunction() : codedValue

Device
+ text() : string
+ value() : coded vocab

Rate
+ value and units() : value (range)
+ value and units per() : value (range)

Dose Timing

Route Site Method

Method of Administration
+ text() : string
+ value() : coded vocab

Individual Dose Timing

Course of Therapy

Site of Administration
+ text() : string
+ value() : coded vocab

Timing Pattern

Route of Administration
+ text() : string
+ value() : coded vocab

Frequency

Duration

Timing Description

Measured Time
+ point in time() : time
+ regularPattern value and units() : value (range)
+ regularPattern value and units per() : value (range)

Circumstantial Time
+ text() : string
+ value() : coded vocab

Dose Instructions

A **Dose Instruction** is defined as "the full set of information that supports the correct administration of a medication to a patient in order for it to have its therapeutic effect". Within this set of information, there are a variety of different concepts represented, such as the amount of medication to be administered, the frequency with which it is to be administered etc. These are termed the component parts of the instruction, and they themselves may have attributes, or sub-types, within them.

A single "dose instruction" may be complex, and therefore may be split into a number of separate **Dosage Instruction Clauses**: each clause can then be split into its **Dose Instruction Components** parts for further structuring. The structured clauses can be concatenated together again, using a mechanism to put the clauses and their

component structures together in the right order, to reproduce accurately the totality of the information of the be a mechanism to put the clauses and their components together in the right order instructions.

Dose Instructions Clause

A Dose Instructions Clause is a single statement that stands "on its own" to describe a single set of dosage instruction information; it will contain a number of component parts. A single Dose Instructions Clause may form the complete Dose Instruction, or two or more Dose Instruction Clauses may be concatenated together to give the complete Dose Instruction, using Sequence Indication to ensure that the Clauses are brought together in the correct order.

A Dose Instructions Clause that has a relationship to another Dose Instructions Clause will have a Conjunction ("or", "then" or "and") and, if it is part of a sequence ("then") it will have an indication of where in that sequence it occurs.

Dose Instructions Components

Within any Dose Instructions Clause, the information contained within the Clause can be divided into Component parts. These Component parts form a finite set of concepts, and are described in the sections below. Rarely will all the Components be present in even a complex Dose Instruction, but some, such as Dose Quantity, are present in the majority of Dose Instructions. Some Components have been further sub-divided into sub-components or attributes of the particular component.

Dose Quantity

The **Dose Quantity** in a Dose Instruction or Dose Instruction Clause is the "amount" of the described medication that is to be administered to the patient at a single point in time (i.e. a single dosage administration act, which may itself be a Dose Instructions Clause).

A Dose Quantity is usually expressed as a numerical value and an explicit unit of measure; however sometimes the unit of measure is implicit (e.g. the "one" in "one to be taken three times a day" is actually "one tablet" [or one capsule etc.]). Note that the expression of Dose Quantity value may be a range: e.g. "2-6 tablets", "100-200mg", "one to two puffs".

Note that the expression of some Dose Quantity information is such that it may appear to be a "dose limit"; this should not be confused with the "Quantity Upper Bound" as described below. For example the statement of "up to three tablets" is

actually a Dose Quantity range of "1-3 tablets"; it is describing the acceptable range of the dose quantity for a single administration.

It is vital that the Dose Quantity component has consistency with the description of the medicine to which it relates. This is discussed in detail below.

Examples of Dose Quantity:

> one tablet
> two puffs (actuations)
> 25 - 50mg
> one 5mL spoonful
> 750microgram/kg bodyweight

Dose Quantity Upper Bound

The **Dose Quantity Upper Bound** in a Dose Instruction or Dose Instruction Clause describes the upper limit of the amount of a medicine that may be given in a specified period of time; it is usually used when there is some degree of optionality in how the medicine may be administered.

