Clinical trial information: developing an effective model of dissemination and a framework to improve transparency

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Declaration of Originality

I, Maria Helena Korjonen, 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.

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Abstract

Purpose

The research aim has two parts: Firstly, to characterise and evaluate clinical trial information and the dissemination of that information by constructing a conceptual model structuring the processes of information generation. Secondly, to test the model by identifying the dissemination methods used, consider their effectiveness and what factors affect dissemination. The research findings contribute to outline a framework of recommendations with an optimal model of effective dissemination for improved transparency in clinical research.

Design and methodology

Based on the literature review, a conceptual model was constructed outlining the structure of information generation throughout the clinical research process. A mixed approach with qualitative and quantitative studies were undertaken to form a comprehensive picture of the dissemination of clinical trial information and in order to test the model.

Key findings

The model identified that clinical trial information is very complex, scattered across many resources and many factors affect how, where and what clinical trial information is disseminated. A model of effective dissemination and a framework of recommendations for improved transparency in dissemination were drawn up for three areas; regulations and standards, communication planning and the organisation of clinical trial information.

Limitations

This research has been done during a time of significant and rapid change in the clinical research environment and therefore this thesis is a snapshot of a time when new web tools allows for information to be disseminated rapidly. A series of small studies were made to gather an overall picture of information transparency in clinical

trials as we lack evidence in these new areas.

Originality/value

There is no existing conceptual model that explains and tests the dissemination and transparency of clinical trial information. Models can structure processes, suggest improvements in the processes and be used as a basis for further research.

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1. Chapter 1 Introduction to this PhD thesis

1.1. Introduction

The purpose of this introductory chapter is to outline the statement of the problem and the motivations for this study by indicating its importance and relevance for the fields of information studies, publishing and clinical research. The aims and objectives of this research are explained and the research questions defined. An outline of the thesis by chapter is also provided.

1.2. Statement of the problem

The crisis at the core of this study is that there is little trust in the clinical research process. Part of that distrust is that clinical trial information is scattered across a variety of resources, and sometimes information is not made publicly available at all. There is no existing model that explains the clinical research process and the information that is generated throughout clinical trials. This research firstly aimed to model the information generated in clinical trials. Once the model was built, the second research aim was to test the model in order to examine the possibility of improving the dissemination of that information and to provide a framework of recommendations for an optimal model for effective dissemination.

Clinical research is a very regulation heavy environment in which to work. Even though research is global, the environment remains fragmented with various regulations affecting research. These regulations are global, national and regional, some requiring adherence to legislation across regions. There are also ethical guidelines on biomedical research to ensure patient safety and the ethics of research subjects. Understanding these regulations and requirements were essential before embarking on this research process and in order to build a model that shows how information is generated throughout the research.

Clinical research into a new promising entity is a long and expensive process which generates a lot of information, which are disseminated in various ways. The dissemination of clinical trial data is affected by various forces, regulations, guidelines, research objectives, research results, market needs, funding agreements,

pressures and so on. Dissemination activities can take many forms, such as presentation at conferences, via promotional material, in published papers or more informally via the web and this research identified rapidly emerging methods of dissemination which is changing the process of dissemination and access to information. The methods used are not flawless and there is evidence of where dissemination has been less than ideal. The clinical research process has come under scrutiny by the press with various recent court cases on issues such as falsified research data, non-publication of research data, misguided marketing claims etc. Again it was important to this research to understand the issues that affect clinical research today and perhaps get an insight into what may have caused those issues.

It is clear that clinical trial information is scattered across many different resources and that many resources lack standards for the organisation of clinical trial information and that there is poor control of such information. This research needed to show how complex clinical trial information can be and therefore how difficult it is to disseminate it and the reasons why it may not be disseminated. Some of these issues are wider than the clinical research community and are embedded in the scholarly communication process, e.g. who is responsible for research information and its storage?

There is a change in the scholarly communication and the information behaviour of researchers. The digital environment allows researchers to disseminate information not only through traditional scholarly communication methods, e.g. journals, but also in informal ways using social tools or by publishing informal reports or grey literature. The boundaries between formal and informal publishing activities are blurring. There are issues around quality of such material, searching and finding it, version control and ownership etc. but the point is that the web has opened up possibilities of informally disseminating clinical trial data rapidly. It became clear that there is an urgent need to address what it means to publish on the web.

1.3. Motivations for this study

The researcher of this PhD has worked within the pharmaceutical industry and during that time wrote her MA thesis on evidence-based medicine (EBM) from an information professional's point of view. At the time EBM became a force in

pharmaceuticals as NICE had recently been set up and changing the existing pharmaceutical sales model of convincing the physician to prescribe to providing evidence to NICE of the effectiveness of an intervention. NICE draw up intervention guidelines on cost-effective treatments and prescribing decisions are usually made based on these guidelines[i]. This was also the time of the *dot.com* boom, the web became an everyday tool to share information to a larger audience and there was no longer a need for visiting your GP for medical information and indeed no need for the GP to call the pharmaceutical rep for information. When moving onto working for the professional body of clinical researchers, it became clear that the world of information is changing rapidly but that research and researchers do not necessarily follow with it. Not deliberately, but because of too much too quickly and the inability to keep up. The public is increasingly information hungry, expecting to access information when they need it. Web 2.0 and other emerging developments are making interaction with information, other people and with researchers possible. Traditional one way communication has transformed into two way communication, making communication more interactive. I believe that this is an age of where transparency in clinical research is expected, information needs to be shared, including research design, objectives, results and summaries of findings. The main motivation for this study was an attempt at documenting some of these changes and review how new initiatives aim to make research more transparent.

An objective was to model the drug development process and show the complexity of information *generated* before, during and after a clinical trial and the kinds of output that information takes. Clinical research is an increasingly complicated area involving many individuals for many years, and as new regulations and ethical guidelines require more procedures within a clinical trial, research is becoming fragmented and potentially more confusing for the public and researchers themselves.

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[i] Note: The new government in England is changing the healthcare service with PCTs disappearing in 2012 and GPs given responsibility for their own budgets. The way in which NICE works is also under review. These changes may mean that prescription may change in the near future.

It was important to try to establish the reasons behind the distrust in the clinical research industry and arguments for more transparency in the research process. There are many factors that affect dissemination, e.g. organisational and journal publication policies and guidelines, economic and geopolitical pressures, regulations, the quality of the information generated in clinical trials, and the quality of the research itself, and many more. To what extent do these factors affect dissemination?

The question '*what is publication in the electronic environment?'* also provided a motivation for this research. It seemed a useful exercise to compare discussion about the scholarly communication process with that of communicating clinical trials. The research therefore draws extensively from research into information dissemination, investigations into the trust concept and the scholarly communication process. Rapid developments in the digital environment allow researchers to disseminate new forms of scholarly material, using various new methods such as blogs, discussion forums, own research web pages etc. It seemed interesting to investigate if there is a change in dissemination behaviour. Is the divide between formal and informal scholarly communication increasingly blurred as has been stated? The journal model has not changed dramatically, even with the possibilities of the Internet, but how long can the current journal model last? An examination of methods and processes to disseminate may tell us which methods are best fit for purpose, e.g. which methods are best suited for disseminating clinical trial information?

There are many methods used for dissemination and I wanted to investigate what determines the selection of information for dissemination and the selection of dissemination methods. With the rise of the Internet we increasingly discover medical information when searching online. To what extent do researchers use dissemination opportunities available online? Different search experiment online over a period of a few years revealed that access to clinical trial information online has increased enormously. It will be interesting to see if electronic dissemination methods may increase and even replace the traditional methods of scholarly communication, e.g. publishing a journal article.

By evaluating strategies of dissemination, methods used, factors that affect dissemination and in examining current practice it seemed useful to document that

understanding of dissemination of clinical trial information in a PhD. It also seemed possible to use this evaluation as a basis to provide a recommendation and framework for improving the dissemination process.

1.4. Scope

The topic of dissemination could potentially be a huge area of research within information studies or clinical research. In order for this to be a manageable PhD there are some inclusion and exclusion criteria that were set.

Inclusion

- This research aims to demonstrate aspects of discovery and characteristics of clinical trial information not all biomedical information.
- Clinical trials and research are global processes with many global factors affecting them. This research gives an overview of clinical trial information with no specific references to specific regions, unless it is useful to do so. Differences in regions are explained, in particular when discussing regulations.
- It is looking at primary methods of dissemination, e.g. methods where the researcher aims to get a clinical trial published or the results released.
- Information is global, when searching for information, in particular on the web, we may not always think about the origins of information. Clinical research is also a global industry and many clinical trials are multi-centred, e.g. take place in many countries, or regions within countries. In this PhD I compare different regions where relevant, e.g. FDA (USA) and EU studies. Much published literature comes from the US and where possible I have done some UK or EU studies to offer comparison.
- Trust and quality are two concepts that are important to information dissemination and will become even more important aspects when engaging with information in the future in particular online. These concepts are referred to where relevant.
- The scholarly communication process is referred to and changes highlighted when reviewing methods of dissemination and the assessment of their fit for purpose within clinical research.

Exclusion

- It attempts to establish what pre-conditions are needed for effective access to clinical trial information, but does not cover details of information needs and information literacy skills of specific groups of people, e.g. the public.
- It does not examine secondary resources that systematically review clinical trials, e.g. libraries that review clinical trials, *Cochrane Library* or *National Institute for Clinical Excellence (NICE)*. They are mentioned briefly where relevant.
- This research does not extend to looking at dissemination or complications of information dissemination in developing countries, with efforts to reduce the digital divide and the lack of efforts in sharing clinical trial data with clinical trial participants world-wide.

1.5. Choosing diabetes and obesity for research

In order to conduct manageable studies for this research, it was suggested I narrow down the scope of research to a key therapeutic area. There are reasons for selecting diabetes and obesity as an area of research for this PhD. According to many organisations, the obesity epidemic is an enormous global problem which is spiralling out of control. The UK has a large amount of overweight and obese people, conditions that often continue to develop into type II diabetes. Approximately one in every five adults in the UK is overweight, and one in 15 is obese, and this figure is climbing. The cost to the health service of diabetes and related conditions is growing and complications of diabetes are very costly to treat. Patient numbers with complications of obesity were thought to have doubled between 2005 and 2010 according to data analysed by the Foresight team[ii]. It is likely that more people will be seeking out new interventions for obesity including clinical trials and very likely turn to the Internet for information seeking.

[ii] The Foresight team analysed data from health survey England on obesity data, published on http://www.idea.gov.uk/idk/core/page.do?pageId=8267926 [Accessed 1 June 2011].

1.6. Geographic coverage

There are three distinct regions in clinical research, identified by the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, ICH[1] for short. These regions are the EU, USA and Japan. The goal of the ICH is to promote international harmonisation on technical requirements of clinical trials. ICH has also extended membership to non-ICH countries, who may their own regional partnerships to harmonise clinical trials. Although this harmonisation partnership exists, within the ICH, within regions themselves (like in the EU) and in other forms of partnerships, clinical trials are very different within the regions due to differing requirements, laws and guidelines. This makes clinical trial information a difficult area to research as there are constant reminders that things are not the same within these different regions or countries.

Information is global and the development of technologies allowing information to freely flow regardless of borders makes it an interesting topic to research within such a regulation heavy environment which is clinical research.

Much research that I draw upon for this PhD will be global, cross-regional or national. There is an attempt to stay within the three ICH regions and not venture into the non-ICH regions and as the exclusion criteria already mentioned, not cover the differences between developing and developed countries where there are many information issues that would make research for this thesis too much. Furthermore there is an attempt to compare the EU region to the FDA region, in particular where I have found research that has taken place in the US but not in the EU. In some cases I have also conducted research into what is happening in the UK, in particular where pointing out the always changing environment in which we live. The change of government affects healthcare nationally. Changes on an EU level have to be incorporated into national law or regulations. Changes in the FDA region may affect the EU, and certainly affects clinical trials taking place in the US sponsored by an EU company, or studies in the EU sponsored by a US company. This complexity highlights the need for harmonisation across regions and clearer guidelines to those conducting research. The global demand for information from clinical trials will increase and this PhD is timely considering the growth of online tools and opportunities to disseminate information in real-time online.

1.7. Research questions

When the research first began, my initial research questions were around themes. The themes allowed me to organise my research and explore how I could best present the research. After the initial literature review and organisation of information discovered around these themes, I identified gaps and questions that I needed to answer. These became my research questions. After draft 2 of this thesis, I was able to simplify and improve the research questions and arrange my research into appropriate chapters addressing the research questions in turn.

The research questions became:

1. What is clinical trial information?
2. What do we mean by dissemination?
3. What methods are used to disseminate information?
4. Why is a particular method chosen and what factors affect information dissemination?
5. What is effective dissemination?
6. Can we improve the dissemination of clinical trial information and make the process more transparent?

1.8. Research aim

The two-part research aim became: firstly, to characterise and evaluate clinical trial information and the dissemination of that information by constructing a conceptual model structuring the processes of information generation. Secondly, to test the model constructed by identifying the dissemination methods used, consider their effectiveness and what factors affect dissemination.

1.9. Research objectives

The objectives of the research were:

- Model the drug development process and the processes by which clinical trial information is generated, stored and disseminated

- Critically analyse the different methods used to disseminate clinical trial information and summarise the factors that affect dissemination
- Through a survey of clinical research professionals, and the examination of publication policies within organisations, explore the understanding and practice of registering and disseminating clinical trial information
- Conduct Internet search experiments to assess how information is scattered
- Evaluate different tools for discovering clinical trial information on the Internet
- Make a recommendation for how the dissemination of clinical trial information could be improved and more transparent.

1.10. Contributions of this study

It is clear that when starting this research, little had been published around clinical trial registration and issues of sharing research results. Still to date little previous research studies of the kind in this thesis have been published and pulling together research studies in this way has proved valuable in getting an overall picture of clinical trial information.

Although many models exist for the scientific communication process, no one has as far as I am aware modelled the clinical research process and the information generated throughout clinical trials. The conceptual model will be useful to those who provide training on clinical trials and for anyone who needs a quick overview of the research process as well as for building upon as new research findings emerge.

I selected the obesity and diabetes topics for the various studies as these diseases are growing in our communities and therefore it is likely that in the future more information will be needed by the public who are looking for health information and by professionals who need clinical evidence on these disease areas. Obesity and diabetes have not previously been used for these types of studies in published literature.

This thesis offers a range of recommendations for improvements to the clinical research process in making it more transparent. It is hopefully a valuable document that offers an insight into the situation of disseminating clinical trial information

over a period of five years and what the issues are from an information professionals' point of view. It is hoped that these studies form a basis for future research.

The research has also highlighted the lack of consistent terminology in this field of study, and this could be an area in which the information profession could provide an input to improve how we search for and find information about the process of clinical trials and the information from clinical trials.

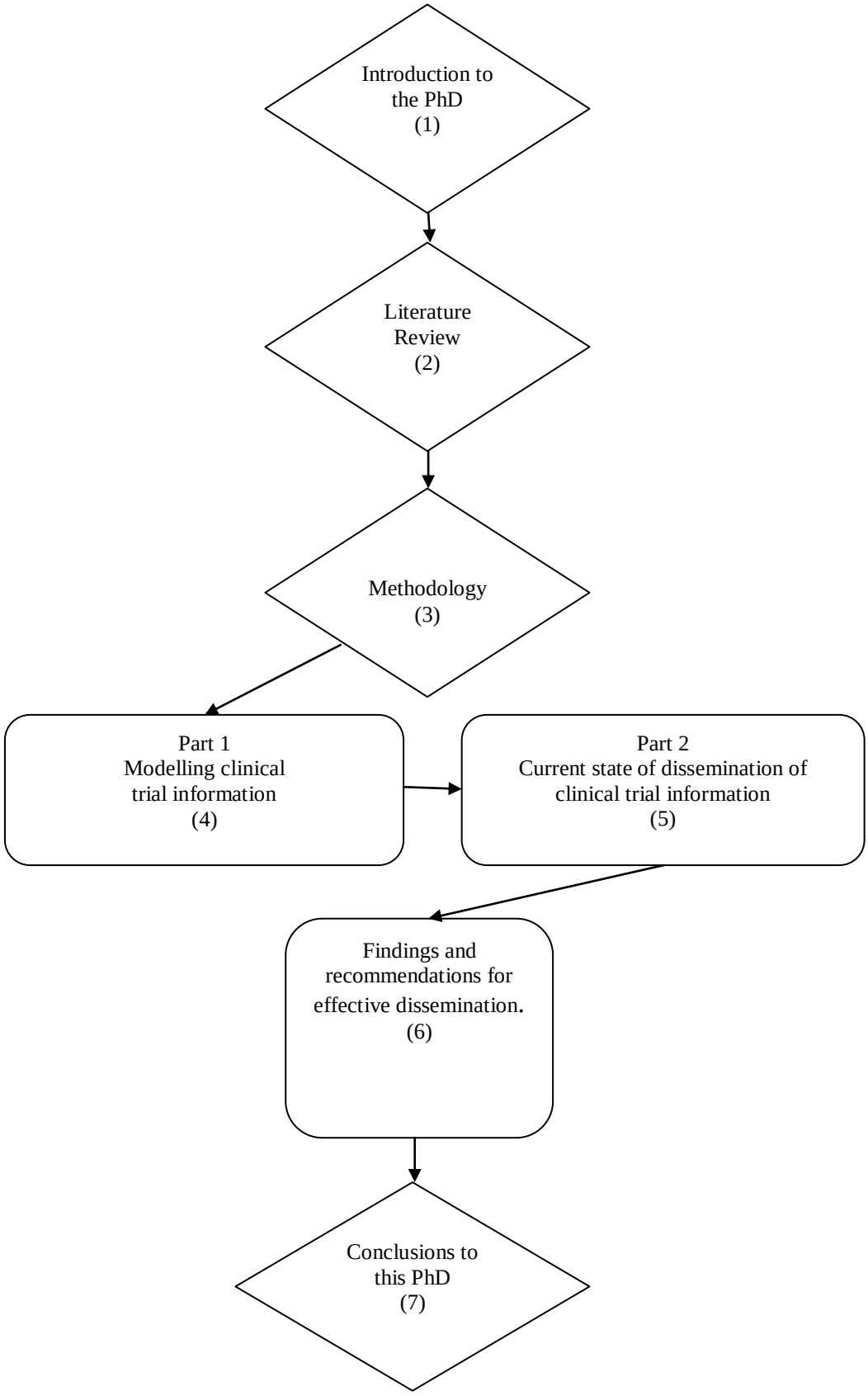
The research has highlighted the evolution of publishing with online methods used for disseminating clinical trial information and I have made a suggestion for an improved definition on what it means to publish to include the new methods.

I hope that this study contributes to an understanding of the complexity of clinical trial information and what happens to the information that is generated throughout the process. I also highlighted the many interlinked issues between clinical research and informatics, e.g. around data standards, intellectual property, trust, information literacy and behaviour etc.7

1.11. Thesis outline - flowchart

A thematic approach has been taken when compiling the research findings. Information and research results are discussed in themes, replicated from the literature review, and which follows the order of the research questions.

The thesis is divided into 2 parts of 7 chapters (in brackets below), appendices and a bibliography.


Introduction to the PhD (1)
Literature Review (2)
Methodology (3)
Part 1 Modelling clinical trial information (4)
Part 2 Current state of dissemination of clinical trial information (5)
Findings and recommendations for effective dissemination. (6)
Conclusions to this PhD (7)

Chapter	Content of chapter
1	Introduction to the PhD, statement of the problem, motivations for the study, research aim and objectives, contribution and research questions.
2	Literature review, setting the scene, introduction to clinical research and introduces concepts used through the thesis and describes information resources used for this research. Literature is also introduced throughout chapters 4, 5, 6 where it is central to the discussion around my research findings.
3	Describes the research methodology adopted in order to respond to the research questions, each study is introduced with its study design and limitations.
PART 1 4	Explains the drug development process and introduces clinical trial information. The conceptual model of the clinical research process and information generated within the process is introduced. Responds to research question 1.
PART 2 5	Tests the model constructed in part 1. Provides the evidence to illustrate the current state of clinical trial information dissemination. It summarises the dissemination methods used, what factors affect dissemination and how effective the methods are. It also critiques the concepts of dissemination and publication. The concept of trust and how this is linked to the dissemination of clinical trial information is discussed. The results of a survey of clinical trial professionals provide an insight into the practice of clinical trial registration and dissemination. Responds to research questions 2, 3, 4 and 5.
6	Provides the framework of recommendations and an effective model of dissemination, which may lead to a transparent research culture and ultimately improves public health. Responds to research question 6.
7	Concludes the research and addresses the research questions, limitations and future research suggestions.

1.12. Conclusion to Chapter 1

This chapter was an introduction into the research undertaken for this PhD. It outlined the statement of the problem and the motivations, the aims and objectives of the research and the research questions. An outline of the thesis by chapter was also provided.

2. Chapter 2: Information sources and literature review

2.1. Introduction

This chapter serves as an introduction to the thesis. It describes in detail what resources were used to find relevant research and terminology used clinical research and also in this research. The literature review, which is organised around the research questions, introduces briefly what is known, controversies, highlights specific gaps and questions that needed answers.

2.2. Resource discovery

A number of resources were used to find suitable literature for the review.

Literature in *life sciences*, and *clinical trials*, is indexed in *PubMed* (or *Medline*) but can also be found across many non peer-reviewed sources that cannot be searched for in a bibliographic database. Some of these sources are magazines published for the clinical research audience, e.g. *International Clinical Trials*, *Applied Clinical Trials*, etc., but also grey literature such as conference presentations, reports, websites, blogs, e-newsletters, newspaper articles etc. The Internet, mainly the search engine *Google* and *Google Scholar*, and hand searching through the bibliographies of books and references of published papers and grey literature aided the discovery of other research but it was a time-consuming activity. A large amount of time was spent weeding out unsuitable literature.

It was also necessary to search in other subject disciplines that cover publishing and electronic communication, the *publishing* and *library and information* fields in particular. The databases searched were *LISA*, UCL's *MetaLib* allowing a cross search across a variety of databases, e.g *SCOPUS*, *Web of Science* etc.

The following broad search strategies were used in different databases:
"clinical trial*" AND (information OR data)
"clinical trial*" AND (information OR data) AND (disseminat* OR publish* OR report* OR communic* OR public*)
"clinical trial*" AND (registr* OR bank)

Many other narrower searches were run where necessary in particular in areas where concepts such as *trust*, *transparency*, *regulations*, *policies* and specific topics are discussed.

A number of other resources were also consulted, such as clinical trial registers, email correspondence with clinical trial professionals, conversations with peers, authority websites, regulations, ethical guidelines, journal publisher websites etc.

2.3. Terminology and difficulty with classification systems

The *Medical Subject Headings* (MeSH) from the US National Library of Medicine is a reasonably well developed classification system used in Medline and PubMed. However, there are difficulties with the lack of terminology when researching the clinical research process, including the administration or management of clinical trials, the profession of clinical researchers and so on.

Terminology available when searching the MeSH for *clinical trials* are:

- Clinical Trial
- Clinical Trial, Phase I, Phase II... etc.
- Clinical Trials Data Monitoring Committees
- Controlled Clinical Trial
- Early Termination of Clinical Trial
- Meta-Analysis

And when searching for MESH terminology for *clinical research*:

- Biomedical research
- Clinical research
- Clinical nursing research
- Clinical research protocol
- Nursing Methodology Research

Terms that are often used for clinical trials are simply not covered by the classification system in Medline. This was also experienced across other databases that were searched for this thesis. One study comparing indexing of randomized

trials in Medline with EMBASE found that 80,000 records out of nearly a third of a million records had not been indexed as randomized in Medline[2]. The lack of terminology available to index material has been discussed by others, the lack of terms used in indexing means that many articles that are relevant to a search are missed out[3;4] and the quality of indexing of clinical trials in electronic databases has been said to be poor[5] and that search sensitivity and precision within databases should improve[4].

A major challenge in finding relevant resources is the lack of an established thesaurus suitable for searching for information on *clinical trials* and *dissemination* or *publishing*. *Clinical research*, *clinical trials, clinical investigation* and *clinical study* or just *trial* are used interchangeably, sometimes with a combination of terms, e.g. randomised trial, human study etc., and literature searches bring back an overwhelming amount of papers that are reporting from clinical trials rather than on the process and management of the clinical trial.

This thesis refers to the *clinical research professional* who is a person involved in the creation and management of clinical trial information and may constitute many types of individuals like authors (those reporting on clinical trials), managers of clinical trials, clinical trial site staff, statisticians, research staff etc. These individuals are based in different organisations like national health services, pharmaceutical companies, research companies, academic institutions etc.

Publishing, *reporting*, *communication, disclosure* and *dissemination* are terms that are also used interchangeably making searching complex. This thesis concentrates on the term *dissemination,* which is the interactive process of spreading information using one or many methods. Communication is referred to frequently in literature and therefore also in this PhD where deemed necessary, in particular where published literature refers to the scholarly communication cycle. More terms that caused difficulty are the newer concepts of *repositories, databases, clinical trial register/registry* or *clinical trial banks* as there is no standard terminology as yet

developed, although the World Health Organization (WHO) has developed a definition trying to standardise the way in which registers are referred to[iii].

Knowledge, *information*, *data* and *publication* were also search terms used to narrow down results in some searches. As scholars use different terminology for these types of similar methods or tools, searching became increasingly complex and time consuming. It was also noted that when suitable references were found, many were poorly indexed (lack of metatags and keywords on websites and within published and grey literature) and it is very likely that many citations go unnoticed due to poor indexing, lack of standards and terminology as described above. The difficulty of finding common terminology has also meant that it was difficult to choose the most suitable terminology for use in this thesis, however throughout there will be explanations of terms and these are also discussed more in-depth in the literature review next.

2.4. Literature review

The purpose of the literature review is to introduce the world of clinical research and the dissemination of information. It will summarise and highlight specific topics that will be discussed in later chapters.

The literature review will begin by exploring clinical research and clinical trial information. It will then discuss dissemination, publication and scholarly communication. It moves onto discussing methods of dissemination and what is meant by effective dissemination. The trust and quality concepts are introduced and then it will introduce the factors that affect dissemination. The literature review sets

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[iii] A clinical trials register is the formal record of an internationally agreed minimum amount of information about a clinical trial. This record is usually stored in and managed using a database. A clinical trials registry is the entity that houses the register, and is responsible for ensuring the completeness and accuracy of the information it contains, and that the registered information is used to inform health care decision making. A clinical trials registry is more than its database. Source: http://www.who.int/ictrp/faq/en/index.html [Accessed 26 Feb 2011]

the scene by introducing terminology, existing research and highlight the areas that this research will examine.

2.1. Criteria for selecting material included in the literature review

For this thesis an exhaustive review with selection citation was adopted[6]. The criteria for selecting the material included in the literature review was to collect and summarise the most relevant information, published and grey literature, that address the themes identified in the research questions, papers that provided useful background information to issues, highlighting gaps and that inspired me to ask questions. They also serve as core papers that drive this research forward, in a way outlining the journey of the research. Other literature is also covered in later chapters. The reason for not including everything in the literature review is that many papers required greater discussion in relation to the research that took place for this thesis. It would be illogical to introduce them early on when setting the scene.

The first searches were run before officially commencing this PhD in 2006 when drafting the research proposal. The initial searches were incredibly broad to include aspects of research which have since been removed due to constraints and narrowing of focus, e.g. literacy skills, fraud and research misconduct and research in developing countries. The first sift identified key papers around my themes. Once I had organised my research in themes, and the final research questions were set, I revisited my literature review, updated it with new papers and removing those that were no longer considered key papers. The first literature review chapter was written as a draft to guide me in my research. Literature searches were then conducted on a regular basis including hand searching cited references. The final searches were run in November 2010 updating the existing bibliography, although a few references were added post Nov 2010 if anything 'new' was published and inclusion was seen to add to this thesis.

2.2. Validity of material

It is difficult to establish the validity of content in literature and specifically in content found on the web or in unpublished grey literature. By adopting the

exhaustive review with selective citation I made the literature review more manageable and allowing the use of grey literature. Grey literature can be contaminated with personal opinion of the author and may not have been through peer review. A critical appraisal of any citations was required. The goal during the critical appraisal was to identify central issues or a line of argument within a theme. I focused on findings of literature, based on some substance or evidence, and if the material fitted in with the rest of the literature identified around that theme. I wanted to take a neutral perspective and not introduce bias to the critical appraisal process. I have highlighted contradictions in conclusions or around issues throughout the thesis where such was present.

2.3. Reference Manager – a bibliographic tool

For this research the bibliographic tool Reference Manager 12 was used to collate all bibliographic information, and annotated notes, and the final catalogue contains 1022 citations referred to for this PhD. The 'Reference Type' field was used to distinguish between types of material collected, e.g. journal article, online source etc. I could also use the 'Notes' field available to write own comments. References were imported if possible from *PubMed* or from .txt files, or catalogued manually.

2.4. Clinical trials information and terminology

The term "clinical trial" was first used by the British Medical Research Council in early 20th century[1;2]. Some scientific studies comparing treatments were performed in the 18th and 19th centuries, e.g. smallpox, cholera, with the most notable interventional trial being that of James Lind, a surgeon, in 1747 involving 12 patients who had scurvy at sea[7]. The first true randomised clinical trial was conducted by the British Medical Council in 1948 involving 100 patients studying streptomycin's effect in the treatment of tuberculosis[8].

Very briefly described here, clinical research answers research questions into the efficacy and safety of medicines. A promising entity is selected to go through phases of research (clinical trials) to establish its behaviour. A clinical trial is the gold standard into the discovery of new medicines and devices, or *interventions* as I will refer to them, testing their efficacies before being marketed.

Clinical trials, or clinical studies, or clinical investigations, exist for a number of different interventions, such as medical devices, herbals, food, medicines and nutritional items etc. Due to differences in the way in which trials are regulated and performed in these areas, this thesis concerns itself with the broader environment of clinical trials and not specifics of particular research entities or areas. This thesis may refer to a new potential medicine as an *'investigational medicinal product' (IMP)* but in general it will refer to *interventions*.

The average cost of researching and developing a new chemical or biological intervention was 1,059 million € in 2007, and R&D expenditure globally has been estimated at $127.2bn[9] in 2010. There are around 107,000 individuals working in pharmaceutical R&D in the EU and the pharmaceutical industry funds thousands more researchers in the health care and university setting[10]. Because of the costs involved in developing a new drug, profits must be made in the sales of those drugs to sustain the product lifecycle. Only one in 10,000 entities successfully becomes a marketed drug, which makes the industry risky but also highly profitable if there is success with one intervention on the market. We do not know how many clinical trials are conducted annually around the world. According to some rough estimates, 100,000 clinical trials were underway in 2007 with a growing amount of clinical trials taking place outside Food and Drug Administration (FDA) in the US and European Medicines Agency (EMA)[iv] in the EU regions[11]. Recent estimates have suggested that every year approximately 4,000 clinical trials are authorised in the EU, meaning that around 10,000 clinical trials are ongoing at any time[12].

There are many research designs that may be appropriate for a clinical trial, however every trial must be scientifically sound and incorporate ethical principles regarding the treatment of research participants[13]. Although there is no standard for what a well-designed and well-executed clinical trial looks like, it has been said that the randomised controlled trial is ideal[14]. However, there is no methodology for assessing the quality, validity and relevance of a clinical trial including RCTs and

[iv] Used to be called the European Medicines Evaluation Agency (EMEA)

many RCTs exclude certain patient populations, e.g. women, children and the elderly[15-17]. Other study types, e.g. meta-analyses and expert reviews are also additional sources on evidence of treatment efficacy[17]. RCT methods are not applied to all therapy areas, a study shows that the cardiovascular, cancer, asthma, post-operative and anaesthetic therapy areas most often employ RCT methodology in trials[14]. More important is the concern is for the quality of the trial itself and the quality of the trial reporting[16]. Furthermore the way in which trials are conducted and how they are reported are changing over time, and therefore it will be difficult to develop tools, e.g. policies, standards, checklists and guidelines, that can be flexible with the types of trials that exist and how they develop over time.

There is no exact definition of *clinical trial information*. Chapter 4 will explain the components of clinical trial information and therefore provide a definition of clinical trial information in the context of this thesis. *Information* is a very broad term which is interpreted differently amongst different people. It is sometimes described approximately as being (1) raw data (2) specified and organised for a purpose (3) presented in a context to give it meaning (4) or that leads to an increase in understanding.

The results from trials, *raw data*, are analysed and interpreted. The data and their interpretation become information, and also evidence, of what we know about the intervention. This information is documented, disseminated and published in various ways, e.g. as supplementary material to a journal article, deposited in a repository, published on a website or shared ad hoc by researchers[18]. In healthcare, health practitioners use the best available evidence together with their expertise to make treatment decisions, coined *evidence-based medicine* (EBM). Without access to current best evidence, a patient (who we are all at some point in our lives) is at risk because of out of date practice by health practitioners[19]. Data are vital in the reconstruction of a research process and to evaluate the research process, and data can be manipulated to generate new datasets or for re-analysis[20].

The scientific validity of data, such as peer review, assumes the sharing of data and research methodology, or protocol, with other scientists who validate each other's theories[21]. Sharing of research data is problematic due to intellectual property

concerns, data protection reasons (if personal information is present) and difficulty in sharing data using appropriate standards. However, sharing of data is increasingly being expected in particular as research is becoming more data-intensive and rich[22;23]. It has also been argued that sharing research data is an ethical must and improves trust in research for transparency effort[24]. I discuss more about sharing research data in chapter 4.

Clinical trials improve medical practice but some of the barriers to practicing EBM are poor access to clinical trial information as well as the volume and complexity of trials taking place[25;26]. Comprehensive *systematic reviews* attempt to bring together results of clinical trials to offer an evidence-based summary of findings for a specific therapeutic area. Systematic reviews do not always include information that is unpublished or exist in formats such as grey literature. Because not all clinical trials are published and all data are not disseminated, the scientific evidence base becomes skewed during systematic reviews. Selection bias, the decision to disseminate certain results but not others impact systematic review results. Systematic reviews, if they did include information from unpublished trials may show a different outcome, even suggesting completely different treatment advice[27-31]. Examples of systematic reviews are the *Cochrane Reviews*[32], which aim to limit bias and error in reviews. The Cochrane Library contains around 4500 synthesised original studies. However, the Cochrane Collaboration estimate that at least 10,000 reviews are needed each year to keep up with healthcare interventions and at least 5,000 need to be updated each year[32]. It is a recommendation that systematic reviews should include grey literature and unpublished information, but in order to do this, the data and information must be made publicly available.

This thesis will define what clinical trial information is in more detail in chapter 4, by discussing research data, research information and other information that is relevant in clinical research. It will describe the process by which this information is generated and how that information is currently made available. It also addresses the factors that affect selection of information and the challenges of sharing information and data.

2.5. Conceptual models, diagrams and road maps

Conceptual models or process models, e.g. diagrammatic descriptions of systems, are designed and used to show how different resources interact within a process or between processes[33]. According to Jun *et al.*, the value of process modelling is to assist the understanding of a process in order to identify areas of improvement and also to help document existing or planned processes to ensure a shared understanding[33]. Research into functions of scientific theory and conceptual theory by Bunge[34] and covered in research by Jarvelin and Wilson[35] suggests that conceptual frameworks integrate separate parts of knowledge, guide research (existing or new) and map an area of reality.

"The speed of progress in science has always been strongly dependent on how efficiently scientists can communicate their results to peers and lay persons willing to implement these results in new technology and practices. "[35] Several models have been developed for the scientific communication process, notably Hurd[36] who accounted for the effects of the Internet on communication, e.g. listservs, self-publishing on the web and repositories, Sondergaard *et al.*[37] also including the effects of the Internet, Tenopir and King[38] who looked at the scientific publication process, Bjork's[39] models looking at the scientific communication process as an information system and of course Wilkes'[40] model of dissemination reviewed specifically in this thesis. Bjork stated that there is a clear need for models that structure overall scientific communication that can be used as a basis for comparing with other studies and building on integrating results from other studies[39].

All methods of models have their advantages and disadvantages and Jun *et al.* examined the eight most common methods of process modelling used in health care and through an evaluation survey reported perceptions for their usefulness and utility[33]. According to their findings, the most easily understood diagrams were flowcharts, process content diagrams and the stakeholder diagrams. Flowcharts are the diagrams that most people are familiar with. However, it has been said that not one single diagram can effectively capture every aspect of a complex process[33]. Equally not one model can directly argue to be valid, being representative of a process and providing exact findings[35]. A model is a simplification of one view of reality[41]. It is suggested that multiple diagram types, or multiple diagrams with

different diagrams for different sub-activities as part of one large context diagram, should be use to deal with complex processes and inter-linked tasks, people and information[33;39].

For this thesis, three models in particular are introduced. First, the Wilkes' model of dissemination (p. 40), which I adapted to represent the dissemination process of clinical trials. Second, the model of trust adapted from online banking (p.171) to outline how trust or distrust forms during the dissemination of information. Trust is a key concept which is discussed in this thesis in relation to clinical trial information and sources of information because I am trying to establish what are the reasons why there is a crisis of trust in clinical research. Third, I produced a conceptual model of information that is generated and disseminated in the clinical research process (p.93and Appendix A). This third model aims to describe simplistically what information is generated through clinical trials and what happens to it and is a backbone to the discussion of this thesis. I am not drawing on models on information behaviour, which attempt to describe information-seeking activities and relationships between activities in seeking information, as we have identified in the scoping section to this thesis that I am not in detail researching information literacy skills or access to information (p.21).

2.6. Dissemination, publication and scholarly communication

Terminology

Scholarly communication (e.g. forms of communication employed for research) is used by scholars for many reasons. Scholarly communication refers to an iterative process where scholarship is communicated, used and developed within a community[42] and how scholars used and disseminate information through formal and informal channels[43]. It is part of the research culture including linked linked to career advancement, collaborations on projects, publishing and engagement with the public.

The terms *dissemination, reporting, disclosure* and *publication* are increasingly used interchangeably. *Dissemination* is a description of activities during the scholarly communication process of which publishing or sharing data and research are parts in the dissemination cycle. *Publication* is defined as a formally recognised work,

contributing to knowledge and which is a responsibility of a scientist[44]. The process of a publication begins when an author publicly presents work, via a conference, posting on a web page or another type of announcement. Part of the process of publishing is the ability of peers to critique it. The terms *reporting* and *disclosure* also appear in relation to clinical trials. *Reporting* is the formal method whereby results or particular data are reported to the authorities, or the final results are provided to the authorities at the end of a clinical trial. *Disclosure* refers to what extent the data, or information about a clinical trial, are made publicly available.

This thesis examines the communication cycle as a whole but with specific concentration on the *dissemination process* of the output from clinical research, the information produced within a clinical trial, about the clinical trial and its methodology and the data generated, the research results. The thesis also refers to *disclosure*, in particular during the examination of factors that affect dissemination. Dissemination is one part of knowledge transfer and understanding the science of dissemination can improve the design and process of clinical trials[45], in particular to make dissemination effective and faster.

It is increasingly difficult to distinguish between formally and informally *published* or *disseminated* material in particular with the growth of use of the web for dissemination activities. The scholarly communication process can be divided into three stages[46]: communication within informal networks usually through electronic media[47], conference and preprint dissemination and lastly formal publication in a scholarly journal (figure 1).

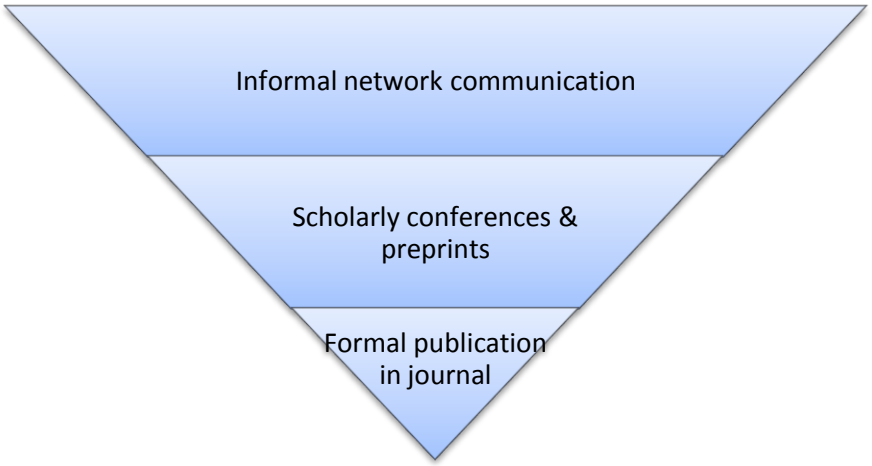

Figure 1: Scholarly communication process of three stages

Both publication and dissemination suggest that information is presented to an audience using a mode and process to do so. Dissemination means an interactive exchange between researchers and defined target groups[48]. There are two parties involved, the information provider and the information recipient. It is more than distribution (pushing out information) and for dissemination to be effective information is implemented in practice[49]. Several models have been developed looking at the scholarly communication process (see section on models 1.17) and specifically Bjork[39] has developed thirty-nine diagrams of the scientific communication process, including dissemination activities. Not one model can fully represent all processes. Wilkes'[40] linear description of dissemination (figure 2) was chosen for this thesis as it represents communication and dissemination in as a simple flowchart, which represents the basic components of dissemination. It can easily be adapted for how dissemination has changed and how it will change in the future. His original model of 1997 is slightly outdated and does not take into account the Internet 'revolution', however this thesis will make a recommendation of how the model could be updated in Chapter 6.

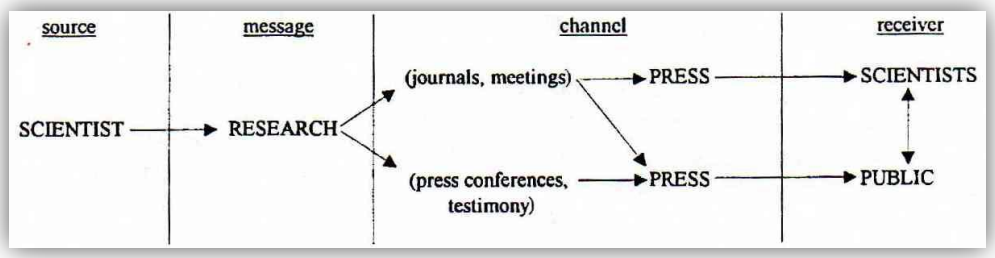

Figure 2: Wilkes model of dissemination (1997)

Introduction into dissemination issues

"Critical to seeking clinical information is the credibility of the source, followed by relevance, unlimited access, speed and ease of use."[50] Liberti, Erdelac and Papaj continue to say that barriers to finding needed information is too much information, lack of specific information and navigation or searching difficulties[50]. Clinical trial information is scattered across a number of resources and there are factors that affect dissemination which have been investigated by others, some introduced in this section. In order to understand what is happening with dissemination of clinical research we must look at what is happening in publishing, how researchers communicate their research and theories behind dissemination.

A study reviewed the aim of publishing and the evolution of publishing[51]. It concluded that publishers are blocking the advancement of science as there is a high cost to access research, but they argue that scholarly journals still have a role to play in scholarly communication. The research questions what constitutes publication in the electronic environment, a question also posed by others[44;51] and which will be addressed in this thesis and which it will aim to respond to. Without a definition; the quality, integrity and authentication of electronic scientific information will be difficult to determine[44]. Further research supported by Joint Information Systems Committee (JISC) has made an attempt at clarifying the term *scholarly publication* providing a suggested list of criteria which can be used as a check list against emerging formats to establish if they are scholarly publications[52]. I will revisit what it means to publish several times in this thesis and a review of the definition will be given in the recommendations in chapter 6.

A recent report by RIN found that UK researchers across many disciplines publish very little but they communicate their research in many different ways with different factors affecting their decision in how to communicate[53]. The report claims that research funders' requirements and institutional guidelines are not that influential when making a decision on dissemination and that the scholarly journals are increasing their dominance over other methods of dissemination as publishing in a journal is an effective form of communication and secures recognition from peers. The report also recognised that researchers also use working papers, reports and presentations at conferences to disseminate research but these methods have lesser status. Scholars publish research as part of the need to communicate their research and there are many reasons for communicating research, e.g. for career advancement where publication of either a few or cumulative papers define academic careers[54], and an ethical obligation to publish clinical research results[55], etc. This thesis will examine how clinical researcher professionals disseminate clinical trial information and examine how effective are the methods used.

A meta-ethnographic study was conducted into effective information dissemination in a crisis[56] looking at dissemination theory. The research proposed a model of social marketing, including training and education, with accompanying multi-method dissemination strategies. The meta-ethnographic method was not successful in establishing effective dissemination methods however it identified some key factors that relate to effective dissemination, which this PhD will draw upon and expand on. As the meta-ethnographic method was not successful in the identification of methods and their effectiveness, it was discarded a as a method for this PhD but could perhaps be used in future research to build on this research (see Conclusion, section 1.60).

"*The scientific literature is a record of the search for truth*"[57]. There is an expectation that research is a public good that should be made available online[58]. Ng wrote of the utopian ideal of scientific research published with online availability of full-text, access to every researcher anywhere, interlinking of all papers and citations, full searchable, retrievable papers, access to all research data and free access for all forever[51]. Online repositories or databases meet some parts of such demands. According to Lawrence[59] there is statistical evidence that electronic

publishing has enabled wider dissemination of information, there is a clear correlation between the number of times an article is cited and the probability that the article is online. Access to organised information online means that researchers can identify and use information that is relevant which improves communication and scientific progress. Every day, 400,000 users access 700,000 articles in PubMed Central [60]. Zerhouni said that the digital revolution in life sciences had led to greater data and knowledge production through information sharing services.

