The Implementation of a Digitally-enabled Care Pathway for the Recognition and Management of Acute Kidney Injury

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Declaration

I, Alistair Connell, 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.

Για την Κλάρα

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Firstly, I wish to thank the staff and patients of the Royal Free London NHS Foundation Trust. To the Nephrology and PARRT teams: thank you for your enthusiasm and engagement. Most importantly: Chris, I'll never be able to thank you enough for your support.

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Abstract

I developed a digitally-enabled care pathway for Acute Kidney Injury (AKI) management for patients in secondary care, incorporating a mobile detection application, specialist clinical response team and care protocol. Using time-series regression, I measured changes in clinical outcome and economic data from adults with AKI before (May 2016-January 2017) and after (May-September 2017) deployment at the intervention site and at another not receiving the intervention. I extracted process of care data from casenotes and compared two nine-month periods before and after implementation (January to September 2016 and 2017, respectively) using pre-post analysis, and qualitatively evaluated the impact of using the care pathway on the working practices of users and on their interprofessional relationships using inductive and deductive thematic analysis of semi-structured interviews. There was no significant step change in the primary outcome (serum creatinine recovery to ≤120% baseline at hospital discharge). Among process measures, times to AKI recognition and treatment of nephrotoxicity improved significantly ($p<0.001$ and 0.047 respectively). Among secondary clinical outcomes, the hospital-wide cardiac arrest rate fell significantly at the intervention site (OR=0.55, 95%CI=0.38-0.76, $p<0.001$), but difference-in-differences analysis with the comparator site was not significant (OR=1.13, 95%CI=0.63-1.99 p=0.69). Mean healthcare costs per patient admission were reduced by £1,631 (95%CI=-£3,218;-£44 p=0.044), not including costs of providing the technology. Interviews suggested that the pathway improved access to patient information and expedited early specialist care. Opportunities were identified for more constructive planning of end of life care due to the earlier detection and alerting of deterioration. However, the shift towards earlier detection also highlighted resource constraints at the intervention site, and some clinical uncertainty about the value of intervening at this stage.

Impact statement

Acute Kidney Injury (AKI) is the generic term for an abrupt deterioration in kidney function. It is common, occurring in up to one in five emergency admissions to hospital. In its most severe form, AKI can lead to organ failure and death. However, even in milder forms, it is associated with a range of poor outcomes, including significantly longer hospital stays and a lifelong reduction in kidney function. The financial burden of AKI on NHS services in England alone is thought to be in excess of £1 billion per year, which is greater than the costs attributable to breast cancer. In 2009, a national enquiry found that care in patients with AKI could be described as “good” less than half the time. In particular, the enquiry identified significant delays in recognition of the disorder, poor management of complications, and deficiencies in access to specialist care.

In collaboration with DeepMind Health and the Royal Free London NHS Foundation Trust, I developed a novel care pathway for patients suffering from AKI. This centered around a smartphone app called Streams - built by DeepMind Health - capable of diagnosing cases of AKI in real-time and of delivering patient-specific alerts directly to a team of kidney and intensive care specialists. I created a process by which such alerts were used to drive a structured bundle of care that ensured patients at the Royal Free received the care they needed as fast as possible.

I worked with the UCL Centre for Human Health and Performance and Department of Applied Health Research to evaluate the impacts of the care pathway. Reliability and speed of AKI recognition improved, as did the timeframes in which some key treatments were delivered. Pathway implementation was also associated with a significant fall in the cost of care delivery for patients with AKI. Staff estimated that using the Streams app to look up blood results for their patients while on the move saved them up to two hours per day.

At a time when the NHS is under unprecedented financial and operational strains, these results offer an exciting glimpse into the possible benefits that technology can bring to patients and caregivers alike.

Four manuscripts detailing this work have now been published:

- Connell A, Montgomery H, Morris S, Nightingale C, Stanley S, Emerson M, et al. Service evaluation of the implementation of a digitally-enabled care pathway for the recognition and management of acute kidney injury. F1000Res. 2017;6: 1033.
- Connell A, Montgomery H, Martin P, Nightingale C, Sadeghi-Alavijeh O, King D, et al. Evaluation of a digitally-enabled care pathway for acute kidney injury management in hospital emergency admissions. NPJ Digit Med. 2019;2: 67.
- Connell A, Raine R, Martin P, Barbosa EC, Morris S, Nightingale C, et al. Implementation of a Digitally Enabled Care Pathway (Part 1): Impact on Clinical Outcomes and Associated Health Care Costs. J Med Internet Res. 2019;21: e13147.
- Connell A, Black G, Montgomery H, Martin P, Nightingale C, King D, et al. Implementation of a Digitally Enabled Care Pathway (Part 2): Qualitative Analysis of Experiences of Health Care Professionals. J Med Internet Res. 2019;21: e13143.