A common expression of Dose Instruction information that uses this Component in its type/pattern is: "Take two tablets every 4-6 hours when required, to a maximum of eight per day". The "eight tablets per day" is the Dose Quantity Upper Bound. The Dose Quantity Upper Bound therefore has two distinct parts: the total amount (dose quantity) of medicine that forms the limit or "upper bound" and the time period that the amount can be administered in. A Dose Instructions Clause may occasionally have more than one Dose Quantity Upper Bound; if this is the case, they will be stating the maximum cumulative dose for different periods of time, for example: "maximum of 20mg in 24 hours, and 100mg in one week".

Note: Conceptually it would be possible to specify a "lower bound dose quantity" (for example: take a minimum of 300mg per day), however, in analysis, no actual examples of this type of instruction have yet been found.

Examples of Dose Quantity Upper Bound:

> Up to 6 tablets in 24 hours
> No more than four sprays in one hour
> Maximum of 500mg per day
> Maximum of 250mg in one week
> To a lifetime limit of 100microgram/kg bodyweight

Dose Timing

The **Dose Timing** in a Dose Instruction or Dose Instructions Clause describes "when" the medication is to be administered to the patient.

Description of "Timing" of medicines administration is possibly the most complex of all the components of Dose Instructions. In order to be comprehensive of the full range of variables, such that *as much information as is possible* could be made machine processable if required, it is necessary to analyse and document fully each type of "Timing" description separately, even though these are often concatenated and flow easily in human speech as if they are seamlessly one. It is likely that, in actual applications, some types of Timing information will be designated as too complex to replicate fully in a machine readable way and therefore should continue to be communicated only through text. This is a legitimate decision, but it must be made with full understanding of what is being set within any machine readable boundary, and what is outside. This understanding can only be obtained if the full analysis is documented.

There are three paradigms to be considered in the understanding of the timing of medicines administration: the "what is being timed", which may be "individual dose timing" or "course of therapy", the type of "time pattern" – the "when" and "how long" - being described, and the "timing description" being used to describe the actual time information, which may be "measured time" or "circumstantial time".

What is being timed: "Course of Therapy" Timing and "Individual Dose" Timing

When a medicine is used to provide healthcare to a patient, as a "therapy" (a treatment, a patient management intervention), the medicine may be administered once (only), or it may be administered a number of times, which may be either a limited number of times, or it may be ad infinitum. There is therefore a requirement to describe the Timing of this "Course of Therapy".

Similarly, there is a requirement to describe the Timing of *each time* a medicinal product is administered, within a Course of Therapy; with is the Individual Dose Timing; for example, a diuretic given regularly to treat hypertension is given "once daily, in the morning" where the "once daily" is the Timing of each Individual Dose.

A single "one off" administration of a medication (such as an infusion of streptokinase, or a pre-medication), in terms of this analysis, could be considered to have a "course of therapy" component, but, because it is only a single administration, its description is identical to the description of its individual dose timing.

A Note on Vaccination: Vaccines are usually administered according to an agreed schedule, with the Frequency of Individual Dose Timing being anything from one month to 5-10 years. It is a matter for national (public health) consideration to determine how to describe each schedule, and it is important to have consistently represented information for public health management. For example: it is possible to describe the course of therapy for the "triple" of diphtheria, tetanus and pertussis as the initial three doses given at monthly intervals from age 2 months, with the pre-school and school-leaving boosters being described as separate individual doses and courses, or alternatively the full 18 year schedule be considered the course of therapy.

Time Patterns: When and How Long - Frequency and Duration

For each of the Course of Therapy and the Individual Dose, there are two types of Time Patterns that can be used to describe their timing; these may be used separately or together, and are "Timing Frequency" and "Duration".

Timing Frequency describes **when** the individual dose or course of therapy occurs, Timing Duration describes for **how long** the individual dose or course of therapy takes.