The digital environment is changing the scholarly communication process, blurring the informal and formal modes of communication, through tools such as blogs, WIKIs, discussion forums, websites and allows for sharing of information and commenting by peers. There is evidence that there is a definite move away from publishing in monographs and books, which declined over the last five years, into publishing in journals or disseminating online[61]. Graham includes electronic media and informal network communication in the new scholarly communication cycle[46]. The electronic environment satisfies the rapid need to publish research but also because electronic dissemination of data allows scholars to re-use, manipulate and verify research[18]. One critical research objective became to establish to what extent clinical trial information could be found in the online environment and if informal communication methods were used for disseminating clinical trial information.

What do we mean by effective dissemination?

To effectively disseminate information means to distribute into implementation, e.g. the uptake of new research findings[49]. Effective dissemination is also an interactive exchange between researchers and the audience that the information is intending to influence[48] . There are several challenges in effectively disseminating findings from health research, e.g. the time required to keep up-to-date with new research and organisational barriers in changing existing practice[62]. The uptake of new research findings has been described as haphazard and unpredictable[63]. There is therefore a requirement to understand the knowledge acquisition process and behaviour of an individual who has needs for new knowledge. Part of knowledge acquisition is the individual's information literacy skills and their awareness of knowledge sources. Miller and Mangan identified two styles of information seekers; the *monitors* who actively seek out information and want high information input and *blunters* who

prefer less information[64;65]. In psychology, the theory of planned behaviour (TPB) explains attitude and behaviour in individuals and has been used in advertising, marketing and healthcare[66]. TPB is useful when planning dissemination, implementation and evaluation strategies[67] where there is a need to understand uptake of new information.

According to Duggan and Banwell[56], when planning a communication three things must be considered:

1. Targeted dissemination, e.g. target a specific audience with a perceived need for knowledge.
2. The role of opinion leaders in dissemination
3. The willingness to change as a result of new knowledge.

This thesis will look at effective dissemination and related theories by examining publication guidelines and organisational policies on disclosure and communication of clinical trial information. By doing this I can establish how to make dissemination more effective and at what stage communication strategies and the dissemination of information is planned.

2.7. Methods of dissemination

It is presumed at the outset of this PhD that there is a public need to access information about clinical trials as there have been requests and calls for clinical research to be made more transparent. It must be said that it is always going to be unlikely that all information generated in a clinical trial will be made publicly available. The data sets of clinical trials are complex and data analysis concentrate on answering the research questions in the approved clinical trial protocol, other information is recorded but kept 'on file' or discarded when irrelevant. A choice is made on what information is selected for reporting and dissemination and what methods are used for this purpose. The selection of information occurs to ensure the right type of information is available to the right type of audience at the right time[68]. Dissemination is therefore 'effective' when it aims to influence an audience. Duggan and Banwell identified a combination of factors that affect effective dissemination[56], and suggested that these factors are considered when preparing a communication. This research identified further factors to add to Duggan and Banwell's factors, a

major one being the timing of delivery of information and the method chosen for delivery discussed later. These new factors are relevant in particular when looking at new online types of methods used for dissemination of information investigated more in this thesis. This research will examine existing methods that are used for disseminating clinical trial information and establish if they are fit for that purpose.

The journal as a method for dissemination

The journal has existed for hundreds of years as a tool to disseminate research findings and opinions and is a key component of the scholarly communication process. Each year more than two million research articles are published in journals[69]. Journals are a key source of research information[70] and papers are used as sources in promotions, advertising, reports and other outputs. For this thesis we define journals as the peer-reviewed regular publications that disseminate research findings. The methods used for disseminating clinical trials information are many and the journal is a trusted method to provide peer-reviewed evidence-based information. The European Commission has made a claim that the traditional model of journal publishing is failing scientists because scientific research is offered with limited access at high cost[71], subscriptions are increasing and the number of journals are increasing. Are therefore our current methods of dissemination effective?

Information is disorganised and cannot be found when health professionals need it[72]. Other negative comments state that the journal is restrictive, lack methodological rigour and is limited in discussion[73;74]. It has also been accused of being a pharmaceutical marketing tool[75;76]. However, others have said that publishing research in a journal is the only way to get research checked by peers, through the peer-review process, editorial process and that publication guidelines helping organise information[77;78].

A disputed way in which we identify top medical journals today is based on citation metrics and impact factors, where a high impact factor suggests a journal is a 'top' or key journal[79-82]. Much research has looked at the role of the impact factor and there has also been research around the identification of core journals in different therapy areas[14;79;80]. Part of this research is about identifying the type of journal that publishes clinical trials or perhaps the choice of journal to publish in made by the

researcher. It will identify the core journals, and their impact factors, used for disseminating clinical trial results in diabetes and obesity, to establish if high impact factor journals publish the majority of diabetes and obesity clinical trials. A method to establish a core set of journals is bibliometrics, which applies statistical methods to communication forms[83]. Some bibliometrics studies have taken place looking at either a specific disease area or a specific health journal: RCTs in pato-biliary disease[84], literature of AIDS[85], RCTs in organisational interventions in healthcare[86], RCTs in surgery[87], core literature on AIDS in women[88], cases in general practice in general medical journals[89], citation pattern in the *American Journal of Epidemiology*[90], RCTs in *Intensive Care Medicine*[91]. One study specifically examined randomized controlled trials (RCTs) in all areas of health sciences[14]. Research has shown that although many clinical journals publish high-quality original studies and reviews, articles were concentrated in a small subset of journals which varies according to health discipline[92], this is confirmed in a study looking at where the core RCT literature is published, concluding that the core is concentrated in a small number of journals with diversified subject coverage[14]. The same study also shows that many of the important articles were published in broad-based healthcare journals rather than discipline or topic specific journals. A study conducted in 1999 which found that the best quality evidence on paediatric clinical practice is found in a large number of medical journals, but that seven journals were cited most frequently[79]. Another study showed that the dissemination strategies of pharmaceutical-sponsored and non-profit sponsored oncology studies did not differ, both published in low impact factors peer reviewed journals[93]. Falagas and Alexiou identified that 60% of the top 25 journals, as ranked by the ISI impact factor (IF), only publish reviews and summaries of past research whereas the journals with much lower IF publish the best original research, but are not cited frequently[81].

Clinical trial registers as a method of dissemination and online access to information

The term ‘clinical trial disclosure’ refers to publicly available electronic databases that present information on new clinical trials at inception, e.g. *clinical trial registries* and results of completed clinical trials; usually referred to as results *databases* although hybrids exist of both and there is no agreement on correct

terminology so in this thesis I have adopted Foote's[94] and WHO's terminology and refer to them both as clinical trial registries and abbreviated to register or registry for ease. These registries are publicly available repositories of information and data. Clinical trial registries can be public or private and managed by not-for-profit or commercial organisations. They differ from databases that are maintained by *competent authorities* (regulatory bodies), such as *EudraCT* in the EU, where *clinical trial applications* (CTAs) are submitted electronically and information shared amongst authorities and *research ethics committees*.

The inception of clinical trial registries was as a result of a combination of things. In 1974 Mary Lasker asked the National Cancer Institute to publish a book listing all ongoing cancer treatment protocols in the US, updated every six months. This would allow physicians to identify open trials in which their patients could enrol[95]. Tom Chalmers extended this idea to include registers of clinical trials with an aim to reduce bias in the reporting of trials[96]. "Both recognised an enormous gap in the dissemination of good information and both hoped to speed the delivery of the best new treatments to the patient."[97]. In 1997, a computer-based approach called the trial-bank system was suggested because scientific evidence was not transferred effectively or efficiently from the bedside[98]. Such a bank would not only aid presentation of clinical trial information, it would also help with recruitment into trials allowing the public to search these banks. Another reason for establishing registers was to improve transparency of clinical research so that information would be available on the type of trial and investigational medicinal products (interventions) used in the trial. This is very useful as not all trials are formally published in journals and it allows the user to find information about both trials that have been published and those that remain unpublished[99].

"However, no comprehensive system currently exists for tracking, organising, and disseminating information on clinical trials."[100] The current largest clinical trial registry is *Clinicaltrials.gov* set up by the *National Library of Medicine* (NLM). The set up of this first independent register was a result of the *FDA Modernization Act*[101] passed in November 1997. Between May and October 2005 the NLM reported that the number of registrations in ClinicalTrials.gov increased by 73% from 13,153 to 22,174[102]. On the 9th of February 2009, the register contained 68,223 clinical trials

from around the world[v] an increase from May 2005 by nearly 420%. On 12 February 2011 the register had 102,817 registered clinical trials from 174 countries. The site has around 50 million page views per month, with 65,000 visitors per day[vi].

There is not one comprehensive system for tracking, organising and disseminating information about ongoing clinical trials[103]. Clinical trial registries have been in existence in some format or other since the 1960s[97] and there are "hundreds of such registers worldwide" today[100] some set up for specific diseases, or for a specific country and with different aims[103;104]. In 2006, an attempt at collating a list of clinical trial registers was made for the book *Clinical Trial Registries: a Practical Guide for Sponsors and Researchers of Medicinal Products*. The editor, Mary Ann Foote [94] said; "...the problems faced by a patient in terms of deciding what web sites to search about information for a clinical trial for a particular disease." Thirty-nine registers were listed in the publication and divided into international and government sites, oncology group sites and sponsor sites.

Liberti et. al[50] argue that in the current time we should be able to create a clinical trial register model that provides a comprehensive up to date listing of results from all concluded clinical trials globally. It would provide a comparative view of all available data in an easy to understand table that could be printed, saved or used. This information would provide 24/7 access to clinically relevant patient treatment information with all the data as evidence. Unfortunately as Liberti et al state, no single register fulfils this vision as a single source repository of data using uniform standards or good enough search engine[50]. The WHO admits that it is impossible to consider one single register suitable to all diseases and aims, instead they have set up the *International Clinical Trial Register Platform* (ICTRP) (see figure 3) in 2007 to "ensure that a complete view of research is accessible to all those involved in health care decision making, this will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base"[105]. The ICTRP is a meta-register allowing the user to search across primary registers. The primary

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[v] http://clinicaltrials.gov/ [Accessed 9 Feb 2009]

[vi] http://clinicaltrials.gov/ [Accessed 13 February 2011]

registers would ‘deduplicate’ and translate information into English from associate registers.

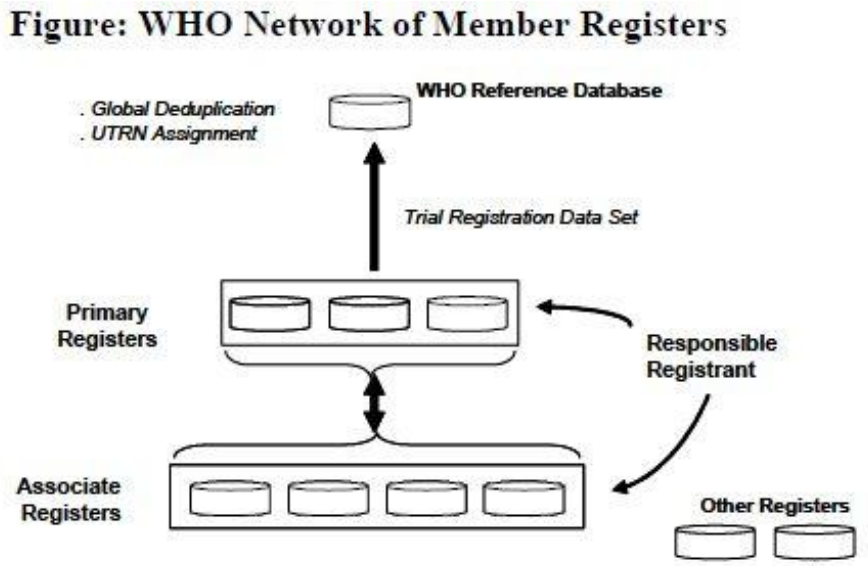

Figure 3: The ICTRP structure proposed by the WHO[104]

Although results databases can provide the public with useful clinical trial information, current prescription drugs used by the public will not be listed in the clinical trial database[106], because the huge effort involved in uploading old drug information would be difficult to implement. Any drug approved before 27 September 2007 that was no longer involved in trials after this date are not required to be registered[107].

A more serious area is that there are legal requirements in the FDA region that state that for confidentiality reasons certain information cannot be released on drugs that are undergoing development, even if there is serious concern for the safety of individuals who may be taking that drug already available on the market[106]. This contradicts ethical standards which makes it unacceptable both ethically and scientifically to withhold information about the safety of efficacy of marketed drugs from the public[106].

Another highlighted concern with results databases is that they do not contain information on unapproved products. Trials may not have been approved by the authorities if a drug application was withdrawn for safety or economic reasons, or

clinical development may have stopped for some other reason. At the moment, this information is not released publicly in any format. Wood suggests that after a 2-year period, all such data should be posted as two year inactivity must be a long enough period for protecting confidentiality[108].

Both Wood and Decullier et al also identified that there is a lack of dissemination of Phase I results[106;108]. Clinical trial registries facilitate sharing of trial information but previously Phase I trials were not required to be registered and results not shared. Potentially the lack of sharing of such information can cause unnecessary serious adverse reactions in patients where drugs of similar type are used in other trials. It would also be useful if such information was shared from a commercial point of view, as studies may have been discontinued for economic reasons which could then be re-used in new studies by other companies to the benefit of scientific development[108]. In fact, it has been highlighted that clinical trial registration does not ensure submission of trial results[109].

Several studies have analysed websites containing information about cancer clinical trials[110-114]. In 2002, Manheimer[103] examined the completeness and accessibility of ongoing drug trials for prostate or colon cancer in the UK. He concluded that existing clinical trial registries were not meeting existing user needs as many ongoing drug trials were not listed. A examination by Monaco and Krills[112] of cancer centres websites concluded that websites that provided information about cancer clinical trials were providing limited content and the reading level of the information was at college level. They also concluded that searching several online registers to identify trials was cumbersome and time consuming due to search capacities of the websites, lack of standardisation and clarity of the language used to describe the trials. Frequently drug names, phase of testing and condition treated were missing.

Another study in 2007 evaluated online resources for cancer clinical trials[113] and it found that the resources varied greatly regarding information provided and called for an improvement to content, design and presentation of clinical trials. A further content analysis into cancer clinical trial search tools in 2008 also found that functionality and content varied greatly[114]. In 2011, the *Cochrane Collaboration* compared protocol or entry in a clinical trial registry with the content of its published

report, which revealed that there are often discrepancies between information in the protocol and trial registry entries and what is covered in the published reports[115].

This thesis will assess the usefulness and effectiveness of clinical trial registries in providing clinical trial information and there is a comparison made of functionality within different clinical trial registries. Diabetes and obesity clinical trials were used for this research as these therapeutic areas have not been investigated previously and it is assumed that in the future this type of research will increase. The risk of diabetes due to obesity is rising and there will be increased information needs for research into these areas from the public, health professionals and governments.

The Internet as a method of dissemination

There is no doubt that the invention of the Internet has changed the way in which information is disseminated. The Internet is expanding with a number of diverse resources related to clinical trials that can be accessed by anyone. New and improved technology allows information to be published and disseminated quickly. Alternative methods of dissemination to the traditional methods, e.g. journals, are growing, e.g. blogs, web 2.0 social media sites, personal websites etc.

A lot of information on the web is disorganised making it time-consuming and costly to search for information and it has been said that health professionals cannot find it when they need it[72]. The quality of information provided on the Internet is disputed in research, it allows for erroneous ideas to be disseminated widely which may have harmful effects[116] although a recent piece of research indicates that the completeness and accuracy of online medical information has improved[117]. Other research states it is a recommendation that patients are referred to websites that are reliable and provide accurate information by a health professional[118;119]. Nevertheless, the Internet is useful in tracking down unpublished and ongoing clinical trials, even if the information is not peer-reviewed[120] and this research shows what type of information was disseminated and on what type of websites by conducting simple searches using publicly available tools online.

Research has been done into the way in which the public access information about clinical trials. It has been said that the primary source of information about clinical trials is the patient's physician[121;122]. One study concluded that individuals rather turn to the Internet for information than to a health professional[123]. Another study showed that patients prefer conversing with a health professional via a portal or email and this type of communication enhances the physician-patient relationship[124]. Research has also shown that physicians feel uncomfortable speaking to patients about clinical trials[121;125]. It is important to note however that each individual has its own unique information needs, which complicates how well physicians are able to communicate information about clinical trials to them[121].

The Internet has revolutionised the way patients access health care information[113;114;126], learn more about health and make decisions about their condition. We need a better understanding of patients' information needs regarding clinical trials, and their information research behaviour, so that we can better present the information to them[112]. More research is being done looking at the attitudes and trends of the public and their access to information. The *Pew Internet Project* studies the social impact of the Internet and they surveyed 'health seekers' in 2000 and 2002 which revealed that half the respondents would turn to the Internet for health information[127].

In a study into patients' usage of a University of Washington Orthopaedics and Sports Medicine Website, the reasons were to find information about a condition, a treatment or symptoms[128]. "Eight in ten Internet users have looked for health information online, with increased interest in diet, fitness, drugs, health insurance, experimental treatments, and particular doctors and hospitals."[129] One study estimated that 12.34 million health-related searches are conducted worldwide every day on the web[130]. In 2004, 23% of Internet users have searched for experimental treatments or medicines compared to 18% in 2002[129].

Physicians use the Internet to find medical information too. According to one study physicians access targeted sites rather than search engines[131], e.g. research databases, medical journals and portals. A review[132] of the information-seeking behaviour of physicians spanning over ten years 1996-2006 shows that physicians still use

colleagues and print evidence in information-seeking, although this research did not specifically ask physicians regarding finding out about clinical trials.

The role of media in dissemination

The media remains important in disseminating information about science. Physicians and the public often find out about new medical research through the media[133-137]. Prior to 1960 the press didn't report widely on medicine[138]. However, over the last thirty years the public interest in medicine has changed[40]. The New York Times increased its coverage of medical articles by 250% between 1968 and 1978 and 425% between 1969 and 1988[40]. Journal editors began to see that media coverage is valuable to attract attention and increase subscriptions, building brand recognition[139].

These days the market is flooded with press releases, sometimes deliberately vague or even misleading[40]. It is recognised that the journal press releases are also prone to exaggeration[133]. A study showed that only 23% (29/127) of the press releases included study limitation and 65% (83/127) included results[133]. It has been recommended that press releases should put research results into context, provide study limitations, reveal author's competing interests and provide absolute results[133]. Seven out of nine medical journals routinely issue press releases[133].

It has been argued that not many sources provide *true access*[106], the existence of reports available to the public and a database which allows the public to conveniently and accurately access those reports. According to Wood[106] there are three types of resources in the US that meet the criteria of providing true access to clinical trial results, e.g. links to reports and published papers:

1. PubMed or other bibliographic databases with indexes of publications
2. FDA analyses and documents on the FDA website (in Europe we would rely on our research ethics committees or EMA posting such documents)
3. Existing industry databases such as the GSK results website[140] or the PhRMA results database[141].

Wood also recognises that the clinical trial register *clinicaltrials.gov* will become an additional source of true access information, however, it does not yet contain

complete sets of clinical trial results. The public would be better served if they were provided with comprehensive reports and reviews for all interventions after approval including for additional applications, e.g. new indications etc[106]. On 30 November 2010, the EMA in the EU announced that they will release all business documentation related to clinical trials electronically for public access, e.g. clinical trial reports, once a procedure concerning an intervention has been finalised[142].

We know that clinical trial information is disseminated in many ways and this thesis will examine some of the different dissemination methods; abstracts, the journal, the Internet, media and clinical trial registers, to try to understand why these methods are chosen for dissemination and what affects choice of method.

Abstracts as a method of dissemination

There are many kinds of abstracts, e.g. the most obvious ones being a summary of a report published on a website, the abstract found in journals describing the content of a paper, conference abstracts for a presentation or a poster and abstracts in press releases, but there are more types of abstracts than these mentioned here. An abstract is meant to summarise the key findings and the 'take away' message and is usually used as a teaser to attract a specific audience or to provide the key information quickly for those who do not have time to read the full script, if there is one. In fact we know that readers sometimes assess a clinical trial on the abstract alone[143]. Abstracts given at meetings are a useful way to disseminate new information quickly[144].

An identified problem with abstracts is that they have been found to underreport findings that are covered in main paper[145;146], 37% of errors found in abstracts of psychology journals could be seriously misleading[147] and some abstracts contain data that are inconsistent with the rest of the paper or even missing altogether in the main text[148]. It has also been found that of abstracts presented at meetings many fail to publish two to five years after presentation[149-153] and identified reasons for non-publication have been investigated, e.g. trial still active, lack of time to write, disputes with other authors[151;154]. One study looking at gastrointestinal abstracts given at conferences found that papers accepted at that conference were more likely to be published later on than abstracts that were not accepted for presentation (54%

vs 34%) and the same study found that abstracts reporting statistically significant results were likely to be published in journals with higher impact factor[154].

One study concluded that conference abstracts are time-consuming to find and that the content are of questionable value. However they may provide some value in health technology assessments if during a systematic review other sources containing relevant information are limited[155]. Data presented at conferences should be treated with caution[144].

Abstracts are provided on the web in clinical trial registries, on websites and on conference websites as well as other types of websites. Posting abstracts in clinical trial registries is still reasonably new and although it is advisable to post an abstract within 24 months of a trial end (as well as law in the US), some publishers consider some abstracts as *publication*[156] making the posting of an abstract difficult for researchers who wish to publish in a journal.

It has been suggested that the CONSORT checklist for writing abstracts could improve the content of abstracts in journals[143] and that peer reviewers and editors of journals should ensure that abstracts represent the full-text article accurately[157].

For this thesis, I examined the quality of content in journal abstracts and the value of different kinds of abstracts in the dissemination of clinical trial information. These findings were fed into the final recommendations provided in chapter 6.

The relevance of concepts such as trust and quality

When disseminating research findings it must done in such a manner that recipients believe that the information they are receiving is trustworthy, only then can information influence and change practice.

Various definitions of trust exist. Rotter[158] defined trust: "a generalised expectancy held by an individual that the word, promise, oral or written statement of another individual or group can be relied on." The dictionary[159] defines trust as: "Firm reliance on the integrity, ability, or character of a person or thing".

Misztal [160] explained that concepts of trust can be grouped into three:
1) individual attributes, such as feelings, emotions and values
2) social attributes, such as common goals (within an organisation for example)
3) public value, such as institutional trust.

Day[161] identified the behaviours that either damage or build trust (Table x).

Trust is linked to quality. In science we ensure quality by using a variety of methods, e.g. peer review or alternatives, review boards who can assess quality, impact factors that show journal quality. By ensuring quality, we ensure trust.

Quality is "Easy to recognise... difficult to define." [162] Quality exists when we talk about products or services; it means that either a product or a service exceed our expectations. It's difficult to define quality but we often see its absence; either a product breaks or we have a poor service in a delivery for example. If quality isn't taken seriously, a 'good enough' approach is usually adopted [163]. The quality concept became popularised in the 1970s, when Japan provided products that customers wanted; well designed, reliable, available and reasonably priced [163].

The British Standard 4778[164] defines quality: "The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs." In other words, what one person wants in a product or service will differ to what another person wants depending on his/her definition of fitness for purpose. Quality is the concept of an object having a purpose for which it's fit and is linked to what the customer wants or needs [163], e.g. the definition I will use in this PhD is that "quality is fitness for purpose"[163]. The studies in this thesis will look at how 'fit for purpose' existing methods of dissemination are for disseminating clinical trial information (chapter 5) and recommendations for the optimal dissemination model will be presented (chapter 6).

Behaviours of trust: damaging or building

There are behaviours by individuals or organisations that either damage or build trust. These trust-damaging and trust-building behaviours have been taken from Day and Rennie[161].

Table 1: Trust behaviours

Trust-damaging behaviours
Unwarranted interference
Excessive criticism (especially in the public arena without right of reply)
Coercive or threatening behaviour
Dishonesty or disingenuity
Wilfulness or recklessness
Trust-building behaviours
Mutual recognition of accountability
Shared vision
Explicit strategic objectives
Tactics left unstated
Free and frequent flow of information

To have confidence is slightly different from trust. Confidence builds over time and comes from trust. Renn and Levine stated "Confidence denotes the subjective expectation of receiving trustworthy information from a person or an institution."[165] If what is received is not trustworthy, confidence will be replaced by uncertainty and create a climate of distrust. The concept of trust has been researched in particular in relation to the commercial sector, such as the trust placed in banking. A model called "five levels of trust"[166] was developed for Internet banking showing how confidence and trust is formed. I have adapted this model to include what factors, behaviours (Table 1), affect trust in the environment in which clinical research takes place and the public opinion of research (chapter 5 p.171).

Quality indicators in dissemination

There are different kinds of indicators of quality that are relevant in this thesis when thinking of dissemination of clinical trial information.

Examples of good clinical trial quality indicators are good trial design and conduct of trials according to Good Clinical Practice (GCP)[167] and Good Manufacturing Practice (GMP)[168] standards. Unfortunately there are few checks available to check

quality of trial design, although the Ethics Committees will review trial design before approval of a trial. It is worth noting that Ethics Committees usually consist of some volunteers from the public without specific expertise of trial design. Informed consent, e.g. making a decision based on enough information, is an important part of gaining trust from those taking part in a clinical trial and an important aspect of GCP. The goals of the research and the institution conducting the research need to be believed in, and the public need to feel that they can place their trust in them. Trust could easily be called into question if people felt that their confidence was not being kept and if they felt that medical information was being used for commercial gain[169] and confidence would improve if competing interests were disclosed[170]. Trials are increasingly audited and inspected by authorities to ensure trials are managed to good research standards.

Dissemination methods, such as journal articles, are also using standards to assure quality. Quality indicators to assess quality in publications have been identified by Liberti[171] and Kling and McKim[42]:

- Results of clinical trials; quality of information provided
- How well data supports key concepts
- Methods of delivery: open access, pre-print
- Format of output: website or journal
- Persuasive writing; marketeer writing, investigator/researcher
- Journal publication: impact factor or what type of journal and the reputation
- Institutional support: who was it funded by?
- Reputation of publisher, author or institution of author
- Corner cutting: did the results get published too quickly with poor review
- Is there advertising attached to the article or a sponsored supplement?
- Structural and presentational aspect
- Target journal/audience, therapeutic area
- Peer review and publication guidelines of journal
- Use of available checklists to aid authors in writing papers, such as *CONSORT*[143]
- Long term access/preservation; will it be access after a number of years,

preserved indefinitely?

To establish its usefulness for science, a publication needs to have been vetted to ensure quality[42;52] and to establish a high level of trust among readers[44]. This process is equally essential for electronic documents and websites, perhaps more so in view of the vast quantity of available information and the difficulty in identifying and access them.

A concern has been expressed over ghost-writing and guest-authorship of clinical trials in journal articles. Both are said to harmful to the public and institutions and the paper cannot be trusted or accurately judged [172;173]. Ghost-writing has been relatively common, e.g. the results of a trial have been written up into a peer-reviewed journal by someone who conducted some work towards the paper but not accredited authorship. In a study by Goezsche et al, there was evidence of ghost authorship in 91% of trials approved by ethics committees between 1994 and 1995[173]. An opposite argument is that ghost-authorship is better than the paper not being published at all as physicians are becoming busier and medical writers have the skills to write and analyse data [174]. Guest-authorship is when individuals are invited to appear as authors on a paper, when they have had very little input into writing the paper, possibly a head of department or a key opinion leader. It has been argued that guest and ghost authorship can make a drug look good[175], either through an author's influence as a subject expert or as a professional medical writer who knows what should be pushed in papers, e.g. marketing messages. Most journals now demand transparency of authorship asking for each contributor to be acknowledged[176].

The usefulness of peer review

The usefulness of peer-review is a debated area within publishing. Peer-review has long been used as a way to assess quality and accuracy of a paper, and for journals[77], although even fraudulent papers have made it through the peer review system[177;178] and there is no evidence that peer-review is improving quality[77;179]. BioMed Central, the science, technology and medicine publisher, operates an open peer review model. This together with their open access to research model, attempts to link together

research, pre-publication information with peer review[180]. The organisation *Sense About Science* state that peer-review is essential to assess scientific quality [181]. To improve transparency of peer review, attempts at open peer review, e.g. via electronic means on websites were tried but failed[182]. Peer review has also been argued to be crude[178]. Peer review, although not perfect, is stated as our best option for the moment of ensuring quality of papers[183] although this is disagreed by others[69]. An issue with peer-review is that it's incredibly slow and there has been recent debate over reviewers remaining anonymous, when in fact conflict of interest may affect the peer review process[184].

Quality standards of websites and online content

There have been proposals for sets of rules (ethic codes) and quality criteria for medical websites, as a way to assure certain quality for them, more prestige for the compliant sites, and more trusted sites visitors. Some examples of ethics codes are: *the Health on the Net Foundation (HON) Code of Conduct*[185], presented in 1997, and standards on managing information from NISO[186]. The *Information Standard*[187] is a new certification scheme in England for health and social care information providers and producers which when approved can use an approval logo on information resources that can be recognised by users of that information. A slight concern with the Information Standard is that it is run on a commercial basis (there is a payment involved in signing up to the standard) and it is also reliant on the government policy approval process. If the government changes, the standard is under review. It may therefore not be supported long term. The *JAMA benchmarks*[188] have been used to assess technical quality on websites[189]. It has been suggested that designing a website with technical quality indicators can help users establish content quality, e.g. accuracy of the information provided[189].

Quality of clinical trial registers/registries/databases/results databases

There is general concern over the varied quality and consistency of registers[190] and lack of leadership, data and monitoring[191]. The quality of clinical trial registers is suffering due to incompleteness of records, missing records, missing critical information and non-compliance by researchers uploading information. It has also been stated that the industry looks like they are complying with new regulations on registered trials but actually hinders the release of too much information[190].

These concerns mean that registers do not aid public access to clinical trials and their results because true access depends on the existence of links to reports or published papers within those databases[106] and reliable information within the databases themselves. Limitations placed on the availability of information result in the limited efficiency of registers[192] and therefore we must question if registers aid the public at all[94]. Although efforts have been made to release clinical trial data for the public good, we have not identified what the public wants out of clinical trial registers[193]. According to research, patients only access registers less than five minutes and look for very specific information[193].

The WHO has drawn up a quality standard of required datasets for registries containing information about clinical trials and suggest that Clinical trial registries should report twenty datasets, WHO Trial Registration Data Sets or TRDS[194] and registries that do not meet those standards are not included as approved primary registers on the ICTRP meta portal for registers[105]. However, Clinical trial registries must apply to be included and are not checked against this standard unless an application has been made.

As part of this PhD a study in comparing the recommended 20 data TRDS with a selection of registers and an analysis of content will reveal any quality concern with clinical trial registers.

2.8. Factors that affect dissemination

There are many factors that affect dissemination of clinical trial information; legislations and regulation, publication guidelines, selection and publication bias, effective dissemination, pressures in the research environment and transparency issues.

Transparency issues in dissemination

In order for research to be transparent there must be trust in the research that has taken place. Transparency is affected by issues such as funding, behaviour that either increase or decrease trust, career progression, publication or selection bias etc. A selection bias of what information is chosen for dissemination is necessary as it

would be impossible to disseminate all information in a clinical trial and it would not be of interest to everyone anyway. The authorities who approve drug applications do not have the resources to read or publish all information provided. The product dossier produced early on is provided to the authorities containing what is thought the relevant information needed for approval of an intervention. There have been media coverage of cases where crucial clinical trial information was withheld from authorities[195-197], which has had detrimental effects on clinical research and the companies concerned. We must remember that researchers have to deal with many protocols and clinical trials across many different countries and reports in different languages, which is a challenge to control[198].

Disclosure policies

Research ethics guidelines have provided statements about sharing or reporting clinical trials, although not covering this in detail and no specifically about disclosing information to the public or about publishing. Several developments in the 1990s and into 2000s have provided guidelines on structure and content of clinical study reports, checklists for reporting randomised controlled trials (RCTs). In 1994 the first International Committee Medical Journal Editors (ICMJE) Uniform Requirements for manuscripts submitted to biomedical journals was published. These together with organisational policy on publication of research address issues that unfortunately have occurred in research.

Publication guidelines

Issues within the complex relationship between the pharmaceutical industry and peer reviewed journals led to the actions and initiatives to encourage best practice and eliminate unacceptable behaviour[199]. Unacceptable behaviour includes not declaring conflict of interest, not naming authors (ghost authorship) or paying non-authors to be listed as authors to attract readers (guest authorship), falsifying data or publication bias (such as selective reporting of some results). Even though publishers use peer review as an additional check of content of manuscripts, there was a need to provide stricter guidelines to authors on their submissions. Journals themselves have author guidelines to aid authors when submitting a paper for publication. But there are also other guidelines available within medical and clinical research that lay out best practice for publishing results.

Regulations

International declarations, conventions, directives, and various national laws and rules regulate research ethics and researchers' ethics. But laws and directives do not usually specifically provide guidelines on how and what to disclose and publish apart from data to the national authorities relevant to the new drug application.

Pressures

There are several kinds of pressures that affect clinical research and the dissemination output as a result. There is evidence of research pressure to publish research findings, to advance one's career, but there are also geo-political pressures and commercial pressures.

Researchers are under enormous pressure to publish their research findings. It is time consuming to write and get a paper published. In a study of time to publication for clinical trials, trials with positive results took four to five years to publication and trials with null or negative results took six to eight years to publication[200]. Recent findings from other studies shows that some trials never reach publication[201;202] and according to Dwan *et al.* the total amount of studies published was less than 50% on average between 1998 and 2008[27]. It has been suggested that researchers sometimes do not publish research with insignificant results or negative results as they are not of interest to anyone or they [researchers] lack the time to publish[203] and the pharmaceutical industry has been accused of publishing only positive results[204]. A study also showed that time to publication is delayed if the results of the trial are presented at a scientific meeting[205]. It is clear that researchers are pressurised from an ethical point of view to report findings to the public, but also pressurised from a funding point of view with stakeholders' stock value being affected by sales. The researcher needs full permission from the owners of that data, or the funders, to provide all this information. In some cases this could also mean lengthy informed consent exercises with patients whose data may be made available, sometimes after a trial took place, if data sharing had not already been made clear during the consent procedure. Company disclosure or publication policies may also indicate where to publish and what journals are the preferred places of publication.

Unfortunately, scientific misconduct and fraudulent cases in biomedical research have come to light[206-208]. Scientists were until recently considered more honest than ordinary citizens and were an elite and that they could regulate themselves[209;210]. Journals, authorities and clinical research organisations now have guidelines to monitor for misconduct and fraud[211].

Unfortunately not all trials can include all types of patients from different minorities and nationalities. We often have little information about how the intervention will react in the individual patient who is unique, it is impossible to group all patients into one category. There are pressures to provide data of trial results in children [212] in incapacitated adults[213], those patients who are suffering from disease and need available drugs and in patients from ethnic minorities. There is also pressure for information to be provided to all (for free) and various initiatives exist providing information to developing countries[214]. This thesis will highlight some factors that affect dissemination of clinical trial information and understanding these factors help towards providing a recommendation for improving transparency.

2.9. Can we improve the transparency of disseminating clinical trial information?

The requirement for improved transparency in the publication of clinical trial results began in the 1980s when Simes published his concerns for reporting bias within publications[215]. Since then several other concerns have been made public; underreporting, guest and ghost authorship, falsified data etc. In 1990 Chalmers stated his concerns for underreporting of clinical trials and claimed that this was scientific fraud[216]. It has been argued that clinical trials funded by profit making organisations, such as industry, publish only positive results[27;76;217] or that trials with positive results are published sooner than negative results[200]. However, arguments have been made in other studies that the journal only wants to publish results that will immediately change practice[218]. For the sake of transparency it has been said that all results should be published, whether positive or not[216;219].

It has also been highlighted that the use of key opinion leaders as guest-authors and promoters (of a particular product) to improve acceptability of new research results or in short to make a drug look good[175]. These opinion leaders are respected at

conferences as speakers, act as drug or therapeutic area experts and often publish in their area of expertise. A publication strategy conference highlighted that the main concerns in the publication of clinical trials are off-label promotion, false efficacy claims and kickbacks, where physicians are paid to appear as authors of papers or as key opinion leaders[220].

According to a statement by the Royal Society, scientists should consider the interest of the public when deciding when and how to communicate research results[221], not their own commercial interests. In order to improve transparency and to further the understanding of clinical trials, scientists should provide implications of research to the public and ensure timely and appropriate communication of the results. A report warns of drawing attention to clinical trial results too early, as an awareness over a product before it reaches the market could have negative commercial impact[222]. The report also suggests that there should be a core communications team that already at the pre-clinical stage make plans for customised messages for the timing and varying information that needs to go out depending on the audience.

Society is facing a crisis of trust[223]. According to sociologists and journalists there are signs of mistrust even at familiar institutions or individuals and consumer no longer trust business or products and patients no longer trust their doctors or hospitals. O'Neill states that we live in a culture of suspicion of accountability and transparency[223]. However it will not improve our trust if we constantly expect individuals to declare their accountability or ask for proof that everything is to be trusted[223]. Several sources confirm that the public distrusts the pharmaceutical industry[193;224-227]. In clinical trials, informed consent of the research subject is an important part of gaining trust. In the clinical setting trust is tied to the interpersonal caring attributes of the provider and confidence in their competence[228] and trust in someone depends on the circumstances[229]. Renn and Levine stated "Confidence denotes the subjective expectation of receiving trustworthy information from a person or an institution."[165] If what is received is not trustworthy, confidence will be replaced by uncertainty and create a climate of distrust. In clinical research, the difference between a positive and negative climate has great impact in how the drug development process is managed, including communication of results.

The question of whether we can improve transparency and improve how clinical trial information is disseminated is one research question that this thesis will respond to. It has been argued that the clinical research community has failed to respond to the widespread distrust[225] although there are clear signs that publishers, researchers, medical writers and the like are introducing efforts in improving reporting of clinical trials. Reporting tools, guidelines[176], Clinical trial registries[193;230], data sharing, publication of all research findings and publication planning[220] are components of improving research transparency.

Chapter 6 pulls together recommendations based on the findings in this thesis on how clinical research can be made more transparent when it comes to dissemination information from clinical trials.

2.10. Conclusion to Chapter 2

This chapter described in detail the resource discovery process undertaken for this thesis. The literature review is organised around the research questions and summarises what is known about the topics and what was to be included in this thesis, specifically gaps that needed responding to. The review also provides information about controversies in the topics and definitions to terminology used in literature and in this thesis. I now move onto the research methodology for this study and the choice of studies to answer our research questions.

3. Chapter 3: Research methodology

3.1. Introduction

The purpose of this chapter is to describe the approach to the research, the design of the methodology and to discuss the methods and procedures employed for data collection and analysis. The chapter explains the reasons for a more qualitative rather than quantitative approach to the research design drawing information from both *health informatics* and *clinical research* as subject areas. It will cover how the research was broken down into segments of smaller studies that were undertaken in order to reach the goal of having a comprehensive picture of how clinical trial information is disseminated It will also described the methodology of the studies undertaken and any problems encountered.

Desk-Based Research

A large amount of time was spent on literature searches and reviews in the beginning of the research process. It was part of the research process to revisit the research questions and objectives as the main issues and themes were revealed during the initial phase of reading literature and narrowing down the scope of the thesis.

Approach to the research

It was clear early on that this study would require an examination of a variety of aspects relevant to clinical trial dissemination. The study had to be broken down into segments of smaller studies, and the results drawn together with the literature review to form a comprehensive picture of how clinical trial information is disseminated and to model it. From that a conclusion could be drawn on how dissemination could be improved. (See figure 4 for studies and data collection methods.)

Validity of research

Throughout planning the research for this thesis, ideas, methodology and research experiments were checked or discussed with experts. All aspects of the research were discussed with my supervisor, Professor Ian Rowlands. Other experts that were consulted were:

- Vanda Broughton, Department for Information Studies UCL
- Nadine Lott, Regulatory Affairs, Merck-Serono Pharmaceuticals

- Ida Sim, Associate Professor in Residence Director, Center for Clinical and Translational Informatics, University of California San Fransisco
- Elizabeth Wager, Chairperson COPE and Consultant at Sideview
- Adam Jacobs, Director and Dianthus Medical Limited
- Andrea Palluch, Medical Writer
- Faiz Kermani, BioPharm International Clinical Trials Advisor
- Sue Fitzpatrick, Education Manager Institute of Clinical Research

Research Design

The study adopted a mixed methods approach and used qualitative and quantitative techniques to examine the dissemination of clinical trial information. Using the two methods complemented each other[231] and helped to understand dissemination practices and perceptions of the practices. Collecting diverse types of data and information using different methods provided this study with a broader understanding of the complexities of clinical trial information, dissemination and factors affecting dissemination.

Data Collection Methods

Both primary and secondary methods were used to gather data and information. Primary methods used include collecting data through experiments, talking to and surveying clinical research professionals and drawing on researcher's own experience from working in a pharmaceutical medical information department and later in a clinical research environment, whereby knowledge of the process of a clinical trial and key information generation and dissemination has been learnt. Secondary methods, data collected by others[232], involved reading published and unpublished material relevant to clinical research found in the literature review.

Quantitative methods

The quantitative methods in this study involved collecting data in a survey and analysing the data with the Statistical Package for Social Sciences (SPSS) as well as minor data sets from smaller studies using Excel. Excel was also used for the creation of useful tables, graphs and figures with SPSS analysed data. The findings in the quantitative analyses were used to compare or complement findings of

qualitative methods. When I have presented research findings and data in this thesis, I have specified in the figures if I am showing numbers (n=) or percentage (%).

Qualitative methods

The qualitative methods used in this study were applied to more accurately describe how clinical trial information is disseminated and interpret choice of dissemination by those who work with clinical trial information and those who disseminate it. This thesis predominately consists of qualitative methods as the research questions are such that it would be difficult to design research methodology that explains the dissemination of clinical trial information with quantitative data alone.

3.1. Research ethics permission

Most research for this thesis involved collection of study data not involving human participants, therefore not requiring ethics approval.

The survey of clinical research professionals involved collecting data from human participants. I sought ethics approval from the UCL Research Ethics Committee, who responded that permission is not required as I did not intend to identify the participants and it was a survey based on behaviour. The UCL ethics approval exemption *part d* therefore applied[vii]. The UCL research ethics standards comply with the Framework for Research Ethics[viii].

[vii] Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behaviour that is not exempt under paragraph (c) of this section, if the human participants are elected or appointed public officials or candidates for public office http://ethics.grad.ucl.ac.uk/exemptions.php [Accessed: 16 January 2012]

[viii] http://www.esrc.ac.uk/about-esrc/information/research-ethics.aspx [Accessed 16 January 2012]

3.2. A mixed methods approach to the research

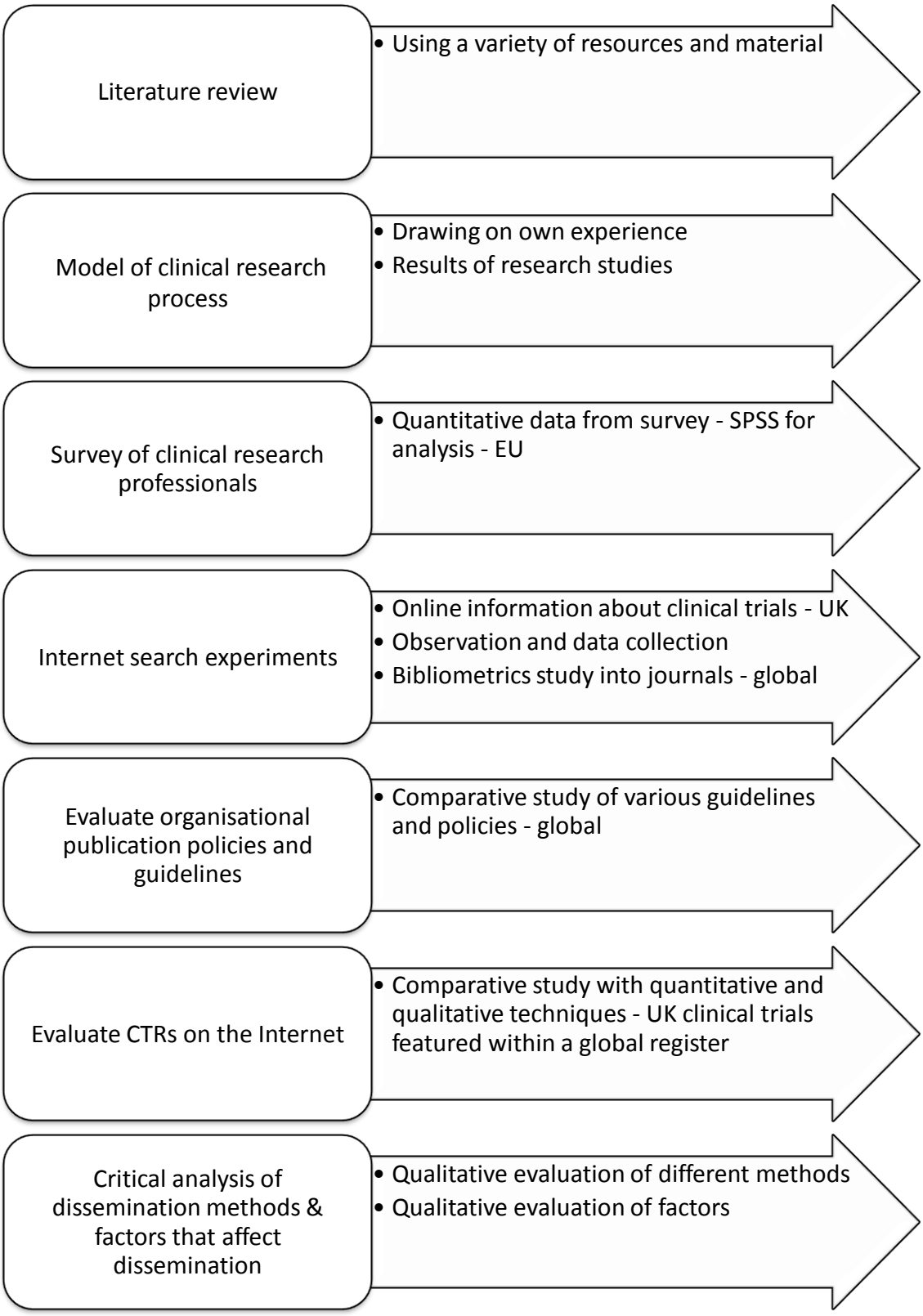

Figure 4: Overview of research design and data collection methods plus geographic coverage

3.3. A model approach

There are many written documents describing the regulatory authorities' approval process for a new intervention undergoing research and subsequent launch onto the market[233]. However, no one as far as this researcher is aware no one has modelled the clinical research process highlighting important points in the clinical research process where key information is produced and the type of output it takes. Constructing a conceptual graphical model of the clinical research process and the information generated throughout it could act as a road map for discussions concerning the aspects of making information available. The model constructed is outlines activities and output. The scope of the model is the information generation from the beginning of the research process, through the clinical trial phases to the post-marketing phase of studies that may take place once the intervention is already on the market. The model shows both publicly and confidential information that is generated. The model is tested in part 2 of this thesis where the methods used for dissemination are examined and the factors that affect dissemination. The model will also form the basis for our final recommendation of how dissemination of clinical trial information can be improved and become more effective. (See figure 7 for model or appendix A for enlarged view.)