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Abbreviations used

ADQI: Acute Dialysis Quality Initiative

AKI: Acute Kidney Injury

AKIN: Acute Kidney Injury Network

BGH: Barnet General Hospital

CKD: Chronic Kidney Disease

CQUIN: Commissioning for Quality and Innovation

DMH: DeepMind Health

ED: Emergency Department

EHR: Electronic Health Record

GFR: Glomerular Filtration Rate

GLM: Generalized Linear Model

HL7: Health Level 7

ICD: International Classification of Disease

IQR: Interquartile Range

ITU: Intensive Treatment Unit

KDIGO: Kidney Disease Improving Global Outcomes

LIMS: Laboratory Information Management System

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NSAIDS: Non-steroidal anti-inflammatory drugs

OR: Odds Ratio

PARRT: Patient At Risk and Resuscitation Team

PLICS: Patient Level Information and Costing System

RFH: Royal Free Hospital

RFLFT: Royal Free London NHS Foundation Trust

RIFLE: Risk, Injury, Failure, Loss, End-stage

RRT: Renal Replacement Therapy

SCr: Serum Creatinine

UCL: University College London

US: United States

95%CI: Ninety-five Percent Confidence Interval

Chapter 1: Introduction

The kidneys are critical to multiple domains of homeostatic regulation in the human. The functional unit of the kidney - the nephron - comprises the glomerulus and renal tubule. The glomeruli work continuously to filter approximately 180 litres of fluid each day from the circulation through complex oncotic, haemodynamic, and electrostatic factors[1]. Filtrate is then delivered to the renal tubules, where tightly controlled transport processes control urine composition and volume, regulating extracellular fluid volume and composition according to homeostatic requirements. Waste products, acid, and excess salt and water are thus excreted as necessary, and electrolyte (and acid/base) balance precisely controlled[2]. The kidneys are also essential for the homeostatic regulation of systemic oxygen transport (erythropoiesis being stimulated by the secretion of the exocrine hormone erythropoetin) and of diverse systems through the hydroxylation of vitamin D, whilst also contributing to gluconeogenesis[2].

Acute kidney injury (AKI) is a sudden loss of kidney function. The syndrome of AKI has long been recognised; in 1941, Beall *et al.* contributed a landmark report on the syndrome (Figure 1.1), describing rhabdomyolysis in patients with crush injuries suffered during the Blitz[3]. The authors recognised that a reduction in renal function often continued after resolution of circulatory shock, suggesting injury to the renal parenchyma. They confirmed this on histological examination post-mortem, by demonstrating tubular damage due to myoglobin precipitation[3].

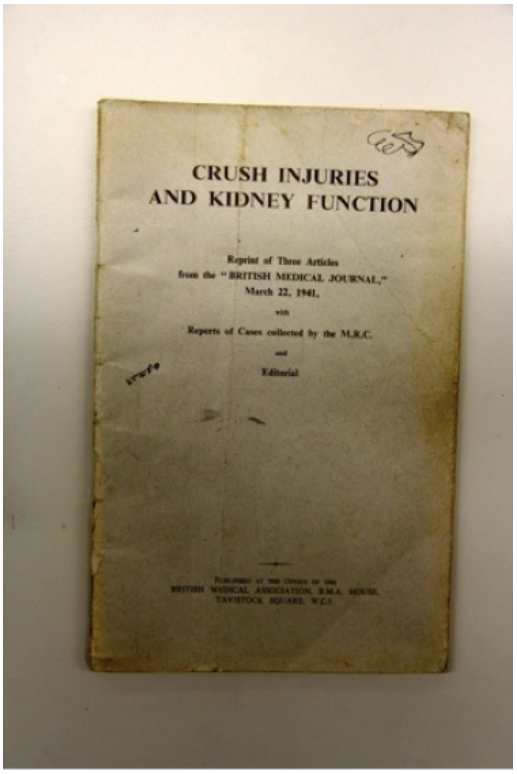

Figure 1.1: **Photograph from Eric Bywaters' archive reprint of original British Medical Journal article, 1941** (personal image)

Significant progress has been made in our understanding of the cellular mechanisms that contribute to AKI in the decades that have passed since this landmark report. So, too, has our ability to monitor and manage its consequences: in resource-rich countries, renal replacement therapy (RRT) is now widely available, while supportive care has been enhanced through the provision of modern critical care services. However, incident rates of AKI continue to rise[4], while outcomes associated with this syndrome remain poor for many patients[5]. Frustratingly, effective therapeutic interventions specific to AKI but generic across its causes have remained elusive[6].