Timing Frequency, particularly for a series individual dosage administrations, may be described using a timing pattern; for example, an instruction of "twice a day" describes individual dosage administrations as happening "two times within a 24 hour period", or "every 8 hours", or at a specific time or times: "at 2pm and 6pm". However, for a single, non-repeating administration, the timing frequency may be a single point in time, for example "at 8am" or "stat" or "2 hours before surgery".

Timing Duration can be used both for an individual dose and for a course of therapy; for individual doses, it is usually only relevant for infusion or nebulisation, most other administrations are taken to be instantaneous; for example in the Dose Instructions Clause "give 500mg over 15minutes every 6 hours" the "over 15 minutes" is the duration of each individual dose of 500mg given. Timing Duration is more commonly used in description of Course of Therapy; for example the "for five days" of an instruction "take two daily for 5 days".

Timing Description: Measurable Time and Circumstantial Time

The nature of the timing of medicines administration may be described in relation to "measurable time" in some way or another. This may be described by reference to a distinct point or points in time either within an unspecified day (e.g. at 6pm) or in a partially specified day (e.g. at 6pm tomorrow) or within a fully specified day (e.g. at

6pm on 14.2.2005). Measurable time may also be specified in terms of patterns of measurable time, as in "three times [within] a day", in which "a day" is a pattern of measurable time, i.e. 24 hours, or as "every 8 hours". Note that, for Dose Instructions, most time patterns involve a 24 hour day, but weekly, monthly and annual patterns are described; indeed, for vaccination, longer patterns (e.g. every 5-10 years) may be described using this same method.

Alternatively, the "when" of medicines administration might be described in relation to conditions or events or circumstances that will, have or do occur, and that form a trigger to start, stop or in some other sense have influence over when a medicine is administered. For example: "starting one week before travel" – the event is that is the timing trigger for medicines administration is "travelling" and the medicine administration must commence one week before that event occurs.

In any one Dose Instruction or Dose Instructions Clause, the various components of Dose Timing (individual dose or course of therapy; frequency or duration) may be described using measurable time description, using circumstantial time description or using a combination of the two.

Types or Patterns of Circumstantial Time

There are various types or patterns of Circumstantial Time used in the description of Dose Timing that can be recognised and described.

Preconditions

A Precondition describes when an event will or will not occur, in relation to the presence of a particular circumstance or event. There is therefore an absolute dependency on a certain event or activity or clinical condition occurring or taking place to describe the "when" (either Frequency or Duration) of an Individual Dose or Course of Therapy.

Many of the Individual Dose Frequency statements that use the Circumstantial Time pattern of precondition are descriptions of clinical conditions that the medicines administration is being used therapeutically for. For example: "take two tablets to relieve fever" implies that the medicine will only be administered if there is the "precondition" of fever being present. In these cases, the Precondition may "qualify" (that is, be stated in addition to) a Dose Timing described using Measured Time. For example: "Give one tablet once daily, if the pulse rate is above 80 beats per minute" states that that the medication must only be given at its Measured Time Frequency of "once daily" when the Circumstantial Time clinical precondition of the patient having "a measured pulse with a value of greater than 80 beats per minute" is met.

A Precondition may have a *Measured Time phrase* within it, but that Measured Time phrase does not describe either a Frequency or Duration but a "time interval" between the precondition and the administration. For example "Give two hours before the procedure" is an Individual Dose Frequency described using the Circumstantial Time pattern of precondition, whereby the medicines administration has "the procedure (happening)" as the precondition, and the "time interval" being "two hours before".

Trigger Conditions

A Trigger describes when an administration *may* occur, in relation to the presence of a particular circumstance or event. In contrast to the "Precondition", which describes how the Dose Timing **is** controlled by the precondition, the "Trigger" allows some optionality to be present. Because the condition or event is a trigger that "allows" rather than "requires" the medicine administration, it is often expressed with the words "if" or "when" and therefore includes some very common instructions, such as "Take two tablets every four to six hourly, *when required for pain relief"* as well as rarer more complex examples.