3.4. Survey of clinical research professionals

A survey (Appendix G) aimed at clinical research professionals who work with clinical trials was designed to ask them (1) about their knowledge and understanding of clinical trial dissemination activities and relevant regulations and policy and (2) about actual practice and timing of different dissemination activities, e.g. the release of clinical trial data, clinical trial registration, posting of results etc. At the time of the survey, WHO had called for the voluntary registration of all clinical trials[234], and even though registration of clinical trials had been made mandatory in the state of Maine in the USA[235] it is not a legal requirement anywhere else. It was uncertain if clinical trials were registered and if so where, and how results of clinical trials were disseminated and specifically more information about what clinical research professionals know about their own organisations, e.g. if they have a publication policy and if so what is the policy on disclosure? Do they post results on their own websites?

The survey questions were drawn up firstly based on information and data needed to respond to the research questions for this doctoral thesis. The survey questions were discussed and tested with two experienced clinical research professionals and medical writers, Liz Wager of *Sideview* and Adam Jacobs of *Dianthus Medical Limited*. The survey questions can be found in Appendix G (p.253).

Population of the Study

A study in the dissemination of clinical trial information has to take into account those who work with clinical trial information to establish what they know about the dissemination of clinical trial information including clinical trial registration. Persons involved in the creation and management of clinical trial information constitute many types of individuals like authors (those reporting on clinical trials), managers of clinical trials, clinical trial site staff, statisticians, research staff etc. These individuals are based in different organisations like national health services, pharmaceutical companies, research companies, academic institutions etc. Generally each organisation has a different set up in what roles are involved in the different parts of disseminating clinical trial information. Departments such as regulatory affairs collate the final product dossier of a new medicine and notify the regulatory authorities, the marketing department use the data to draft promotional material and the medical department use the research findings as evidence to provide to healthcare professionals requiring evidence as base for treatment.

Sampling and Sampling Strategies

One of the difficulties of this study was to reach the right people in a variety of organisations. The respondents were selected using purposive sampling, e.g. a predefined group. Purposive sampling was used to detect clinical trial information dissemination within a wide range of affiliations and across departments with individuals working in different roles. Individuals belonging to particular membership bodies were chosen because they are likely to have some knowledge of reporting in clinical trials which enabled detailed exploration of the dissemination of clinical trial information. However the actual sample population is unknown.

Sample Size

The survey was announced and distributed by the Institute of Clinical Research (ICR), European Medical Writer's Association (EMWA) and the Pharmaceutical Information & Pharmacovigilance Association (PIPA). It ran between 20 August 2007 and 7 October 2007. These organisations had a total membership of 7,113 of which only a small number would find the survey relevant to their work and therefore be the target audience of this survey. The survey had 938 hits, 159 partial responses and 309 complete responses.

Three filters were set before analysing numbers (see figure x). Incomplete responses (n=159) were removed. A limit was also set to responses from the EU as there were only 40 responses outside the EU. The regulatory environment is quite different in other areas outside the EU. Drawing conclusions of actual practice of clinical trial registration would be difficult without considering the regulatory environment. A filtering question was also asked in the survey of whether the survey was relevant to the respondent's work. The point of this filter was to remove individuals (n=171) who may not had sufficient experience or knowledge of trial registration and dissemination. This left 98 survey responses for analysis.

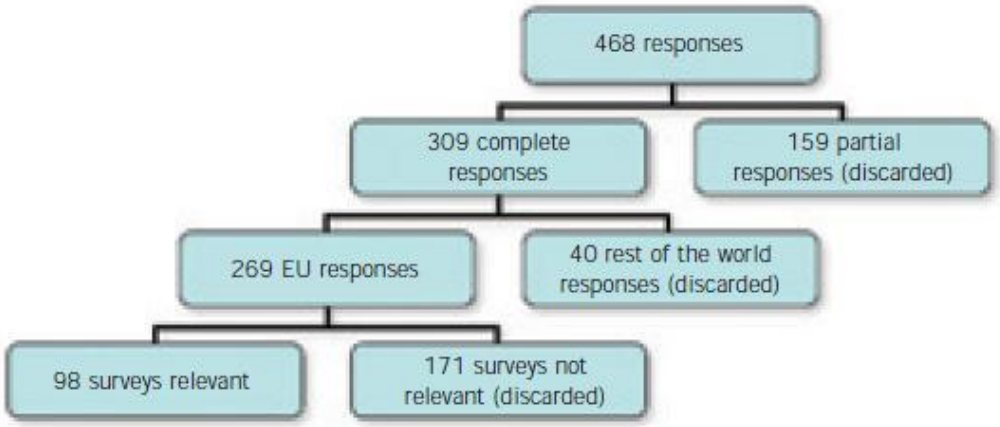

Figure 5: Flowchart of responses to survey (n=98)

Data collection and instruments

The survey was deployed using Zoomerang online (see Appendix G for survey). Online surveys are low cost, easy to deploy as well as easy to collect data from. It

was not feasible to send out print questionnaires to such a large amount of people. Zoomerang was chosen as it was the survey tool used in-house in the researcher's organisation and made design and deployment easier.

Data analysis was done using SPSS as described earlier in the section on 'Quantitative methods'. Data was then exported into Excel for creating tables, figures and charts.

Limitations and problems encountered

The Internet gives the opportunity to conduct surveys more efficiently and effectively than traditional print methods. However, using only a web-based survey does create risks, in particular the self-selection of respondents, which may result in a sample that does not represent the targeted population and we must also assume that not everyone has access to a computer or the web which could reduce the potential sample[236;237]. Another difficulty with web-based survey is the difficulty in calculating a response rate.

Even though the design of the survey was checked with experienced clinical research professionals, some of the terminology within questions was ambiguous. Clinical trial registration is relatively new and the terminology (as explained earlier) is not used consistently by the clinical research community. For example, a question on 'releasing research results early' can mean different things, e.g. release prior to publication in a journal or releasing results before the end of a clinical trial. Assumptions cannot be made on what respondents assumed it meant and so interpretation must be cautious. However, a follow-on question asked respondents to describe how research results were released early meaning prior to end of trial, providing some responses that can be interpreted.

Another after-thought is the complexity of the survey. Since the questions ranged from clinical trial registration to disseminating clinical trial results, it may have benefited from being a briefer survey followed by in-depth selective face-to-face interviews. The appendix to this thesis contains the published paper of the survey results (Appendix I), the survey questionnaire (Appendix G) and a poster with findings (Appendix H).

3.5. Online information about diabetes clinical trials – an evaluation of website results from a Google search

We know that the Internet is increasingly used when trying to find medical information. The aim of this study was to 'mystery-shop' to try to find clinical trials for diabetes in the UK and examine the types of websites, the reading level of the content and date the website was reviewed (if dates were given). The result will reveal the types of information about clinical trials that is disseminated on the web by using one of the most commonly used search engines.

Data collection and instruments

Using Google, I limited our search[ix] to diabetes clinical trials as with our other studies in this thesis. I also limited the search to the UK. The search terms: *diabetes clinical trial* (not using boolean operators or ""). The first twenty websites listed from Google were selected for examination. The decision to only analyse the first 20 results was because the average searcher rarely go beyond the first page of returned results[238].

Limitations and problems encountered

This type of search is only a snapshot in time as more content is added to the web and indexed by search engines every day. The results examined were true for the date the search took place and if repeated regularly will produce a different result. Nevertheless, it was an interesting exercise providing an idea into how information is scattered across a variety of online resources and fits the objectives of this thesis.

3.6. Evaluate existing publication/disclosure policies of organisations

The decision as to how clinical trial information is disseminated or to what extent data from clinical trials are released, are covered in publication and/or disclosure policies of organisations, institutions and journals. For this thesis, I will refer to them all as publication guidelines. There are three sets of publication guidelines that this thesis refers to. First there are the guidelines issued by authorities or authoritative sources, e.g. ICH GCP (good clinical practice) guidelines[167] or ICH E3[239] is a guideline regarding formatting and reporting of research to authorities. Second there

[ix] Search conducted 19 July 2008

are guidelines drawn up by journal publishers or research groups, e.g. the ICMJE guidelines[176] or the GPP guidelines[240]. The ICMJE guidelines are comprehensive with regards to reporting and writing up research. Both these types of guidelines aim to provide recommendations to clinical researchers on reporting clinical trial results and findings to the authorities and the public including the scientific audience. The third type of guidelines are organisations' internal guidelines, e.g. guidelines for researchers within a pharmaceutical company or an institutional statement of disclosure of research results. The Pharmaceutical Research and Manufacturers of America (PhRMA) issued their principles of disclosure[241] of clinical trials, based on the ICMJE uniform requirements advising their members (pharmaceutical companies) to adopt the principles or adapt them into their own policies.

For this thesis, I investigated these three types of guidelines in two studies to establish their content of coverage and recommendations for dissemination of clinical trials.

Study 1: Pharmaceutical companies' guidelines

The first study was a comparative analysis of ten large and small pharmaceutical companies' publication guidelines[x], comparing the content of them to the recommended ICMJE requirements[176]. In the survey of clinical research professionals, questions regarding publication guidelines within organisations as well as external guidelines were asked and responses useful for comparison in this analysis.

Each year a list is published of the top 50 pharmaceutical companies in the world is published[242]. From this list five large and five small (based on number of prescription drug sales) companies were randomly selected for this study. Initially it was investigated whether or not the companies had a disclosure policy or not (Table 2). Policies were found on companies' websites and if they were not found, the company was contacted by email to request a copy of their policy.

[x] The policies were downloaded or read online between May and July 2007.

Table 2: Companies selected for analysis and whether they had a public policy on disclosure

Company	Public policy of disclosure	
Five large companies	**Yes**	**No**
P1. Pfizer	√	
P2. GSK	√	
P3. Novartis	√	
P4. AstraZeneca	√	
P5. Sanofi-Aventis		√
Five small companies		
P6. Merck Pharmaceuticals (KgaA)	√	
P7. Eli Lilly[xi]	√	
P8. Roche	√	
P9. Amgen International	√	
P10. Ipsen Ltd.		√

Data collection and instruments

The ICMJE provides a uniform list of requirements of a manuscript submitted to one of its member journals. In this study, these requirements were used for comparison against the publication or disclosure policies. Publication guidelines were compared against the headings of the ICMJE requirements (Table 3) to establish if they have incorporated the uniform requirements within their guidelines.

[xi] Eli Lilly has a policy on the conduct of clinical trials which includes some disclosure information

Table 3: ICMJE uniform requirement headings used for comparison

Using external contractors for drafting publication
Conflict of interest
Obligation to communicate negative results
Obligation to register clinical trials Phase I-IV
Preparing manuscript for publishing
Registration of Phase I studies
Commitment to communication of results
Acknowledges official guidelines (e.g.PhRMA/ICMJE)
Posting results on a public database
Admits commercial sensitivity
Identifies database where registering trials
Gives timeline when results will be released
Discusses interim or preliminary results
Talks about publication of results
Internal review of abstracts/scripts
Discusses delayed publication
Sharing of protocol with journal editors
Authorship of publications
Peer review
Communicating outside peer-review journal

Information analysis also extended to: title of policy, year of publication, availability on the web, full text of policy publicly available and the coverage of the policy.

A coding scale was used for scoring the findings:

0=no coverage,
1=some mention
2=yes covered

Each publication guideline then had a total score, providing an insight into its coverage.

Study 2: Authority guidelines and clinical trial specific guidelines (publishers or research groups)

This second study into guidelines aimed to create a chronological timeline of the release of guidelines that have affected the dissemination of clinical trial information. The timeline supports this thesis argument that there is change in how clinical trial information is disseminated and helps to answer the research question about what factors affect what is disseminated.

Data collection and instruments

The information to produce the timeline in Figure 20 (p.154) came from a review of literature which provided the dates and titles of relevant guidelines. The timeline identifies the different guidelines with colour-coding. It also includes important events (black) in clinical research. Each guideline was read and summarised to provide a brief background into how they may affect clinical trial dissemination. The survey of clinical research professionals also asked individuals to identify guidelines that they are aware of, which ones that they use and the usefulness of the guidelines. These findings are supplemented by literature searches. The findings may help identify some of the issues that exist in clinical trial dissemination.

Limitations and problems encountered

The results of the survey (section 1.19) also provide a small insight into which guidelines are known by clinical research professionals. The survey asked users to evaluate guidelines usefulness which is a question asking for their personal opinion. It is not evidence enough of a guidelines' usefulness to only refer to opinions of a sample. There would be more clout if there was evidence of which guideline(s) were officially adopted by organisations. Very little such information exists, although there is some evidence provided by the authors of the GPP[240] and ICMJE guidelines[176], as they formally publish lists of organisations which have approved their guidelines on their websites.

With regards to organisational guidelines, it may be that organisations did not model their guidelines against the ICMJE principles. However, these guidelines were chosen in this study as most peer-reviewed journals that publish clinical trial results expect papers submitted for publication to adhere to these principles. Therefore the assumption was taken that organisations would cover the same topics within their guidelines as those of the ICMJE.

Not all pharmaceutical companies have publication guidelines, or these are not made available to the public. Two of the ten companies studied here did not have public policies. They were removed from further study. One company had a policy on the conduct of clinical trials, which included disclosure, and this one was included in the study.

3.7. Critical analysis of the methods used to disseminate clinical trial information

The methods used to disseminate clinical trial information are many. A key observation in this thesis, which is argued throughout, is that clinical trial information and data are scattered around various resources, mainly online (Figure 6). Of interest in this thesis is how dissemination is changing with the invention of new tools on the Internet and new developments in publishing. How have these new developments affected the way in which research is disseminated and are the methods fit for purpose?

Figure 6: Scatter of clinical trial information

To establish if methods used to disseminate are fit for purpose, an evaluation of traditional methods and new or recently developed methods took place. With traditional methods, I mean those methods used prior to the Internet, e.g. peer-reviewed journals, conference meetings etc. With new methods I mean those that have developed in the electronic era with the help of the Internet, e.g. clinical trial registries, online tools such as blogs and websites etc.

3.8. An evaluation of methods used for dissemination

Individual but related studies took place to evaluate different dissemination methods. The research objectives were:

1. An examination of the journal as a suitable tool for disseminating clinical trial results, a bibliometrics study to establish what journals are core clinical trial journals and what information the abstracts of published papers contain.
2. An examination of electronic alternatives to traditional dissemination methods.
3. An examination of clinical trial registers; their quality and content

Responses in the survey of clinical research professionals are used to compare with findings of the above analysis.

Study 1- Part 1: Journal as a tool of dissemination: A bibliometrics study - Bradford's law applied to Scopus search

The literature review showed that some bibliometrics studies have taken place into specific disease areas or a specific journal, but not into the obesity and diabetes therapy areas. The first aim of this bibliometrics study was to establish what journals cover the subject of obesity and diabetes clinical trials; the number and the titles of core journals to get the most relevant articles in the field. I have already established that clinical trial information is scattered around a variety of resources and journals. This study may show which and how many journals covered by a bibliographic database will supply a certain percentage of journals relevant for a specific topic. It will also tell us what type of journals are the core set that cover information about clinical trials in the area of obesity and diabetes.

Bradford's law of scattering comprises one law of bibliometrics. In knowing the core journals that cover our subject, it may help to understand the type of journals that cover our topic and to see if the core set is large or small. It's important to remember that the Bradford nucleus or core of journals continues to develop as a topic matures, if the graph that is generated is mostly linear, the topic is still in a stage of development. A *Groos drop,* the Bradford curve is an S-shape and droops at the end, could indicate of an incomplete nature of the bibliography examined[243], but Braga states that a *Groos drop* could indicate the maturity of the subject area[244].

Data collection and instruments

Bradford's law was applied on the results from a search on the database *Scopus* to establish core journals. *Scopus* was selected as it provides a useful citation tracker tool, one which does not exist within *PubMed*. The search terms were: *humans, obesity, diabetes, 2008.*

In order for *Bradford's law* to work in this study, the search had a limited time span (articles from year 2008 only), the subject is well-defined (clinical trials, obesity, diabetes) and the bibliography must be complete, although it has been stated that a complete bibliography is difficult to achieve[245]. Scopus is a relatively comprehensive database listing medical and scientific articles.

Study 1 – Part 2: Journal as a tool of dissemination: Eigenfactor score applied to PubMed search

In this part of the study the objectives were to examine the types of journals that publish the most clinical trials in the area of obesity and diabetes, and if those that publish the most clinical trials have the highest impact factor. The objective was also to examine the abstracts of published papers to establish usefulness, was sufficient information provided about the clinical trial in the abstract, e.g. type of trial, IMPs used, methodology, main findings, clinical trial registration number, declaration of funding etc.

The *Eigenfactor Article Influence Score* calculates measures the relative importance of the journal on a per-article basis. It is the journal's *Eigenfactor score* divided by the fraction of articles published by the journal. That fraction is normalized so that

the sum total of articles from all journals is 1. The mean Article Influence Score is 1.00. A score greater than 1.00 indicates that each article in the journal has above-average influence. A score less than 1.00 indicates that each article in the journal has below-average influence.

Data collection and instruments

A PubMed search was conducted on 14 June 2009 using the search terms: *obesity* and *diabetes*. Filters were set to 'clinical trials', 'humans', and '2008'. There were 80 citations that matched this search. The abstracts and journals published in were analysed for the following information: publisher, the impact factor, the *Eigenfactor Article Influence Score* (referred to as Eigenfactor score from hereon), country of author(s), transparency of sponsor and funding, if clinical trial registration number was given, evidence of type of study published and the language of the article. This search did not use a *Bradford analysis* but used the impact factor and *Eigenfactor score* (found in the Science Journal Citation Reports from Thomson Reuters[xii]) instead and it was an interesting comparison between the *Bradford analysis* on Scopus and the *Eigenfactor score* from PubMed result to establish if the same journals came up as core journals.

Limitations and problems encountered

I cannot be sure of how authors select publications to submit their clinical trial paper. By examining impact factors I cannot determine the choice of journal. I cannot therefore draw conclusions on suitability of a journal as a method of disseminating clinical trial results on behalf of the author.

Journals use different abstracting methods and do not necessarily use an IMRAD[xiii] structured abstract making it difficult to quickly find relevant parts of the abstract for analysis.

[xii] http://thomsonreuters.com/products_services/science/science_products/scholarly_research_analysis/research_evaluation/journal_citation_reports [Accessed 26 Jul 2009]

[xiii] IMRAD stands for **I**ntroduction, **M**ethods, **R**esults **A**nd **D**iscussion

Using two different methods in analysing journals to establish a core journal set proved interesting. It is known that the impact factor can be manipulated and that journals that publish reviews and summaries tend to have higher impact factor due to higher citations than journals that publish original research. However, journal value is more than just its impact. Coleman suggests that journal value is multidimensional and citations alone which drive impact factors do not capture other value factors such as costs and benefits, e.g. the scientific value must be developed in a fuller model[246]. Furthermore, impact factors cannot be used for other methods of publishing, and there is a need to develop a model of showing scientific value in other types of publication activities. Similarly, the Eigenfactor score aims to measure influence. However, influence is more than citing articles and the rank of a journal.

Study 2: Examination of electronic alternatives as dissemination methods

The objective was to establish what the electronic alternatives are compared to publishing in a journal and in particular find out if blogs or other social tools were used to announce clinical trial results.

Data collection and instruments

As an online search experience, *Google* was used with the search terms: *clinical trials* AND *results* and a limit set to year 2008. There were 4,290,000 results matching this search. Looking at the results, it was difficult to establish what type of online page or document it was, unless the URL specifies so in its path name, e.g. using words like blog, press release, publications etc. Therefore clicking on links was required to establish what type it was. The overwhelming result count means that only links that seemed suitable were visited and recorded.

Limitations and problems encountered

Many alternative methods to disseminate clinical trial information are available using the Internet. It is evident that by using an Internet search engine we can discover clinical trial results, however, it is time consuming and difficult to conduct a search that will bring back relevant articles as search engines do not yet allow for more sophisticated searching. The different types of web pages that exist also make it difficult to determine ownership, quality, publication date, authorship and relevancy of content.

It was not obvious when reading blogs and random web pages that came up through the Google search who the owners were and if they were researchers or representing research institutions. It is known that researchers use blogs or other kinds of web presence to be transparent about their research in particular to those funding it[53]. There is some evidence that researchers are also using new social tools such as Twitter, to list research, papers and researchers[247].

The research does not show if dissemination has changed over a specific time period. That type of research is difficult to conduct as some electronic tools online do not have date stamps on when information was uploaded.

Study 3: Evaluation of clinical trial registries on the Internet

Clinical trial registries are repositories of data and information about current and closed clinical trials and sometimes also the results of the trials (abstract and references of published papers). The aim of the register is for the sponsor of a clinical trial to record information about clinical trials, which improves transparency and allows users to search for information about clinical trials. There are many clinical trial registries in existence, with different content, structure and functionality. Clinical trial registries are a link between the clinical trial, the formally published results, the authorities and the public.

As publishers now recommend[176] that clinical trials are registered before publication of results in a journal, it was important to review this type of dissemination method of clinical trial information. For this thesis an evaluation of ten different clinical trial registries took place during a time of sudden increased interest in clinical trial registries. There was a sudden growth in registers coming to the market and their purpose was debated in published literature. My research also took place before *Clinicaltrial.gov* became the largest register in use and recognised as the default register for clinical trials and before the WHO launched the *ICTRP* metaregister, a combined register, of other existing clinical trial registries[105] allowing for cross-searching. The focus of the research was to establish the functionality of the clinical trial registries and assess the quality of the content.

Data collection and instruments

To make the study manageable, these research questions were set:

- What clinical trial registries are relevant for this study when you want to find open clinical trials in type 2 diabetes and obesity in the UK?
- According to the evaluation tool[114] used, does the register provide suitable functionality and tools to enable the user to find information?
- Does the register meet the criteria of the WHO by providing information in the WHO recommended 20 datasets (TRDS) (Table 4)?

Table 4: The WHO 20 minimal dataset (TRDS)

WHO 20 minimal dataset
1. Primary Register and Trial ID #
2. Date of Registration in Primary Register
3. Secondary ID#s
4. Source(s) of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor(s)
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title
11. Countries of Recruitment
12. Health Condition(s) or Problem(s) Studied
13. Intervention(s)
14. Key Inclusion and Exclusion Criteria
15. Study Type
16. Date of First Enrollment
17. Target Sample Size
18. Recruitment Status
19. Primary Outcome(s)
20. Key Secondary Outcomes

The study began by compiling a list of clinical trial registers by using a four step process to identify and select for review web sites that offer clinical trial search tools.

Step 1: Sites recommended by diabetes related organisations

Step 2: Online search using Google to expand the site list. Most Internet searchers

start with a search engine and Google is the most widely used search engine
Step 3: A Medline search
Step 4: Information from experts in the area, e.g. lists or published information.

Eligible resources

Resources had to contain information about diabetes clinical trials available in the UK. Websites reviewed are not limited to those based in the UK but must contain information about diabetes trials in the UK. Sites were excluded if they did not allow the user to search or at least display information about current (ongoing or open and recruiting) trials.

Search conducted to find relevant clinical trial registries

A search was conducted[xiv] in *Medline*, on *Google* and on known diabetes websites and supplemented with clinical trial registries known to researcher. In *Medline*, the search terms used were: "clinical trial" AND "diabetes" AND ("database" OR "register") without result. New terms were: "diabetes" and "database" with the limits "2006-8" and "UK" yielded 11 results. On *Google*, the search terms were "clinical" "trial" "database" "diabetes", and pages from the UK radio button was selected, were used in *Google* yielding a total of 137,000 websites. Site links on the first two pages of the *Google* findings for each search were considered as users rarely go beyond the first page of returned results[238]. Organisations that promote diabetes care that were consulted for further clinical trial registries were *Diabetes UK*, *Diabetes.org.uk*, *Diabetes Action* and *Juvenile Diabetes Research Foundation International*.

In total 11 clinical trial registries were considered relevant to the study.

Table 5: List of Clinical trial registries relevant to searching for diabetes clinical trials

[xiv] The search took place 7 July 2008

Site	Link	Source	Country of origin
Clinical Trials.gov	http://www.clinicaltrials.gov/ct2/search	recommended	US
IFPMA portal	http://clinicaltrials.ifpma.org/no_cache/en/myportal/index.htm	recommended	Switzerland
Current Controlled Trials	http://www.controlled-trials.com/	recommended	US
ISRCTN	http://isrctn.org/	recommended	Global/HQ London
MRCT	http://www.controlled-trials.com/mrct/	recommended	
UKCTR	http://www.controlled-trials.com/ukctr/	Google	UK
Pharmaceutical Industry Clinical Trials Database	https://www.cmrinteract.com/clintrial/	recommended	US
UKCRN Portfolio	http://public.ukcrn.org.uk/search/	recommended	UK
ICTRP (WHO)	http://www.who.int/trialsearch/	recommended	Global
Centerwatch	http://www.centerwatch.com/	recommended	US
MedTrials	http://www.medtrials.co.uk/	Google	UK

Note: ISRCTN, MRCT and UKCTR (now called UKCTG) are available to search within the Current Controlled Trials register. Please also note that CRMInteract ceased to exist 31 Dec 2009.

Tool to compare clinical trial registries: Range, content and quality markers

There are no validated tools to evaluate content and form of Internet information. The *JAMA* benchmarks quality rating scale[188] or the DISCERN Instrument[248] were not suitable for this study as it was not an evaluation of websites but specific databases on websites. For this study I based our content evaluation tool on one used by Atkinson *et al.* in the search for clinical trials[114]. The tool developed by them reviews functionality and features of websites with clinical trials looking for:

- Basic search tool
- Advanced search tool
- Registration options
- Presentation of results
- Additional site content.

Limitations and problems encountered

It is not difficult to find clinical trial registries by searching Google, however it is difficult to know suitability of a register without visiting it and attempting a search first. Some of the clinical trial registries suffered from technical problems, e.g. search not working as it should. Many clinical trial registries had rudimentary search engines and different terminology was used making it difficult to make a search similar in all clinical trial registries. Sometimes it was impossible to know if a study was still open or closed. Other difficulties were that sometimes the country could not be selected when searching.

This study is also a snapshot in time but shows an interesting picture of registers at a time when their growth and development was at its infancy. It is difficult to judge the quality of registers from different organisations with different agendas, level of funding and management time invested. It was still a valuable exercise in identifying recommendations for registers to be fit for purpose in chapter 6.

3.9. Discover factors that affect dissemination

The objective was to discover the factors that affect dissemination, e.g. what determined which method was chosen for dissemination, why were other methods not chosen, what was disseminated and why? By understanding the forces that affect dissemination, it will allow us to address the potential issues in drawing up recommendations for future dissemination.

Data collection and instruments

Two methods were used to help discover the factors affecting dissemination. A literature review into existing research or claims made about the dissemination process is supplemented with comments made by clinical research professionals in the survey described earlier.

Limitations and problems encountered

Much of the literature reviewed contains personal comments and emotional statements, sometimes very negative comments against the publishing and pharmaceutical industry. To what extent these comments are based on scientific truth is difficult to determine. Another research method for this topic could have been to select a sample of clinical trials recently published and approach the authors asking specific questions about their dissemination activities and behaviour and researching their organisations' policies on dissemination. However, for this thesis there was not enough time to conduct a more comprehensive study.

3.10. Conclusion to Chapter 3

This chapter summarised the research methods adopted to address the research questions and objectives set for this thesis. Many studies were small scale, but necessary to get an insight into the dissemination process of clinical research professionals: the traditional methods and new methods that have been developed

mainly with the help of the Internet, factors that affect dissemination and the fitness of purpose of the methods used for dissemination. The chapter describes the objectives of each study, the data collection methods used and limitations encountered with each study. The research findings of these studies and the literature review are discussed in chapter 4 and 5 with recommendations presented in chapter 6.

PART 1

4. Chapter 4: Modelling clinical trial information

4.1. Introduction

Chapter 4 is the first chapter in which I will try to make sense of clinical trial information and explain the complexity of information within the clinical research process. Chapter 4 and 5 are arranged around the themes as introduced in the Literature review chapter (Chapter 2) and in order to respond to the research questions. This chapter will define clinical trial information. The findings presented here responds to the first research objective to model the clinical trial process and what type of information is generated throughout the clinical trial. The conceptual model of information generation and dissemination is presented as a backbone to discussing clinical research, regulations and the information that is produced in the various phases of clinical trials. There is special emphasis placed on discussing research data, the evidence of a clinical trial, and issues around raw data, sharing of data and ownership. This is followed by a brief introduction into the heavily regulated clinical trial industry which impacts on information dissemination as will be seen in later chapters. I draw on references introduced in the literature review and new references not previously discussed will be introduced to compare with findings of research done for this thesis and to add to the discussion.

4.2. What is clinical trial information?

Clinical research answers research questions into the efficacy and safety of medicines. A promising compound is selected to go through phases of research (clinical trials) to establish its behaviour. A clinical trial is the gold standard into the discovery of new medicines and devices, testing their efficacies before being marketed. The results from trials, research data, are analysed and interpreted and if successful form the basis for new drug applications. Throughout the drug development a large amount of clinical trial information is *generated* in the different processes that a compound or entity is put through. That clinical trial data consists of complex information and data that are connected to one another. This generated information is adapted or repurposed for various use and some publicly released in a

number of ways, although it is unknown how much research information is publicly released.

Clinical trial information can be broken down into four components of information generated:

1. Information about the clinical trial, e.g. name of entity, type of trial, number of patients, research questions, funding etc.
2. Information sought during a clinical trial, e.g. efficacy data, dosage information, side-effects etc.
3. The final results of a clinical trial, the data.
4. The interpretation of the research process and data and their output, e.g. the written summary of a trial, a published paper, the evidence of efficacy and safety etc.

These components, and surrounding issues, will be explained in more detail in this chapter and are key to discussion throughout this thesis. When this thesis refers to clinical trial information it includes all these components of information.

4.3. A conceptual model of the clinical research process and information generation

For this thesis, a graphical model has been constructed (figure 7, or see appendix A for larger scale) as a road map to understand the phases of clinical research and output of information generated during the different points of the lifecycle of a new intervention. The model is showing the path of a typical intervention, but of course the model can vary considerably depending on things that affect research, e.g. research aims, type of intervention and events etc. The model consists of a pre-clinical phase (a) and the clinical phases (b). The clinical phase section is split into a number of types of phases, phases 1 – 3, all which seek out to answer specific questions about an entity. The arrow represents the clinical research process starting at year 0 with the selection of an entity that shows potential. The end of the arrow represents the end of research, e.g. the launch of a new medicine on the market and the end of the research lifecycle. It is unlikely to be an 'end' as often research continues but for illustrative purposes I mark an end when an intervention is approved for sales on the market. It can take on average 12 years and cost around

$1billion to bring a new medicine to the market, although due to economic pressures the time can now be as low as seven years due to the pressure to generate revenue to bring more entities through development[249] as well as priorities to finding suitable interventions to pressing diseases.

In this thesis I refer to '*information generation*' where during the various phases of clinical research information about the entity is discovered and when output becomes *evidence* of how the research took place, the research findings, data etc., which is then disseminated and published in various ways.

4.4. Model walk-through

As an entity continues through the phases, more information is generated, indicated with the thickening of the arrow. Along the way, there is some key information output, shown by yellow diamonds on the arrow. There are also decisive moments between the phases of whether or not to continue developing the entity, a decision of go/no go that depends on research findings so far, continuous funding, opportunities to recruit subjects for trials and so on. Phases may also overlap and there may be more than one clinical trial in each phase.

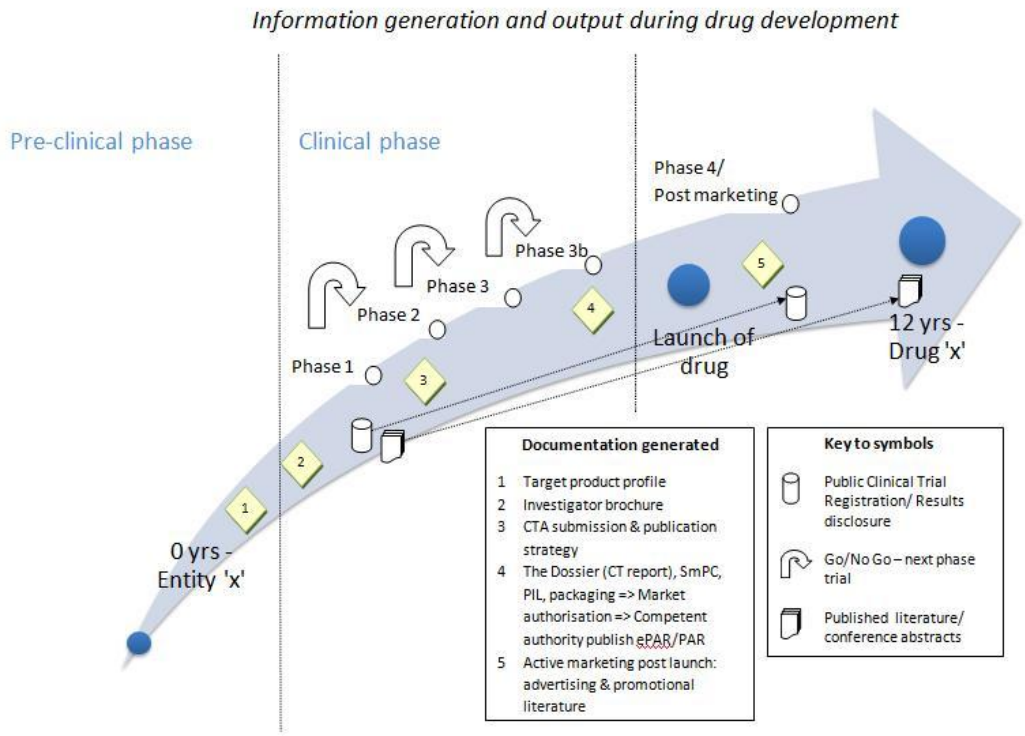

Figure 7: Constructing a conceptual model of information generation and dissemination for a new intervention undergoing clinical research

(Available in larger scale in appendix A.)

The pre-clinical phase – understanding disease

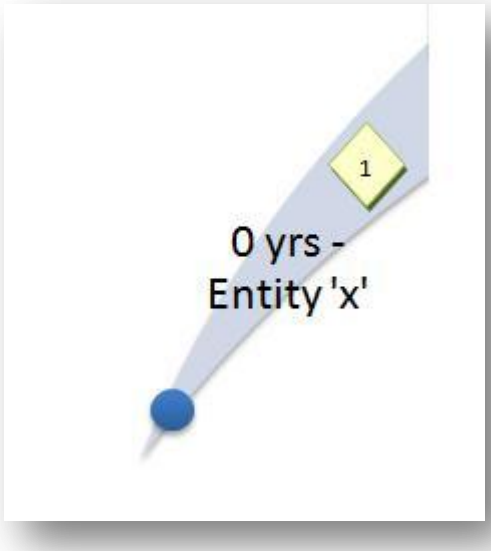

Figure 8: Pre-clinical phase: 'entity x' at 0 years - (1)Target product profile produced

In the pre-clinical phase (Figure 2), the first step in drug development is to find a promising entity. This requires an understanding of disease, pharmacology and using computer technology and chemistry. Numerous entities are tested and computer modelling helps establish what entity shows promising signs. Why a particular entity is selected for development depends on economic, political and other agendas. It is likely that the entity chosen fits in with the existing drug portfolio or it may be sold off to another company who will develop it further. It will need to generate a financial profit and be worth investing time and effort for a final product. There may also be cultural-political pressures to develop drugs, e.g. a drug for a disease affecting a large population, e.g. HIV, or an unexpected breakout of a disease, e.g. flu.

Early in vivo tests are carried out in living animals, usually rodents, to demonstrate the safety of a suggested medicine. In vitro tests, using cells and tissues in an artificial environment, are also done to assess safety and effectiveness of an intervention. Computer models are also used and can in some cases replace in-vivo and in-vitro tests. The drug regulatory authorities (or competent authorities) require certain safety tests to take place before humans are exposed to a new entity. Information that is generated during the pre-clinical phase includes toxicology and safety information. This information generates a 'target product profile'(marked with diamond 1). This information is used to support a submission of a clinical trial application (CTA) (in the US this is called an Investigational New Drug (IND) application). Usually before a submission is prepared, the sponsor company (a pharmaceutical company or research organisation) holds discussions with the competent authorities to discuss the potential of the new entity. No information about the entity is publicly disseminated at this stage.

Information about the clinical trial itself

Each clinical trial has to be approved by an ethics committee and by the competent authority in the country of which the trial will take place, and by the EMA if it is a trial taking place in the EU. When a Clinical Trial Application (CTA) is made, certain amount of information has to be provided about the clinical trial for an assessment of whether the clinical trial should go ahead and the design of the trial is

ethically sound. Information has to be provided on the name of the entity to be studied, what the research objectives and aims are, how many patients will be studied, what type of trial it will be, how the trial will be managed, where it will take place and so on. If any of these pieces of information change at any point before or during the clinical trial, an amendment must be applied for and approved. The procedure for applying for a clinical trial and an amendment are highly regulated. This information is stored in databases and can be accessed by any competent authority which needs to access it. Some of this information may also be released in public clinical trial register. Registration usually takes place before subject recruitment for a clinical trial begins.

The clinical phases – testing in humans

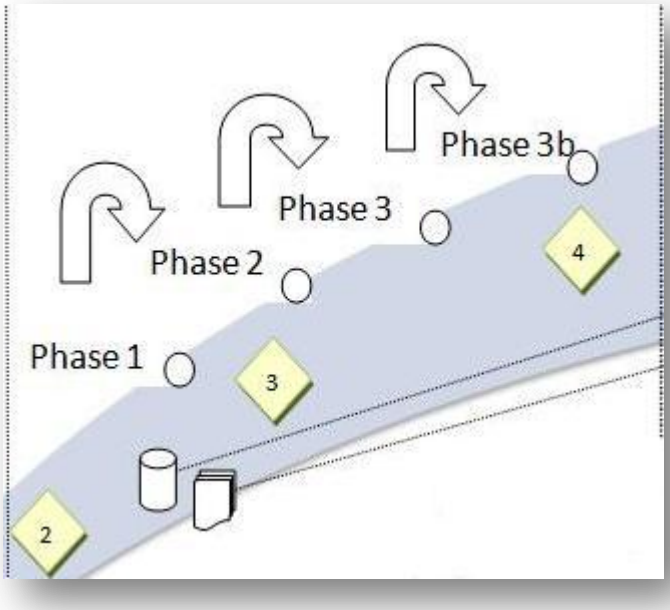

Figure 9: Clinical phase: information heavy phases – (2) Investigator brochure (3) Clinical Trial Application (CTA) (4) The dossier

Phase 1 in healthy volunteers

The sponsor company will seek out investigators (researchers) and investigator sites that are suitable to carry out trials in healthy volunteers. There has been much discussion around the use of healthy volunteers with ethical questions being raised surrounding the type of volunteer, e.g. healthy males. There have been calls to

extend trials in Phase I to women, children and the elderly. Investigator brochures are produced providing background information about the entity and information about the clinical trial and the objectives. The clinical trial may be registered in a public register to attract trial subjects and investigators. The phase 1 studies are looking for tolerability and pharmacology of the drug.

During the trial, all data are fed back to the sponsor company who analyse them and report any possible adverse events information. The results of the trial are sometimes posted on a public results database within 12 months post-trial, according to guidelines[250]. There is actually no regulation in the EU forcing sponsor companies to register clinical trials in the public domain, but there are guidelines recommending to do so[97;250;251]. Results are sometimes released before the end of the trial, e.g. at a conference during a presentation, sometimes with great media speculation on the success or failure of the drug. (I discuss dissemination of clinical trial information fully in chapter 5.)

The success of the drug in phase 1 will determine whether or not it will continue into Phase 2. In fact this question of go or no go is asked after each phase. This is the most volatile aspect of a trial, as a no go means the research is abandoned and information generated so far may not be disseminated in any way apart from what is submitted to authorities in end of trial documentation. The sponsor company is likely to begin planning the publication strategy when drafting the protocol for the next phase, and it's suggested that planning should begin early, but even the planning process is currently actively debated in the clinical research environment[220]. Usually, the research questions and aims in the original clinical trial protocol form the basis of the structure for the final paper reporting on the trial once a trial has ended.

Phase 2 in a small number of patients who suffer from the condition

For each clinical trial a separate protocol and CTA must be filed and approved by the ethics committees and regulatory authorities. (The first CTA application is marked with diamond 3 on Figure 3, although it will be a regular occurrence between phase 2 and 4, including possible amendments to the protocol.) The role of the ethics committee is to review the drug development procedures of any ethical issues that

may arise from any of the activities. A clinical trial must demonstrate that the anticipated benefits justify any risks.

In phase 2, the entity is tested in a few hundred patients who suffer from the condition the new drug is intended to treat. The aim is to identify the optimum dose, method of delivery and to reconfirm patient safety. Patients are monitored and assessed frequently. Many drug trials fail at this stage when a drug proves ineffective or has unwanted side-effects.

Conference abstracts and posters are presented whilst clinical trials are ongoing. The media report from conferences and disseminate wider than the intended research community, results sometimes covered in the popular press. Papers may be published on the results, but unfortunately some 'failed' trials are never published[252;253]. With failed trials we mean trials that failed to show successful results, expected results or even trials that may have ended for some reason, e.g. safety concerns. I discuss dissemination methods and factors that affect dissemination in chapter 5.

Phase 3 in larger patient population

During phase 3 information about the effects of the drug on organs and efficacy are monitored. This is the final step before regulatory approval for a new drug. Researchers aim to confirm findings from phase 2 trials in a larger patient population and continue to study safety data. These studies can last two to 10 years and involve thousands of individuals across many sites and countries. Approximately 10% of drugs fail in phase 3 trials.

Data from phase 2 and phase 3 trials are compiled into the 'product dossier'. (This is marked by diamond 4 on Figure 3.) The Summary of Product Characteristics (SmPC) is an executive summary of the evidence of the intervention that has been verified in clinical trials and Patient Information Leaflets (PILs), providing a summary of evidence in a format that is easy to understand in inserted into packaging, labelling for packaging are all produced and submitted with the dossier to the regulatory authorities to obtain a marketing authorisation. The application contains information on chemical makeup, manufacturing process, pharmacology,

toxicology, human pharmacokinetics, results from clinical trials and all the proposed inserts and labelling.

In accordance with the Directive 2004/27/EC[254], the EMA publishes information online, including summaries of clinical trials, on products assessed by the Committee for Medicinal Products for Human Use (CHMP). Any positive opinion given by the CHMP is published in the first instance as a Summary of Opinion. More detailed information is published later, following the granting of a Marketing Authorisation by the European Commission as a European Public Assessment Report (EPAR)[255]. The MHRA also publishes this Public Assessment Report (PAR) in the UK online[256]. In both cases the reports are prepared by medical writers and commercially sensitive information or confidential information is removed. The sponsor company has the opportunity to comment on the report before it's published. The information is available to the public and contains a summary written in an easy to understand language for the public. This summary, SmPC, PIL and packaging information is provided in all EU languages. The time scales vary depending on which authority is dealing with the application, but in the EU this usually takes up to 60 days but may include lengthy discussions and questions between the authority and sponsor company.