In this chapter, I will outline the definition, epidemiology and pathophysiological features of AKI, before detailing how the syndrome is currently managed according to its primary causes. I will then describe deficiencies in existing paradigms of care. Finally, I will suggest how these might be addressed.

Definitions of AKI

AKI was previously known as *acute renal failure*, a term implying severe or total loss of organ function. However, evidence of the association between adverse clinical outcomes and apparently mild reductions in kidney function led to the formulation of the alternative term *acute kidney injury*[4], which incorporates a spectrum of severity, from mild renal dysfunction to that requiring RRT.

Historically, multiple definitions of AKI existed in the literature, resulting in variation in reported prevalence and difficulties in comparing the outcome of clinical studies. The first attempt to standardize the definition of AKI took place at the 2nd *Acute Dialysis Quality Initiative* (ADQI) consensus conference, resulting in the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria, published in 2004[7]. These stratified patients into categories of severity based on how much the serum creatinine (SCr) or glomerular filtration rate (GFR) differed from the patient baseline. The criteria also included two clinical outcome categories for any patient requiring RRT (*Loss* + *End Stage Kidney Disease*), each defined by how long patients had been receiving RRT. The Acute Kidney Injury Network (AKIN) criteria were published in 2007[8]. These built on the RIFLE criteria by broadening the definition of AKI, acknowledging that small changes in SCr occurring over 24 to 48 hours were associated with a substantially increased risk of mortality e.g. individuals with a SCr increase of 27μmol/L experienced a 70% increase in the risk for death relative to patients with little or no change in SCr. Additionally, any patients on RRT were included in Stage 3 (independently of changes to SCr or urine output) and changes in GFR were no longer used, discouraging the incorrect use of changes in estimated GFR for AKI diagnosis. In 2012, the RIFLE and AKIN criteria were effectively merged in a classification proposed by the Kidney Disease Improving Global Outcomes (KDIGO) consortium[9]. These criteria also clearly specified the time-periods in which changes in SCr should take place in order for AKI to be diagnosed and its severity defined.

In 2013, the UK Acute Kidney Injury Consensus Conference issued a recommendation that,

> "*A national group should be established to develop agreed standards … including an agreed definition of AKI based on the KDIGO classification and a standardised methodology for*

the derivation of baseline serum creatinine."[10]

As a result, an expert panel convened and agreed a standardized definition of how baseline SCr should be defined. In 2014 (under the auspices of their "Think Kidneys" Programme), NHS England and the UK Renal Registry produced a Patient Safety Alert mandating its use across England[11]. Definitions used for each criterion are given in Table 1.1.

Name of criteria	Stage	Criteria
RIFLE	Risk	● ↑ in SCr of 50% from baseline ● ↓ in GFR of 25% from baseline ● Urine output <0.5 mL/kg/h for 6 hours
	Injury	● ↑ in SCr of 100% from baseline ● ↓ in GFR of 50% from baseline ● Urine output <0.5 mL/kg/h for 12 hours
	Failure	● ↑ in SCr of 200% from baseline ● increase in SCr of >44.2μmol/L if baseline SCr is >353.6μmol/L ● ↓ in GFR of 75% from baseline ● Urine output <0.3 mL/kg/h for 24 hours ● Anuria for 12 hours
AKIN	Stage 1	● ↑ SCr of 50% from baseline ● increase in SCr of ≥26.5μmol/L within 48 hours ● Urine output <0.5 mL/kg/h for 6 hours
	Stage 2	● ↑ SCr of 100% from baseline ● Urine output <0.5 mL/kg/h for 12 hours
	Stage 3	● ↑ SCr of 200% from baseline ● increase in SCr of >44.2μmol/L in 48hrs if baseline >353.6μmol/L ● Urine output <0.3 mL/kg/h for 24 hours ● anuria for 12 hours ● Initiation of RRT, regardless of SCr or urine output
KDIGO	Stage 1	● ↑ SCr of 50% from baseline in 7 days ● increase in SCr of ≥26.5μmol/L in 48 hours ● Urine output <0.5 mL/kg/h for 6 hours
	Stage 2	● ↑ SCr of 100% from baseline in 7 days ● Urine output <0.5 mL/kg/h for 12 hours
	Stage 3	● ↑ SCr of 200% from baseline 7 days ● SCr >353.6μmol/L with either: ↑ SCr of 50% from baseline in 7 days, or increase of ≥26.5μmol/L in 48 hours ● UO <0.3 mL/kg/h for 24 hours ● Anuria for 12 hours ● Initiation of RRT, regardless of SCr or urine output
NHS algorithm	Stage 1	● ↑ SCr of 50% from baseline ● Increase of ≥26.5μmol/L in 48hours
	Stage 2	● ↑ SCr of 100% from baseline
	Stage 3	● ↑ SCr of 200% from baseline 7 days ● current SCr >353.6μmol/L with ↑ SCr of 50% from baseline