> **Comment**: *There is a considerable element of judgement required to discern whether a particular dosage phrase constitutes a precondition or a trigger. A precondition is "tighter" in that it "requires" the administration to start/stop/continue if the related observation it is true, whereas the trigger is "allowing" the administration to start/stop/continue if the related observation it is true. Whether clinicians, patients and systems can or should be able to truly differentiate this difference in clinical practice is as yet unclear for dosage information.*

Examples of Dose Timing Components:
Measured Time Examples:

Individual Dose Timing:
Frequency:

    every 6 hours [q 6 h]

    three times a day [t.d.s]

    daily

    twice a week

    every 4-6 hours (frequency range)

    not less than every 8 hours (minimum value of frequency range only)

    up to four times a day (maximum value of frequency range only)

Duration:

    give 500mg over 30 minutes every 6 hours

    30mg via syringe driver over 12 hours

    mix into a bath of warm water and immerse body for 30 minutes

Course of Therapy Timing:

Frequency:

    apply twice daily for 1 week; repeat at monthly intervals

    one daily for the first 5 days of each month

Duration:

    one to be taken three times a day for 5 days

    apply sparingly for 7-10 days

    take twice daily for 2 months

Circumstantial Time Examples:

Individual Dose Timing:

Frequency:

    after each loose stool

    before each nappy change

    before sexual intercourse

    when the cytotoxic infusion has been completed

Duration:

    for the duration of each dressing change

Course of Therapy Timing:

Frequency:

    for each acute attack of gout

Duration:

    from one week before until four weeks after travelling

    during an acute attack of gout

    take one every 4 hours, for up to 10 doses
        (although the Course of Therapy Duration *could* be

calculated as a Measured Time value, using the Measured Time information,

but described as it is, the Duration is bounded by "a number of doses having

been taken, which constitute the "circumstances" of the duration)

Combinations of Timing Descriptions:

    Give one tablet once daily, if the pulse rate is above 80 beats per minute
(precondition on Individual Dose Frequency)

    Inject 5mg subcutaneously every 6 hours when required to relieve migraine

Objectives and Goals

The **Objectives and Goals** information in a Dose Instruction or Dose Instruction Clause describes the Objective or Goal of that particular Dose Instruction or Dose Instruction Clause. The Objective or Goal information may relate to any of the other components of the Dose Instruction Clause, but common patterns relate the Objective or Goal to the Dose Quantity, Rate of Administration and/or the Dose Timing components.

There are two distinct patterns for Objective and Goal information in Dose Instructions; these are Maintenance Objective and Final Objective.

Maintenance Objective

A Maintenance Objective in a Dose Instructions Clause describes a requirement to (achieve and) **maintain** a particular circumstance or condition. There will be some optionality in Dose Quantity, Rate of Administration or Dose Timing (usually a range value in one of these components) and the Maintenance Objective gives the criteria that should be used to determine the actual value of the component from within the range. For example, in the Dose Instructions Clause "Infuse 2-5micrograms/kg/min to maintain systolic blood pressure at greater than 70mmHg" there is a range value for the Rate of Administration component, with a Maintenance Objective stated as "to maintain systolic blood pressure at greater than 70mmHg"; therefore the instruction is to adjust the Rate of Administration within the stated range in order to maintain the systolic blood pressure at a level that is greater than 70mmHg.

Final Objective

A Final Objective describes in a Dose Instructions Clause describes a requirement to **achieve** a particular circumstance or condition, (at which point the administration may cease). There will be some optionality in Dose Quantity, Rate of Administration or Dose Timing (usually a range value in one of these components) and the Final Objective gives the criteria that should be used to determine the actual value of the component from within the range. For example, in the Dose Instructions Clause "Take one tablet every morning until the bleeding stops" there is an implicit statement about the Duration of the Course of Therapy (a Dose Timing component) in that the therapy should continue "until the bleeding stops"; therefore the "Final Objective" is "the bleeding stops".