Phase 3b, comparator or pharmacoeconomic studies and phase 4 or postmarketing studies

Sponsor companies may also choose to conduct further studies such as pharmacoeconomic, comparative, new strengths and formulations. Additional information, and evidence, in particularly published information generated can provide beneficial in improving marketing efforts, in providing cost data to decision-makers and to extend market authorisation for other strengths. Formulary decisions made on behalf of national health services in the UK require suitably strong evidence of the medical as well as cost benefits of a new drug. If a drug fails to be approved by treatment and national formulary decision-making bodies, such as National

Institute of Clinical Excellence (NICE)[xv], it can have economic repercussions on the sponsor company who will not be able to get their drug prescribed.

Market authorisation can be rejected by the authorities. The sponsor company will be provided with reasons why and information that could be provided for re-approval. This could mean conducting additional trials, such as a Phase 4 post-marketing study to examine risks and benefits of a new medicine in a population, or to assess long term effects of drug exposure, or evaluate the effects in paediatric patients (Figure 4).

Product launch after market authorisation

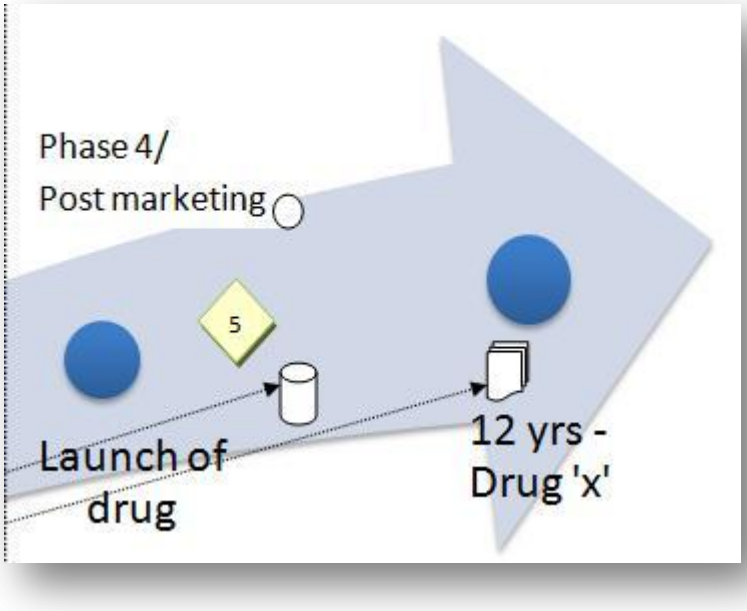

Figure 10: Launch of drug: post marketing studies – (5) Active promotional period

The intervention is officially launched once it has had successful market authorisation by the relevant competent authority. In the EU, the regulation of medicines is harmonised, where submission for market authorisation can be done to the EMA and makes it valid across the European Economic Area (EEA). There are

[xv] As this PhD is written, NICE is under review under the new coalition government and NICE guidelines may not have as strong an input on prescribing as GPs take control of own budgets whilst PCTs are phased out by 2013.

still some national procedures for some interventions, which must be checked with each national competent authority directly.

The information in the product dossier is used when preparing a promotional plan or submission to a prescribing authority (diamond 5 in Figure 10). A company can produce literature, advertising and questions and answers that may be received by prescribers or other health professionals. Promotional material can include reprints of published papers, 'detail aids' which is a product profile brochure, and other materials to help with presentations or submissions to formulary decision makers, e.g. NICE. In the UK, the Association of the British Pharmaceutical Industry (ABPI) Code of Practice guidelines[257] restrict what kind of promotions the pharmaceutical industry is entitled to. At the time of writing this, the code has strict guidelines on marketing and promotions which are designed to protect the health professional and the public of irresponsible marketing. There is now less of a requirement to use a sales force to sell products in the field because authorities such as NICE are making health technology assessments and write recommended treatment guidelines that are used by the health services. Individual sales pitches have been eradicated. Currently the sponsor company invests more time in formulary submissions and in educating health professionals, although this may change as health services are under regular review and due to other forces.

4.5. Validation of the model

The model in its current shape has not been validated in detail but three colleagues[xvi] provided useful feedback which led to the model evolving into this third version. All models have limitations[34;35]. The main emphasis on this model is to show the information produced throughout the various phases of research. More in-depth activities, such as type of communication activity or activities of participants could be included but would also make the model more complex. It is not easy to test a model in its entirety as different participants of the clinical research process may have a different perspective on the process that they are involved with. This model is

[xvi] Sue Fitzpatrick, Education Manager Institute of Clinical Research; Nadine Lott, Regulatory Submissions Manager, Merck Serono; Andrea Palluch, Independent Medical Writer.

a diagram of the overall process of clinical research and it may be useful for others to consider diagrams of sub-activities. A model such as this one can contribute to examining many aspects of the clinical research process, by creating a model of sun-activities in each section and adding additional resources and participants required. This way we can measure:

- Time spent on activities
- Number of participants required
- Costs of each activity and a total cost
- Quality of information output
- Type of information output and whether public or confidential
- Roles of individuals etc.

The thesis will now move on to discuss the specific components that make up the information within the model.

4.6. Clinical trial data – the raw material and evidence

A large amount of data are generated during clinical trials. Data are raw materials of information and are evidence of the research that has taken place. There is a lot of discussion around research data, in particular around sharing the data, making them publicly available and if all data should be published. Clinical trials generate data showing the efficacy of an intervention in a particular population, for a particular treatment. These data are analysed and some used as evidence to back up a claim, or respond to a research question made when disseminating the results of a clinical trial. Without data, we cannot make a claim that an intervention is effective in a treatment. As data are the raw material of research information, they need to be accurate enough for their purpose, they must be relevant to a decision, they must be timely, accessible and digestible[258].

Raw data – before they are processed

Raw data are the primary output of any research before anyone has made the data usable or retrievable[259]. Data are vital to evaluate research results, reconstruct the events and processes leading to them[260]. Lyon[20] described the scholarly knowledge cycle and the creation of data. Original data, such as numerical data are created in experiments or surveys in a clinical study. Additional processes may follow such as selection of an initial data subset with repetition of experiments or re-analysis and

possibly manipulation or editing of images or models creating modified datasets. Data are raw materials derived from research information and may never fully analysed by the researchers who generate them[261].

Sharing of data – benefits and methods

There is an ethical and scientific goal of sharing research data, in particular in clinical research, with the objective of accelerating dissemination of trial data making the results available sooner and enabling patients to benefit[262]. The goal to facilitate access to information culminated in the invention of the clinical trial registries which allow for sharing of data and other clinical trial information. Sharing data is useful for different kinds of groups and for differing reasons:

- those who are looking for clinical trials to partake in, to find out if the research results look promising (in case they suffer from an illness and are looking for treatments)
- those who have participated in a trial, to satisfy that their contribution to research was recorded
- for clinicians, researchers and anyone else who have an interest in clinical trial data to keep themselves up to date, to enable them to treat patients with the latest evidence at hand, to know what pharmaceuticals are up and coming etc.
- Those who wish to continue research building on existing data.

By sharing data we can also avoid research duplication and science can move faster by building on existing research that has been shared. By sharing data, the data will be re-analysed[263] which can improve concentration into specific research questions[264]. Auffray argued that there are large amounts of unused datasets available in laboratories and much of these data remain unused although they may be useful in other contexts[265]. There is also potential for experts adding more data and annotations to previous datasets[263] and developing knowledge this way between academics and industrial partners creating open access repositories or 'data warehouses'[265]. Data must be shared to avoid unnecessary duplication of research. In fact Lyon argues that other researchers and students in higher education will want more access to research data in particular as the life sciences is becoming more data-rich and because future e-science will be more data-intensive and collaborative[20].

Researchers are expecting to access published output and research [261;266]. Journals and other organisations are also expecting data to be shared [263]. There are some publishers that insist that all data are published online for access[265].

Lyon states that the availability of original data will raise standards associated with the publication of research as the review of accuracy of data will be more transparent, access to research will increase the speed of dissemination of research activity allowing data to be re-used and original data of published work will be available to those undertaking learning activities[20].

Many agree that clinical trial data should be available to the public, including to the research participants of studies, as the information, including for the safety of public will improve the reputation of the industry for their transparency efforts[267;268]. When disclosing research results to those participating in a study, it is important to take into account the possible negative effect the results may have if the results were undesirable, or not effective[267]. A study[24] showed that participants of clinical trials usually want to know the outcome of the study but 33% misunderstand the meaning of results or were unsure of their significance. Awareness of the results was through the media (29%), by post (26%), via a healthcare provider 19%). More participants learned about the results through the mail than through a healthcare provider. Another study[269] shows that research results are rarely communicated in a timely or effective manner. Most participants found out study results via the phone (73.1%) when they prefer a personal contact.

There is agreement in general however that sharing of data is not always possible: time constraints in formatting data, lack of standards, where to release or publish data, concerns over debate arising over data analysis, e.g. that re-analysis may impact on future research, informed consent issues over acquired data and intellectual property issues, e.g. the sponsor does not want data released as it may affect patent [106;264;270] or ownership questions[271]. There are also issues such as patient privacy[20;271], where data protection and copyright apply. Raw data from clinical studies are often thousands of pages long causing space problems, such as within print journals that cannot publish all data or the non-existence of institutional

repositories to store data. Fortunately the online environment has made storage possibilities nearly endless, in particular with cloud computing.

The pharmaceutical industry has been seen to be against the public release of product information prior to the product has been approved by the authorities[251;264;270;270]. The main concern is around intellectual property of confidential information and there is also the opinion that a lot of the information generated, e.g. results, are not suitable for the lay public to read anyway. In a survey conducted in Oct 2007 as part of this PhD[xvii], respondents stated that they did not disseminate unfavourable results for several reasons; it was not company policy to do so, they felt there was no need to disseminate unfavourable results, they thought that results may harm the organisation's reputation and peer-reviewed journals had rejected publishing the results (more information about this survey in chapter 6).

Methods of sharing data

Since the invention of clinical trial registries, data from clinical trials are posted on results databases and there are guidelines suggesting they should be published within 12 - 24 months of study completion[250]. Only half of published papers make their data publicly available on the Internet[20] and these data are scattered across many websites, not retrievable from one place (more on scatter in chapter 5). There are also arguments that if data are raw, incomplete or not considered 'useful' by those who own them, then there is no point in sharing data[20;258].

ClinicalStudyResults.com[141], led by the *Pharmaceutical Research and Manufacturers of America* (PhRMA), argue that there is no point sharing data that is meaningless to those who read it, and this includes data from Phase I, and some Phase II trials, as well as raw data. Evidence, if only as data, encourages a false sense of scientific accuracy and objectivity[258]. Therefore study summaries are published and shared on clinical trial registries, rather than raw data, although there may be developments on this in the future.

[xvii] The perception and practice of publishing clinical trial results survey was conducted between Aug-Oct 2007 and details of the survey are in chapter 6.

A recent US law states that all clinical trial data will be publicly available within 12 months of the end of a clinical trial[272]. The ICMJE journal editors[176] suggest that all trials published in their journals (any trials around the world) should release the results in clinical trial registries or results databases within 24 months of the end of the trial if it has not already been published in a peer reviewed journal by that date. The submission to the register should be in the form of a short abstract which will not be considered pre-publication[273] which concerns journal editors. Journals do not like publishing original papers already published elsewhere (duplication). If the authors/sponsors submit detailed results to the results databases, this could be considered as publication by the ICMJE editors and submitted articles could be rejected based on this. This suggests that those that have to comply by US law will post results as required and those trials not conducted for the US market can choose to follow the ICMJE guidelines. The next few years will see much unpredictable change of these regulations and guidelines.

Examples of repositories are the *GenBank*[274] and the *National Institute of Diabetes and Digestive and Kidney Diseases* (NIDDK)[275], a catalogue for samples, DNA and genetic materials and a number of registries, e.g. *Clinicaltrials.gov*. Associated problems with repositories can be identifying what data are original and what may be manipulated data[276]. Other problems are the search mechanism, poor structure and variance in quality and format (discussed in chapter 5).

The eBank UK project[277] which ran between 2003-7 aimed to develop an information architecture for providing access to electronic resources in the UK, linking research data with other derived information. The project harvested metadata about research data from institutional repositories. The role of institutional repositories is for researchers to deposit, disseminate and preserve data. Several projects[278-280] that looked at the concerns of depositing data show that academics are reluctant to share data due to intellectual property, quality and cultural issues.

Ownership or stewardship of data

Challenges in the field of repositories include issues of data preparation, curation, storage and preservation of data[18]. Repositories still lack the technical and institutional framework to support data sharing.

Because of the reluctance of researchers to share data in the past there have been examples of where we have been unable to attribute research to specific researchers, as there is a lack of evidence of who the originator of data was. The data banks or repositories are an obvious solution to this as they can help with confirming ownership and/or originator, removing doubt of who should be acknowledged.

Scofield suggested we replace the word ownership with stewardship as ownership of data may mean hoarding of data and that the person owning the data is responsible for the quality of it, which is not good for an organisation[281]. As an example, Scofield mentions company sales data that may be owned by an employee, not allowing other colleagues to access and manipulate the data. The consequence may be having several different versions of the data and in different formats. Stewardship means that someone is responsible for checking data, for its accuracy therefore ensuring that the quality is maintained[281].

According to recent report, policy on effective stewardship is needed for key players involved with research data[282]. The key players are researchers, libraries, publishers, research sponsors, university and research institutions[282]. According to the report, the five principles of stewardship are: roles; standards and quality assurance; access, usage and credit; benefits and cost-effectiveness and; preservation and sustainability.

4.7. Why do we need clinical trial information?

The evidence from the clinical trials, e.g. information generated, is used to prove efficacy of a product in treating a disease. In evidence-based medicine (EBM), health practitioners use the best available evidence to make treatment decisions. Data on their own may not be useful without interpretation and subject knowledge. The best available evidence together with treatment expertise is what makes the practice of evidence-based medicine possible[19]. Full research information behind the data is needed together with the data, showing why the research was done, the aims and outcomes. The ability of other scientists to validate each other's theories is what confirms validity of research[21]. The data and the scientific validity of trials, such as the ability to repeat the trial and peer review of such trials, are key aspects to ensuring EBM. We must be aware, however, that there cannot be clinical trials for

every type of patient, therefore we have populations in which we don't know how an intervention will behave. Therefore information from trials cannot by itself determine efficacy in a patient. It must be combined with expertise.

The information that is generated in a clinical trial is not always what we need to know in order to change practice [283;284]. There is an information gap between what is needed to know and what is actually produced in a clinical trial. Without access to current best evidence, a patient (who we are all at some point in our lives) is at risk because of out of date practice by health practitioners[19]. EBM should identify the best treatment, e.g. efficient and appropriate, to maximise the quality and quantity of life for a patient. Clinical trials, generating information about treatment, improve medical practice but some of the barriers to practicing EBM are the poor access to information about trials as well as the volume and complexity of trials taking place[25;26].

4.8. A basic overview of clinical trial regulations

It is important to provide a basic overview of the regulations surrounding clinical trials, as they have an impact on how clinical trial information is disseminated, not necessarily obvious this early on in the thesis but it will be clearer in the next chapter where I discuss factors that affect dissemination. The clinical research industry is strictly regulated by authorities, with directives and legislation for clinical trials[285] and for good clinical practice[286] in the EU regulated by the EMA. Other regions, outside the EU, have their own regulations and guidelines, so international research and related activities such as marketing are controlled by the authorities in other countries, e.g. the Food and Drug Administration (FDA) in the USA. There is other legislation that may apply in drug development such as manufacturing and quality assurance. Furthermore, the industry is heavily referring to several guidelines related to clinical research. The International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH)[1] brings together the European, American and Japanese regions to harmonise guidelines and requirements for clinical trials to avoid duplication of unnecessary research. ICH has guidelines in four categories: quality topics (Q), safety topics (S), efficacy topics (E) and multidisciplinary topics (M) (Table 1).

Table 6: ICH guidelines topics [1]

Q "Quality" Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)	S "Safety" Topics, i.e., those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)	E "Efficacy" Topics, i.e., those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)	M "Multidisciplinary" Topics, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5)

In clinical trials, the 'E' topics are particularly important, relating to the process of conducting research and the use of the human subject. The 'E6' Good Clinical Practice guideline[167] is the gold standard in clinical research.

The *Declaration of Helsinki*[287], referred to as 'the Declaration', first adopted by the *World Medical Association* (WMA) in 1964, is a statement of ethical principles relevant to the conduct of research involving humans or their data or material. These principles have been re-examined and updated several times, most recently in November 2008. One issue with the Declaration which has caused much debate is that the 1996 version of the Declaration is referred to in the EU Directives and in UK statutory instruments, which is against the advice of the WMA. The FDA refers to the 1998 Declaration. This ongoing debate has recently led to the US FDA rejecting the use of the Declaration of Helsinki in April 2008[288]. The 2000 (with a commentary added in 2004) Declaration stated that industry should conduct trials with placebo with extra care, as it was considered unethical to refuse subjects access to treatment. Industry prefer testing against placebo because equivalence studies (drug against drug) are very expensive and time consuming, and it is easier to show that a drug is better than placebo than with existing therapies. Another issue with the Declaration has been that it was written by the WMA for physicians. Many people involved with clinical trials are not physicians and it is questioned whether or not the Declaration applies to all those involved in the research or only physicians. A recent WMA consultation promoted these issues for discussion.

Other events have shaped the changes in clinical research reporting (see figure 5) The *CONSORT* statement[289] in 1996 was designed as a checklist to improve the conduct and reporting of Randomised Clinical Trials (RCTs). In 1997 it became US legislation to register all trials involving "serious or life-threatening diseases" according to the *FDA Modernization Act* (FDAMA)[101]. *Clinicaltrials.gov*, a clinical trial register, was set up by the *US National Institutes of Health* (through the NLM) as a requirement of this law. In 2003 a group of clinical research professionals and medical writers from around the world drafted the Good Publication Practice guidelines[290], providing guidelines for authors and medical writers on how to report results when publishing clinical trials. In 2004 *GSK* were fined for withholding clinical trial data from publication and to improve transparency set up the first commercial clinical trial registry on their website. This controversial incident also sparked the *International Committee of Medical Journal Editors* (ICMJE) to publish the first ICMJE statement[251] on registering clinical trials in a clinical trial registry as a pre-requisite of publishing a paper in an ICMJE journal. The pharmaceutical industry made recommendations via the Joint Position Paper[250] in 2005, between IFPMA, EFPIA, JPMA and PhRMA trade associations that all their members should adhere to transparency standards. The position paper agreed that all clinical trials should be registered (apart from exploratory studies, e.g. Phase I) and that results for all clinical trials (apart from Phase I again) should be made available within 12 months of study completion. In 2008 this has been changed to include Phase I trials[291].

In 2005 in the US the *Fair Access to Clinical Trials* (FACT) Act[292] was proposed suggesting the disclosure of results , but it never became law. In the same year the state Maine in the US issued legislation[235] that all trials carried out in Maine should publicly disclose information about clinical trials that are or have been approved by the FDA.

It is unnecessary to list all regulations but bear in mind these main developments and other events that have had an impact on dissemination and which are determinants in how dissemination is changing.

4.9. Conclusion to Chapter 4

Part 1 aimed to characterise and evaluate clinical trial information and the dissemination of that information. It answered the first research question 'what is clinical trial information'. It introduced the conceptual model which identifies the development lifecycle of a new intervention and outlines what key information is produced in clinical trials. A lot of information is produced throughout processes of clinical research and information is complex. I have identified four components of information, generated in clinical trials, information about a clinical trial, information sought in a clinical trial about the intervention, results from clinical trials and the interpretation of findings. The information is interconnected and we need all these pieces of information as evidence behind a new intervention in order to practice EBM. If we do not have all the pieces, we may not know the relevance of a clinical trial in a particular patient population, and we may not be able to replicate a trial or compare it to another one.

There are large amounts of clinical trial data, and with related information these can cover several thousand pages. This information is the raw materials of research which is never fully analysed or made available to others. Sharing data has been proven to be useful to several groups and for different purposes. We avoid research duplication, allow further research of existing data and there is a new expectation that data can be shared in repositories made available online. Sharing of data can improve research interpretation accuracy through peer review of data. Sharing of data is labour intensive and without standards in formatting, the interpretation of data can be very difficult. There are other issues affecting sharing such as informed consent, data protection, intellectual property issues and others.

I briefly introduced clinical trial registries. There are ongoing discussions around what data should be shared, the value of sharing data and their format, e.g. summaries of clinical trials are easier to digest than raw data, and such raw data may harm if not interpreted accurately. Repositories can also act as a way to confirm ownership of research projects and protect research findings and allow stewardship of data to protect their quality.

The chapter introduced events, regulations, guidelines and legislation. There are many new initiatives in clinical research to make the process more transparent, e.g. registering in a clinical trial registry before the trial commences and provide some detailed information, e.g. about the aims of the trial. This chapter has summarised that information is disseminated, and reported or published in various ways, before and after clinical trials have ended. Next, part 2 will test the model by identifying the dissemination methods used, consider their effectiveness and what factors affect dissemination.

PART 2

5. Chapter 5: Current state of dissemination and publication of clinical trials

5.1. Introduction

As we have seen in the Part 1, a lot of information is generated in clinical trials and the outcome of clinical trials form the foundation for evidence-based medicine. The goal of clinical research is improve health delivery. In order to improve health delivery reports of clinical trials needs to influence its audience and this can only happen if all research is disseminated. Reports of clinical trials are difficult to find and in some cases do not exist in the public domain. In order to improve health delivery practice this gap between research and health delivery must be addressed. This chapter reports the findings of the research looking at the methods of dissemination and factors that affect dissemination.

Part 2 will test the constructed model from the last chapter by identifying the dissemination methods used, consider their effectiveness and what factors affect dissemination. The findings presented in part 2 are responses to the research questions what range of methods are used to disseminate clinical trial information, what factors affect how clinical trial information is disseminated, including attitudes and practices of dissemination and how effective a particular method is for dissemination. To respond to these questions research objectives included: through search experiments assess where clinical trial information is scattered, and how it was found, followed by critical analyses of the methods used for dissemination and the factors affecting dissemination. The responses to the survey of clinical research professionals were also analysed to understand practices of dissemination but also attitudes of clinical research professionals towards dissemination. Through an analysis of publication policies and survey responses we will know more about factors that affect dissemination and this is compared to information found in literature reviews. The responses to this research questions will put the model to test in order to identify how we can make the information from the research process more transparent.

5.2. True access to clinical trial results

According to Wood[106] there are three types resources that meet the criteria of providing true access to clinical trial results, e.g. links to reports and published papers: PubMed or other bibliographic databases with indexes of publications, FDA analyses and documents on the FDA website (in Europe we would rely on our research ethics committees or EMA posting such documents) and existing industry databases such as the GSK results website[140] or the PhRMA results database[141].

I will review the scatter of clinical trial information across many resources next in this chapter.

5.3. Scatter of clinical trial information

Information is disorganised and health professionals cannot find it when they need it[72]. At the beginning of this research a research objective was to establish the methods used to disseminate clinical trial information and confirm the extent of the scatter of clinical trial information across many resources. It was also suggested that a lot of information would exist online and a large part of research included investigating this possibility.

As the model of clinical research information shows us (Figure 11 and Appendix A), a lot of information is generated throughout the research process some which remain confidential and will never be publicly released. Information can exist in print and electronic copy.

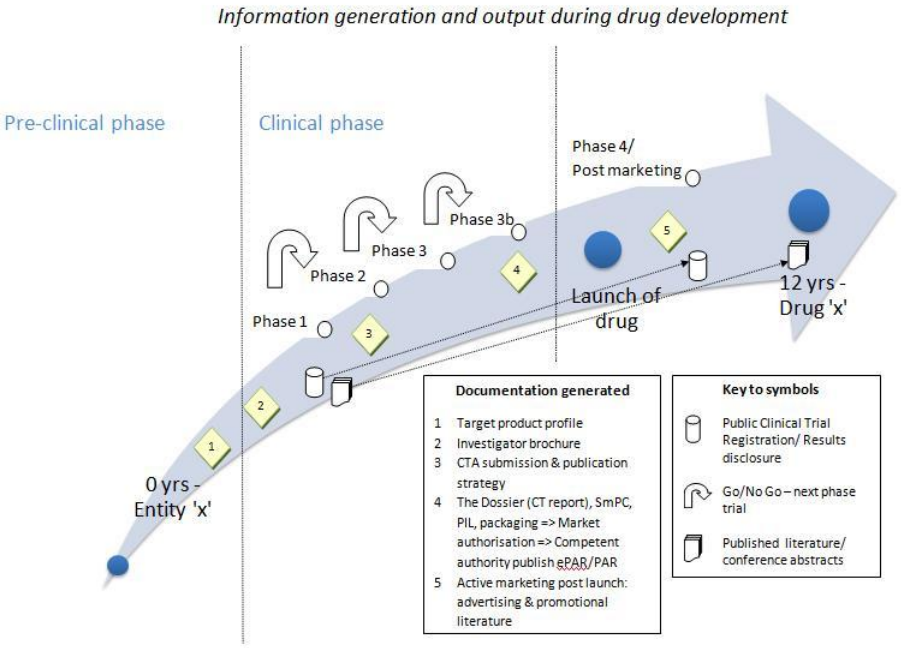

Figure 11: Clinical research process information generation and output

What methods of dissemination can be found searching Google?

The model does not give us a comprehensive picture of all the methods used for dissemination. Eysenbach et al evaluated the usefulness of Internet searches to identify unpublished clinical trials[120]. They found unpublished studies on departmental and institutional websites, personal web-pages of academic researchers, conference proceedings, announcements, press releases, unreferenced papers and patient recruitment sites. They concluded that authors will leave "digital footprints" on the web from various parts of the research process. To find out what types of resources contain clinical trial information in diabetes, a simple Google search experiment[xviii] took place first in 2008 and then again in 2010 to compare the findings.

[xviii] Search took place 19 July 2008

The search conducted in 2008

The search was limited to diabetes[xix] clinical trials in the UK. The search terms used were: diabetes clinical trial (not using boolean operators or “”). The aim was to identify types of digital content and whether the content directed the user to a clinical trial register or repository. The search brought back a large amount of websites (n=504). The first twenty websites were selected for analysis (Table 7) because it is known that users rarely go beyond the first page of returned results[238].

Table 7: 2008 Types of websites discovered when searching for diabetes clinical trial in the UK using Google (n=20)

Type of site	n=
Jobs (vacant)	2
Commercial (money making)	3
Journal/Magazine	3
Personal website (patient blog)	1
Information resource (database/portal)	2
PR/news	9
Total	**20**

Five resources were removed as proved duplicates leaving 15 resources for analysis.

The following information was gathered about each site:

- Institution or organisation behind the site
- Format (e.g. document, portal, journal)
- Date of last review (if provided)
- Reading level grade (SMOG)
- Does the site list or attempt to forward the user to clinical trials, e.g. a repository/clinical trial register?
- Focus of the website.

[xix] Continuing with the obesity/diabetes theme of the research

Table 8: Types of resources found in Google search experiment 2008

Unique sites found					
Institution	**Format**	**Date of review**	**SMOG grade**	**Link to clinical trials**	**Type of site**
UKCRN	.pdf	20/05/08	13.8	No	PR/News
Datamonitor	HTML	29/11/07	15.25	No	PR/News
Diabetes Research Network	HTML	don't know	13.18	No	PR/News
Ingenta Connect	HTML	don't know	15.85	No	Journal
LeadDiscovery	HTML	don't know	15.8	No	PR/News
BioPortfolio	HTML	don't know	N/A	No	PR/News
ATTRACT	HTML	don't know	16.49	No	Information resource
Clinical Discovery magazine	HTML	don't know	14.62	Yes	Journal
Oxford Radcliffe	.doc	don't know	N/A	No	Job site
Knowles Consultancy search engine	HTML	don't know	N/A	Yes	Commercial
Success City search engine	HTML	don't know	N/A	Yes	Commercial
Newcastle University	HTML	01/04/05	16.64	No	PR/News
Search Medica	HTML	don't know	N/A	No	Information resource
Phillip Makepeace	HTML	don't know	13.49	No	Personal
RDL Scientific	HTML	don't know	N/A	No	Job site

Reading levels (SMOG)

A SMOG calculation of each site was performed[xx] to reveal level of education expected to read and understand the content found in the search in 2008. The SMOG grades reveal that all sites that could be measured expect some American college level literacy[xxi]. Two evidence-based sites scored above 16 which expect university level literacy. Not all resources were measurable if insufficient textual content was provided.

The results from 2008 show that there is a mixture of websites that contain the words diabetes clinical trial, e.g. job vacancies, press releases, magazines, news sites etc. Only three sites referred the user directly to a site that contained information about clinical trials. This shows that it can be quite difficult for a user to search and find relevant websites, if they are looking for diabetes clinical trials.

The search conducted in 2010

The same search as the one in 2008 was conducted[xxii] in 2010 limiting results to the

[xx] http://www.literacytrust.org.uk/campaign/SMOG.html

[xxi] Since this calculation was performed, a UK equivalent SMOG calculator has been introduced: http://shop.niace.org.uk/readability.html

[xxii] 11 September 2010

UK.

Table 9: Types of resources found in Google search experiment two years later (n=20)

Insitution	Format	Link to clinical trials	Type of site
Diabetes clinical trial unit	HTML	yes	Organisational website
UKCRN diabetes clinical trials	HTML	yes	Not for profit research
Diabetes Research Network	HTML	yes	News story
Diabetes Research Networking	HTML	yes	Patient information
NHS Choices	HTML	yes	Patient information
Diabetes Research Network	HTML	yes	Patient information
Veeda Clinical Research	HTML	no	Commercial clinical research
Financial Times	HTML	no	News story
Next Generation Pharmaceutical	HTML	no	News story
Biocompatibles	HTML	no	News story
British Geriatrics Society	PPT	no	Presentation
Daily Mail	HTML	no	News story
Juvenile Diabetes Research Foundatic	HTML	yes	Patient information
BMJ Evidence	HTML	no	List of references
NHS Choices	HTML	yes	Patient information
UKCRN	HTML	no	News story
Medical Research Council	HTML	no	News story
Nottingham Clinical Trials	HTML	yes	Patient information
Times Online	HTML	no	News story
Trials Journal	HTML	no	Journal

Table 10: 2010 Type of websites found in Google search

Type of site	n=
Presentation	1
Journal/Magazine	1
Organisational website	3
Information resource (database/portal)	7
PR/news/newspaper	8
Total	**20**

Comparing findings in 2008 with 2010

Not surprisingly the results are very different from the search in 2008. Two years later, Google has become more sophisticated in its search mechanism and in general clinical trial registers have also become more prominent on the web. There were 333,000 relevant web pages to the search compared to only 504 in 2008. This shows that the information available on the Internet about diabetes clinical trials is increasing rapidly.

When comparing the type of information that is found, the information found in 2010 is much more geared towards providing public information about clinical trials, whether to patients or professionals, and the content brought back is much more relevant to what a user would expect to see when searching for diabetes clinical trials. When the search results were brought back, Google first of all provides a top level list of scholarly articles that are relevant as well as sponsored links at the top of the page and commercial links (advertisements) to the right.

Nine websites in 2010 compared to only three in 2008 provide information or links to clinical trials that are recruiting, or a listing of clinical trials.

5.4. Resources that provide information about clinical trials: a map

A more comprehensive picture of the scatter of clinical trial information across various resources is shown in figure 12. This list, or map, has been compiled by me throughout a number of years working in the industry. This research has identified that a few of these stand out as being key resources for individuals looking for clinical trial information.

Figure 12: Map: Scatter of clinical trial information across a number of resources

Looking at the resources in figure 12 we see a mix of formal and informal dissemination, or communication, methods. Journals and books are considered formal communication modes[293]. It is also known that new communication methods developed within the Internet are blurring the formal and informal methods. Young *et al.*. and Halliday argued that the distinction between raw data in grey literature and peer-reviewed articles can be difficult[52;294] in particular in the digital environment where information presentation can make it look as though it is a formally published piece of work and from a trustworthy source. Without a definition; the quality, integrity and authentication of electronic scientific

information will be difficult to determine[44]. Examples of material that is published on the web include conference proceedings, preprints, theses and reports. It is clear to state that the electronic environment makes these resources more accessible and according to Halliday fulfil some of the functions of a scholarly publication more effectively for timely communication[52].

5.5. Current methods used in dissemination

This section will cover the methods used for dissemination. This is different from resources that aggregate information and re-present it in another format, from an access point of view. The clinical research professional decides on an appropriate method to disseminate suitable for his audience. Information of course subsequently ends up in other forms of resources, secondary sources, e.g. bibliographic databases such as Medline that provide abstracts which will not be covered here. There are some resources that fit into both categories, a primary method of dissemination and a secondary source, e.g. an aggregating resource, such as news services and pipeline information, which will be covered here.

Journals that disseminate clinical trial information

According to Griffin and O'Grady[70] scientific journals are a key source of information on medical research. Published papers are used as original reference sources in pharmacopoeia, advertisements and promotions[70]. The journal has existed for hundreds of years as a tool to disseminate research findings and opinions and has been a key component of the scholarly communication process. Original research data is usually presented at conferences and subsequently published in peer reviewed journals[152], although we know that not all conference presented data is subsequently published[153;200;295]. Each year more than two million research articles are published in medical and scientific journals[69]. There are many journals, around 17,000 biomedical journals in publication with 4,000 of these indexed on Medline[49], of these around 114 journals specifically publish influential clinical trials[296]. It can be argued that there is a need for more journals as research areas are growing and separate themselves away to create their own topic areas.

Bibliometrics to establish core journals

To establish which core journals are used for publishing clinical trials in obesity and diabetes, a bibliometric study took place using *Bradford's law*[243]. The Bradford distribution model shows how a subject's literature is distributed among journals, with a core and further scatter[14]. In knowing the core journals that cover our subject, it may help to understand the type of journals that cover our topic and to see if the core set is large or small. Data was analysed from *Scopus*. Using *Scopus*, a search was conducted for articles published in journals on the subject of clinical trials narrowed down to obesity and diabetes published in 2008 resulted in 557 articles covered on *Scopus*. This study was not looking at growth of literature in this topic area but aiming to establish the core set of journals published in and the characteristics of those journals.

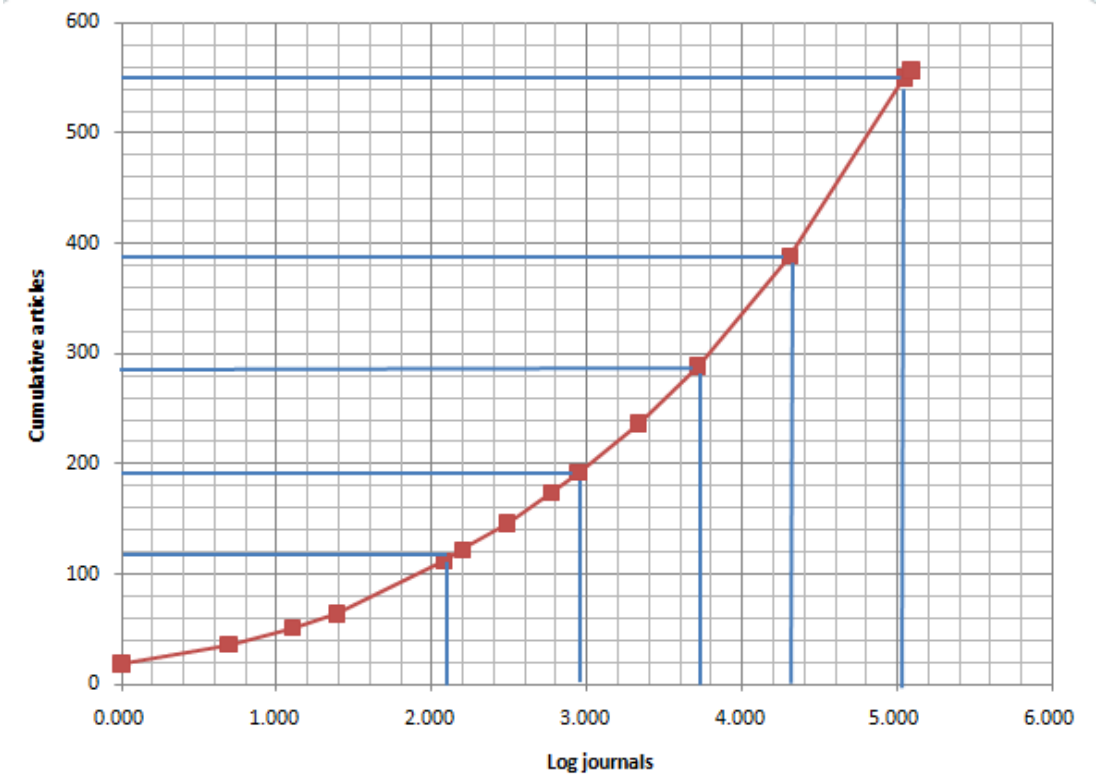

Figure 13: Bradford distribution of articles to journals in Scopus with five zones identified

Table 11: Data table from Bradford Analysis of core journals in obesity and diabetes clinical trials

			y-axis		x-axis
Journals	**Articles**	**Total**	**Cumulative articles**	**Cumulative journals**	**Log journals**
1	19	19	19	1	0.000
1	17	17	36	2	0.693
1	15	15	51	3	1.099
1	13	13	64	4	1.386
4	12	48	112	8	2.079
1	10	10	122	9	2.197
3	8	24	146	12	2.485
4	7	28	174	16	2.773
3	6	18	192	19	2.944
9	5	45	237	28	3.332
13	4	52	289	41	3.714
33	3	99	388	74	4.304
81	2	162	550	155	5.043
7	1	7	557	162	5.088

Although there are a large amount of journals that publish the results of clinical trials in diabetes and obesity, a very small amount of core journals (n=8) account for 112 articles (20%) of published clinical trials according to the Bradford analysis done for published clinical trials in obesity and diabetes found in the database *Scopus* (Figure 13 and Table 11). We can see that 557 articles were published in 162 different kinds of journals.

There is a pattern in numbers of journals: 8: 19: 41: 74: 155, meaning the Bradford multiplier is 2; the number of journals has to double to add another 100 articles. The analysis reveals a typical Bradford curve which suggests that it is a well developed field. Had the graph been linear the topic is still in development.

Table 12: Five zones of journals identified

	Journals	**Articles**	**% of refs**
Zone 1	8	112	20.1
Zone 2	19	80	14.4
Zone 3	41	97	17.4
Zone 4	74	99	17.8
Zone 5	155	162	29.1

The core journals (zone 1) that were identified in the Bradford analysis can be seen in table 13 below.

Table 13: Eight core journals (zone 1) identified in Scopus (112 cumulative articles) and impact factor

Journal title	Impact factor (IF)
Diabetes	8.398
Diabetes Care	7.349
Diabetes Obesity and Metabolism	4.126
Current Atherosclerosis Reports	1
Current Diabetes Reports	1.56
Clinical Cornerstone	Unknown
Obesity	2.762
Expert Review of Cardiovascular Therapy	2.991

A second study examining the journal as a tool of dissemination was conducted in PubMed to compare with the findings of the Bradford analysis.

The 80 abstracts found were published in 58 unique journal titles. Some journals were specialist in the cardiovascular, diabetes and lipids areas. Six journals published three or more of the abstracts (n=25, 43%) (Table 14) of which three are society or association journals and these have higher impact numbers than the commercial publishers' journals.

Table 14: PubMed study of core journals that published ≥3 articles in the subject of diabetes and obesity clinical trials

Articles (n=)	Journal title	Impact factor (IF)	Eigenfactor metric influence score	Publisher
6	Diabetes Care	7.349	2.508	Am Diab Ass
5	Obesity	2.762	0.845	Nature
4	Diabetes	8.398	2.989	Am Diab Ass
4	Diabetologia	6.418	2.180	Springer
3	Am J Clin Nutr.	6.740	2.246	Am Soc for Nutrition
3	Diabetes Res Clin Pract	1.888	0.572	Elsevier

The Bradford analysis suggests that researchers publish the majority of their clinical trials in eight core journals, three of which were also identified in the PubMed analysis. I can therefore identify three journals as being core in publishing clinical

trials in obesity and diabetes: *Diabetes Care*, *Obesity* and *Diabetes* with impact factors 7.349, 2.762 and 8.398. These three journals are subject specific and not broad-based healthcare and they have differing impact factors, one low and two higher. Therefore these research findings confirm findings of McKibbon[92] where healthcare disciplines such as nursing, internal medicine, general practice and mental health publish in small subsets of journals but do not concur with the finding that many important articles for all disciplines were published in broadbased health care journals. However, further analysis of the *Scopus* data in the latter zones (Table 13) may reveal more broad-based healthcare journals. This PhD study findings are more in line with the those of Falagas *et al.* who found that the majority of articles were not published in journals with the highest impact factor[82] and Barbui *et al.* who found that high impact factor journals do not publish the highest quality RCTs[297], where quality was measured by using the *Jadad instrument*[298] and the Cochrane quality criterion and Costa *et al.* who reached the same conclusion looking at physical therapy clinical trials[80].

There are some limitations attached to these two studies. I selected Scopus initially, as Scopus provides useful citation tracker information and I performed the Bradford analysis based on this data. I then wanted to search PubMed, which I consider a more comprehensive bibliographic database, to see if the results were similar and to confirm my findings in the Scopus search. I chose not to run the Bradford analysis on the dataset from this search, but to use Excel to analyse the data. I compared numbers of articles between journals (see Methodology). Comparing the two results, three journals came up in both searches as core for the topic. I used this as an confirmation of the results of the Bradford curve.

Abstracts

The study of the abstracts found in the PubMed search also identified some interesting details about published clinical trials. As has been discussed earlier, there is no agreement on terminology within clinical research. When searching for published literature containing information about clinical trials various different subjects headings are used to identify papers. In the Pub Med study out of the 80 studies, 45 (56%) were key-worded as *Randomised Controlled Clinical Trials*. The

rest were marked up as *clinical trials*, *multicenter trials* or *comparative studies* and sometimes a combination of these terms.

Sometimes the abstract is all that is read and it does not always contain all the necessary information[73;147;299;300]. Abstracts should have comprehensive structure and metadata attached to make it easier to find and ready.

The study of abstracts within this thesis revealed the lack of standardised content required in abstracts. ICMJE declared that the publication of an abstract of around 500 words is not considered pre-publication[176] and that such abstracts can be disseminated as the researcher wishes, but many journal abstract vary greatly in length and content. Other abstracts are often published at events where researchers present findings from clinical trials and these abstracts make their way to the press and other aggregated news sources who report on information provided to them. It is obvious that although some recommendations exist for the format and content of abstracts, e.g CONSORT[301] or IMRAD structured[xxiii], many journals and event organisers have their own guidelines for what should be in the abstract rather than using a set standard. A study reported that only 66% (160/243) articles reported a source of study funding [69]. Furthermore, papers that disclosed funding sources were of higher quality than those that did not, where quality was assessed based on journal circulation, impact factor, citation rate and journal acceptance rates. Funding should be considered when assessing the usefulness of an article [69;302]. It has been identified that abstracts often underreport in some aspects of a clinical trial[145;155;157;303] but most abstracts analysed here provided useful information on methodology, results and conclusion of the trials.

In the PubMed study, only four out of 80 (5%) abstracts listed clinical trial registration numbers. This makes it difficult for people reading abstracts knowing if the trial was registered or not. If trials are registered more information about the study can usually be found in the clinical trial registry, including data and other published papers. By providing the registration number we can also more quickly

[xxiii] IMRAD stands for **I**ntroduction, **M**ethods, **R**esults **A**nd **D**iscussion

spot duplicated papers published about the same trial, or related articles with data from the same trial. Some of these published clinical trials may of course have taken place long before it was a requirement to register all trials, e.g. phase I and medical device trials, in which case a registration number may not exist, but then this should be noted.

Abstracts should also report on all aspects of the trial[145]. Some of the abstracts declared funding, but not all journals collect this information from authors and the information provided in the citation did not make it clear if a study was commercially sponsored or not. Declaring funding is an important aspect of making research transparent and would be helpful if provided in abstracts.

Access to full text articles

Access to full text journal articles has been a long debated issue in medicine with many institutions, organisations and other bodies getting involved in the discussion[71]. It is such a large issue that it would be impossible to discuss it in its entirety within this thesis. This thesis concerns itself with it by analysing decision-making of methods used to disseminate clinical trial information. The decision-making process may include access issues, e.g. access for developing countries, institutional guidelines determine choice etc. The open access movement[180] as we refer to it as has made access to clinical trial information easier from a user point of view, but possibly more difficult for a researcher who may have to pay to publish. This move from 'user paid' to 'author paid' model has made journals more complex for users who have to find out if they have access to a paper or not at the point of access. In the analysis of the PubMed abstracts, only 28/80 (35%) articles offer free full text access. Five (6%) articles did not carry a link to an electronic version or webpage of the journal and 47/80 (59%) articles asked for a subscription or pay online.

Journal – fit for purpose?

We assess fit for purpose in journals by looking at how quality is defined. The quality of journals is identified by articles that have higher citation rates and high impact factors, higher circulation and low acceptance rates[69].