Table 1.1: Definitions of AKI

Epidemiology

AKI affects over 13 million people worldwide per annum, the majority of whom live in resource-poor countries[12]. However, this is almost certainly an underestimate, due to the prior lack of a standardised definition and absence of comprehensive data[5,12]. Furthermore, published incidences (themselves disproportionately from resource-rich countries) vary widely, possibly relating to differences in populations studied. In resource-rich countries, AKI affects up to 15% of hospital admissions and 20% of patients admitted to hospital as an emergency[13]. Within hospital cohorts, the profile of AKI differs between emergency admissions and surgical, nephrology and critical care patient cohorts[14], with older patients being particularly susceptible[15]. Around two-thirds of such cases begin in the community but are diagnosed in-hospital[16]. In a recent retrospective study, hypovolaemia and sepsis were together the primary aetiological factors for 35% of cases, with cardiorenal syndrome causing 19%, obstructive uropathy 8%, nephrotoxic drugs 7%, tubulointerstitial nephritis 4%, and rhabdomyolysis and glomerulonephritis 2% each[17]. In many patients, however, multiple mechanisms may exist in parallel.

Pathophysiology

Considerable pre-clinical research has been undertaken into the cellular and molecular mechanisms of renal injury, associated inflammation and repair.

In the context of sepsis, the paradigm that AKI results purely from reduced renal perfusion is no longer valid. Indeed, AKI has been demonstrated in the context of *increased* total renal blood flow. The renal microvasculature is thought to play a more important role in the development and propagation of AKI[18]. As well as meeting high tissue energy demands, adequate oxygen supply is key in the production of nitrous oxide and reactive oxygen species necessary for the physiological regulation of organ function; disruptions to the provision of these compounds results in pathogenic effects[19]. Damage to the vascular endothelium impacts on the synthesis and release of such key compounds, but may also increase vascular permeability and adhesion of platelets and leukocytes that may further

reduce oxygen delivery[20]. The renal mitochondria are also thought to play a central role in AKI pathogenesis. The proximal tubule has a limited capacity to perform anaerobic glycolysis, making it highly sensitive to anaerobic insults. Mitochondrial damage is also implicated in AKI in the context of sepsis, and in response to nephrotoxins such as gentamicin and cisplatin[21].

However, whilst pre-clinical research has improved insight into pathophysiology, improvements in fundamental knowledge of disease mechanisms have not, in general, resulted in translation to the introduction of new and effective therapeutic agents[6]. Furthermore, animal models are limited in the degree to which AKI pathogenesis reflects that in humans[22], which represents a heterogeneous group of conditions and rarely has one distinct cause. Multiple mechanisms may exist in parallel (e.g. where ischaemia, sepsis and nephrotoxicity co-exist), a fact that may complicate both recognition and effective management. In clinical practice, therefore, it is useful to consider how multiple factors might have contributed to the development of AKI, and how each may be addressed.

Management of AKI

Risk assessment and prediction

The risk of developing AKI depends on both the vulnerabilities of the patient, and the nature of any renal insults. A host of background risk factors may increase susceptibility of the kidney to injury, or reduce the ability of the patient to maintain renal perfusion and oxygenation in the face of systemic illness. These risk factors include Chronic Kidney Disease (CKD), advanced age, concomitant administration of drugs known to be harmful to the kidneys, diabetes, and coexisting liver, cardiac or vascular disease[23]. Tools have been developed to prospectively assess risk at patient level. However, many are limited to specific clinical scenarios; predictive scores for heart failure, high-risk surgery, and contrast-induced AKI were summarised in a recent review[24]. Artificial Intelligence (AI) holds considerable promise in this field. Through analysis of multiple dynamic variables, it may be possible to prospectively predict the development of future AKI in multiple clinical contexts in real-time,

and in turn to prompt early targeted intervention[25]. However, such technologies have not yet been validated in prospective clinical studies.