Examples of Objectives and Goals:
Maintenance Objective:

    Dose Quantity:

Give 1-4mg daily to keep the INR between 3-4

Rate of Administration:

Inhale at a rate of 1.5-4 litres/minute to maintain adequate peripheral oxygenation

Dose Timing:

Inhale one puff up to six times a day to control the wheezing

Final Objective:

Dose Quantity:

Take 10-25mg four times a day until there is no breakthrough pain

Rate of Administration:

Infuse 100-250ml/hour until urine output is greater than 50ml/hour

The Route-Site-Method Complex

The "Route-Site-Method Complex" describes the "where" and "how" the prescribed medication is to be administered to the patient.

In order to have its desired therapeutic effect, an allopathic medicine must in some way come into contact with some or all of the body of the patient. The Route-Site-Method Complex component of a Dose Instruction or Dose Instructions Clause describe the route into the body, where on the body the medicine makes it entry/contact and/or the method of administration to be used. This allows the prescriber to give specific direction to the patient and/or parent/carer/healthcare professional about "where" or "how" to administer their prescribed medication.

The Route-Site-Method Complex is can be further decomposed into the three separate components of Route of Administration, Site of Administration and Method of Administration; in any one Dose Instructions or Dose Instructions Clause, all, one, two or none of the components may be used dependent on the medication prescribed and the intent of the prescriber.

Examples of the Route-Site-Method Complex:

One tablet three times daily (none)

Inject (method) 100mg/5mL IV (route = intravenous)

Apply to the affected area (site) with gentle massage (site = "affected area" and method = apply with gentle massage)

Instil (method) two drops into the left eye (site) twice a day

Inhale (method) two puffs four times a day

Route of Administration

The Route of Administration describes which way that the administered medication should take to get into the body or into contact with the body and constitutes part of the "where" (the other part being site – see below).

There should be no implication that a route of administration is or can be taken as synonymous with a description of the "final destination" for an administered medication; the route of administration can only be a stylised description of the path taken.

For example, an oral antibiotic may be used to treat a severe infection on a toe; the oral route is used to get the medicine to be able to reach and treat the infection in the toe. For some specific routes of administration, there may be an incidental sense of "final destination", for example an ocular administration usually occurs when treatment of an eye condition is required. Note that this can in no sense be taken as definitional: rectal administration of a medicine may be for a local effect (a steroid foam for treatment of colitis) or for a systemic effect (metronidazole for treatment of infection). The route of administration of a medicine should only be a description of the path taken; the end may or may not be implied.

Examples of routes of administration include: "oral", "rectal", "ocular", "intravenous (IV)", "subcutaneous (SC)".

Site of Administration

The Site of Administration describes the specific area of the body "where" the medication is to be administered. The site can be seen as the particular anatomic location where an administration activity happens (or has happened). It can be stated specifically, for example including laterality (e.g. apply to the right eye; inject into the left antecubital fossa vein) or stated more generally (e.g. apply to the affected area(s)).

Site of Administration is a distinct and separate concept to Route of Administration, Route of Administration being the "way in" to the body and the site the specific area in/on the body where the "way in" is located. In some Dose Instructions or Dose Instructions Clauses, if the Site of Administration has been stated very explicitly, the Route of Administration may be being implied rather than explicitly stated itself. For example, a Dose Instructions Clause that states "instil one drop into the right eye twice a day" has a Site of Administration of "the right eye" which implicitly indicates an ocular Route of Administration.

Just as the Route of Administration is a description of the "path taken" and carried no implication as to the sense of a description of a "final destination"; so the Site of Administration is a description of where the administration happens, not the site of action of the medication; although as for route, there are some examples where the site of administration is also a description of the site of action (for example, administration to the right ear is likely to imply a site of action in the right ear).