Journals improve the quality of research papers using three methods; instructions to authors, peer review and the editorial process [77].

Improved publication guidelines and editorial standards within journals are attempts at improving the quality of papers published in journals. Journal editors have changed requirements for acceptance of manuscripts to include the transparency of authorship, e.g. declaring authors and acknowledging other contributors. This will lead to less cases of ghost-authorship and guest-authorship which has been said to harmful to the public and institutions and the paper cannot be trusted or accurately judged [172;173].

The usefulness of peer-review is a debated area within publishing. Peer-review has long been used as a way to assess quality and accuracy of a paper although even fraudulent papers have made it through the peer review system[177;178] and there is no evidence that peer-review is improving quality[77;179]. Peer review, although not perfect, is the best option for the moment of ensuring quality of papers[183] although this is disagreed by others[69]. An issue with peer-review is that it's incredibly slow and there has been recent debate over reviewers remaining anonymous, when in fact conflict of interest may affect the peer review process[184].

The journal model with articles that are trying to please every type of reader with the same length articles not providing all information that may be required for those with needs for information is not working[74;98;304] and it has been said that it is time that journals change their role in disseminating clinical trial results[74]. Articles are restrictive in nature; "confusing tables, use acronyms, sometimes lack methodological rigour, do not discuss findings in broader context and this is frustrating"[73]. Nevertheless, the journal is considered the second most important resource to some health professionals[305]. Journals are also important as evidence where published papers are required to form evidence, such as in assessments of new technology or treatment. Journals try to be useful tools for health professionals in their practice but have little success in changing practice[49] and journals have rarely been tested for their effectiveness in conveying information[306]. It has been suggested that the journal can be replaced by systematic reviews and institutional repositories that deposit papers written by scholars[294].

Even in 1974 it was stated that the role of the journal is changing and that the publication speed is of vital importance to those conducting research[307]. Publishers of medical journals should explore co-operation so that findings of clinical trials could be shared, reducing the 'scatter' of medical information, and journals should only publish well-conducted clinical trials providing the clinical bottom-lines[49]. Journals could publish summaries of pre-appraised evidence and evaluative research articles representing higher levels of evidence with potential to change practice[49]. In order to survive, publishers need to adapt to new formats and respond to the digital developments[183].

News services and pipeline information

The news media plays an important role in which to make drug development information available quickly to a wider audience. The news media are an important source of information about medical research for the public and even some physicians[308;309]. The public and many physicians learn about new medical research through media rather than medical journals[133;308]. The news distribution can have a positive or negative impact upon sponsor companies, the researcher or medicines themselves as well as journalists with benefits if the story is sensationalised[310]. An analysis of media coverage showed that pharmaceutical scandals can impact research efforts even when a study isn't linked to the scandal itself[311]. Therefore, media coverage of research can also set the agenda for future research.

Prior to 1960 the press didn't report as widely on medicine[138]. However, over the last thirty years the public interest in medicine has changed[40]. The New York Times increased its coverage of medical articles by 250% between 1968 and 1978 and 425% between 1969 and 1988[40]. Journal editors began to see that media coverage is valuable to attract attention and increase subscriptions, building brand recognition[139]. Providers such as *NHS Choices, NHS Evidence* and *Bandolier* (an independent journal) disseminate information around new treatments and disease specific research.

Drug development information is a commodity and has for many decades been sold through subscription services such as drug pipeline resources, e.g. journals, abstracts

or electronic news feeds to the sectors that need drug information for a variety of reasons such as competitor scanning, current drug development and in the case of decision-making as evidence for efficacy. Such resources have grown and are more freely available via news/pipeline websites or portals, e.g. Drug Discovery News[312]. Pharmaceutical industry pipeline sources can be searched for information about drugs in development but these sources contain non-standardised information and sometimes very little data making it difficult to search[103]. Pipeline sources are still used to find out about products undergoing development, these sometime contain information not available on a clinical trial registry. The main reason for this may be that there is pre-clinical information that exists prior to clinical trials. Pipeline sources are often subscription based although some exist free on the Internet. This type of information is expensive to produce and highly valued in particular for competitor information.

The providers of such information often make income through other means such as publishing journals, sponsorship and advertising. Medical journals have been a primary source of medical information to the pipeline resources but also to news media. Clinical trial registries are now becoming an alternative resource for both those seeking the information and those making it their business distributing it.

These days the market is flooded with press releases, sometimes deliberately vague or even misleading to get media attention[40] and some do not provide sufficient information[308]. Data in newspapers are presented in such a way that the findings are exaggerated[136;313] and according to Woloshin and Schwartz the journal press releases are prone to exaggeration[133]. Seven out of nine medical journals routinely issue press releases and only 23% (n=29/127) of the press releases included study limitation and 65% (n=83/127) included results[133]. In a study[313] of news stories reporting on research presented at scientific meetings, it was found that the news items often omit basic study facts, e.g. study results, study design and study size. Another study found that press releases report basic study details, usually preliminary findings presented at conferences, but often do not disclose study limitations[314]. It is suggested that press releases should put results into context, provide study limitations, reveal author's competing interests and provide absolute results[133]. Medical journals should

ensure quality of content of press releases as physicians and the public often find out about new medical research through the media[133-137].

The media report topical drug news with an impact on lifestyle rather than with medical implications and journals issue press releases that they know the journalists will be interested in[40;133;313]. Bad news is more likely to be published in newspapers, and in particular women's health issues[315]. However, a study[316] of US reporters found that more than eight out of ten reporters have no training in interpreting health statistics and one third said that understanding health issues was 'often' or 'nearly always' difficult.

Newspapers can generate false hope and unwarranted fears[310]. In 2002 the hormone replacement therapy (HRT) scare broke in the media of HRT increasing health risks. A study examined the newspaper reports on the topic and found that the stories published were accurate and reported consistently[317]. The media generally get their stories from press releases issued by sponsors and journal editors and the study highlighted the importance of planning strategies when communicating research results to the media, and in particular using reporting intermediaries to translate the science to plain language. One important finding in the study was the lack of communication and guidance directed specifically at medical practitioners[317].

Advertising

Advertising over-the-counter (OTC) drugs, e.g. painkillers, cold and flu treatments etc., in mass media reaches a large number of people. OTC adverts tend not to provide much information about the mechanism of action, details of clinical trials or information of educational value[318]. There is also some indication that advertisements in medical journals aimed at medical professionals make promotional claims that are not substantiated with references[319]. Clinical trials are also advertised through media, in particular on the radio asking for volunteers for new treatments.

Industry has long been blocked to advertise prescription drugs and claims to patients in the EU due to EU directive 2001/83/EC, echoed in the voluntary Code of Practice[257] in the UK. There is a discussion to allow for more advertising and provision of information by the pharmaceutical industry to the public in the EU[320].

Only the US and New Zealand allows direct to consumer advertising (DTCA) at this point in time.

A link has been identified between published papers and drug promotion [76;321]. It has been suggested that publishing papers is merely another method of promoting a particular drug, in particular if there is the opportunity to publish a supplement of inferior quality to parent journal[322] which can be given to healthcare professionals in marketing efforts. Some journals allow the placement of an advert in the same journal as the results article making marketing claims[323;324].

There are arguments for and against the industry providing advertising and information to the public. As we have seen, the industry holds a great deal of information and is able to offer useful information on its product to information-hungry public. The European Commission has stated that there is a lot of varied quality information provided by relevant authorities throughout the EU and as the public turn to the Internet the information is not reliable and not always understandable[325]. However, it has been argued that the information will not be objective. Those against the industry advertising to the public suggest two other options: an expansion of information offered by community pharmacists and more patient-to-patient information offered via a controlled website such as healthtalkonline.org[xxiv ; 326], offering patient experiences combined with advice from health professionals. In 2008 the European Commission ran a consultation on DTCA with the result that a proposal has been submitted to the Parliament for decision to provide detailed guidance on what DTCA is allowed and identify types of information dissemination methods appropriate for member states, in particular provide a distinction between advertising and provision of information where this could be blurred.

The physician-patient relationship

People make treatment choices themselves[123;327]. Some personal published accounts exist that provide some insight into the behaviour of individuals looking for trial

[xxiv] http://www.healthtalkonline.org/ Previously known as DIPEx [Accessed 7 January 2012]

information[327;328] for personal use or to pass on to someone that they know. It has been suggested that the primary source of information about clinical trials is the patient's physician[121;122].

Physicians are generally aware of existing clinical trials or may know which companies are conducting relevant clinical trial, should a patient ask. There is evidence to show that patients now turn to the Internet rather than a health professional[123] for medical information, including treatment decisions. Patients also prefer conversing with a health professional via a portal or email[124]. In fact, a study shows that physicians feel uncomfortable speaking to patients about clinical trials[121;125]. Each individual has its own unique information needs, which may complicate how well physicians are able to communicate information about clinical trials to them[121]. As our map of information scatter shows (figure 12 in section 1.45), and the result of our Google searches indicate (section 1.44), a lot of information about clinical trials can be found on the Internet and there are many websites that provide patient information on clinical trials.

Pharmaceutical companies and provision of information

Pharmaceutical companies through their medical information or scientific departments have the expertise of dealing with patient enquiries about their personal medical condition, although in the UK it is practice to refer such individuals to their physician as discussing personal medical conditions with patients is prohibited by the Code of Practice[257]. It is possible however to provide the patient with a summary of product characteristics (SmPC) or patient information leaflet, although these are also available via the web, e.g. EudraPharm[329] maintained by the EMA. Information to patients on clinical trials is rarely provided directly, but it is suggested to the patient that they discuss requirements with their doctor to whom information can be sent or patients are recommended to search for suitable trials on clinical trial registries.

With the advent of the Internet, there was scope for pharmaceutical companies to provide more information to patients via a website. An example of such a website is Amgen[330]. Pharmaceutical companies use the Internet to set up product specific websites, where allowed, with sections separated for health care professionals and

for patients, and they also sponsor educational patient websites as well as some public health initiatives. A current example of how the pharmaceutical industry helps with disease awareness activities is via sponsorship of the FAST stroke adverts in the media[331]. The adverts together with educational material offered by The Stroke Association are sponsored by GE Healthcare. GE Healthcare is a supplier of diagnostic imaging equipment used to detect stroke amongst other things.

In 2007, the European Commission suggested that industry could have a greater role in provision of information to patients[325]. Although the term 'advertising' isn't used in the plans, the Commission suggest that information should be objective. The EU consultation launched in 2007 was met with both negative and positive comments, generally it was felt that the industry could not be expected to provide balanced or comprehensive information and that the information will be more in the form of advertising. A survey in the US on public perception of advertising showed that many individuals assume that information in advertising is checked by some agency[332] which of course is not the case. However, we know that in the UK the Code of Practice provides guidelines with regards to product promotion including the Internet and provision of information to the public. There are of course difficulties in regulating information on the Internet with an abundance of product information of drugs and treatment in existence and accessible to all regardless of who they are and where they live.

The pharmaceutical industry provides much information to physicians on new and existing drugs. Information is delivered in different formats, e.g. mailings from pharmaceutical companies that go out to physicians[308], educational events on therapeutic areas often in combination with a drug launch, visits from medical representatives who bring clinical papers and a detail aids, conference posters and presentations and promotional material providing some basic information on a drug. Much of this type of drug promotion has undergone change. As drug prescribing was done less by individual physicians and more by organisations such as NICE, there is no need for a medical representative to sell product efficiency to a physician in order to get prescription. However, change of Government in England in 2010 has seen yet another change in responsibilities. Although NICE retains its role in assessing products and therapies and issue treatment and prevention guidelines, the

general practitioner through consortia has resumed the role of commissioning services within the practice from 2013.

There has also been much discussion around pharmaceutical sponsorship of educational events[333;334]. The discussion has led to PhRMA limiting pharmaceutical sponsorships and separating such funding decisions from marketing decisions[335]. This was followed in 2008 by Pfizer announcing it will no longer sponsor profitable third party companies running courses, but will continue to sponsor medical school, medical society and teaching hospital courses[336].

There is no doubt that the Internet and the invention of clinical trial registries have revolutionised the way in which information about clinical trials can be found. The pharmaceutical industry provide clinical trial summaries on their websites and some companies have their own clinical trial registries, or databases, showing what current clinical trials are available and what the results were of previous trials which allows the physician and patient to discover suitable trials and potential treatments more easily[140]. Still, in the EU there needs to be better and shared standards on what information, where and how, pharmaceutical companies are allowed to provide information publicly.

Patient organisations and charities

Patient organisations and charities are ideal places where details on patient and public information needs can be assessed and responded to. Medical research charities put great effort into improving public understanding of science, including clinical trials, and other charities provide information into public health, aiming to prevent disease but also inform regarding treatment. Many research charities and patient associations in the UK are members of the Association of Medical Research Charities (AMRC). The organisations inform on different scientific developments, provide patient information leaflets, publish blogs and involve the public in research activities.

Without patient involvement in setting the research agenda, researchers could not be sure the research conducted is relevant to patients' needs[337]. Unfortunately not all patient associations, or charities, are consulted on research projects. The European

Cancer Patient Coalition (ECPC) has suggested a model of collaboration between industry, academia, patient groups and the European Health Commissioner[337]. The UK 'Best Research for Best Health' report also outline plans to involve patients groups in medical research[338]. Many patient organisations, like Diabetes UK, fund research and also provide information to patients about clinical trials. In the UK the research networks supported by the National Institute for Health Research provide useful information about clinical trials to the public, e.g. the Diabetes Research Network website[339]. In the recent years a large amount of websites have been built aimed at the public to provide a wealth of information on health related issues, including clinical trials, e.g. *NHS Choices*[xxv] and aimed at professionals, e.g. *NHS Evidence*[xxvi].

The library

Patients use libraries to find medical information[340-342]. The public library is a trusted public institution where people go for information and could play an important role in the provision of health information[341], in fact, partnerships between public libraries and the NHS exist[xxvii]. For public librarians it is a challenge to organise and provide patrons with evaluated information[340;342;343]. Although researchers do not disseminate information with libraries in mind, information that they produce such as clinical summaries, patient information and healthcare professional information are disseminated via electronic libraries, portals, directories and evidence-base websites, which are undoubtedly found by library patrons and staff.

In the UK the *Clinical Knowledge Summaries* (CKS) website[344], formerly known as *Prodigy*, aims to provide some medical information on behalf of the then called *National Library for Health*, now called *NHS Evidence*. As can be seen here, there are rapid changes in ownership and titles and it can be difficult to remain up to date. It is not exactly clear how the public use these websites and whether they speak to their physician about information that they find by using their websites.

[xxv] http://www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx

[xxvi] http://www.library.nhs.uk/KnowledgeManagement/page.aspx?pagename=CONCLINTR

[xxvii] http://www.yorksandhumber.nhs.uk/news.php?id=282 [Accessed 19 January 2012]

Many hospitals have a medical library or education centre that supports the health professionals who work there but also have an active involvement of providing information to patients and help with collating information[345]. In England the *NHS Evidence* website also attempts to bring together relevant information for professionals. Trials of patient kiosks[346] in health surgeries and hospitals provide patient information through electronic means although these are not standard in all surgeries. In the US, information is also being embedded in the electronic patient record that can be downloaded by the patient[347]. There have also been trials of telemedicine where information is disseminated via TVs or mobile devices. Information dissemination via mobile devices is on the rise as it is the method most easily available at reasonably low cost to the user.

The *James Lind Library*, an online library, was set up to improve public and professional knowledge on fair tests of treatments in healthcare. It has a unique library into the history of clinical trials and provides documents and research via the website[348].

Unfortunately little published information exists specifying the types of questions patrons have when visiting libraries. Although, it is likely that patients ask for information on clinical trials as many patient organisations provide information on their websites about clinical trials, indicating that it is a frequently asked question.

The Internet – information about clinical trials online

The Internet helps resource discovery and can be used to publicly disseminate clinical trial information. The challenge lies in trusting information posted on the Internet. Information technologies are ideal tools for disseminating information but "they dislocate our ordinary ways of judging one another's claims and deciding where to place our trust"[223]. The Internet houses a growing number of diverse resources related to clinical trials that can be accessed by anyone. With the proliferation of health information on the Internet it is likely that the public, as well has health professionals, try to find information about clinical trials on the Internet. It is thought that 79 percent of Internet users have actively searched online for information of a health topic[129]. It is estimated that 12.34 million health-related searches are conducted worldwide every day on the web[130]. In 2004, 23 percent of

Internet users have searched for experimental treatments or medicines compared to 18 percent in 2002[129]. Online access to information about the availability of clinical trials creates an expectation that the information will be comprehensive, because the web is not restricting content or forces formats like journals do. There has also been an expectation of improved subject recruitment into trials with more online information available [110].

There needs to be more research into where on the Internet patients go to find information about health, medicines or treatment and what kind of information that they download. The study for this thesis into what resources can be found when searching *Google* shows that patient information, news and clinical trial portals appear high on the results list. We know that website data and statistics show increased visitors numbers, e.g. in 2009 *Clinicaltrials.gov* has 40 million page views per month with 50,000 visitors daily[xxviii], and there are also increased visitors to free online databases like *PubMed*. Between Jun 2007 and Feb 2009 interactive searches on *PubMed* jumped from 54,663,426 to 67,406,898[xxix]. It is likely that there is a steady increase as individuals have more readily access to computers but we do not know who these individuals are and their reasons for going online.

A study tried to establish how often patients of a rheumatology clinic search for health information on the Internet[123]. Thirty-seven respondents (27%) out of 138 patients had used the Internet for medical information in the past year. 83 percent had found useful information, 54 percent found information that they had not previously known and 31 percent preferred using the Internet to their doctor or nurse for information (see also the doctor-patient relationship p.129).

Physicians use the Internet to find medical information too. According to one study physicians access targeted sites rather than search engines[131], e.g. research databases, medical journals and portals. Other research shows that physicians are increasing their use of the Internet to find clinical information and news[349].

[xxviii] http://clinicaltrials.gov/ct2/info/about [4 April 2009]

[xxix] http://www.ncbi.nlm.nih.gov/About/tools/restable_stat_pubmeddata.html [6 Apr 2009]

Even though a review[132] of the information-seeking behaviour of physicians spanning over ten years 1996-2006 shows that physicians refer to colleagues and hard-copy evidence when seeking information in general and it is likely that physicians also turn to the web when looking for clinical trials. Eysenbach has suggested that the Internet is useful in particular when looking for unpublished or ongoing clinical trials[120].

An objective for this PhD was to identify the online 'alternatives', as opposed to the traditional methods of dissemination such as journal articles, that are used to disseminate clinical trial information. My Google search showed that information about clinical trials on the Internet is increasing rapidly and with more information made public. In particular it is interesting to see the use of more informal methods and some web 2.0 'social tools', e.g. blogs, discussion forums etc. are being used for disseminating clinical trial information (table 15).

Table 15: Types of methods used for disseminating clinical trial results on the Internet

Academic personal pages
Blogs with unidentified owners
Conference proceedings
CTRs
Discussion forums
News blogs
Newsletters posted on websites
Personal blogs from sufferers
Portals for trade magazines
Pre-publication press releases
Pre-publication reports
Result summaries on pharmaceutical websites
Slides from presentations

5.6. Current practice of dissemination of clinical trial information: a survey

Data from a survey of clinical research professionals provide an insight into the current practice of dissemination of information and also gives us a snapshot into their knowledge of regulations and tools to assist with dissemination. I draw upon the responses to the survey questions to compare with our literature review findings. The 98 respondents to the survey work predominately in the pharmaceutical industry or contract research organisations, but there were also respondents working for the

national health service, in not-for-profit/academic research and as contractors. The respondents live in the EU. The job roles of those responding were varied (table 16).

Table 16: Job role of respondents in survey (n=98)

Job role	n=
Other	9
Medical writer	11
Medic/Scientist/Researcher	11
Product manager	1
Clinical Research Associate (CRA)/ Project manager	16
Clinical Research/Clinical manager/Director	37
Statistician/Data manager	2
Regulatory/Quality	2
Nurse/Pharmacist	2
Admin/support role	4
Operations/process	3
	98

The survey of clinical research professionals asked respondents to identify various methods that they used for disseminating clinical trial results (table 17).

Table 17: Survey data: Dissemination methods for clinical trial results (respondents n=98)

Method	n=
Blog/wiki	1
Online discussion groups	2
Repository	5
Newspapers/magazines	6
Advertising	9
Website (external)	13
Reprints of journal articles	18
Open access journal	19
Promotional material	19
Standard letter sent out to physicians	25
Meetings/conferences exhibition	40
Press release	41
Website (own)	42
One of the top five medical journals	45
Conference presentation	61
Conference abstract/poster	73
Other peer-reviewed journal	80

The responses show the most common methods used for disseminating clinical trial results are through a peer-reviewed journal, through conferences and via websites. Although it also shows that researchers are using online alternatives to disseminate information, such as blogs, websites and through discussion forums.

5.7. Online tools – clinical trial registries

Computer-based clinical trial registries improve information flow[98] and registrations have increased nearly 420% from year 2005 to 2009 in *Clinicaltrials.gov*[xxx]. Several studies have analysed websites containing information about cancer clinical trials[110-114]. Some of these websites provide tools, e.g. a database or clinical trial registers that can be searched for information about clinical trials.

Atkinson *et al.* studied cancer clinical trial search tools online to establish how easy it was to use these tools available to the public[114]. The outcome of this study was that online search tools do not adequately facilitate providing information about the clinical trial process and there was great variety between different tools. Till *et al.* conducted an exploratory evaluation of online resources for Canadian cancer trials[110]. The outcome of the study was a statement that online sources should strive to make access to clinical trials simpler and reliable.

In 2002, Manheimer[103] examined the completeness and accessibility of ongoing drug trials for prostate or colon cancer in the UK. He concluded that existing clinical trial registries were not meeting existing user needs as many ongoing drug trials were not listed. A examination by Monaco and Krills[112] of cancer centres websites concluded that websites that provided information about cancer clinical trials were providing limited content and the reading level of the information was at college level. Another study in 2007 evaluated online resources for cancer clinical trials[113]. This study found that the resources varied greatly regarding information provided and called for an improvement to content, design and presentation of clinical trials. A further

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[xxx] In October 2005 *Clinicaltrials.gov* contained 13,153 registrations and in February 2009 it contained 68,223 clinical trials[xxx].

content analysis into cancer clinical trial search tools in 2008 also found that functionality and content varied greatly[114].

5.8. Clinical trial registers – study of functionality and content

No similar studies of functionality and content of diabetes and obesity clinical trial registries have been published and therefore a study into this area could establish if the issues are comparable across registers containing information and diabetes and obesity clinical trials. This research wanted to confirm if similar findings apply to clinical trial registries containing information about open or ongoing clinical trials available in the UK. The evaluative study of the content and functionality of clinical trial registries took place with eleven eligible clinical trial registries.

In order to measure functionality and quality of content, two measures were used: 1) a tool evaluating functionality and 2) a list of recommended datasets to evaluate quality of content. There are no validated tools to evaluate content and format of Internet information. This study used a website feature tool used by Atkinson *et al.* in the search for cancer clinical trials[114]. The tool reviews functionalities and features of websites for the following features being available:

- Basic search tool
- Advanced search tool
- Registration options
- Presentation of results
- Additional site content.

The *World Health Organization* has recommended that 20 WHO datasets are provided at the time of registering a clinical trial in a clinical trial registry[350] and these fields were used as a comparative standard for quality of content in a clinical trial registry in this study.

The outcome of the evaluative study shows that the clinical trial registries varied considerably in what features and functionality they offered to the user..

To summarise the key findings; some clinical trial registries provided minimal tools to aid the searcher in discovering information (see research data in appendix B).

- Ten out of 11 registers offered a search tool, but only three out of 11 offered an advanced search tool.
- Two out of 11 registers required the user to register on the site prior to searching.
- The sites that offered advanced search functionality provided many search field options, e.g. terms, phase, condition, study type, dates of registration etc. Even the sites that offered very basic search tools tended to provide a list of search terms or keywords to use.

Obviously functionality of a site is dependent on the software in place and level of funding available to the register owners. Technical difficulties affected some registers and many of them did not offer any help with searching.

The same keywords were used in each directory search: 'diabetes' AND 'obesity' AND 'United Kingdom'. The expectation was that the results list would display studies and the status of those studies, so that open or recruiting studies could be selected. This was not always the case, sometimes it was impossible to know if a study was still open or already closed. Other difficulties presented themselves, such as selecting a country. When comparing results, the different registers did not contain the same clinical trial content. This suggests that the content policy of a register needs to be declared on the site to the user.

The result display varied amongst the registers. Two of the sites provided the results as narrative rather than in data sets; *CenterWatch* and *MedTrials*. These two sites aimed at recruiting subjects for trials, rather than providing structured output of information.

Using the *World Health Organization* twenty recommended TRDS as a comparator, table 18 (and appendix C) shows what data was found when searching across the registers. The table also shows how many diabetes and obesity clinical trials were found in the UK, and the number varies greatly between registers. The *CenterWatch* register, MedTrials and *ClinicalConnection* had a zero result, therefore not comparable to the TRDS and excluded. The three *Current Controlled Trials*

registries had similar output so have been grouped as one in this table, leaving six registries that were analysed for fields and content.

If a clinical trial registry had a matching TRDS field, and if content was available in the results, they received a 'tick'. If no data was provided, even if the field was there, the register did not receive a tick. The numbers of ticks were calculated at the end. Using this method to assess quality of content, the register with the higher number of ticks therefore offer better output of information than those with lower ticks and can be considered to offer better quality content.

Table 18: Comparison of the WHO TRDS and register data fields and review of content provided within registers

(Larger image in appendix C)

URL	ClinicalTrials.gov	IFPMA	Controlled Trials	CMRInteract	UKCRN	WHO ICTRP	CenterWatch
# recruiting trials on diabetes & obesity in the UK	4						
WHO minimal dataset*							
Primary Register and Trial ID #	√	14	28 (but doesn't specify open, closed)	101 but doesn't let you specify open closed etc.	34 (diabetes type II)	5	0 for the UK
Date of Registration in Primary Register	√						1 for US obesity+diabetes
Secondary ID#s	√	√	√	x	√	√	
Source(s) of Monetary or Material Support	√	√	x	x	x	√	
Primary Sponsor	√	√	x	x	√	√	
Secondary Sponsor(s)	x	√	√	x	√	x	
Contact for Public Queries	√	√	√	√	√	√	
Contact for Scientific Queries	x	x	√	x	x	x	
Public Title	√	√	√	√	√	(not complete information)	
Scientific Title	√	x	√	x	x	x	
Countries of Recruitment	x	√	√	x	x	√	
Health Condition(s) or Problem(s) Studied	√	√	x	√	√	√	
Intervention(s)	√	x	√	√ (regions)	√	√	
Key Inclusion and Exclusion Criteria	√	√	√	√ (not very clear)	√	√	
Study Type	√	√	√	√ (sometimes given)	√	√	
		√	√	x	x	√	
		√	√	√	√	√	
Date of First Enrollment	√	√	√	x	√	√	
Target Sample Size	√	√	√	√	√	√	
Recruitment Status	√	√	√	x	√	√	
Primary Outcome(s)	√	√	√	√	√	√	
Key Secondary Outcomes	√	√	√	x	x	√	
Total data sets provided	18	18	17	9	14	17	

The *Clinical Trials.gov* and *IFPMA* clinical trial registries show appropriate data fields in line with WHO recommendations and accurate data within the fields which suggests they are of higher quality than any of the other registers. The WHO *ICTRP* platform was still at early development during this study, and this may explain the lack of data in some of the data fields. The poorest performance was from *CMRInteract* which failed to provide some of the basic information such as registration date, funding, inclusion criteria and the title of a clinical trial. However, *CMRInteract* ceased to exist after 31 Dec 2009, some time after this study took place.

Many clinical trial registries in this study did have similar data fields as that of the recommended WHO TRDS. Quite disappointingly, some registers were lacking

checks and review as fields had been left blank or mandatory fields contain inaccurate information. In a field requesting the name of the study drug, some other word had been provided and fields for contact names and telephone numbers were blank.

The WHO *ICTRP's* register received a low score against its own criteria in this study. However, the *ICTRP* is meta-register searching across a network of registers. Therefore we can assume that if data fields or data are missing from the results of a search in the *ICTRP*, then it is because the data field or data do not exist in the original register from which *ICTRP* aggregates its information.

This evaluative study, which is a snapshot in a time of fast development for registers, shows that some registers' technical capabilities are crude and with regards to content many fields were left blank and some fields carried irrelevant information, perhaps the details were not known or they did not want to provide it (for confidential reasons). Some key information was sometimes missing, such as contact information, drug name and the name of the study. Results and type of information offered varied from site to site and it was difficult to interpret the data provided. This finding is in line with similar studies[112;114]. The study by the *Cochrane Collaboration* in 2011 also confirms that information in published reports of RCTs is not the same as that provided in the protocol or the entry in a clinical trial registry[115].

The absence of a comprehensive standardised registers creates problems for clinicians and patients seeking information about clinical trials[103]. Research also shows that trial registration does not ensure the timely availability of accurate trial results[351-354] because records remain incomplete and are not updated with information even after publication of results and they need to be able to provide information at the point of care.

The results of the recent studies of websites have been that finding search tools was easy, but using the tools was more complex and many sites also used difficult medical and research terminology[114]. It was suggested by several investigators[110;111;114] that developers of search tools should get input from patients

to simplify and enhance search options and to share tools with clinicians and health professionals on how best to integrate these tools into the health care encounter[113;114].

The US activist group Public Citizen conducted a study of registers in 2007[190]. The study included 22 registers of which four were publicly accessible and the rest private websites. They found that the privately run registers lacked consistent design and were of varied quality. It was also felt that these registers were an attempt by the pharmaceutical industry to be seen to comply with new guidelines on trial legislation but in fact hinder the release of too much information. Another concern has been that registers lack data on trial leadership and contact information and are not monitored to ensure completion of mandatory fields.[191]

There are now developments to link the most used register, Clincialtrials.gov, with results databases from the FDA, NLM and NIH websites. This is because of section 801 in the Food and Drug Administration Act enacted in September 2007[272] which mandated the expansion of Clinicaltrials.gov to include results information of trials.

There is a move to make the Clinicaltrials.gov website the comprehensive source of trial information. In a three year development plan starting in 2009, the website will develop a comprehensive results database that may or may not be combined with the registration database. The complexities in creating a clinical trials register including registration and results information, are that there are a wide range of trial designs making it difficult to match their information up with fields, and the information within the database is not peer-reviewed, interpreted or explained[106]. A register complements existing methods of disseminate and releasing results on such databases are not considered pre-publication of data complying with publishers' requirement of only publishing original research.

Perhaps strange to the public, the legalities surrounding the Clinicaltrials.gov database were set by legislation in the US and only applies to clinical trials taking place under the FDA authority, e.g. for the US market. Nevertheless, studies from around the world are registered on the Clinicaltrials.gov database, which has developed into the largest clinical trial registry in existence. The difficulty is in

imposing US legalities on trials conducted in the EU for the EU region. The EU has no similar legal requirements for trial registration and posting of results.

5.9. Usage of clinical trial registries – survey results

The survey of clinical research professionals for this study hoped to find out what registries were used for registration and posting of results.

Results databases were set up for results to be posted and some are separate from clinical trial registries. Some example results databases are: clinicalstudyresults.org by PhRMA, lillytrials.com by Lilly, ctr.gsk.co.uk by GlaxoSmithKline (GSK).

When survey respondents were asked if the last clinical trial was registered the response was that 60% (n=59) said yes it was registered, but 24% (n=24) did not register the trial and 15% (n=15) did not know. 71% (n=37) registered the clinical trial on clinicaltrial.gov with the remainder registering their trials on other registries. When asked if the sponsor of the clinical trial have their own registry available online, 22% (n=22) said yes and 60% (n=59) said no. The remainder did not know.

It was also not common practice for the sponsor to post results on their website 56% (n=55) although 31% (n=30) of respondents stated that the sponsor did.

5.10. Social media and networks

Online information and networking tools are reshaping research but we do not really know to what extent these are used for disseminating clinical trial information or if they are likely to replace what we think of as traditional methods of dissemination, e.g. the journal. Scientists use emails, blogs, Twitter, wikis and social networks when collaborating and sharing information. Research into this kind of scholarly activity is taking place and there have been references to how social media is changing scholarly communication[355].

A recent survey showed that researchers believe social applications will have a major influence on the future of research [356], although it identified that there needs to be work on quality indications, validation of users and credibility is needed to attract

researchers. Another survey of scientists show that since the shift of the millennium, email is being used for research related tasks and is central to scientific work[357].

Research in the US shows that the usage of medical data online by physicians will increase [358]. According to their research, physicians visit pharmaceutical websites, use e-detailing and the younger physicians post content online. There is a growth in usage of mobile devices and content such as news and journal content is downloaded by physicians [358] and the researchers conclude that the portable' on demand' content model is likely to replace traditional resources.

5.11. Reports by the regulatory authorities

Interventions that are tested in trials are submitted for approval with European Public Assessment Reports (EPARs) giving an overview of the clinical trial. EPARs are important additional sources of information about a clinical trial, in particular as only 35% of all RCTs between 1999 and 2005 of approved new medicines were published [359]. The EPARs can be found online from the EMA in the EU. Some drug companies present the clinical study reports on their websites, however there is no evidence that this detailed report (usually 30 pages or more) is the best format for the public[94].

5.12. Choice of dissemination method and factors affecting dissemination?

As we have seen in the previous section there are many different methods available to disseminate clinical trial information. What determines where information is disseminated? This was a very important question to examine as the answer to this question will help with making recommendations at the end of this thesis. A further question was about what clinical trial information is disseminated. The two question fit together as it was part of the investigation to examine if what was disseminated affected where it was disseminated.

Research for this PhD discovered many initiatives and events that have shaped the way in which clinical trial information is disseminated. As discussed earlier, clinical trial regulations are complex and requirements vary in different countries.

Researchers have to deal with protocols and information from clinical trials that are taking place in many different countries and with reporting in different languages, a challenge to control[198]. They also have to deal with different regulatory requirements. The regulatory framework in which researchers work have an impact on dissemination. Other initiatives have included publication guidelines, which set standards of what should be disclosed and how to address reporting and dissemination.

An interesting discovery in this research was the role of pressure and its effect on dissemination. Several types of pressure could be identified ranging from economic to geo-political. There are forces at play affecting dissemination and the choice of a particular dissemination method. A number of factors through various studies that will be discussed covered in this section (Table 19). A factor which has impacted on dissemination and shaped the current practice of dissemination is transparency, a need to declare everything from funding to methods to results. Linked to transparency but also to behaviour of individuals within the research environment are the concepts of trust and confidence.

Table 19: Factors that affect dissemination and choice of method

Factor	Description
Legislation and regulation	• Requirement to register trials • Requirement to report on outcome • Research regulations
Publication guidelines	• Journal or research group guidelines • Industry/authority guidelines • Internal disclosure guidelines
Transparency	• Selection and publication bias • Career progression • Funding • Trust • Behaviour • Fraud
Effective dissemination	• Quality • Timing • Time to publish • Target audience
Pressures in the environment	• Economic: funding, sales/performance, cost • Geopolitical: ethics, global trials, regulations • Social: individual opinion

5.13. Awareness of legislation and regulatory framework behind dissemination

The clinical research environment is heavily regulated with a number of processes and guidelines in place to support the clinical trial activity. The EU has its own directives that outline how clinical research should be conducted, but there is very little guidance on how the information generated should be disseminated. Guidelines have instead come from other sources, such as ICH E3[239] which provides guidance on reporting to authorities with specific details on reporting safety information. The WMA Declaration of Helsinki (2008)[360] provides some vague instruction to register the clinical trial and to share study outcomes with those who partook in the trial. The clinical research environment has still not agreed to accept the 2008 declaration, many still referring to the one dated 2004 and the FDA in the US has completed

abandoned the Declaration[288]. ICMJE[176] and the WHO[194] have provided more comprehensive guidance on publication in journals and clinical trial registration.

The respondents in the survey for clinical research professionals were asked to rate their understanding of current practice of registering and disseminating clinical trial information to which 85% (n=83) felt that they were reasonably or mildly confident in their understanding of these practices. 9% (n=9) individuals stated that they were not at all confident. When examining this further, the least confident individuals worked in the national health service and pharmaceutical industry. Data did not show any trend towards a particular role being the least confident as most individuals felt that they had some confidence.

Many new initiatives during the 1990s relate to ethical guidelines or legislation and in the 2000s we see the emergence of publication guidelines (Table 20).

Table 20: Timeline of the various guidelines and important events relevant to transparency

Year	Event
2010*	GPP2
2008🗀	Declaration of Helsinki (update)
2007*	ICMJE statement (update)
2007⚑	WHO ICTRP (launch)
2006*	Council of Science Editors guidelines
2005*	EMWA guidelines
2005*	WAME guidelines
2005🗀	EU GCP Directive
2005*	Ottawa Declaration II
2004🗀	EU CT Directive
2004*	Ottawa Declaration I
2004⚑	First Clinical Trial Registry (GSK)
2004*	ICMJE statement
2003*	Good Publication Practice (GPP)
1999*	COPE guidelines
1997⚑	Clinicaltrials.gov set up
1997🗀	FDA Modernisation Act
1996🗀	ICH E3
1996*	CONSORT
1996🗀	ICH GCP (E6)
1996🗀	Declaration of Helsinki
1994*	AMWA
1989🗀	ICH conceived
1964🗀	Declaration of Helsinki (first published)

Key

🗀	Clinical research ethical guidelines
*	Publication guidelines
⚑	Other events

5.14. Publication guidelines

International declarations, conventions, directives, and various national laws and rules regulate research ethics and researchers' ethics. But laws and directives do not usually specifically provide guidelines on how and what to disclose and publish apart from data to the national authorities relevant to the new drug application. The issue of declaring all clinical trial data has been debated for a long time with a wish to eliminate unacceptable behaviour and encourage best practice[57;199;361-363].

Unacceptable behaviour includes not declaring conflict of interest, not naming authors (ghost authorship) or paying non-authors to be listed as authors to attract

readers (guest authorship) and falsifying data or publication bias (such as selective reporting of some results). It started with Chalmers declaring that underreporting research data is scientific misconduct[216] and nearly twenty years later he claimed selection bias should be outlawed[364].

This research has identified and refers to three types of publication guidelines.

- Clinical research ethical guidelines, e.g. ICH E3 reporting guidelines
- Publication or reporting guidelines, e.g. by journals or research bodies
- Organisational internal disclosure guidelines, e.g. those by sponsor companies

A comprehensive list of guidelines with further information referred to in this research is given in Appendix D.

Looking at Table 21, we can see that the first clinical research ethic guideline is the Declaration of Helsinki in 1964 concerned with patient safety and that clinical trials should be conducted ethically. Table 21 (below) gives an overview of main events that have shaped publication guidelines and the path to transparency.

Table 21: Events that have shaped the evolution of publication guidelines

1997	FDAMA Law, Section 113 (USA)	A Clinical Trials Data Bank should contain the following information: (1) Information about Federally and privately funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases or conditions, (2) a description of the purpose of each experimental drug, (3) patient eligibility criteria, (4) a description of the location of clinical trial sites, and (5) a point of contact for patients wanting to enroll in the trial, all in a form that could be readily understood by the public.
2004	GSK sued for withholding negative data from paroxetine trials	As a consequence of the event where GSK were found guilty for not disclosing results from paroxetine trials, GSK set up the first pharmaceutical clinical trials register online where all results are publicly disclosed.
2004	Ottawa statements I & II	The Statement outlines the fundamental principles for trial registration (Part I), operational aspects of the protocol registration (Part II, in progress) and of results reporting (Part III). Part III has been drafted and is under consultation.
2005	WHO calls for registration of all trials (worldwide)	The WHO held several consultations in 2004 on trial registration. In Jan 2005 the WHO started a project to set standards and advocate for compliance. The WHO launched a portal as a meta register of clinical trial registries in 2007.
2007	Enhancing drug safety and innovation act: register all new trials and disclose all trial results (USA)	This is a bill in the United States to amend the Public Health Service Act and the Federal Food, Drug and Cosmetics Act to improve drug safety. This is the first stage of the legislative process where the bill is considered in the committee.
2007	FACT: register new trials and disclose trial results of studies with serious and life-threatening diseases (USA)	The Fair Access to Clinical Trials Act (FACT) of 2005 asks for a databank of clinical trials registered accessible to patients and healthcare professionals for information related to ongoing clinical studies as well as a results database with results of all publicly and privately funded clinical trials regardless of outcomes. Introduced Feb 2006 S.470 or FACT Act would require the FDA to expand on the clinicaltrials.gov database to incorporate the above features.
2007	Maine Regulations (USA)	February 2007: The rule defines the obligations of manufacturers and labellers of prescription drugs and biological products to publicly disclose websites information about clinical trials that are or have been FDA-approved for marketing and are or have been dispensed, administered, delivered or promoted in Maine. The final rule further clarifies the required content, timing and location of these disclosures, and indicates for which clinical trials this information is required.

The first 'original' publication guideline is the one produced by the American Medical Writers Agency (AMWA) in 1994 although AMWA has had a Code of Ethics for all its members dating back to 1940[365]. 1997 is a landmark for clinical trials as this is the year the US FDA Modernisation Act states that clinical trials must be registered in a databank which resulted in the invention of the clinicaltrials.gov register. This sparked the production of publication guidelines by the Committee on Publications Ethics (COPE)[366] in 1999, the Good Publication Practice (GPP)[290] in 2003 and the statement made by the International Committee of Medical Journal

Editors (ICMJE)[251] in 2004. Another landmark event in 2004, probably the event that highlighted several issues and concerns with clinical trial reporting, Glaxo SmithKline (GSK) was found guilty for not disclosing results from Paroxetine clinical trials. GSK declared at the court trial that they would set up a clinical trial registry where all their trials and the results of trials would be posted[140]. As a consequence of this event in 2004, PhRMA made recommendations to its members, the pharmaceutical industry in the USA, to communicate clinical trial results publicly via a peer-reviewed journal, abstract submission, oral presentation or other means [367]. In November 2004 the World Health Organization (WHO) called for members to establish a platform to link clinical trial registers to ensure a single point of access and identification of clinical trials. The ICTRP was set up in August 2005 linking primary registers. The Ottawa Statement in 2005 recommended that registration and the release of clinical trial information are necessary to fulfil ethical obligations in research. The Declaration of Helsinki was updated in 2008 with "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject"[360]. Several other guidelines were published thereafter and are regularly revisited for updates.

5.15. Responses from survey of clinical research professionals

In the survey of clinical research professionals, it was established that awareness of publication guidelines written by various research bodies is quite low (Table 22 and Figure 14).

The most used guidelines by respondents are the ICMJE 41.8% (n=41), CONSORT 28.6% (n=28) and GPP 24.5% (n=24) guidelines.

Table 22: Awareness and use of publication guidelines n=98

		Not aware of it	Aware of it but haven't used it	Have used it
ICMJE	Count	23	34	41
	%	23.5%	34.7%	41.8%
GPP	Count	41	33	24
	%	41.8%	33.7%	24.5%
CONSORT	Count	54	16	28
	%	55.1%	16.3%	28.6%
WAME	Count	73	21	4
	%	74.5%	21.4%	4.1%
COPE	Count	84	12	2
	%	85.7%	12.2%	2.0%
CSE	Count	85	12	1
	%	86.7%	12.2%	1.0%
PhRMA	Count	55	23	20
	%	56.1%	23.5%	20.4%
EMWA	Count	69	22	7
	%	70.4%	22.4%	7.1%
AMWA	Count	82	11	5
	%	83.7%	11.2%	5.1%

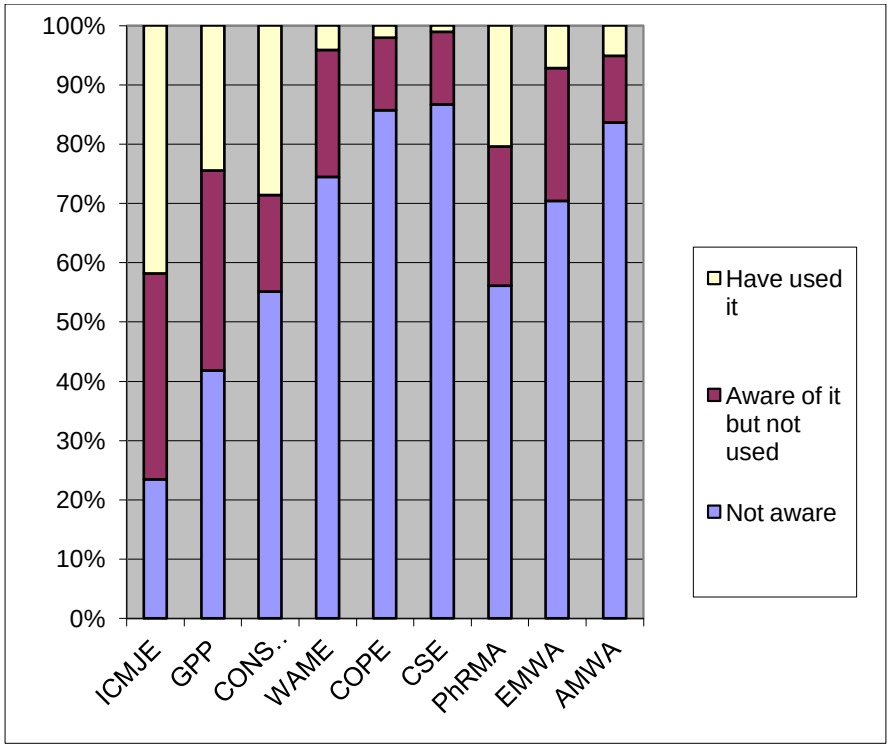

Figure 14: Awareness and use of guidelines % of respondents in a survey

Respondents were also asked to rate usefulness of guidelines where the ICMJE (n=33), CONSORT (n=30) and the GPP (n=23) were reported as the most 'useful' to 'very useful' guidelines (Figure 15).

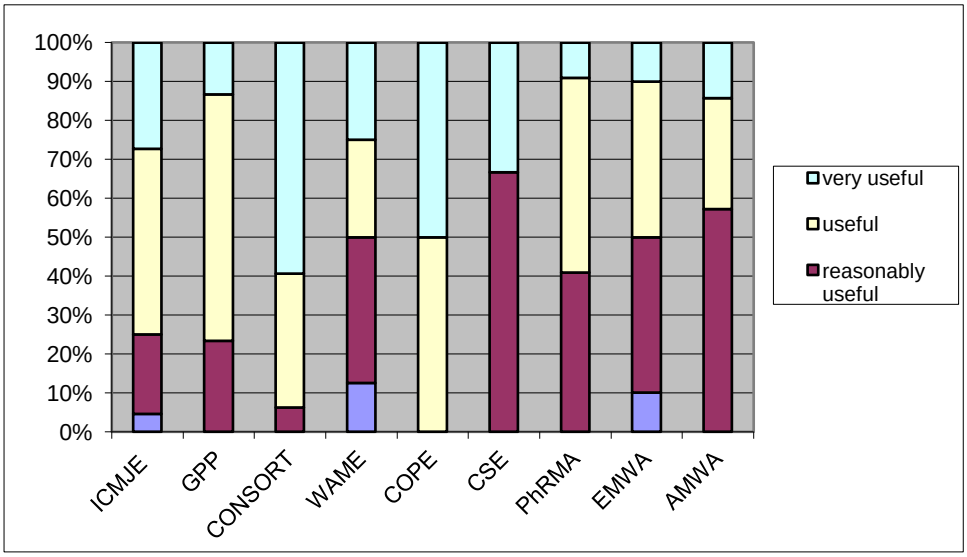

Figure 15: Guidelines used and their usefulness % by respondents in a survey

When asked if the organisation, in which the respondent works, has a publication policy, 72% (n=71) responded that they do. Rather worryingly, 10% (n=10) did not even know (Table 23). It is surprising that 17% (n=17) state that they do not have a publication policy.

Table 23: Publication policy within organisations n=98

	n=	%
Yes	71	72.45
No	17	17.35
Don't know	10	10.20
	98	100

When cross referencing the availability of publication policy against organisation it was established that those organisations that had a publication policy were pharmaceutical, clinical research or device companies (75.4% (n=61)) as well as academic/not-for-profit organisations (88.9% (n=8)). Those that did not have policies were individuals working as contractors (58.3% (n=7)) and 8 pharmaceutical companies (13.1%).

5.16. Pharmaceutical disclosure policies

During the GSK trial and the recommendation by PhRMA for industry disclosure guidelines, many pharmaceutical companies drafted and published their own guidelines to cover what information they will disclose about clinical trials.

To establish to what extent the policies cover the issues identified for disclosure, the ICMJE uniform requirement headings were used for comparison with pharmaceutical disclosure policies selected for analysis[xxxi](Table 24). Ten policies were randomly selected from ten pharmaceutical companies, of which five were larger (by sales) and five smaller[242].

Table 24: Publication or disclosure policies of pharmaceutical companies in the study

Company	Year of policy
1. Pfizer	2002
2. GSK	2003
3. Novartis	2005
4. AstraZeneca	Not provided
5. Sanofi-Aventis	N/A
6. Merck harmaceuticals (KgaA)	2005
7. Eli Lilly	2005
8. Roche	2005
9. Amgen International	2005
10. Ipsen Ltd.	N/A

Note: Sanofi-Aventis and Ipsen Ltd. do not have public policies of disclosure. Eli Lilly's policy covers the broader conduct of trials.

[xxxi] Analysed between May and July 2007

Table 25: Comparing pharmaceutical disclosure policies against ICMJE Uniform Requirements headings for quality of content

	Pfizer	GSK	Novartis	Astra-Zeneca	Merck KgaA	Eli Lilly	Roche	Amgen
Coverage								
Using external contractors for drafting publication	2	0	0	2	2	0	0	0
Conflict of interest	0	0	0	2	0	0	0	0
Obligation to communicate negative results	2	2	1	0	0	2	2	2
Obligation to register clinical trials Phase II-IV	2	0	2	2	0	2	2	2
Preparing manuscript for publishing	0	2	0	2	0	0	0	0
Registration of Phase I studies	1	0	0	0	0	0	1	1
Commitment to communication of results	2	2	2	2	2	2	2	2
Acknowledges official guidelines	2	2	2	2	2	2	0	2
Posting results on a public database	1	0	2	2	0	2	2	2
Admits commercial sensitivity	2	0	0	0	0	0	1	0
Identifies database where registering trials	2	0	2	0	0	2	2	2
Gives timeline when results will be released	2	0	2	0	0	2	2	2
Discusses interim or preliminary results	0	1	0	0	0	0	0	0
Talks about publication of results	2	2	2	2	2	1	2	2
Internal review of abstracts/scripts	2	2	0	0	2	0	0	0
Discusses delayed publication	2	0	0	0	2	0	2	0
Sharing of protocol with journal editors	2	0	0	2	0	0	0	0
Authorship of publications	2	2	2	2	2	0	0	0
Peer review	0	2	0	0	0	0	0	0
Communicating outside peer-review journal	0	1	0	0	0	0	2	2
Total	28	18	17	20	14	15	20	19

This table is also available in Appendix E.

Rating scale used for comparison

0	No coverage
1	Some coverage
2	Comprehensive coverage

Table 26: Scores of analysis of disclosure policies against the ICMJE criteria

Company	Points scored
Pfizer	28
AZ	20
Roche	20
Amgen	19
GSK	18
Novartis	17
Eli Lilly	15
Merck KGaA	14

Using a scoring system to analyse the quality of the content points were awarded on coverage of headings identified by the ICMJE. Out of a possible score of 40, the eight guidelines analysed performed poorly. Specifically some policies stated that they will not provide commercially sensitive information, e.g. name of investigational product, title of the study or how many subjects are in trials. Some of them also said they do not release interim results and will only share results once the study has ended. Some policies stated that non-publication will occur if a study has ended prematurely, if there is insufficient data or if the data are invalid. Some

companies are happy to publish results sooner than study end if the data are medically important.

It seems that during the analysis of the content disclosure policies with that of the ICJME publication guideline, the content of those policies do not provide comprehensive guidance to clinical research professionals or possibly internal policies conflict with publishers' guidelines. This suggests that professionals writing papers or planning communication/dissemination activities may be experiencing pressure or difficulty when determining what to disseminate. It was surprising that professionals were not always aware of external publication guidelines and also did not rate them very useful.

5.17. Selection and publication bias

Selection and publication bias refers to a decision to select information that will be published. This has traditionally encompassed publishing in a journal although we can extend this argument to a method of dissemination that is accessible by the public. It is recognised that medical journals in particular publish content that is affected by a form of bias[368]. However, we know that information disseminated on the Internet will be biased, affected by things such as owner of the website, the editor/author and their own opinion and any other influences that may affect the content[130]. It has been argued that researchers need more comprehensive guidelines to aid them in the reporting of results to avoid any kind of bias[369], although we know there are several comprehensive guidelines available to researchers (as seen in the previous section) we also know that they are aware of some of them but not others.

There are different types of selection bias, e.g. the selection of which studies to publish based on their results. It has been shown that studies without statistical significance (negative results) are less likely to be published[217;218;370] and that profit-making organisations only publish positive results[27;76;217]. There is also a selection bias on which data are selected for publication, withholding some data, e.g. some do not agree that data from Phase I trials are worth publishing[295] or that some outcome data are not published[27]. Scientific misconduct such as fraudulent research claims [207;371-373] may be unfortunate outcomes of pressures for various reasons. Pressure to publish or end of funding means that the researcher may take shortcuts [211]. There is

also a selection bias which affects in which journal results are published, where journal prestige affects choice[374]. There is also current debate around editorial bias, to which extend the publisher rejects studies for publication[204;218;375].

Examining bias is difficult through a survey. However, in the survey of clinical research professionals, one question asked respondents if in a recent trial showing unfavourable (negative) results, the results were disseminated in any way (Figure 16).

35% (n=35) said that they disseminated the results in a peer-reviewed journal. Only 14% (n=14) said that they did not disseminate them at all.

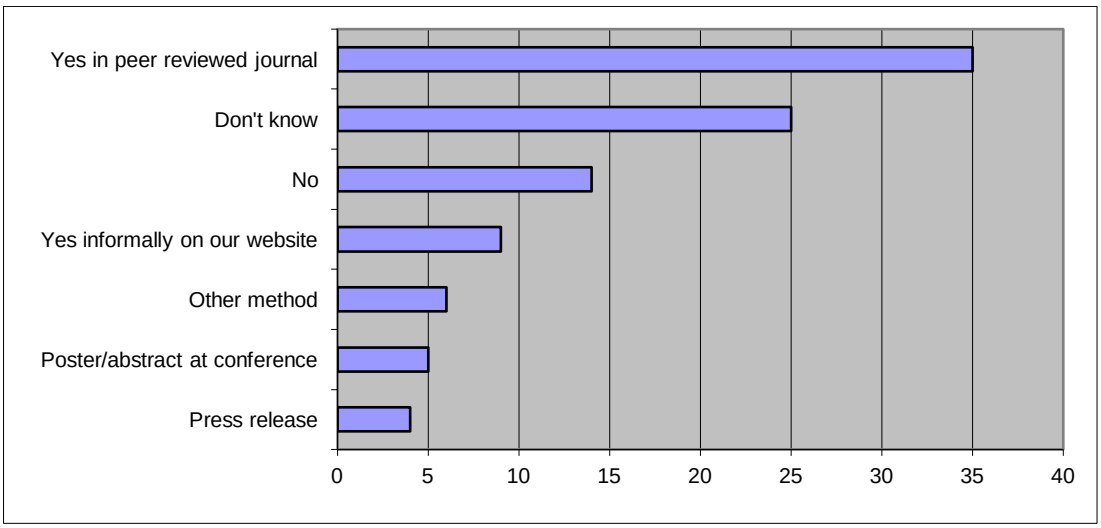

Figure 16: Dissemination of clinical trial results that were unfavourable/negative (n=)

Five respondents identified the reason for not disseminating unfavourable results as not being company policy to do so. However, they also identified that the journal to which they submitted the results rejected the publication (n=3) and admitted that releasing such data may harm the company reputation (n=4). Only 16 survey respondents provided an answer.

It must be argued that a selection bias of what is disseminated is necessary, as it would be impossible to disseminate all the clinical trial information generated, as we have seen a very large amount of information is generated in clinical research. It is unlikely that all that information would be of interest to anyone and we know that

raw research data is not necessarily that useful without interpretation or research design information[376]. But perhaps an argument is that as long as that information is publicly available at request, even if not disseminated, it would improve transparency. To improve transparency, all results should be published whether positive or not [201;216;219]. Underreporting or not reporting at all is recognised as research misconduct, and in particular as this can lead to seriously misleading recommendations for clinical practice and new research [216].

5.18. Does impact factor play a role in selection of journal when disseminating clinical trial information?

The impact factor has been used as a method to establish the impact a journal has on the community it serves. It has been suggested that impact factor plays a role in which journal a researcher decides to publish in as it authors seek to profit from publication[81]. It has also been suggested that journals are nothing but marketing tools where the authors publish for their own professional benefit in journals that impress[76] and that journals foster the careers of researchers[377]. It is likely that authors select what journal to publish in based on impact factor, publication time span between submission and print of article and to improve their scientific merit[81;378-380]. If an author publishes frequently, the likelihood is that there will be a high volume of self-citations, contributing to a higher impact factor for the journal[81]. It has been argued that journal publishers reject authors that do not publish frequently for this reason[81]. Cynics have said that authors of scientific papers publish to get their own name in print and to serve their own needs, rather than a reader's[381] and it has been stated that science, not marketing, should guide us in writing scientific papers[382].

The impact factor has become our way of measuring not only a journal's worth, e.g. quality, but also researchers' activity. The impact factor has become a way to measure a journal's, and a paper's, scientific worth although it has been argued that the number of citations as a quality measure is questionable [383;384]. The impact factor of a journal may have a role in decision making on where an article is submitted[374;378]. It is possible that research published in a top medical journal with high impact factor will be trusted more than the research published in a less well-known publication[206] and that authors who want their research to be identified as

evidence of good quality choose to publish in high quality research journals[53;69]. The sponsors of clinical trials need to sustain drug development and need funding for this[249] and publishing is usually part of a funding application. Although, Coleman states that journal attraction power, consumption power and author associativity[246] are indicators of journal value rather than impact factor and he suggests that the scientific value of a journal must be developed in a fuller model. Impact factors also cannot be extended to other dissemination activities outside publishing and so the model must show scientific value of other activities too.

For this thesis, the analysis of the journals that publish the majority of clinical trials in diabetes and obesity (section 1.46) does not suggest that impact factor plays a role in selection of journal for publication of a clinical trial as I would have expected to see the majority of papers published in journals with top impact factors. It seems, at least in the discipline of obesity and diabetes that clinical trials are published in three journals that are subject specific. Societies and institutions have released statements to say that the choice of journal where primary research results are published is not relevant, as long as certain criteria are met by the researcher: that the results are made publicly available within three months of publishing and that the publication will be stored in an electronic repository after publication[271;385;386].

5.19. How effective are the methods chosen?

"Dissemination activities seek to strengthen awareness and enhance the impact of research findings amongst relevant target audiences"[49] and dissemination aims to influence policy makers or force decision-making, which creates a change in behaviour in the recipient[48].

By effectiveness in this thesis I am examining the methods used to disseminate and if they are fit for purpose for clinical trial information. The following section discusses fit for purpose and how effective the current dissemination methods are.

Influencing decision-making

The reason for dissemination is to actively spread information to a defined target group and to do so effectively that information has to be taken up in implementation, to influence decision-making. I have already looked at factors that affect

dissemination of clinical trial results, e.g. influences including political and economic pressures, existing policies, administrative feasibility, timing and bias.

According to Duggan and Banwell[56] these influential factors can be broken down into internal and external by provider of the information and by recipient (table 27).

Table 27: Factors influencing effective dissemination

Provider		**Recipient**	
Internal	**External**	**External**	**Internal**
Effectiveness measures	Cultural constraints	Perceived relevance of the information	Recognition of need for new knowledge
Change in behaviour	Socio-economic factors	Interaction with information	Information seeking style
Change in attitude	Other sources	Participant enrolment in the strategy	Awareness of information sources
Change in knowledge	Reinforcement of existing knowledge	*Environment*	Willingness to change as a result of new information
Cost	Research based information		*Information literacy skills*
Evaluation	*Method chosen for delivery*		*Access to resource*
Time for research & delivery	*Tools for influencing*		

Italics=additional factors identified by this research not included by Duggan and Banwell

According to Duggan and Banwell, not one factor is crucial for effective dissemination[56], but that there is a combination of factors that is important. This thesis has identified a further four factors (in table 27 in italics).

- Tools used for influencing, e.g. opinion leaders or social tools such as websites, Twitter, blogs. In public health there is evidence of where social

marketing campaigns involving social tools are used to change public health behaviour, e.g. reduce obesity[387].

- The environment in which the recipient is receiving the information, e.g. under a stressful situation or very little time to absorb the information[388].
- The recipient's information literacy skills also affect absorption of disseminated information, e.g. searching for information using various tools and the interpretation of the content and context of information[130].
- Access to the information, e.g. access to full text or Internet access in particular for healthcare providers[214].

Scientific evidence is only one aspect of information that influences policymaking, as can be seen in how NICE make technological assessments of interventions in England[389]. It is not only the efficacy of the drug that matters, it is also the economic evidence and how it fits into other treatments that are on offer. Also, sometimes there is not sufficient evidence for a particular drug, decisions must be made based on incomplete evidence and sometimes quickly[390]. Sometimes new information may be adopted on the proviso that further information will be forthcoming, e.g. further research data. Research results and information have limited time in the limelight and often it is not known when an update will be made available, so there is a very short time in which to impress and influence. The information disseminated is likely to be more successful if the information was founded upon existing research and therefore reinforces the recipient's existing knowledge[56].

New treatment recommendation is often slow in uptake. In the 1970s and 1980s several randomised trials into a particular condition which suggested change in treatment practice were not adopted until nearly 20 years later by one of the Royal Colleges in the UK[391]. Certainly, NICE makes evidence-based treatment decisions on behalf of the National Health Service, e.g. what drugs are recommended in what treatment. However, NICE relies on access to the right type of evidence for new interventions and treatment suggestions in order to make a ruling on application in practice.

Barriers that may affect dissemination are existing assumptions, e.g. about the audience, and the need for homophilous communication[56;392]. There are identified barriers to effective communication, either cultural, e.g. existing ideals or emotions, or socio-economic, such as education and status[56]. Environmental barriers have been ignored, e.g. the environment in which the information is received can cause stress or not be ideal as identified by Wilson[388]. Most physicians have less than 15 minutes to discuss diagnosis and treatment with a patient, in which the doctor is the only source of information for the patient[388]. Interruptions or lack of time can be significant barriers of time, e.g. a press conference, or a discussion that takes place in intense situations with little time.

Influencing through effective dissemination

To effectively disseminate information means to distribute into implementation[49]. There are several challenges in effectively disseminating findings from health research, with several stakeholders to satisfy: health professionals, policy makers, current and future consumers. Effective dissemination is also an interactive exchange between researchers and those that the information is intending to influence[48] .

It can take many years for research results to be disseminated, by which time the information is not relevant or when information is needed quickly, the speed of delivery may impact practice. The timing of the delivery is also important. If research is not delivered timely at the point of need, it may no longer be useful. According to Coomarasamy *et al.*, clinical medical journals are not effective in motivating practitioners to change practice mainly because what is published is not valid or relevant with patient care[49]. It is also possible that clinical trial results are not reaching practicing physicians. In 1979 a paper in JAMA highlighted a survey of primary care physicians' awareness of an important diabetic retinopathy study[393]. The results showed that only 33% of physicians had treated their patients correctly according to new study results published 18 months earlier. Two other papers in 1981 stated that clinically significant research results that were published did not reach the practicing physician[394;395]. These days, the publication of clinical trial results can have a "rapid and dramatic effect on treatment patterns"[396-399]. In 2004 the Women's Health Initiative (WHI) trial was stopped early due to evidence that harm is associated with hormone replacement therapy in postmenopausal women,

which caused widespread panic amongst HRT users. It is also the case that researchers are more likely to find out about medical research through the popular press [400]. However, there is evidence of where publications have taken many years to be incorporated into clinical practice or where new evidence has not made any change to existing practice[401;402]. An example of where research was disseminated quickly, is the Million Women Study[403]. In this study, it was discovered during the clinical trial that HRT caused an alarming rise in severe long-term side effects. The results were published rapidly in various ways: by press release and in a peer-reviewed journal, causing a sudden reduction in the prescription of HRT.

One key paper[401] aimed to examine the dissemination plan of a major clinical trial which had the potential immediate applicability in public health, the ALLHAT's trial. The study concluded that there is a need for a comprehensive plan to influence prescribing practices and that this planning should be part of the planning for the clinical trial.

What are the implications of research in practice? In order to improve transparency and to further the understanding of clinical trials, scientists should provide implications of research to the public and ensure timely and appropriate communication of the results. There is an identified need for evaluation into dissemination and implementation strategies to estimate efficiency[62]. There is also a concern over communicating research results too early. A report warns of drawing attention to clinical trial results too early, as an awareness over a product before it reaches the market could have negative commercial impact[222]. The target audience must see a relevance of the material to them and be able to interact with the information[56].

Research from *Thomson Pharma* revealed that GlaxoSmithKline (GSK)'s publishing practices between June and August 2006 made more impact than any other pharmaceutical company. They published nearly 80 articles of which 32% created an impact on the attitudes or product knowledge of prescribing physicians[404].

It has been established that the journals are still considered important by physicians in obtaining information[305], although professional meetings and conferences are

considered more important and colleagues come closely after journals. Dissemination of trial results should be intensive[401] and in order to impact practice behaviour efforts apart from journal publication should take into account drug promotions, recommendation from colleagues, guidelines, and use multiple methods such as detailing by opinion leaders, community based methods, provide patient guidelines etc.[405;406].

Dissemination activities should seek to "strengthen awareness and enhance the impact of research findings" amongst target audiences[407]. Medical journals could improve influence in practice by reducing the number of journals in existence and by journal articles being published in the right journal for their content[49]. To avoid the danger of practice-changing to results released at conferences or pre-submission, it has been suggested that more journals should publish rapid review and publication of those trials that are likely to change practice, and that publication should not be delayed[396].

The web is a breeding-ground for new ideas, products and services. Websites are set up, change and disappear frequently. We can quickly search and read material on the web, much quicker than we can digest it[408], and it is much easier to come across misinformation on the web with the speed in which we use it. To deal with misinformation on the web Calvert suggested two solutions: that publishers control information flow as they have the experience of this in print formats and that we improve information literacy in individuals.

Blogs are influential forms of web publication and communication and some blogs have media impact and are of commercial value[409]. Blogs are "new forms of mainstream communication" to publish and exchange information and to establish networks[410]. According to data gathered between 2003-4, blog readership in the US increased 58%[411]. However, according to a lifestyle survey done in the US, blog readership did not increase during 2005[412]. We need more data on the use of blogs for those searching for information on the web.

According to Shirky[413], blogs are expected to follow a 'powerlaw' distribution whereby a small group of popular blogs have the highest readership. With time,

distribution becomes uneven so that popular blogs will become more popular, and blogs with less audience will reduce further in readership. The blog's 'value' is determined by multiple factors: the 'look and feel', e.g. how information is presented, the organisation of it, and also the extras a blog can offer, e.g. commentary, polls or other interactive features[409]. These factors and the accessibility of blogs affects the potential of the spread of the blog[414;415]. Another important value factor is the existing community of a blog; e.g. blog friends or links, which shows a trust in a blog[409].

According to research by Giordano *et al.*, an oral presentation at a US oncology conference in 1998 increased the use of taxanes in breast cancer patients before the study was published and also before the drug was approved for this disease by the Food and Drug Administration[396]. Research results are often presented at conferences in advance of publication, and even though they are not subject to independent peer-review, the results are widely disseminated[396].

We are aware that presentations of research at conferences may be limited with information and outcomes may in fact change between the initial protocol and final publication of results[155;416;417], and conference abstracts and posters could be presented throughout the phases of a trial.

Concerns raised by Giordano *et al.*, is that rapid changes in practice based on early results can be premature[396] and the authors suggest that there should be caution exercised and awareness of the power of these meetings to publicise their agenda, using press releases to attract attention. Giordano *et al.* encourages conference organisers and participants to share data from studies presented with as much information as possible for health professionals to study before making practice decisions[396]. A study on taxanes communicated at a conference concluded that there were insufficient data to recommend taxanes for the treatment of breast cancer and yet it did change practice. Giordano *et al.*, provides three reasons as to why the practice changed. The first reason is that this particular study received intensive and positive media coverage. The second reason is that the pharmaceutical company representatives were disseminating the results to oncologists. A third reason was the

type of study: an established research group, a multicenter randomized trial would have added trust.

Conference presentations are often included in technology assessment reviews (TARs), which lead to treatment recommendations, where the presentations provide information that has not yet been published. In a study of presentations and abstracts used in TARs they found that the quality of reporting was poor failing to describe methods of randomisation or blinding of allocation, there were also discrepancies in reporting of results[155].

Continuous medical education (CME) events often communicate the latest research and recommendations. Research shows that dissemination activities have little effect if used on their own[405] although two systematic reviews found that CME events have some impact on practice behaviour[418;419]. This has been disputed in later research arguing that previous reviews were flawed with poor evidence[420]. Even the use of key opinion leaders in changing practice has been disputed[421].

However it seems that a combination of dissemination activities has greater success. The ALLHAT study used persuasive messages by opinion leaders delivered face-to-face and intended to use professional societies, formularies and patients to intervene in practice[401]. The study stated that difficulties in organising opinion leaders, e.g. their availability, early on in a trial, before the results of the trials are known, is very expensive. The study authors suggested that the use of professional associations and public health networks would be useful for wide dissemination activities. Another difficulty is designing the right model of implementing the persuasive messages for the target practitioners. These strategies require long implementation times of six to twelve months in advance. The cost of the dissemination project in the ALLHAT trial was $3.7 million in 2007, which was 4% of the clinical trial budget[401].

It's the role of translational research to ensure that scientific knowledge is extracted from research and translated into use for patients by health care professionals[422]. One of the difficulties with translational research is ensuring the new knowledge is disseminated and affect everyday clinical practice[422]. Woolf argues that there must

be more investment into working out how to ensure that research is translated into practice and should be funded by those sponsoring the research.

An issue also identified by authors is the objectivity of information disseminated, in particular information delivered in the interest of pharmaceutical companies[401] and the role of money in the dissemination of knowledge in the form of paying ghost-authors and it was suggested that academic centres ensure guidelines exist when dealing with commercial studies[283].

In 2006 an incident at Northwick Park Hospital in London where a phase I trial went wrong left six men with multiple organ failure. Not only a shock to the public, but also to industry, this type of incident is highly unusual. The drug had been through several pre-clinical and animal tests without any sign of causing the types of events as was seen in the trial. The Medicines and Healthcare products Regulatory Agency (MHRA) and Ethics Committee had approved the trial protocol. Over many days the media was full of anti-industry commentaries.

In 2004 GlaxoSmithKline (GSK) was found guilty for not disclosing serious side effects of the drug paroxetine: suicidal thoughts in children and adolescents. GSK has been sued by more than 5,000 U.S. citizens since the incident.

In October (2008) Pfizer was found guilty of marketing Celebrex, a cox-2 inhibitor, failing to disclose possible serious cardiovascular side-effects such as blood clots, heart attacks and stroke. They also falsely marketed Bextra, a drug for arthritis, by advertising the drug for use in non-approved uses, namely for pain. Pfizer conducted the trials in dental patients and published the results in a dental journal in 2002. The article and large marketing efforts increased sales. They had to withdraw the drug in 2005 for safety concerns, in particular cardiovascular problems. In the case of Bextra, this was an important historic event where private litigation can hold pharmaceutical companies accountable in a case where the industry regulators have failed to spot scientific misconduct. There is no wonder that the media will cover these stories in detail and that public trust in clinical trials and industry fails.

5.20. Trust and confidence in clinical research

Society is facing a crisis of trust[223]. According to sociologists and journalists there are signs of mistrust even at familiar institutions or individuals and consumer no longer trust business or products and patients no longer trust their doctors or hospitals. "Trust has to be placed without guarantees"[223]. If we are let down or we let someone else down, relationships based on trust are damaged. Therefore we place great emphasis on preventing fraud or deception to deter mistrust; through law, code of practices, examiners, passwords etc. The evidence of mistrust are for example demonstrations, results of opinion polls or the written opinion of someone, we don't have much choice in placing our trust in our day-to-day activities such as drinking tap water, taking medicines or using certain products but O'Neill states that we live in a culture of suspicion of accountability and transparency. However it will not improve our trust if we constantly expect individuals to declare their accountability or ask for proof that everything is to be trusted[223].

Trust is relevant to clinical trial information in several ways. In the clinical setting trust is tied to the interpersonal caring attributes of the provider and confidence in their competence[228] and trust in someone depends on the circumstances[229]. In clinical trials, informed consent is an important part of gaining the trust of a volunteer in a clinical trial, do they understand the process of the clinical trial, including personal risks? The goals of the research and the institution conducting the research need to be believed in, and the public need to feel that they can place their trust in them. Trust could easily be called into question if people felt that their confidence was not being kept and if they felt that medical information was being used for commercial gain[169]. A recent study shows that patient's confidence in their physician would improve if the physician disclosed relationships with pharmaceutical companies and other competing interests[170].

Trust can be hampered by evidence of bias or conflict of interest, lack of transparency and quality, pressures, ethics and geographic location. The scatter of information, the evolution of the Internet and the information skills needed to find and interpret information means it can be difficult for an individual to distinguish between accurate information and marketing claims or even inaccurate information. When reading an article, the goal is to balance strengths and flaws found and

establish an independent thought of whether the message is true[423]. Are the results believable and valid, do they represent the truth?

In clinical research the aim is to disseminate the results of a clinical trial in order to influence, e.g. by providing the right information at the right time for the right audience. Trust is an important issue that must be considered by those who are communication information. The difference between a positive and negative climate of trust can have great impact in a clinical trial, including recruitment of subjects for trials, marketing products and in sales.

5.21. Model of trust

In order to understand how trust/distrust forms, a figure from online banking research has been adapted to fit the dissemination of clinical trial information (Figure 17) to illustrate issues I have discussed in this thesis, including the behaviours of trust shown in Table 1 (p. 57).

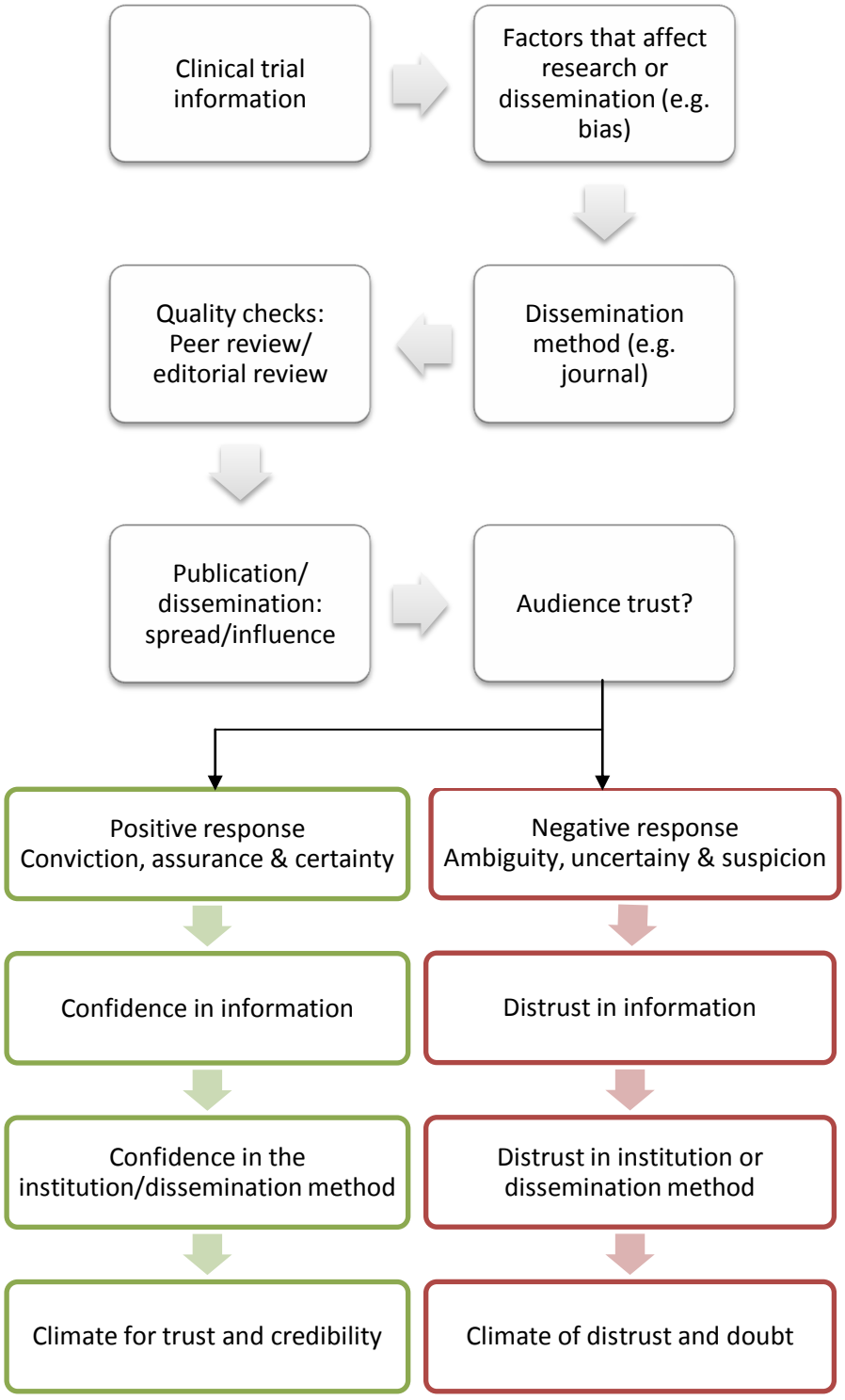

Figure 17: Framework of how trust or distrust forms throughout dissemination – adapted from 'five levels of trust' in online banking[166]

In brief, factors throughout dissemination can affect the trust of the audience. I have discussed factors that affect dissemination in this thesis and they early on affect the researcher and research process, and the dissemination process. The choice of dissemination method can also affect trust, e.g. if communicating via a website compared to via a peer-reviewed journal will affect trust in the audience of that information, as some of these methods may be accompanied by peer review or other rigorous quality checks, e.g. a publication guideline. It may also be affected by previous knowledge or trust in that dissemination method or the author because of their institution or experience. Behaviours affecting trust were discussed in the literature review. There may also be factors that affect the dissemination process during the dissemination stage, how influential the information is that is disseminated and the way in which the information spreads.

The audience now has to decide if they trust the content. Ambiguity, uncertainty and suspicion will lead the author and the institution into a climate of distrust and doubt. Conviction, assurance and certainty will lead the author and the institution into a climate of trust and credibility. In a positive climate, more trust is invested in institutions, which improves the way in which the public behaves towards an institution or their opinions of it. In a negative climate, trust is removed from institutions, causing a climate of distrust and this creates concerns within institutions.

Although simplified here, the results of this research shows that trust surrounds the dissemination of clinical trial information throughout the clinical research process and the way in which trust or distrust forms should be included when planning a dissemination strategy.

5.22. Conclusion to Chapter 5

The findings presented in part 2 are responses to the research questions what range of methods are used to disseminate clinical trial information, what factors affect how clinical trial information is disseminated, including attitudes and practices of dissemination and how effective a particular method is for dissemination. These research questions aimed to test the model constructed and presented in part 1. The chapter began by describing the scatter of information across many resources. The

'mystery shopper' search using Google showed that information about clinical trials is increasingly appearing on the Internet. It identified three core journals that publish clinical trial information from trials in obesity and diabetes which show that research is not just published in top medical journals, e.g. those with high impact factors. The research identified that abstracts and media services underreport aspects of clinical trials. Information about clinical trials can also be found in advertising, promotional literature, via patient organisations and charities. The electronic opportunities have greatly improved dissemination of clinical trial information. The Internet helps resource discovery and health information on the Internet is growing. In particular, clinical trial registries are publicly available but research shows that the content is limited and there is a need for an improvement in the design and presentation of information. There are many factors that affect dissemination of clinical trial information. There are many regulatory requirements as well as institutional policies for reporting on clinical trials. A growth in publication guidelines has improved the publication process of clinical trials but my research shows that there is a lack of awareness of these guidelines and many of them are not considered useful. Effectiveness of a dissemination method is based on the impact of research findings on the relevant target audience and research shows that there is a need to understand dissemination theory as well as the framework for how trust and distrust form when planning dissemination strategies. It is also clear that we need a new definition of 'publishing' to suit the new emerging electronic culture of sharing research. Chapter 6 will pull together the findings from Part 1 and Part 2 to make recommendations on how we can improve the dissemination of clinical trial information and present an optimal model of effective dissemination in order to make clinical research more transparent.

6. Chapter 6: Recommendations for how the dissemination of clinical trial information could be improved and more transparent

6.1. Introduction

In this chapter, the main findings are drawn together with reference to relevant literature and the findings in the studies for this PhD. The goal of the research was split into two parts: (1) to characterise and evaluate clinical trial information and the dissemination of that information by constructing a conceptual model structuring the processes of information generation and (2) to test the model constructed by identifying the dissemination methods used, consider their effectiveness and what factors affect dissemination.

This chapter responds to the final research question pulling together recommendations for how the dissemination process of clinical trial information can be improved and made more transparent. It is not an easy task to make recommendations which impacts on many aspects of communication, some which have existed for hundreds of years, others only a few years. It is difficult to predict the future. There are rapid changes within the information environment with many new opportunities that exist communicating via the Internet. Hybrid publishing models are emerging combining communication and publishing methods. Many improvements have already been made in making the research process more transparent, which is promising. But there is still a need to identify a framework which can go some way towards improving the dissemination of clinical trial information. Within the framework suggested here there is a model outlining the clinical research process and the need for planning communications throughout the process.

Three themes have been identified to outline the framework of recommendation: regulations and standards, communication planning and organisation of clinical trial information. The optimal model of effective dissemination will then be presented to outline the ideal methods used for disseminating clinical trial information. The model of the clinical research process will be re-introduced to include the optimal dissemination methods. The chapter ends with a suggested new definition for what it

means to publish, to incorporate the many new methods of disseminating information that were discovered during this research.

6.2. Framework for improving the dissemination of clinical trial information

The recommendations made in this chapter are aimed at the clinical research community, the organisations and authorities who are involved with clinical trials such as publishers, clinical trial register managers, intervention approval agencies and anyone else with an interest in clinical research process. The framework is intended to provide some guidance into building on existing improvements made to the communication and dissemination process, highlighting development areas that need attention.

The following areas have been highlighted throughout the research as potential improvements that can be made:

- Communication planning as part of the clinical trial process
- Legislation and harmonised regulation around the registration and dissemination of clinical trial information
- Increased dissemination online in structured formats using metadata to improve accessibility and additional links between related resources
- Clinical trial registers to become the key repositories of all clinical trial data and links to other relevant registers and published material in journals
- Data management role – custodian of clinical trial data and information
- Introduction of standards around clinical trial data
- Journals should adapt to the electronic era and work closely with clinical trial registers, linking to data and research protocols
- The role of the journal is to organise published peer-reviewed information and should concentrate on providing content that helps implementing research into practice
- A new definition of what it means to publish will include the different dissemination methods: informal communication, deposited data and information in registers and repositories, communication at scholarly conferences and in abstracts, websites and formal publication

- Scholarly publication is linked to the public good and transparency of research, not to career progression and funding.

These can be further broken down into three themes:

1. Legal requirement of reporting
2. Communication planning
3. Organisation of clinical trial information

These are idealistic recommendations to provide long-term guidance and steer the dissemination process of clinical trial information. These measures can improve the transparency of the clinical research process and information dissemination. If researchers are provided with improved guidelines around clinical trial information dissemination, tools that assist with the dissemination process and have support from authorities and publishers, it is a start towards making the clinical trial information available in a timely and accurate fashion. It will be possible to reduce pressure on researchers and therefore eliminate bias, fraud, mistakes and this will improve how the research process is viewed by the public and increase trust in research. Next, the recommendations in each theme will be discussed in detail.

6.3. Legal requirement of reporting

To improve public trust in clinical research, we must promote the access to information. Legal requirements should be harmonised and implemented globally. One global law on clinical trial reporting and dissemination would reduce fragmentation that is currently occurring. The ethical guidelines that exist to ensure safety in clinical trials should extend to include that it is a legal requirement to share all research data and make them publicly available. All tools and methods that are used for dissemination must be covered under this legal requirement, e.g. an application to conduct a clinical trial should be accompanied by a document certifying that the researcher will register the clinical trial and publicly make the results available and supply a publication plan.

Publishers' and authorities' guidelines on publication and disclosure should be standardised. There are currently many published publication and disclosure guidelines with some of them providing conflicting guidelines or expanded guidance

on a specific topic. The standardisation of these into one comprehensive publication guideline, protected by law, for clinical trials would reduce the confusion amongst researchers of which guideline should be followed.

Already in 1901, Sir Galton suggested that biomedical data should be stored and be accessible to those who wish to verify the work[424]. Currently in the EU, it is a legal requirement to register clinical trials on EudraCT but this register was set up as a closed database for competent authorities only and information within it remains confidential to authorities only. However, there has been agreement that some of these fields will be made publicly available soon. There is also no legislation, apart from in the US, on reporting clinical trial results within 24 months of trial end. The *NHS Constitution*[425] in England aims to improve access to research for the public and research summaries are published on the National Research Ethics Service (NRES) website[xxxii]. They will also be publishing a summary of ethical opinion on the NRES website in the future. There is no framework in place to control registration and posting of clinical trial results or for the long term preservation of clinical trial data. Eysenbach and Sa called for a code of conduct for publication of clinical trial data[426] but one has not emerged.

The ethical and legal issues surrounding sharing and publication of raw clinical trial data need to be worked out. It is not clear even to researchers themselves who owns their data[23]. By registering clinical trials, there is an opportunity to make this type of information transparent by asking who owns the data, funding information and to what extent can the data be reused and manipulated. Clinical trial registers are still not at this stage asking for intellectual property information. In some cases, researchers have argued that they cannot release data without risking the safety of their study subjects. Various groups have also argued that access to raw data is unnecessary as they are poorly defined and there are problems with consent for the release of clinical trial data. It is recognised that individual anonymity can be difficult to achieve completely[176] but that specific items in patient information can be removed when sharing information to go some way towards achieving anonymity.

[xxxii] http://www.nres.npsa.nhs.uk/researchsummaries/ [Accessed 17 February 2011]

The informed consent procedure should include seeking consent on the release of research data.

Data have been said to be more absolute than written conclusions and they can reused to answer other problems[427]. Currently the overall prevalence of sharing research data remains low[428]. Admirably, the Annals of Internal Medicine invented the 'reproducible research initiative' in 2007 which sets out minimum requirements for data sharing to allow reproduction of research[429]. The requirements were for the provision of the original protocol, datasets used for analysis and the computer code required for analysis. Authors can specify the extent to which they can or will share their data and conditions. This type of standard could be adopted by other journals.

Finally, the research community together with publishers and relevant authorities need to agree on standards for the sharing, publication and preservation of research data. These standards should be enforced by a legal framework on the requirement to register a clinical trial and publicly release all research results. The unique clinical trial registration number should be used to identify the clinical trial in publications, on registers and websites and inter-link resources. Funders should make sure that the researcher has followed requirements for trial registration and release of results. Data managers should be the guardians of the data, in data archives, and link the information between registers and other resources where the data are shared or published. They are also responsible for the long term preservation of the data.

Summary of recommendation:

- Ethics committees and medicines authorities to enforce inclusion of plans on the dissemination of data and publication planning in clinical trial application.
- The research community, authorities and publishers to agree on standards for sharing, publishing and preservation of clinical trial data.
- The data manager role to be formalised as custodians of data.
- Funders and data managers of clinical trial registers to monitor enforcement of data sharing.
- Journal editors and publishers to provide standards on the preparation of data and require clinical trial number to ensure that the trial was registered.

- Researchers to obtain consent from patients during recruitment on the publication and sharing of all data.
- Clinical trial registers to adapt their registers for inclusion of data or link to the repository where the data is archived and managed.
- Data archives to adopt data management procedures for long term preservation of data.

6.4. Communication planning

Kahn points out that knowledge transfer begins when a clinical trial is still under design[45], not after the publication of results. A clinical trial should be carefully planned and there is a need to provide information on how research can be translated into practice. There needs to be good quality clinical trial design to provide the necessary knowledge and answers on effectiveness of new therapy areas. Unfortunately there are few checks available to check quality of trial design, although the ethics committees will review trial design before approval of a trial. The conduct of trials should be to good clinical trial practice (GCP) standards and trials should also follow good manufacturing practice (GMP) guidelines. Trials are increasingly audited and inspected by authorities to ensure trials are run to these standards.

Published studies can take years to make it into practice and it is an unpredictable process[63;200], therefore a plan on how to rapidly communicate and disseminate information must be thought of early, even before the start of a clinical trial. In fact researchers should address publication and appropriate reporting guidelines at grant application stage[77] or at the design of a clinical trial[401]. However, it is recognised that planning communication early is costly and funders may not want to do this when results are not yet known[401]. It is important that planning should continue throughout the lifecycle of a medical intervention. The publication strategy and plan should be a part of the clinical trial application which is vetted by the authorities and ethics committees.

Wilkes[40] linear model of dissemination presented earlier (figure 2 p41-2) needs to be revised. Figure 18 is a proposal for a cycle of dissemination to replace the linear

model. This cycle could be used as a basis when embarking on communication planning.