Method of Administration

The Method of Administration gives further information as to "how" the medication should be administered. A "method" can be defined as "a regular and systematic way of accomplishing something". The "Method of Administration" is therefore the particular way of carrying out or accomplishing a substance administration, in that it further defines the process of the medication is to be administered to the patient, whether that is by the patient or by the parent/carer/healthcare professional.

Method description is often an adjective that directly refines the action giving more specific information as to "how" the prescriber intends that medication to be administered; it can be also have a further qualifying description added to the original method in order to fully define the exact method of administration required; for example: "apply with gentle massage".

In Secondary Care, standard charted dosage instructions do not usually have the "method" concept made explicit. However, if a dosage instruction is "written" as opposed to the more common "charting", there may be a method stated. For specialist parenteral administration, it is more common to have some "method" information expressed, even if this is written as an annotation to a standard chart.

Method Qualifiers: As seen in the descriptions above, the Method of Administration may be described or "qualified" by further information that gives more detail about the administration; a method of administration is "application" ("apply" or "to be applied"); this can be further qualified by various adverbs (liberally, sparingly, gently) as required by the situation. Due to the limited size of the vocabulary, however, pre-co-ordinated concepts ("apply sparingly", "inject using piggyback") are used.

Rate of Administration

The Rate of Administration describes information about the "delivery speed" with which a specified amount of a medication should be administered to a patient per unit of time. It is applicable for "continuous" medications only (e.g. liquids, inhaled

gases etc.) since an instantaneous administration does not exist for long enough for it to have a measurable speed at which it is given.

Certain medications, most notably parenteral infusions, may be given continuously over an extended period of time. The rate at which the medication is to be administered may be specified as an alternative to a Dose Quantity and Timing, and is usually used because the exact Dose Quantity to be given and/or duration of the administration is not known.

Examples of Rate of Administration:
> (to be given at) 2litres/minute
>
> (to be given at) 5micrograms/kg/minute
>
> (to be given at) 50ml/hour

Device Use Instructions

Device Use Instructions describe information about administration of a medicine that involves the use of a device.

A number of medicines require their administration to the patient to be assisted by the use of some kind of administration device. This "device use" information is often communicated as part of the Dose Instructions or in a Dose Instructions Clause.

In secondary care, particular named devices may be described as part of a dosage instruction; for example, administration of a particular medication via one specific lumen of a triple lumen sub-clavian catheter, or administration of an antibiotic through a Hickman line.

This component must not be used for "recipe" information for extemporaneously prepared medicines.

Examples of Device Use Instructions:
> Via the nebuliser
>
> Using the vaginal applicator

Additional Instructions/Information

The Additional Instructions/Information component of a Dose Instructions Clause describes any other additional instructive information about the administration of the medicine; it is usually non-quantitative in its nature. It excludes any phrases relating to use of a device in the administration of a medicine, to a "recipe" for extemporaneous preparation of the medicine or to the active method of administration of the medication.

Additional Information/Instructions may give "negative" instructions or information, for example "do not take at the same time as milk or antacids".

Some Dose Instructions and Dose Instruction Clauses contain phrases of instructive information, additional to the defined Dose Quantity, Dose Quantity Upper Bound, Dose Timing, Objectives and Goals Information, Route-Site-Method Complex and Device Use Instructions concepts.

Preparation Instructions form a particular subset of Additional Instructions/Information. A number of medicines require some form of manipulation prior to their administration to the patient; this may be some form of preparation instruction such as dissolution or shaking/agitation of a mixture.

Preparation Instructions:

Preparation Instructions describe manipulation of the medicine prior to its administration, but the preparation is such that it does not affect the expression of the quantity of the medication administered (for example the "dissolved in water" manipulation does not affect the "two tablets" quantity of a dosage instruction that reads "Take two tablets, dissolved in water, every morning").

Examples of Additional Instructions/Information:

"as instructed on the pack"

"titrate according to response"

"with or after meals"

"do not take with milk"

"avoid alcohol while taking this medicine"

"dissolved in water"

"shaken well before use"

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