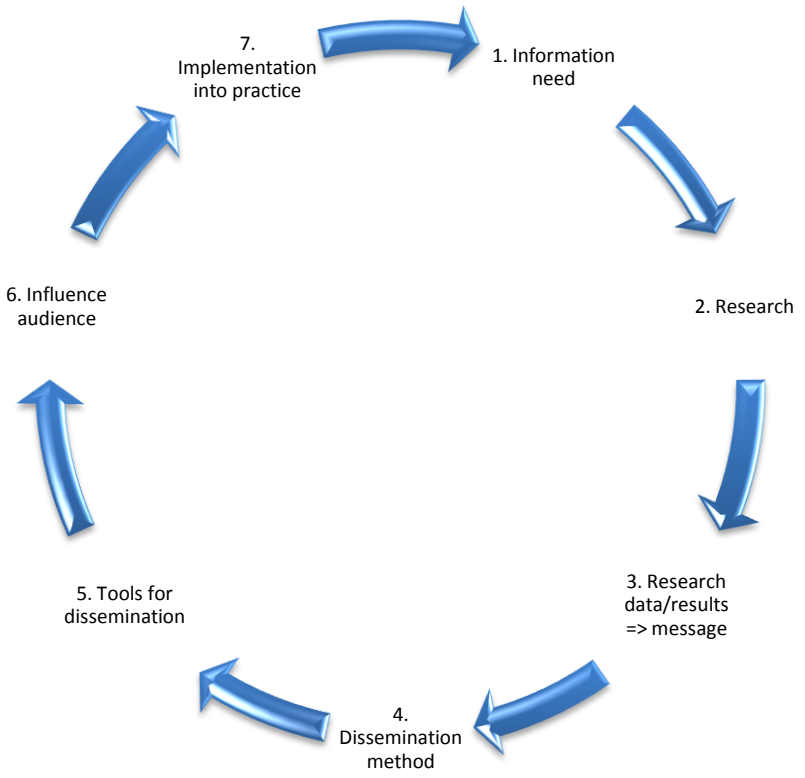

Figure 18: Proposed cycle of dissemination based on Wilkes' linear model of dissemination

Ideally within the research organisation, a team should be identified that has enough awareness of requirements of communication and appropriate tools and guidelines to aid the communication process. They should be supported with appropriate training and material to prepare a communication and dissemination strategy. This core team should be in place already at the pre-clinical stage and make plans for customised messages of timing and varying information that needs to go out depending on the audience.

A key objective in the plan should be to publicly share all research data collected in clinical trials[430]. The plan should not be promotional in nature as "science, not marketing, should guide us in writing scientific papers"[382].

As part of the strategy the team should decide on the appropriate methods used for disseminating clinical trial results and use appropriate theory to efficiently and

effectively disseminate research. There are some aspects that need to be considered during the planning to achieve effective dissemination and influence decision-making (discussed in section 1.60):

- Understand the factors that influence dissemination (Duggan & Banwell)
- Understand the framework of trust and distrust
- Consider the barriers to effective communication: cultural, socio-economic and environmental
- Implications of the research: who is it for, what are the implications, e.g. change in practice, the timing needed for disseminating
- The knowledge acquisition process and information literacy skills of those acquiring the information, consider how to influence practice
- Public interest of the public in the research process, make research as transparent as possible.

The communication strategy should also include interventions and education[35;401] of practitioners for implementation into practice. I know from findings in this thesis that health professionals do not get the information that they need at point of care. Research shows that opinion leaders, public health bodies and large professional bodies should be involved in dissemination activities as these organisations already communicate well with their peers and members.

Other research shows that academic detailing, patient messages, formulary/economic evidence and communication that appeals to clinicians are effective.

The team should also write and disseminate comprehensive press releases to the media scheduled closer to the publication of results[401]. The press releases should report on all datasets reported in the clinical trial register and not adopt a selection bias to exaggerate findings or leave out important risk factors. Ideally, the 20 recommended data sets[350] and all findings (negative or positive) should be reported in a non-promotional and non-sensationalist way.

Publication guidelines help clinical researchers plan their publications and dissemination efforts, and organisational policies provide direction. Informal

guidelines on ethical practices in conducting research together with regulations and legislation should be regularly updated and implemented globally to ensure transparency in research.

Well developed organisational publication strategy or organisational disclosure policies should guide the communication team in planning the dissemination process, and these guidelines should draw upon existing standards and legal requirements of reporting clinical trials.

Finally, each organisational policy or strategy should be publicly shared to improve the transparency of the research process.

Summary of recommendations:

- The communication and dissemination strategy and plan should be planned early in the clinical trial design and at least by funding application stage.
- The strategy should be a part of the clinical trial application process and checked by the authorities and research ethics committees.
- Dissemination planning should continue throughout the lifecycle of the medical intervention.
- A dedicated communications team should be set up at the pre-clinical stage within the research organisation who are responsible for the strategy.
- The team should be supported with training and materials to aid the process.
- The strategy should:
    i) Publicly share all data
    ii) Not be promotional in nature
    iii) Should include interventions and strategy for implementing research into practice
    iv) Involve professional bodies, public health bodies and opinion leaders to communicate the message(s)
    v) Use theory based dissemination strategies that are proven to work in audiences
    vi) Communicate with media in a non-sensationalist way providing all 20 key data sets as laid out in the clinical trial register

vii) Organisational policies on disclosure and publication should be publicly available and draw upon existing standards and legal requirements in reporting clinical research.

6.5. Organisation of clinical trial information

There are many challenges in the organisation of clinical trial data. Clinical trial information is scattered around different resources and sometimes does not exist at all because it has not been published or publicly shared in any way. There are ethical and legal issues surrounding sharing of raw data and information from clinical trials due to intellectual property, data protection. Only 31% of researchers responding to a survey are willing to disclose study protocol and financial agreements[431] and they are also reluctant to disclose all data items[431].

Regulations already exist for the clinical trial process, but these regulations need to be expanded. A legal framework addressing all legal issues and sharing of data in clinical trial registers together with guidelines and standards for communication and reporting would aid the dissemination process of clinical trial information and improve the quality of the data and information as well as the methods used for dissemination.

I have established that the Internet is a useful tool to communicate clinical trial information. This PhD has shown that the Internet is changing the way in which clinical trial information is made available through both formal and informal tools of communication.

This PhD has identified the most effective methods of disseminating clinical trial information which can exist electronically via repositories and the Internet. These methods are shown in Figure 19:

(1) Sharing data and information via clinical trial registers
(2) Providing sufficient information in structured abstracts (journal, conferences or on the web)
(3) Publishing succinct messages including how to implement information in practice through editorials, commentaries, systematic

reviews and case studies published in e-journals or similar online publications.

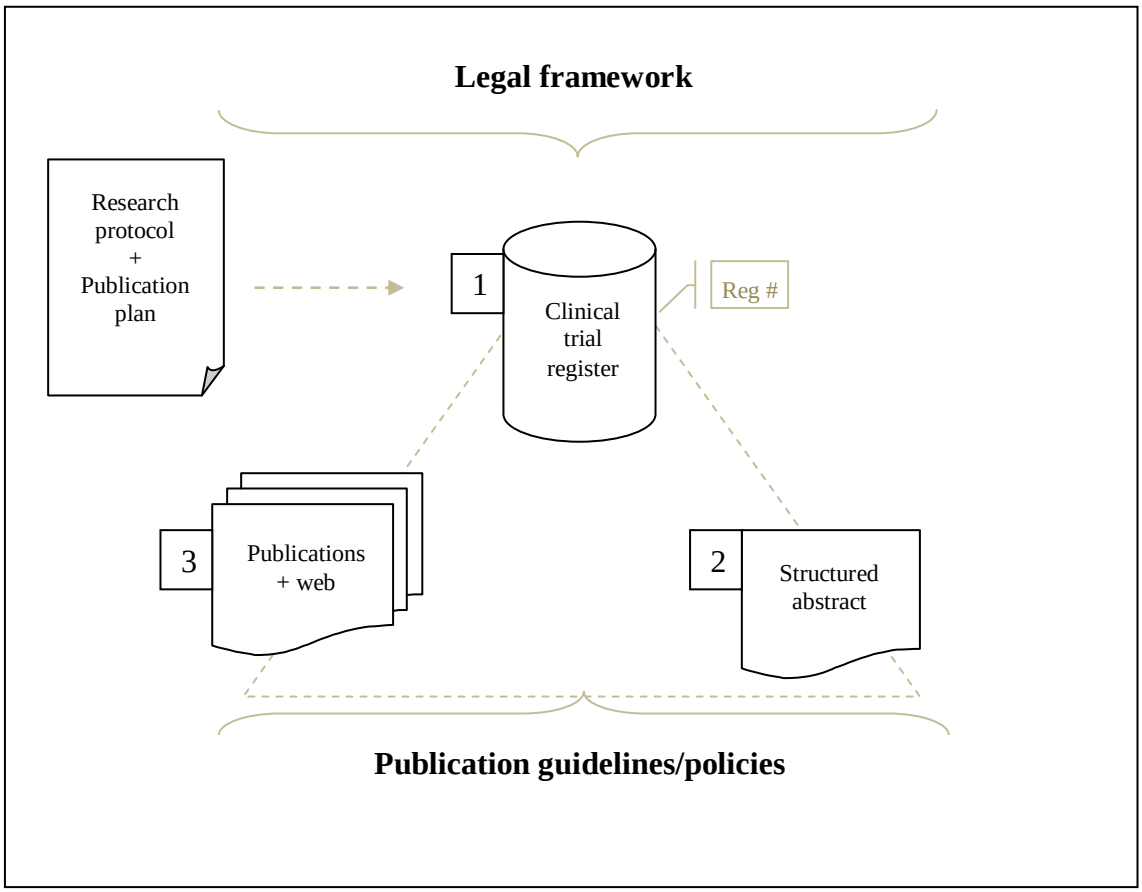

Figure 19: Effective methods of disseminating clinical trial information and inter-linking between resources using the unique clinical trial registration number as connector (Reg #)

All resources should be inter-linked and connected via the unique clinical trial registration number, which is provided at the first point of registration in the clinical trial register. This framework identifies a greater role for information professionals and data managers to facilitate dissemination by interlinking various information resources and appraising literature for validity and importance as well as teaching information literacy skills to those who require access. It also necessitates closer working relationships between information professionals, data managers, researchers, publishers, technical system developers and authorities.

6.6. The Internet – changing dissemination

There is evidence that the dissemination of clinical trial information in changing with the introduction of new types of online dissemination methods. The advancement of technology, and the Internet, impacts on the research landscape of scholarly publishing, policies of research and funding, dissemination of information and progress of science. The Internet allows for increased accessibility, visibility, interactivity and usability of research. The web also lends itself well to interlinking between resources, and linking in this way will improve navigation for the user between the different resources visited. The model of scholarly communication[46] will see an increase in communication through informal networks via electronic media and possibly less formal publication in journals as information is informally published on websites and in clinical trial registers.

The Internet is a very useful tool for resource discovery, albeit informal and formally published information exists side by side and quality concerns have been identified. The Internet makes it easy to be kept up-to-date, through real time access to information in various formats. Online opportunities reduce the lag-time between manuscript acceptance and publication. Publishing a clinical trial takes an average of 4-8 years after the end of a clinical trial and if publishing in print it can take a year from acceptance of manuscript to final print copy. Because of this time lapse, some formats of scholarly communications, such as biomedical information, are more effectively published in the electronic environment rather than print[52]. "Our future is on the web"[183], in particular as data and abstracts can be disseminated immediately online. Currently, clinical trial information on the web appears in many different formats. If research is not formally published, information provided via the web could be provided as technical reports and by providing abstracts, both written for a public and professional audience. The formats should be based on appropriate quality and content standards. New opportunities, as online formats of publication develop, will change the way in which researchers publish. Blogging, writing structured abstracts and organised websites may replace expensive peer-review journals offering no restrictions on format, length and style.

Health information professionals are deeply concerned with the quality and authority of health information found on the web[432]. It is surprising that standards for

assessing web quality and functionality have not yet emerged. Internet communication methods need management, funding, stewardship, structure, stable long-term storage and terminology for retrieval. Eysenbach suggested an open trial initiative to define syntax for publishing trials on the web and ensure interoperability between clinical trial registers and search engines to harvest information on clinical trials[120]. We therefore need to develop a standard terminology for clinical trial information on the web. If these issues were addressed it will improve the quality of information found on the Internet. However, we need standards and checklists in line with those developed for print publications and a recommendation would be to adapt the ICMJE publication guidelines and the WHO 20 data set recommendations into a standard for aiding those who publish clinical trial content online.

Summary of recommendations:

- The Internet is useful for rapid dissemination of clinical trial information, but standards for publishing on the web need to be developed
- Web based information needs to managed, funded and be stable long-term
- We need to develop appropriate terminology for clinical trial information on the web.

6.7. Clinical trial registers – a central system

We recognise that there is no centralised system in existence that brings together all clinical trial information. The advent of clinical trial registers has improved access to clinical trial information and is an attempt at standardising information. Adopting technology itself does not improve healthcare, but the exchange and use of health information to inform clinical decision making at the point of care does[433].

The challenges with registers are many including allocation of resources, the management of registers, the inclusion of standard elements within the register, updating and accuracy of information, completeness of records, intellectual property concerns, data protection and technical challenges. Registers need to be improved to provide accurate and comprehensive information and no doubt the future will see much development in this area led by the World Health Organization.

Clinical trial registers are clearly important in the storage and dissemination of clinical trial information, providing information about new, ongoing and closed

clinical trials. They can ultimately cover the gap between research and practice, linking research information, data and publications. The clinical trial registration number should be used to connect the content to the registered clinical trial in all material that is disseminated. Clinical trial registers are key components of knowledge transfer research allowing monitoring uptake of new evidence and identify barriers to implementation of research into practice. They can also be searched for information on adverse reactions and answer questions into the effectiveness of new research[45].

Clinical trial registration and the availability of datasets will provide some reassurance to the public that clinical trial information is being used for the benefit of all. Clinical trial registers will allow us to spot gaps in research and where funding and research is needed. Registers can aid systematic reviews of literature reducing bias in literature reviews, if all trials are registered, trials with negative results that are possibly not published will not skew a systematic review. The registration of clinical trials can also avoid duplication of research effort and effort can be spent on other studies building on existing registered studies, or answer research questions not already studied. According to JISC 88% of researchers share data even if only with collaborators and informal peer exchange network[434]. 43% of researchers say that they would like to access others' data[434].

The purpose of trial registration is to make sure all data bout a trial are available publicly. Once registered, researchers should regularly update their entries[435]. It will improve further if full details of study design and the clinical trial protocol were shared. Administration time will be cut down for ethics committees, data managers, researchers as all research information is centrally stored and managed by data managers. Comprehensive clinical trial registers aid information access for all, although existing registers are not sufficient to provide the public with information about ongoing trials[352]. At the moment the current lack of funding means that systems are poorly structured, they lack standards and there are no checks on data within the registries. There is a need to improve registers with harmonised standards, starting with the mandatory provision of the 20 recognised datasets, inclusion of trial design and protocol, checks in place to ensure compliance. There is also a need to develop a standard for the technical system set up and management of clinical trial

registers. Currently hundreds of registers exist globally with some overlap, different structure and functionality and little inter-linking between content. Clinicaltrials.gov has emerged as a leading register but after recent evaluation the system has been said to fail patients and clinicians at point of care[352]. It seems appropriate to suggest that the World Health Organization revisit its technical capacity recommendations for registers and set technical standard to enable cross-searching and inter- linking together for professionals and patients to find appropriate trials[352].

Funding of clinical trial registers together with independent management by a not-for-profit body, and the management of standards by the World Health Organization, would improve checks of content and therefore quality. Registries could be funded by a possible combination of pharmaceutical companies and the Government, although others recommend that clinical trial registers are independently managed for improved transparency and to avoid bias. It is also be a recommendation to introduce a formal directory of approved clinical trial registries (according to laid down standards), maintained by an appropriate authority.

During researching for this PhD, the WHO announced their involvement in setting standards and an introduction of the WHO International Clinical Trial Registry Platform (ICTRP)[105] as well as a directory of Registry Networks. The Registry Network currently links to a few clinical trial registries that meet the WHO standards. The WHO standards for registers were issued in April 2009[194]. The current WHO standards in trial registration consist of the requirement of 20 trial registration data sets (TRDS) to be reported[350] in registers, e.g. around the set up of the clinical trial. There is not yet any formal consensus on standards for clinical trial results reporting[226]. There are unfortunately no checks in place for monitoring data entered and no sanctions levied of failed or incomplete entries.

Transparency pressures from journal publishers[251] and legislation in Maine (USA)[235;436] on registration should improve access and quantity of data in registers, although it is unclear if this will be useful to patients and prescribing physicians [8]. Registers need to be up-to-date, easily and widely accessible for anyone. Journal editors should demand registration as a condition of publication and should demand publication of result[218].

Bian also recommends a global network committee with local effort for trial registration to ensure uniform, international consistency in policy and trial registration and therefore data transparency[435]. The data management profession needs to be developed to maintain the clinical trial registration process from clinical research to the archive of clinical trial data.

Only legislation will ensure researchers register their trials and disseminate information accurately and timely[435].

Summary of recommendations:

- Standards for clinical trial registers to be harmonised
- Registers to be connected
- A data management profession to manage registers who perform checks, ensure accuracy and protects the data long-term
- Funding to be in place for registers
- Legal requirement to register clinical trials and provide timely information
- Sanctions in place for non-compliance
- Trial registration numbers link between research registration and publications.

6.8. Abstracts – need to be comprehensive

Abstracts take many forms and are used for many purposes. They may convey information at conferences, for journals, in grey literature, on websites and used in press releases. We know that often only the abstract is read, even if a full paper has been published. The reasons for this are many: many presentations and abstracts from meetings remain unpublished[437], lack of time, no access to full paper, publication language and access to informal abstracts that appear on the web.

This PhD identified that abstracts often under-report clinical trials, not providing important information such as trial design, results, funding information or clinical trial registration number. The lack of this information make abstracts risky document for use at point of care and in systematic reviews. We need standards for abstracts covering the required elements in line with information that is provided in clinical

trial registers and the research questions in the clinical trial design. Abstracts should not be promotional in nature and provide guidance for practitioners. They should also provide sufficient information for patients who may print the abstract and bring to their physician for discussion. It could follow a similar format as a summary of product characteristics[xxxiii] (SmPC) leaflet.

The EQUATOR[438] network is working towards setting standards in reporting research and have made some recommendations for abstract formats. The CONSORT checklist[289] has been adopted by some journal publishers to guide authors in the construction of journal and conference abstracts by providing a minimum list of essential items when reporting the results from a randomized controlled trials. A recommendation in this PhD is that a standard similar to the CONSORT checklist should be developed and widely adopted to aid the drafting of any type of abstract for any clinical trial design.

In particular for media, press releases should provide the same information as abstracts with sufficient details about the clinical trial and not be promotional or selective. It should provide a link to information provided on clinical trial registers, publicly published study reports and key journal articles.

Summary of recommendations:

- Abstracts should not be promotional in nature
- Abstracts should provide sufficient information about clinical trial design and results as well as provide some guidance for practitioners
- A standard for abstracts should be developed to aid drafting abstracts for any type of clinical trial
- An abstract could look something like an SmPC
- The abstract should provide the clinical trial registration number.

[xxxiii] SmPCs are available once a medical intervention has been approved by the competent authorities.

6.9. The journal – effectiveness in dissemination

Journals have complex funding and business models that affect the way in which they disseminate information, via the web and in print format. New business models like the open access model, aim to provide information rapidly at no cost to the user. The format of the journal article has changed very little but journal articles are getting longer and readers' times are getting shorter. The journal has aimed to bridge the gap between clinical research and practice but it is difficult to establish their effectiveness in the dissemination information and it has been claimed that they do not change practice[49] and that the existing journal model therefore is not effective[49]. Time to publication is long, and the peer review process cause delay and introduce further bias. Journal articles lack information on how to implement the research into practice. Not all print journals are fully indexed on search engines and articles are difficult to find. Improved organisation, abstracting (see previous section) and indexing, using metadata, of articles will ensure that papers can be found even if not published in top journals.

The motives of journal publishers, editors and authors are for a good academic reputation and the primary objective is commercial success. Publishers identify the quality of journals by articles that have higher citation rates and high impact factors, higher circulation and low acceptance rates[69]. The actual primary function of the journal is to describe and interpret data and it needs to do this for a varied audience. The journal article is usually of a standard length, a one size fits all, with little flexibility in providing a large amount of information, data or graphics to illustrate content. Journals are selective in their publication of articles, due to editorial policy but also lack of space or specialism. In order to improve transparency of research, journals should publish all research[201] or at least summaries of research that are aids to interpreting results. Journals should not publish papers that seem to be selectively reporting results and they should not allow sponsored supplements that promote products[218]. If possible, the journal business model should attempt to separate product promotion from reporting of clinical trials.

It is the role of the journal to ensure quality of the research it is publishing. It does this through three means: 1) instructions to authors 2) peer review and 3) editorial processes[77]. Authors' guidelines have improved over the last few years to include

requirements for trial registration, and requiring transparency in authorship and funding such as stated in the GPP and ICMJE guidelines. However, ideally authors' guidelines could be standardised to avoid author confusion and wasted effort in rewriting content in line with guidelines. The guidelines should also be in line with current legal and ethical requirements. Peer review has been questioned as a tool for assessing accuracy and for approval for publication, but it is the best system we currently have and needs to remain in place until a viable alternative is invented. Open peer review was tested by Nature and abandoned due to lack of uptake from readers. Journal publishers need to invest more time in the editorial process and developing the peer review process to ensure transparency and fairness. Currently peer reviewers are unpaid, untrained and sometimes inappropriately used, e.g. reviewing information from competitors or do not have the adequate skills to review certain content. We rely on peer-review of published information to be screening content and data to ensure accuracy, reliability and journal editors to check the quality of peer reviewers and other editors used by journals. Some checklists exist to aid authors in writing papers, such as CONSORT[143] which asks the author to discuss trial design and methods used. It is a lot to ask a peer reviewer to accurately be able to comment on statistical analysis of trial results, design of trial, what is reported and how. Journals should not rush to publish manuscripts that have not been through quality testing, as this may cause chaos and sensationalism[439]. They must also insist on checking source data.

The impact factor system does not determine quality of scientific research[379]. The removal of impact factors can remove the pressure on researchers to publish in high impact factor journals. Many organisations are moving away from the impact factor requirement to an expectation that research is published and made publicly available within six months of publication.

It has been suggested that organisational repositories of information can replace journals as they organise information and data better. If repositories are peer reviewed and indexed using better terminology, they can replace the scholarly journal[52]. However, the era of repositories is not here yet and the journal is still a primary method to disseminate clinical trial information.

There is room for both the journal article (summary) and a true object (eg research findings, technical report) to exist alongside one another. By publishing all trials we save time and effort, protect patients who were in those trials and future patients who may rely on those results and will reduce potential bias in systematic reviews allowing all studies to be taken into account. The journal still has an important role to play in reporting clinical trial results but an improved journal model is recommended. If publishers modified their focus, they can concentrate on publishing pre-appraised evidence summaries and clinical bottom-lines. The journal should publish abbreviated findings or abstracts from large robust clinical trials, systematic reviews and clinical bottom lines. They should highlight implementation of new findings, repeat findings in the editorial and allow for opinion in commentaries. They should encourage the publication of case reports. They can publish full articles online and provide translations into other languages. Journal summaries could be linking to clinical trial registers for access to research data, the study protocol and further information about the clinical trials. The summaries should provide information on cost-effectiveness, side-effects and barriers to implementation. These summaries could be disseminated within practices with no copyright needed for dissemination. Journals should link to information elsewhere and therefore reduce the scatter of information[49].

Summary of recommendations:

- The role of the journal remains strong in publishing clinical trial information
- The journal model could change to publish summaries of clinical trial information and to stimulate discussion around clinical trials
- The journal should publish non-promotional articles and supplements
- The journal should not reject publication of negative result studies
- The journal should use its online presence to expand and provide extra value content, e.g. translations, systematic reviews, longer articles, commentaries etc.
- Peer review remains an important aspect of assessing quality of content, but editorial control and checklists (e.g. CONSORT) need to support the peer review system

- The impact factor system does not contribute to quality, an alternative is recommended
- Journals should extensively link to clinical trial information content elsewhere, e.g. clinical trial registers, websites, related articles etc.

6.10. An optimal method and a model of effective dissemination of clinical trial information

The PhD shows that we can improve the dissemination process for clinical trials to make the clinical research process more transparent and information publicly accessible. Ideally we want to disseminate clinical trial information as widely as possible in a timely and efficient manner. Access to research information accelerates sciences, innovation and discovery[440] as well as improves the public trust in clinical research and science.

Based on the findings in this PhD and recommendations in this chapter, the model of the clinical trial process can now be updated to show how we can ensure the effective dissemination of clinical trial information (figure 20 and appendix F for a larger model).

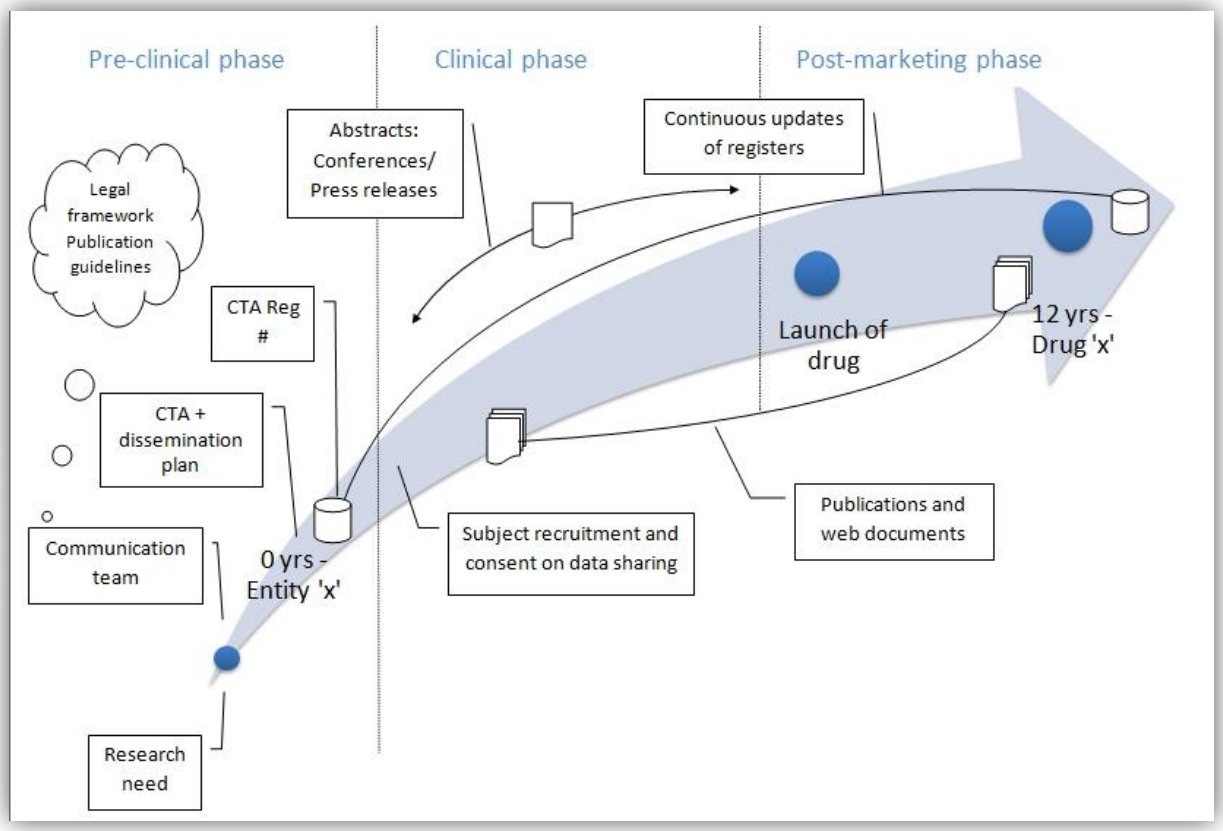

Figure 20: Model of effective dissemination of clinical trial information

Three themes were identified to outline the framework of recommendations for improving dissemination: regulations and standards, communication planning and organisation of clinical trial information. The European Clinical Trial directive has been said to not harmonise European clinical research but has left research fragmented[218]. The existing legal directives also do not adequately support the communication of research findings. We need regulation and standards around the reporting, communication and publication of research. We also need to plan communication earlier on in clinical research. And finally we need to organise clinical trial information appropriately, by sharing and publishing research data and summaries.

6.11. Model walk-through

Pre-clinical phase

A research organisation has identified an information need, a research need. A promising compound may respond to research questions x and y. Even before

clinical trials take place, the compound is undergoing pre-clinical tests. Already at this point a pre-defined communication team who has the relevant training and support through publication guidelines and existing public disclosure policies will draft the dissemination plan.

This plan forms a part of the Clinical Trial Application (CTA). Once the CTA has approval, the phase I clinical trial will be publicly registered in a clinical trial register and obtain a registration number (Reg #).

Clinical phase

Subject recruitment can begin and during the informed consent process, permission will be sought from study subjects for the disclosure and sharing of clinical trial data. During the clinical phase, several clinical trials are likely to take place each with individual research protocols. Data will be analysed, the clinical trial register updated at each trial end, abstracts drafted for conferences, websites and press releases and publications will begin to emerge.

Post-marketing phase

Once the drug has launched, we are in the post-marketing phase during which some other studies may take place. Clinical trial registers should continuously be updated and trials marked ended with the sharing of all data, citations for published research and links to other publicly available quality information on the web.

Within this framework, three optimal methods for organising and disseminating clinical trial information were identified: clinical trial registers, abstracts and publications (journals or web based content). These three methods require responsible management, funding and support to become unbiased and make science transparent.

6.12. Definition for what it means to publish

A research objective for this thesis was to provide a recommended definition of what it means to publish. Research has highlighted that there is a need to define what constitutes publication on the web[44;51]. Without a definition; the quality, integrity and authentication of electronic scientific information will be difficult to determine[44]. We

lack a definition of what it means to publish in view of the changes in publishing and communication opportunities that have arisen with online tools and dissemination via the Internet. Frankel refers to "definitive publication" in the electronic environment, and in order to be definitive the material must be publicly available, peer-reviewed, available within a system allowing long-term access and preservation, material should not be removed, must be identified (ideally with a DOI), have bibliographic metadata, and the relevant communities must be made aware of its existence[44]. Halliday wrote that the electronic environment suits some forms of scholarly communication better and information can be hyperlinked in an integrated transparent network[52]. Online material greatly improves linking directly to other research, e.g. citations[49]. To some extent institutional repositories are addressing these issues and according to the European Commission, the research funding agencies must lead the way in determining researchers' publishing practices [71]. Online archives, preservation standards and repositories ensure the preservation of scientific information[441].

The developments in the electronic environment have created opportunities for new forms of dissemination and are changing the way in which dissemination is done as well as changing how information is accessed. We have not gone into detail about *access* in this thesis, but it is important to stress that the way in which the public and health professionals access information is increasingly becoming similar[113;442].

It is important to take into consideration new developments in dissemination. Traditional dissemination methods as we have seen involved talking informally to colleagues followed by presentations at conferences followed by a final published article. New dissemination methods are more about involving the recipient of the information by targeting information and evidence to a specific audience, e.g. evidence to get a medicine into a formulary or providing updated news about the medicine via a newsletter. Dissemination of information must be planned early on[401].

I propose a definition inspired by those who have made a point of what it means to publish [44;57].

To publish is a recognised work, contributing to knowledge and searching for the truth via a method of dissemination which acts as a record of science.
The publication allows peers to critique and repeat the scientific research activity to complete the scholarly research cycle. Therefore to publish can be in a print, verbal (in the form of presentation, podcast or recording) or electronic format.
The publication should allow for long-term access, be preserved and its existence communicated to peers.

6.13. Conclusion to Chapter 6

This chapter responded to the research question on whether the dissemination of clinical trial information can be improved and make the research process more transparent. Three themes were identified to outline the framework of recommendations: regulations and standards, communication planning and organisation of clinical trial information. The research shows that we can improve and harmonise the dissemination process for clinical trials and make the clinical research process more transparent. By the adoption of these recommendations we can save research time and effort, improve the evidence-base, improve future research, reduce pressure on researchers which leads to improved transparency and public trust in clinical research. Duplication of research will end and research will accelerate. When the entire research process and high quality information output is publicly accessible and transparent the public good will be served. This will lead to a transparent research culture which will ultimately improve public health.

7. Chapter 7: Conclusion to the research

7.1. Introduction

This chapter presents the summary of the research that has taken place for this thesis. Reflections on the research undertaken will be discussed first followed by a discussion around the limitations of the research. A summary of the major findings will be provided with a reflection on current developments in the communication of clinical trials and how this study contributes overall. The chapter ends with presenting suggestions for further research.

7.2. Reflections on the research process and methodology

Clinical research is a regulation heavy environment and information about clinical trials is abundant and very complex. Dissemination activities take many forms and there is a lack of organisation of information, which is scattered across many resources. At the same time developments on the web has made dissemination or publication on the web easier and also made the public expectant to find more information on the web. These rapid developments and opportunities are fascinating and it is clear that regulations, policies and guidelines within clinical research are not up to scratch with telling researchers how to disseminate their research. It was challenging to determine how best to research these issues and monitor developments over a period of 4 years for this study. There were also temptations to get drawn into related issues of dissemination, in particular fraud and misconduct in research as well as economic and political issues such as managing clinical trials in developing countries or in specific disease areas that are either high or not so high on the research agenda but where there is great public need for research.

The literature review was cumbersome, even if interesting. A lot has been published on some of the topics, e.g. opinion pieces on the current regulations of clinical trials, sharing research data, clinical trial registries and the future of the journal. It was difficult however to find published information around clinical trial information and the process of clinical research, an area which has yet to be developed. Many of the resources drawn from for this research come from non-peer reviewed sources, e.g. magazines, the web and reports, not always good quality research. It was difficult to find evidence when a lot of resources consulted are full of opinions of authors.

The literature review was ongoing throughout the research process in particular when following new developments, e.g. clinical trial registration and legislation surrounding clinical trials. There could never be a real 'cut-off' point for running searches for new information, however the final overall check for new relevant references was done in November 2010. A few more recent references have been included as I came across them in early 2011.

In order to find data to establish an evidence-base this research needed to break down the research into many smaller studies. This was time-consuming as each research study had to be considered for its value as a contributor to this study. Most of the studies are snapshots in time providing data and information around issues discussed in this research as many of them were under development, e.g. clinical trial registries, publication guidelines and developments on the web making publishing on the web easier.

The thesis followed a mixed method research approach and used qualitative and quantitative techniques to examine the dissemination of clinical trial information. The study was broken down into segments of smaller studies to draw together a comprehensive picture of how clinical research takes place and the information that is generated throughout the process of clinical research. Collecting data and information through different methods provided this study with a broader understanding of the complexities of clinical trial information, dissemination and factors affecting dissemination. The research findings allowed me to propose a framework for improving the dissemination of clinical trial information to make the clinical research process more transparent.

Six central research questions that were posed and examined in this study:

1. What is clinical trial information?
2. What do we mean by dissemination?
3. What methods are used to disseminate information?
4. Why is a particular method chosen and what factors affect information dissemination?
5. What is effective dissemination?

6. Can we improve the dissemination of clinical trial information and make the process more transparent?

The two-part research aim became: firstly, to characterise and evaluate clinical trial information and the dissemination of that information by constructing a conceptual model structuring the processes of information generation. Secondly, to test the model constructed by identifying the dissemination methods used, consider their effectiveness and what factors affect dissemination.

By exploring the answers to these research questions, this thesis has revealed the status of clinical trial information dissemination by modelling the information that is generated in clinical trials, it analysed the methods used and factors that affect dissemination, it has proposed a framework of recommendations for improving the dissemination of clinical trial information and therefore also making research more transparent.

7.3. Limitations of the research

Some of the limitations were discussed in Chapter 3 where each study's research methodology is described. Briefly summarised here:

Survey of clinical research professionals:

- The use of web-based surveys may miss out on respondents reducing potential sample.
- The use of ambiguous terminology where terms are not used consistently throughout the clinical research community.
- Complexity of survey asking many questions around many issues. May have benefited from a briefer survey followed by face-to-face interviews.

Most of the studies are snapshots of a moment in time, during a period of rapid developments in clinical research during a five year period:

- The clinical trial registries saw a rapid increase in registrations.
- The WHO got involved in setting standards for trial registration.
- New publication guidelines, ethical guidelines and clinical research legislation released.

Rise of web 2.0 or interactivity via the web:

- During the five year research the Internet became increasingly popular for self-publication through social tools, e.g. blogs etc.
- The public are increasingly turning to the Internet to find information about health.
- Regardless of this sudden development, little research has been done around the dissemination of information on the web, although this will probably change in the next few years.

Clinical trial registries – quality of content and functionality:

- The research on registers was conducted at a time when the WHO had not yet announced their involvement in writing standards. Registers were built and disappeared rapidly during a short period of time. However, registers that exist today are still facing similar issues, e.g. standards, technical difficulty etc.

Lack of evidence:

- Many resources used for the literature review were not peer-reviewed and many papers contain personal comments, sometimes very negative, towards publishing and the pharmaceutical industry. It is difficult to determine the evidence for some of these comments.
- There is a lack of evidence in many areas discussed in this thesis. Where possible my research was compared to existing research, e.g. study of functionality and quality of content on clinical trial registries were compared with similar studies looking at cancer information on the Internet and knowledge of clinical trial registration in the survey were compared to similar findings in published survey[443] that took place after the survey presented in this thesis.

Some other limitations were described in Scope (Chapter 1). These were mainly around the need to keep the research focussed on the main aim and not get drawn into relevant, but too detailed, areas:

- Research fraud and misconduct
- Economic and political issues such as managing clinical trials in developing countries or in specific disease areas
- Information literacy skills
- Dissemination or complications of information dissemination, e.g. the digital divide between developing and developed countries
- Legal issues, e.g. copyright and intellectual property
- The scholarly communication process as a whole.

7.4. Summary of recommendations

This study has demonstrated the following 8 findings:

- Clinical trial information is complex sets of information that is generated throughout the clinical research process.
- Although there are some legal requirements of reporting from clinical trials to the authorities, there should be further legalities surrounding the sharing of data and make results publicly available.
- The communication of clinical trial information must be planned early on even before the start of a clinical trial. The communication plan should be to publicly share all research data collected in clinical trials which should not be promotional in nature.
- The most effective methods in disseminating clinical trial information are electronic, these methods are 1) clinical trial registries 2) structured abstracts in journals and on the web 3) publication of succinct message on how to implement research in practice in publications (not necessarily journals).
- Peer review remains an important aspect of assessing quality, but should be accompanied by checklists and editorial control.
- The impact factor system is not helpful in the publication of clinical trials
- All publication methods should interlink to related resources online.
- The definition of what it means to publish needs to change and this includes updating the scholarly communication cycle.

7.5. Reflections on the recommendations

I stated in the introduction of Chapter 6 that it is not an easy to task to make recommendations. The clinical research industry is a major industry with big players such as governments, pharmaceutical companies, research organisations, charities and stakeholders who all have their own personal interest in their work or investment. It is also difficult to predict the future and events that may have an effect on the industry. Within the information environment there are also rapid changes, the Internet is growing and changing providing new opportunities for individuals to express themselves.

The framework that was provided in Chapter 6 was based on the research conducted in this thesis and not dissimilar to some concerns expressed by other experts in the field or issues that have been identified elsewhere. They are not radical but even a small change may impact on the existing routine in clinical research, creating more bureaucracy, taking up more valuable research time, but making research more transparent and improving public access to information.

In order to 'check' the feasibility of my recommendations, they were circulated to a group of 'experts' for comments. These comments proved valuable and give the research some clout. Since writing the last few drafts of this thesis, more transparency efforts are being made in clinical research, some which are very similar to some of my recommendations provided. This is encouraging and satisfying, making the findings in this research significant and providing realistic opportunities for making research more transparent.

7.6. Reflections on current developments in the dissemination of clinical trial information

As stated above, whilst working on this thesis a number developments took place which improved aspects of clinical research and also confirmed findings of my research.

- A paper[443] was published on clinical trial registration which concluded that trialists require further information before making decisions with regards to voluntary trial registrations. A key finding in my survey was that clinical

research professionals have some knowledge but are not always confident when it comes to clinical trial registration. Another paper in 2008 reporting on survey results on public disclosure clinical trial registration identified that public disclosure of funding and the study protocol were issues[431].

- In late 2010 a handbook on clinical trials communication[444] was published discussing the need for planning and writing strategies for communicating clinical trials globally. This is in line with my findings that communicating needs to begin early on in a clinical trial. It also covers the issue of releasing clinical research results.
- Early in the research it was established that there are too many clinical trial registers, the quality of the content is poor, and the scatter of information is large across many resources. The WHO announced in 2007[105] the need to set standards for registers and inter-link registers to make it easier to search for the public.
- New legislation in the US (FDAA) on mandatory trial registration[445] and a paper published on the necessary legislation on trial registration in 2010[435].
- The Declaration of Helsinki was updated with recommendations for trial registration in 2008[360].
- A book was published covering issues around clinical trial registries in 2006[94], showing the need for in-depth information around the issues.
- Published evaluations of clinical trial registers' functionality and content, more recently one paper on clinicaltrials.gov and its failures (these studies are reviewed in Chapter 5).
- The rise of organisations and more meetings around communication of clinical trials, e.g. Equator[73], GPP[240] and several medical writers' associations.
- After finalising the recommendations of the proposed cycle of dissemination above, a paper[35] was discovered presenting thirty-three diagrams modelling different aspects of the scientific communication process. Jarvelin's IDEF0 based diagrams, in particular diagram AO, breaking down the life-cycle of research, and A3, on communicating the results of research, closely resemble my cycle of dissemination and the framework of effective dissemination. The

models presented strongly confirm the need for models to outline research processes.

7.7. Further research recommendation

Since research is a process, it attempts to answer some questions as well as generate new questions.

A suggestion for continuing this research would be to perform further in-depth analyses of aspects of clinical research and information management in order to establish the most consistently effective methods of dissemination for clinical trial information:

- The communication planning in clinical research and specifically what happens to information from research.
- In a meta-ethnographic approach investigate the dissemination of clinical trial information in a specific disease area or perhaps situation, e.g. a crisis.
- The development of a review tool for checking quality on websites that publish clinical trial information.
- The organisation of clinical trial information, e.g. quality and content of clinical trial registers and information found on the Internet.
- Informatics systems and standards that can be helpful in the development of repositories for clinical trial information.
- The opportunities and possibilities of making research results publicly available, e.g. new forms of publishing.

7.8. Conclusion

This chapter has summarised the research undertaken, reflections on the research process, limitations to the research, contributions to the evidence-base and provided further research recommendations.

7.9. Cited material

The British Medical Journal citation style was used for referencing this thesis. These references are cited, sometimes multiple times, throughout the chapters. A full alphabetised bibliography is available in appendix J.

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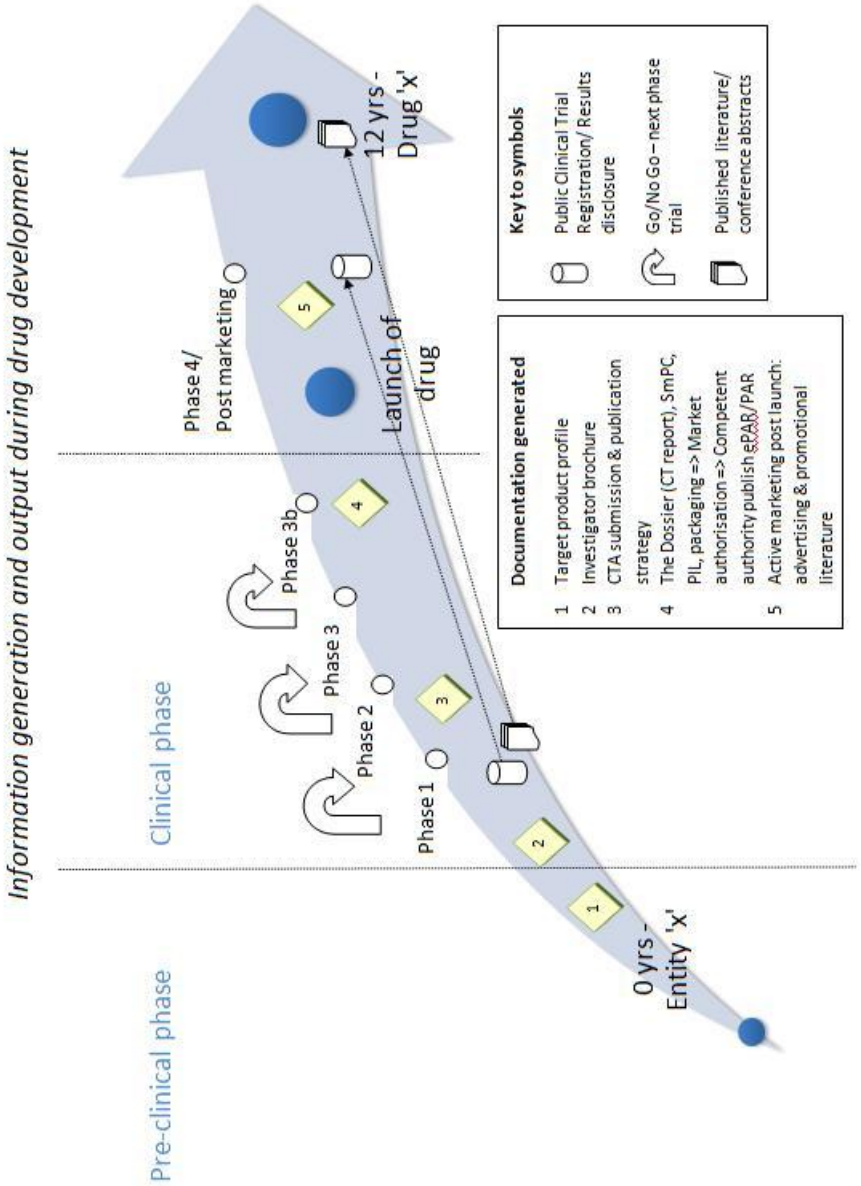
Appendix A: Constructing a model of information generation and dissemination for a new intervention undergoing clinical research



Appendix B Feature and functionality range of clinical trial registries (Part 1 & 2)

Part 1

	Features			Display of fields	
	y = available n=Not available				
CTR	*Basic search tool*	*Advanced search tool*	*Registration*	*Search fields*	*Results display*
ClinicalTrials.gov	y	y	n	Search terms Recruitment Study type Condition Intervention Sponsor Study id Location Age Phase Funding Date registered or updated Study by topic Studies on map Display full text view, tab view, contact locations, related studies	Recruitment and study status given Title Condition Intervention Outcome measures Eligibility Contacts More information Identification number
IFPMA register	y	n	y	Terms to search for (pop up box) Terms to exclude Location	Indication Trial id Trial description
ISRCTN*	y	n	n	Search box Results order Direction Maximum results Display as print friendly	ISRCTN id Sponsor Public title Scientific title Acronym Ethics approval Study hypothesis Study design Country of recruitment Disease Eligibility Status and dates Outcome measures Funding Website Contact details Edit date
MRCT*	y	n	n	Search box Results order Direction Maximum results	Source of record (CTR) +as above

Part 2

	Features			Display of fields	
	y = available n=Not available				
CTR	*Basic search tool*	*Advanced search tool*	*Registration*	*Search fields*	*Results display*
UKCTR*	y	n	n	Search box Results order Direction Maximum results Tick CTR to search	as above
Pharmaceutical Industry Clinical Trial Database	y	n	n	Keyword Or View all records	Company Serial number Brand name Generic name Trial title Objective Therapeutic area Indication Phase Design Source Participating countries Comparators Interventions Patient groups Primary endpoint Sample Status Date Duration Publication status Publication name Contact email
UKCRN Portfolio	y	y	n	Topic Title Chief Investigator ISRCTN UKCRN Study Id Research summary Or Topic search with subtopics list	Title Id number Topic Funding Study type Design Disease Phase Status Sample size Geography Eligibility Investigator name Contact details Sponsor
WHO ICTRP	y	y	n	Title Intervention Condition CTR Recruitment status Primary sponsor Secondary id Countries of recruitment Date registered	21 datasets of the WHO
Centerwatch	y	n	y	Keyword Disease/condition Trial location Or list by disease topic	Written in narrative, no decided data sets. Aimed at recruiting.
MedTrials	n	n	n	Only a list of current trials	Gives narrative Aimed at recruiting.
Clinical Connection	y	n	n	Keyword Zip Distance	City State zip Study summary Eligibility Reward Location Contact number Online form to submit

**within Current Controlled Trials*

Appendix C: Comparison of the WHO TRDS and data fields and review of content provided within clinical trial registers

URL	ClinicalTrials.gov	IFPMA	Controlled Trials	CMRInteract	UKCRN	WHO ICTRP	CenterWatch
# recruiting trials on diabetes & obesity in the UK	4						
WHO minimal dataset*							
Primary Register and Trial ID #	√	14	28 (but doesn't specify open, closed)	101 but doesn't let you specify open closed etc.	34 (diabetes type II)	5	0 for the UK
Date of Registration in Primary Register	√						1 for US obesity+diabetes
Secondary ID#s	√	√	√	x	√	√	
Source(s) of Monetary or Material Support	√	√	x	x	x	√	
Primary Sponsor	√	√	x	x	√	√	
Secondary Sponsor(s)	x	√	√	x	√	x	
Contact for Public Queries	√	√	√	√	√	√	
Contact for Scientific Queries	x	x	√	x	x	x	
Public Title	√	√	√	√	√	√ (not complete information)	
Scientific Title	√	x	√	x	x	x	
Countries of Recruitment	x	√	√	x	x	√	
Health Condition(s) or Problem(s) Studied	√	√	x	√	√	√	
Intervention(s)	√	x	√	√ (regions)	√	√	
Key Inclusion and Exclusion Criteria	√	√	√	√ (not very clear)	√	√	
Study Type	√	√	√	√ (sometimes given)	√	√	
		√	√	x	x	√	
		√	√	√	√	√	
Date of First Enrollment	√	√	√	x	√	√	
Target Sample Size	√	√	√	√	√	√	
Recruitment Status	√	√	√	x	√	√	
Primary Outcome(s)	√	√	√	√	√	√	
Key Secondary Outcomes	√	√	√	x	x	√	
Total data sets provided	18	18	17	9	14	17	

Appendix D Publication guidelines

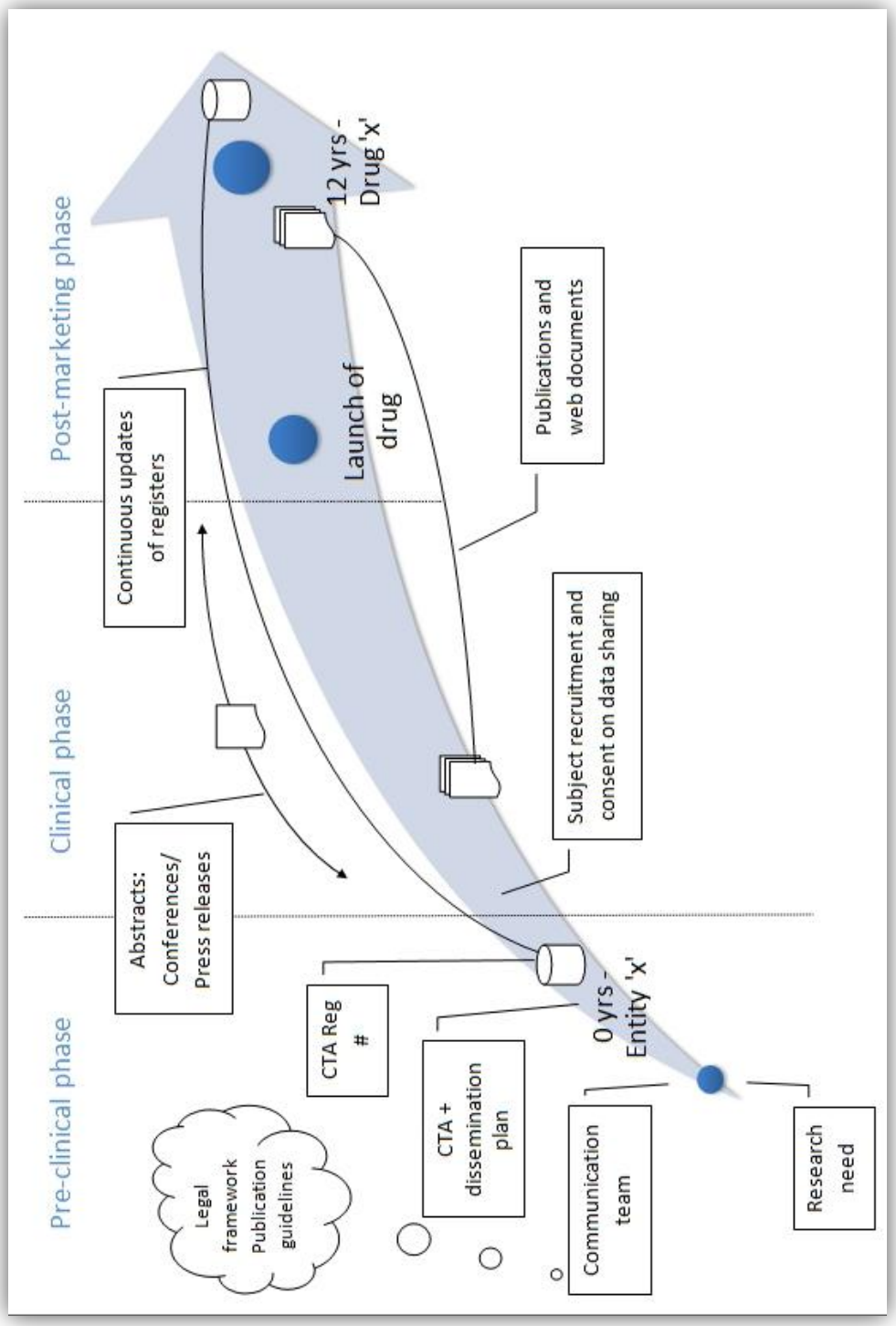
ICMJE Uniform Requirements for registering trials prior to publishing and disclosure (worldwide) 1979	Produced by the International Committee of Medical Journal Editors (ICMJE) to aid editors and authors create accurate and easily accessible reports of biomedical studies. Covers ethical principles of medical manuscripts and the technical aspects of preparing and submitting scripts. First published in 1979 it has undergone revision many times.
ICH E3 (worldwide) 1995	The objective of this guideline is to allow the compilation of a single core clinical study report acceptable to all regulatory authorities of the ICH regions. The guideline is intended to assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy to review. Although it doesn't provide guidelines on how to publish a paper, it has often been quoted as providing the right guidelines for how the content should contain in a publication.
CONSORT statement (worldwide) 1996	The Consort statement is an evidence-based, minimum set of recommendations for reporting RCTs. It offers checklist for authors to prepare reports of trial findings, facilitating complete and transparent reporting, and aiding their critical appraisal and interpretation.
GPP Good Publication Practice for Pharmaceutical Companies (worldwide) 2000	Written in 2000 and circulated to pharmaceutical companies for consultation. The guidelines were designed to increase transparency of processes involved in the publication of industry-sponsored trials and to establish standards. The guidelines apply to publications arising from industry-funded clinical studies of marketed products. In September 2008 Blackwell Wiley announced that the GPP guidelines should undergo review and are seeking collaborators.
PhRMA Principles: disclose trial results of all hypothesis-testing trials (USA) 2004	The Pharmaceutical Research and Manufacturers of American (PhRMA) represent research-based pharmaceutical companies and biotechnology companies. Drafted and adopted these principles to set out its relationship with individuals and other entities involved with the clinical research process. Disclosure of clinical trial results is one chapter out of four principles. These principles were revised June 2004.
IFPMA (International Federation of Pharmaceutical Manufacturers Association) Joint position statement:	January 2005 a joint position statement was signed between the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical

registering and disclosing clinical trials and their results (worldwide) 2005	Industry Association (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA) and PhRMA. They agreed on principles regarding the disclosure of information relating to clinical trials that they sponsor. Covers clinical trial registration and the disclosure of trial results, implementation dates and a compliance statement. They encouraged companies to make public how they will adhere to the signed standards. 2005 and 2006 saw pharmaceutical companies issue their own guidelines or policies with regards to the registration of trials and disclosure.
EMWA publication guidelines (EU) 2005	To define ethical standards for professional medical writers who prepare papers for publication in medical journals. The guidelines provide support for recognised authorship criteria and lay out the professional responsibilities of medical writers to ensure that the papers they write are scientifically valid and are written in accordance with accepted ethical standards.
WAME publication guidelines (worldwide) 2005	A comprehensive policy on publication ethics:; including description of authorship, peer review, editorial decision, originality, scientific misconduct etc. A basis for journal editors to draft their own policies, the document makes recommendations on the best solutions to address ethical problems.
COPE (worldwide) 1999	The guidelines address: study design and ethical approval, data analysis, authorship, conflict of interests, the peer review process, redundant publication, plagiarism, duties of editors, media relations, advertising, and how to deal with misconduct.
Council of Science Editors White Paper on Promoting Integrity in Scientific Journal Publications (worldwide) 2006	The policy was created as a resource as an aid for all editors who are establishing and benchmarking their journals' policies and procedures. It covers roles and responsibilities of all parties involved in publishing and scientific misconduct.
AMWA Code of Ethics (USA) 1994	These principles take into account the important role of biomedical communicators in writing, editing, and developing materials in various media and the potential of the products of their efforts to inform, educate, and influence audiences.

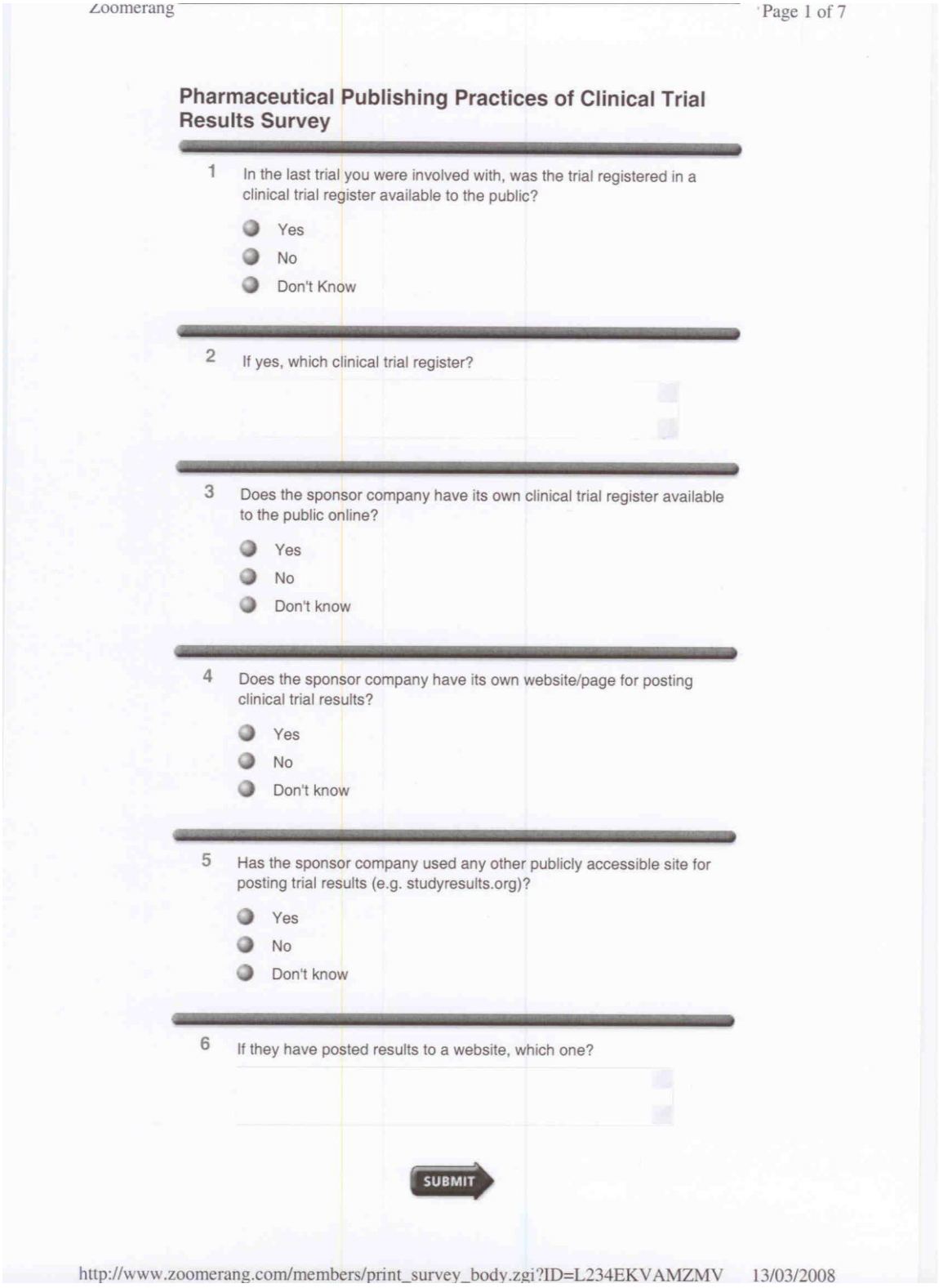
Appendix E: Comparing pharmaceutical disclosure policies against ICMJE Uniform Requirements headings for quality of content

Coverage	Pfizer	GSK	Novartis	Astra-Zeneca	Merck KgaA	Eli Lilly	Roche	Amgen
Using external contractors for drafting publication	2	0	0	2	2	0	0	0
Conflict of interest	0	0	0	2	0	0	0	0
Obligation to communicate negative results	2	2	1	0	0	2	2	2
Obligation to register clinical trials Phase II-IV	2	0	2	2	0	2	2	2
Preparing manuscript for publishing	0	2	0	2	0	0	0	0
Registration of Phase I studies	1	0	0	0	0	0	1	1
Commitment to communication of results	2	2	2	2	2	2	2	2
Acknowledges official guidelines	2	2	2	2	2	2	0	2
Posting results on a public database	1	0	2	2	0	2	2	2
Admits commercial sensitivity	2	0	0	0	0	0	1	0
Identifies database where registering trials	2	0	2	0	0	2	2	2
Gives timeline when results will be released	2	0	2	0	0	2	2	2
Discusses interim or preliminary results	0	1	0	0	0	0	0	0
Talks about publication of results	2	2	2	2	2	1	2	2
Internal review of abstracts/scripts	2	2	0	0	2	0	0	0
Discusses delayed publication	2	0	0	0	2	0	2	0
Sharing of protocol with journal editors	2	0	0	2	0	0	0	0
Authorship of publications	2	2	2	2	2	0	0	0
Peer review	0	2	0	0	0	0	0	0
Communicating outside peer-review journal	0	1	0	0	0	0	2	2
Total	28	18	17	20	14	15	20	19

Appendix F: Model for effective clinical trial information dissemination (also Figure 20)



APPENDIX G: SURVEY QUESTIONNAIRE OF CLINICAL RESEARCH PROFESSIONALS



Pharmaceutical Publishing Practices of Clinical Trial Results Survey

1 In the last trial you were involved with, was the trial registered in a clinical trial register available to the public?

- Yes
- No
- Don't Know

2 If yes, which clinical trial register?

3 Does the sponsor company have its own clinical trial register available to the public online?

- Yes
- No
- Don't know

4 Does the sponsor company have its own website/page for posting clinical trial results?

- Yes
- No
- Don't know

5 Has the sponsor company used any other publicly accessible site for posting trial results (e.g. studyresults.org)?

- Yes
- No
- Don't know

6 If they have posted results to a website, which one?

SUBMIT

Survey Page 1

Pharmaceutical Publishing Practices of Clinical Trial Results Survey

7 What do you agree or disagree with the most when it comes to releasing research results early (e.g. an abstract at a conference or electronic summaries on your website)?

	1 Strongly disagree	2 Disagree a litte	3 Agree	4 Strongly agree
Competitors will use the results to their own advantage	1	2	3	4
Releasing results early is a positive development	1	2	3	4
Traditional print journals disseminate trial results too slowly	1	2	3	4
Published results by themselves are meaningless without analysis	1	2	3	4
Some results can be released early, such as drug safety	1	2	3	4
Results may be misinterpreted by readers	1	2	3	4
The media will publish the results which is good advertising	1	2	3	4
I don't agree with releasing results prior to publication in peer-reviewed journal	1	2	3	4

8 In the last trial you were involved with, were research results released early and if so, how?

- On our website
- Via a conference presentation
- By poster at a conference
- We did not release results early
- Don't know
- Other method:

9 In a recent trial showing unfavourable results, did you still disseminate the results in any way?

- Yes, in a peer reviewed journal
- Yes, informally on our website

- No
- Don't know
- Comment:

10 If you answered no to the previous question, why not? (Select as many as apply.)

- No need to publish unfavourable results
- Not company policy to publish if trial shows unfavourable results
- Unfavourable results may harm our reputation
- The journal we submitted the article to, refused to publish it
- Other, please specify

SUBMIT

Pharmaceutical Publishing Practices of Clinical Trial Results Survey

11 What methods of publishing have you used when disseminating results of a recent trial? (Select as many as apply.)

- One of the top five medical journals (BMJ, NEJM, Lancet, JAMA, Annals of Internal Medicine)
- Other peer reviewed journal not part of the top 5 (e.g. Br J of Cardiology)
- Open access journal(e.g. BioMed Central journal, PLOS Medicine)
- Repository (institutional or academic)
- Website (own – company or product)
- Website (external)
- Press release
- Standard letter sent out to physicians
- Conference proceeding – abstract/poster
- Conference proceeding – presentation
- Blog/wiki
- Newspapers/magazines (eg not peer reviewed)
- Promotional material (such as a Detail Aid)
- Advertising

- Online discussion groups
- Reprints of journal articles
- Meetings/conferences (sales/medical) stand/exhibition
- Other, please specify

12 If you didn't select open access journal, why was this not chosen as a method to publish clinical trial results? (Tick as many as apply.)

- No suitable journal (content or reputation, etc.)
- Not the same impact as a paper or electronic subscription journal
- No opportunity to advertise in journal
- Not company policy
- Concerned about lack of copyright protection
- Not had opportunity
- Page/author charges are too expensive
- Don't know enough about Open Access to publish
- Other, please specify

13 Are you aware of the following guidelines? And if so, which ones do you use in the preparation of publishing an article?

	1 Not aware of it	2 Aware of it but haven't used it	3 Have used it
The ICMJE 'Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication'	1	2	3
The 'Good Publication Practice for Pharmaceutical Companies' guidelines	1	2	3
The 'CONSORT' statement	1	2	3
WAME (World Association of Medical Editors) guidelines	1	2	3
The COPE guidelines	1	2	3
The CSE (Council of Science Editors) guidelines	1	2	3
PhRMA 'Principles on Conduct of clinical trials and communication of clinical trial results'	1	2	3
EMWA guidelines on the role of medical writers			

1 2 3

AMWA Code of Ethics

1 2 3

14 If you have used a guideline in the previous question, rate its usefulness

	1 Not useful	2 Reasonably useful	3 Useful	4 Very useful	N/A
The ICMJE 'Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication'	1	2	3	4	
The 'Good Publication Practice for Pharmaceutical Companies' guidelines	1	2	3	4	
The 'CONSORT' statement	1	2	3	4	
WAME (World Association of Medical Editors) guidelines	1	2	3	4	
The COPE guidelines	1	2	3	4	
The CSE (Council of Science Editors) guidelines	1	2	3	4	
PhRMA 'Principles on Conduct of clinical trials and communication of clinical trial results'	1	2	3	4	
EMWA guidelines on the role of medical writers	1	2	3	4	
AMWA Code of Ethics	1	2	3	4	

15 Does your organisation have a publication policy?

- Yes
- No
- Don't know

SUBMIT

Survey Page 3

Pharmaceutical Publishing Practices of Clinical Trial Results Survey

16 Is this survey relevant to your work (e.g.do you work with publishing

clinical trial results)?

YES NO

17 Rate your understanding of current practices of registering clinical trials and publishing the results.

Not at all confident	Mildly confident	Reasonably confident	Highly confident
1	2	3	4

18 In which part of the world do you do your main work?

- North America
- South America
- EU
- Rest of Europe (non-EU)
- Middle East/Western Asia
- Africa
- South Asia
- South East Asia/Far East
- Australia/New Zealand

19 In the past 12 months, which of these roles have you acted in? (Select as many as apply.)

- Author
- Medical writer
- Referee (peer review)
- Editor
- Member of the editorial board of a journal
- None of the above

20 What type of organisation do you work for?

- CRO
- Medical communications agency
- Pharmaceutical company
- Freelance
- Other, please specify

21 What is your main job function?

- Medical writer
- Medic
- Product Manager
- Other, please specify

SUBMIT

Survey Page 4

Pharmaceutical Publishing Practices of Clinical Trial Results Survey

SUBMIT

Survey Page 5

APPENDIX H: POSTER PRESENTED AT CONFERENCE OF THE INSTITUTE OF CLINICAL RESEARCH MARCH 2008

Perception and practice of publishing clinical trial results: the PPP survey of those involved in clinical trials

By Helena Korjonen, BSc (Hons.), MA, MCLIP
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Doctoral research student at UCL School of Library, Archives and Information Studies (SLAIS) (www.ucl.ac.uk/slais)

Aim

The aim of the survey was to examine current perception (understanding) and practice (reality) of registering clinical trials using clinical trial registers (CTRs), and the dissemination of the results of trials using different methods and timings.

Introduction

Regulations and guidelines surrounding the clinical trial industry rapidly change and it's difficult for individuals to keep up to date. New recommendations of trial registration and the publication of trial results have been made by authorities, governments and professional bodies around the world to improve the transparency of the industry involved in conducting research. Little previous research has been done on the practice of trial registration and dissemination of trial results.

Methodology

468 respondents (n=159 partial responses and n=309 complete responses) completed an online survey of 21 questions between 20 August and 7 October 2007. The survey was distributed via email, announced in journals and linked from a variety of websites, and open to those involved in clinical trials. Respondents were working in a variety of job roles and spread across different affiliations. The majority of responses were from the EU (n=269). SPSS software was used to analyse the survey data.

Results

A selection of key findings[1] are presented in this poster.

Registration of clinical trials and results of trials released (Q1, Q3, Q4, Q6)

This figure shows a comparison between sponsors' own and other publicly available CTRs for registering trials and releasing results.

Column 1 shows that sponsors use both their own n=102 (22%) and other publicly available n=222 (47.5%) CTRs for registering trials. In the case of registering trials, the sponsor uses other publicly available CTRs more than own.

Column 2 shows that sponsors use their own n=148 (32%) and other publicly available n=49 (10%) CTRs for releasing results. In the case of releasing results, the sponsor uses own available CTRs more than other publicly available.

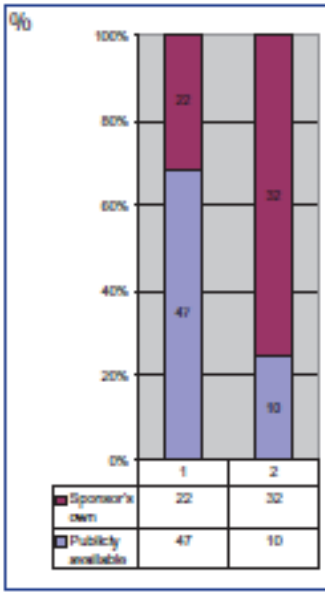


Figure 1: Comparison of the use of sponsors' own vs publicly available CTRs for registering and releasing results (Q1, Q3, Q4, Q6)

1: A summary of the main findings is available as a handout.

Understanding of current practice in registering clinical trials and publishing results (Q17)

The confidence in respondents' understanding of registering clinical trials and publishing results varies: n=97 (31%) not at all confident, n=104 (34%) mildly confident, n=94 (30%) reasonably confident and n=14 (5%) highly confident.

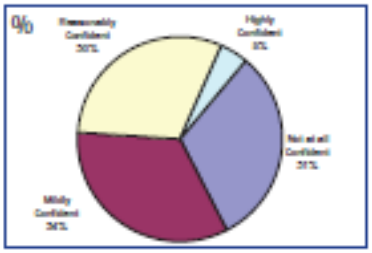


Figure 2: Understanding of current practice (Q17)

Awareness of available publication/author guidelines and if so, which ones do you use in the preparation of publishing (Q13)

This figure conveys that very few of available guidelines are known to the respondents. The guidelines that are known the most and have been used are; the ICMJE Uniform statement guidelines n=60 (19%), Good Publication Practice (GPP) guidelines n=50 (16%), The CONSORT statement n=47 (15%).

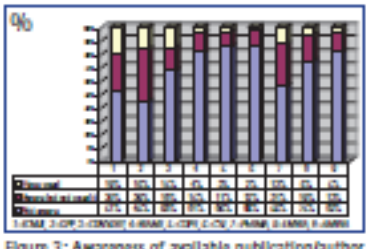


Figure 3: Awareness of available publication/author guidelines (Q13)

Methods of publishing and dissemination in a recent trial (select as many as apply) (Q11)

The top five most common methods used when wanting to release research results are: other peer reviewed journal (not the top 5 medical journals) n=177, conference proceeding abstract/poster n=172, conference proceeding presentation n=149, press release n=139, one of the top five medical journals n=139.

The use of electronic dissemination methods still feature low on the list; website (company or product) n=115, open access journal n=45, other external websites n=43, online discussion groups n=9 and blogs/wikis n=1.

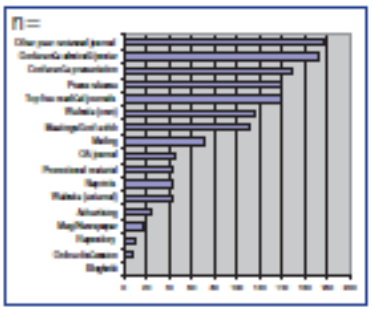


Figure 4: Methods of publishing and other forms of dissemination used in a recent trial (Q11)

Conclusion

The survey results show scope for an information resource to be developed from which individuals working with clinical trials can obtain information on requirements for trial registration and publication of results. The potential exists for authorities and other organisations to collaborate in providing such support. It also suggests that more research should be done on the practicalities and current awareness of trial registration and dissemination of trial results for those who actively manage roles within these areas.

Clinical Researchers: Examination in Progress

Helena Korjonen of the National Heart Forum looks at current practice in registering and publishing clinical trials

The average cost of researching and developing a new chemical or biological entity stood at €1,059 million in 2007, and the expenditure for R&D in Europe was estimated at €26,000 million in the same year (1). There are around 107,000 individuals working in pharmaceutical R&D in the EU, and the pharmaceutical industry funds thousands more researchers in the university and healthcare centres (1).

Law, regulations and guidelines surrounding the clinical trial industry rapidly change, and it is difficult for individuals to keep up with these and whom they affect. Countries have different legal requirements with regards to public registration of clinical trials and different levels of public disclosure of information.

Over the past few years, progress has been made in the public registration of clinical trials, in particular with the push by the International Committee of Medical Journal Editors (ICMJE), stating that trials must be registered if the sponsor intends to publish the results in one of their peer-reviewed biomedical journals (2). In 2000, Clinicaltrials.gov was set up, and is managed by the US National Institutes of Health and the National Library of Medicine. It has emerged as one of the leading CTRs, together with clinicalstudyresults.org, for disclosing results. From 1st May 2004, in line with the new EU Clinical Trial Directive 2001/20/EC (3), sponsors in the EU must, by law, register trials on the European Union Drug Regulatory Authorities Clinical Database (EudraCT) before recruitment of subjects for a trial begins. EudraCT is managed by the European Medicines Evaluation Agency (EMEA), and is only accessible by the competent authorities and the EMEA, although pressures for public access continue.

Finding trial information can be confusing as there is a vast number of registers available, both CTRs managed independently and those managed by sponsors themselves. Controversy surrounding the issue of what data should be provided at the time of registration also exists, and in particular the reluctance of sponsors in providing what they define as confidential or sensitive trial information for fear of losing commercial advantage (4,5). Following advice from PhRMA in June 2004 (6), pharmaceutical companies started setting up their own CTRs, meaning that trial information has become dispersed across many sites and the type of information given varies from site to site, including duplication occurring across many CTRs (7,8).

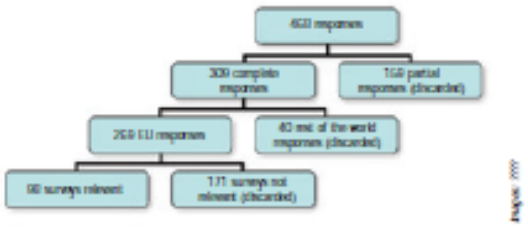
PhRMA made recommendations to its members to disclose study results within 12 months of study completion (9), and this has become law in the state of Maine, US (10). In October 2007, the ICMJE updated its statement to include the disclosure of results, allowing abstracts to be released prior to the final results being published (11).

In May 2007, the WHO announced their International Clinical Trial Registration Platform (ICTRP) for searching across a network of CTRs, thus reducing the need to search single registers separately (12). They have undoubtedly taken charge of setting the standard for CTRs for the future. At present, there is no standard format for trial registers or results databases, which means that some CTRs also display results and citations to published papers.

OBJECTIVES, OUTCOME AND SAMPLE SIZE

The aim of the survey was to examine current perceptions and practices of registering clinical trials using CTRs, and the dissemination of the results of trials using different methods.

Figure 1: Flowchart of responses to survey (n=)



The target audience was clinical research professionals involved in managing clinical trials, such as clinical research associates, administrators and project managers. The main research objective was to find out whether they feel confident in their understanding of trial registration and the dissemination of results. Although the sample was small (n=98) (see Figure 1), the results give an indication of individuals' understanding of clinical trial registration and publication of results.

MATERIALS AND METHODS

Methods and Filters

Ethical approval for this survey was sought, but not required, from University College London. The survey was deployed using Zoomerang on the web. The internet gives the opportunity to conduct surveys more efficiently and effectively than traditional print methods. However, using only a web-based survey does create risks, in particular the self-selection of respondents, which may result in a sample that does not represent the targeted population and we must assume that not everyone has access to a computer or the web which could reduce the potential sample (13,14).

Relevant professional bodies were asked to distribute information about the survey via email, their website and through their newsletter or magazine. These were: Pharmaceutical Information & Pharmacovigilance Association (PIPA) (15), European Medical Writer's Association (EMWA) (16) and The Institute of Clinical Research (ICR) (17). Non-members were also able to access the survey via links on the internet. The survey software recognised IP addresses for those completing the survey, barring an IP address from entering the survey again once submitted.

In total, these organisations had a potential 7,113 members exposed to the survey (EMWA 860 members, PIPA 727 members and ICR 5526 members). The survey was announced in ICR's 'CRfocus', in EMWA's 'Write Stuff', and in PIPA's 'Pipeline'. The survey was launched on 20th August 2007 and closed 7th October 2007. The survey had 938 visits, with a total of 468 responses which consisted of 159 partial responses and 309 complete responses. Incomplete responses from individuals who abandoned the survey were eliminated. Responses from outside the EU were also filtered out in order to analyse EU opinion. Another filter asked individuals to declare if they work with publishing clinical trial results and only those who responded 'yes' to this question were retained for analysis. Ninety-eight responses were from the EU and therefore eligible for analysis (see Figure 1 for responses and filters).

RESULTS

Demographic Data

Out of 98 responses, 63 per cent (n=61) were from industry (see Table 1). (When 'industry' is stated, this is a term encompassing pharmaceutical companies, contract research organisations (CROs) or device companies.) Thirty-nine per cent (n=37) of respondents were clinical research managers or directors, although a wide variety of roles were represented (see Table 2). Finally, 69.4 per cent (n=68) respondents have acted as authors or medical writers in the past 12 months.

Table 1: List of respondents' affiliations

	n=
Medical communications agency	1
Charity/university	9
Freelance/consultant	12
National health service	9
Industry	61
Other	6
Total	**98**

Table 2: List of respondents' job functions

	n=
Medical writer	11
Medic/scientist/researcher	11
Product manager	1
CRA*/project manager	16
CR**/clinical manager/director	37
Statistician/data manager	2
Regulatory/quality	2
Nurse/pharmacist	2
Admin/support role	4
Operations/process	3
Other	9
Total	**98**

* Clinical research associate
**Clinical research

Confidence in Clinical Trial Registration and Publishing Results

Respondents were asked to rate their understanding of current practices of registering clinical trials and publishing the results. Only 6 per cent (n=6) of respondents rated themselves as highly confident, but 47 per cent (n=46) were reasonably confident and 38 per cent (n=37) were mildly confident (see Figure 2, page 96). Nine per cent (n=9) stated that they were not at all confident. The least confident respondents worked in the national health service.

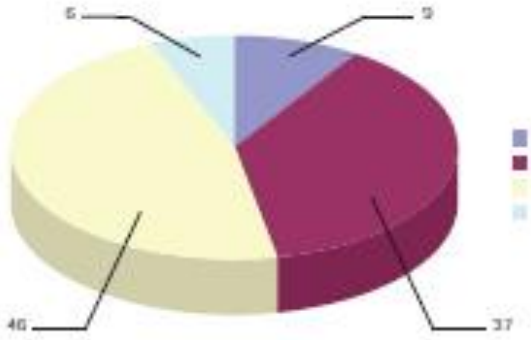
Publication Policies

Seventy-two and a half per cent (n=71) of respondents said that their organisation had a publication policy, leaving 17.5 per cent (n=17) that did not have a policy and 10 per cent (n=10) that did not know. Seventy per cent (n=7/10) of those who did not know if they had a publication policy worked in industry.

Registration in a CTR

When asked about the last trial they were involved in, 60.2 per cent (n=59) stated that it was registered in a CTR, and 15.3 per cent (n=15) stated that they did not know, leaving 24.5 per cent (n=24) that said that the trial was not registered. Clinicaltrials.gov was the most used CTR by 71 per cent (n=69)

Figure 2: Confidence of current practice in clinical trial registration and publishing of results



of respondents (23). While 60.2 per cent (n=59) of respondents said that the sponsor did not have its own CTR available to the public online, 22.45 per cent (n=22) stated that they did.

Dissemination of Results

Fifty-six per cent (n=55) of respondents said that the sponsor did not have its own website for posting clinical trial results; 30.6 per cent (n=30) of respondents stated that they had their own website; 45.9 per cent (n=45) of respondents said that the sponsor did not use any publicly accessible site for posting trial results; and 38.8 per cent (n=38) did not know. Only 13.3 per cent (n=13) of respondents provided a response to which website was used to post clinical trial results to. Clinicalstudyresults.org was mentioned by 3.1 per cent (n=3) of respondents (24).

Releasing Research Results Early

There are many definitions of what is meant by releasing research results early: results that are released before the end of a study (for example at a conference or as interim results), before a trial is published, or perhaps because a trial is closed down early for whatever reason. In the last trial that respondents were involved with, 31.6 per cent (n=31) of respondents said that they released research results early by a poster at a conference and 31.6 per cent (n= 31) said that they did not release results early (see Figure 3).

Respondents were able to agree or disagree to statements with regards to release research results early: 21.4 per cent (n=21) strongly disagreed with 'I don't agree with releasing results prior to publication in a peer-reviewed journal' and 31.6 per cent (n=31) strongly agreed with 'Published results by themselves are meaningless without analysis'. 48 per cent (n=47) disagreed and 52 per cent (n=51) agreed with the statement that 'Releasing research results early is a positive development'.

Figure 3: Methods in which research results were released early

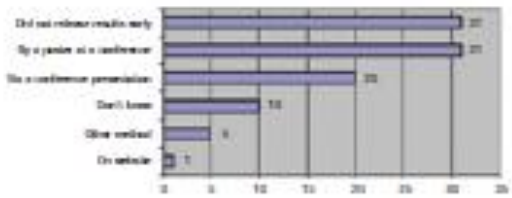
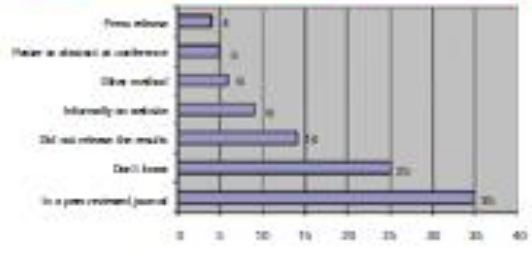


Figure 4: Dissemination of unfavourable results



Releasing Unfavourable Results

Unfavourable results refer to those which did not meet the expected positive outcome. In a recent trial showing unfavourable results, 35.7 per cent (n=35) respondents said that they published the results in a peer-reviewed journal (see Figure 4). Five per cent (n=16) of respondents who said that they did not release unfavourable results said that the main reason for this was that it was not company policy to publish unfavourable results.

Methods of Publishing used when Disseminating Results

The main method used to disseminate research results by 81.6 per cent (n=80) of respondents was to publish them in a peer-reviewed journal. This was followed by 74.5 per cent (n=73) who present results through conference abstracts or posters. Then, 62.2 per cent (n=61) disseminate through conference presentations, 45.9 per cent (n=45) published in top medical journals, and 42.8 per cent (n=42) of respondents used their own websites for dissemination (see Table 3). Only 19.4 per cent (n=19) respondents chose open access (OA) journals, and when prompted 'why not?', 21.4 per cent (n=21) responded that it was not considered to have the same impact as a paper or electronic subscription journal and 28.6 per cent (n=28) respondents said that they did not know enough about open access journals to choose this method.

Awareness of Publication Guidelines

The awareness of publication guidelines varied amongst respondents: 76.5 per cent (n=75) of respondents scored the ICMJE guidelines with the highest awareness. The guidelines that respondents have used and find useful are seen in Figure 5.

DISCUSSION

There are many arguments for why research results should be disclosed. The Declaration of Helsinki (18), which underpins medical research, states that the results (including negative results) should be published and made available publicly. The ICH GCP guidelines which remain the main

Table 3: Methods of publishing used for dissemination of results

	No.
Blog/wiki	1
Online discussion groups	2
Repository	5
Newspapers/magazines	6
Advertising	9
Website (external)	13
Reprints of journal articles	18
Open access journal	19
Promotional material	19
Standard letter sent out to physicians	25
Meetings/conferences exhibitions	40
Press release	41
Website (own)	42
One of the top medical journals	45
Conference presentation	61
Conference abstract/poster	73
Other peer reviewed journal	80

guidelines for the ethical conduct of clinical trials, state that organisations must have a publication policy in place (19). Revealing results so that other researchers are aware of studies that have taken place also ensures that there is not unnecessary duplication of research, and that data can be shared. The under-reporting of trials is a form of scientific misconduct (20). Also, evidence-based decision-making can become biased due to the lack of available results from trials which have a bearing on treatment decision.

The results indicate that respondents are not aware of the sponsors' actions with regards to trial registration, or that the sponsor does not follow current guidelines with regard to trial registration. As previously mentioned, Clinicaltrials.gov (21) was the most commonly used CTR for trial registration. The ISRCTN (22) CTR followed.

Two concerns arose from analysis. The first is that the results indicate that many of the respondents were not aware of the sponsors' actions with regard to the dissemination of results. The second concern is that the sponsors are not disseminating results using CTRs or other publicly accessible sites for posting trial results (such as studyresults.org). However, it seems that sponsors are using their own websites to disseminate trial results. This is confirmed by a statement by PhRMA recommending that pharmaceutical companies disclose their results (9) and a number of global pharmaceutical propriety CTRs exist for example GSK Clinical Study Register (23) and Eli Lilly and Company Clinical Trial Register (24). There was an indication that the sponsor had policies on various processes such as publication policies, releasing research results early and the release of unfavourable results, but some respondents were unaware of such policies.

The results show that the respondents are not clear about the current available publication guidelines on the preparation of publishing. Few guidelines had actually been used by respondents, but these included the ICMJE (25) Uniform Requirements, Good Publication Practice for Pharmaceutical Companies (26) guidelines and the CONSORT statement (27). These three guidelines were also rated as the most 'useful' to 'very useful'. It is possible that the respondents who were not aware of any guidelines, rarely get involved in writing publications.

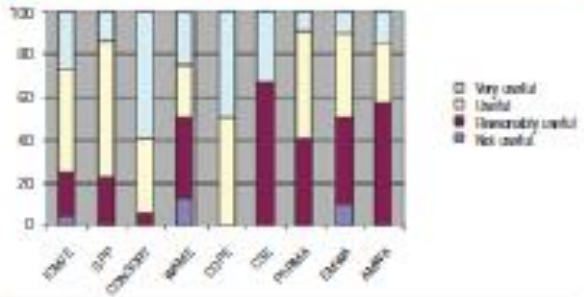
Respondents were asked to select methods used to disseminate the results of a trial. The peer-reviewed journal remains at the top of the list of methods used for releasing the final results, even though there has been discussion about the role of the peer-reviewed journal not being the right vehicle for releasing results (28) and it is known that not all results will be published in a peer-reviewed journal (29). Surprisingly, electronic methods were still featured low on the list for methods used by respondents. During the time of this survey, the ICMJE has set guidelines with regard to the publication of results, such as encouraging abstracts to be submitted to conferences or a website (112), which may change the way in which results are disseminated.

There were a number of limitations to this study, which hopefully future studies will overcome. This was an English language web-based survey, which may have caused a coverage and language bias. An additional problem may have been that a number of respondents did not have knowledge of certain aspects of clinical trial registration and publishing results to be able to answer all the questions.

CONCLUSION

This survey provided an insight into the personal understanding of current guidelines and regulations of trial registration of those working in clinical research, but more studies are needed. Although these individuals are highly or reasonably confident in

Figure 5: Publication and author guidelines used and their usefulness as a percentage



Acronyms and web addresses

ICMJE	Uniform Requirements for Manuscripts Submitted to Biomedical Journals	www.icmje.org
GPP	Good Publication Practice for Pharmaceutical Companies	www.gpp-guidelines.org
CONSORT	Consolidated Standards of Reporting Trials statement	www.consort-statement.org
WAME	World Association of Medical Editors	www.wame.org
COPE	Committee on Publication Ethics	www.publicationethics.org.uk
CSE	Council of Science Editor guidelines	www.councilscienceeditors.org
PhRMA	The Pharmaceutical Research and Manufacturers of America	www.phrma.org
EMWA	European Medical Writers Association guidelines	www.emwa.org
AMWA	American Medical Writers Association guidelines	www.amwa.org

the current practices of clinical trial registration, there is still a small number that do not feel confident, and these individuals tend to work mainly in the health service. The role of the WHO, the ICMJE and many others in setting standards and guidelines in trial registration and public disclosure of results is encouraging and will improve clinical trial reporting.

Acknowledgments

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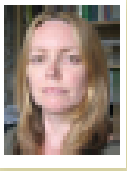
About the author



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