Other investigators have sought to use biomarkers to predict the development of AKI. However, experience of using biomarkers to predict clinical course in other contexts has shown this approach to have limitations. Biomarkers do not outperform diagnostic scores such as CURB-65 in predicting mortality in community-acquired pneumonia[26]. Likewise, urinary, plasma and serum biomarkers for the prediction of AKI also perform modestly[27]: the sensitivity and specificity of assays to predict AKI were 0.51 and 0.79 respectively for urinary interleukin-18[28], 0.881 and 0.474 respectively for plasma neutrophil gelatinase-associated lipocalin (NGAL) in predicting AKI in the context of sepsis[29], and 0.85 and 0.61 respectively for cystatin C in predicting AKI in children[30]. Notably, a score based on biomarkers Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) and Insulin-like Growth Factor Binding Protein 7 (IGFBP-7) has been approved by the US Food and Drug Administration (FDA) as a predictive biomarker in selected patient subgroups. The most recent validation study of this score defined sensitivity and specificity of predicting AKI stages 2 or 3 within 12 hours at a range of scores; for a score of 0.3, they were 0.92 and 0.46, respectively, and for a score of 2.0 they were 0.37 and 0.95, respectively[31]. Several trials have shown its use in conjunction with structured clinical interventions to be associated with a reduced incidence and/or severity of AKI among critically ill cohorts[23,24]. However, the optimal use of this score in more diverse clinical settings remains to be determined.

The use of biomarkers has further significant limitations. AKI is often not the result of a single insult at a single time. Biomarkers are often non-specific; many rise with inflammation (e.g. in the post-surgical setting or sepsis), irrespective of the presence of AKI[32]. Furthermore, the optimum thresholds to prompt clinical intervention are unclear. Their role in surveillance - and the costs involved - therefore remain unknown. No biomarker is currently in widespread clinical use.

Pending further progress in the development and deployment of predictive technologies, clinicians should minimise their patients' exposure to risk where possible and monitor for AKI through measurement of serum creatinine and urine volume.

Prevention of AKI

Among patients at risk of AKI, preventive measures aim to reduce the incidence or severity of disease e.g. potentially nephrotoxic drugs are discontinued or avoided where possible, and any infection treated promptly. The optimisation of fluid and haemodynamic status in patients at risk has been subject to considerable investigation. In this respect, adequate resuscitation is desirable, but fluid overload is harmful and increases mortality[33]. Early intervention to meet pre-specified haemodynamic targets ('goal-directed therapy') has been suggested to improve survival in the context of critical illness (including sepsis)[34,35]. However, trials have not demonstrated any reduction in RRT use among patients with AKI in the context of sepsis[36,37]. The choice of fluid used in resuscitation has also been investigated extensively. Randomised trials have identified no difference in mortality between crystalloids and colloids[38]. However, observational data suggest that strategies seeking to minimise chloride load may reduce the need for RRT[39,40]. More recently, two large trials compared outcomes with balanced crystalloids (i.e. those that have a sodium, potassium, and chloride content close to that of extracellular fluid) or 0.9% saline in non-critically ill (SALT-ED[41]) and critically ill (SMART[42]) adult cohorts. The SALT-ED trial reported an absolute risk reduction of 0.9% in major adverse kidney events with crystalloids, although the primary outcome of hospital-free days before 28 days was no different. The SMART trial demonstrated an absolute difference of 1.1% in favour of balanced crystalloids for the primary composite outcome of death, persistent renal dysfunction or RRT use within 30 days.

Contrast-induced nephropathy (i.e. where AKI develops up to 5 days after the administration to iodinated radiocontrast material), has been extensively documented. The mechanisms by which such materials might cause AKI remain unclear and no specific treatment exists[43]. Preventive measures include minimisation of contrast media volume, the avoidance of hyperosmolar contrast[44], and volume loading[45]. Sodium bicarbonate does not appear superior to saline[46], and oral fluids may suffice for many patients[47]. However, it is worth highlighting that - as almost all studies on contrast-induced nephropathy have significant sources of bias - the importance of contrast-induced nephropathy is still widely debated, and that more recent studies have suggested that the AKI risk attributable to contrast material is modest at most[48].

Detection of AKI

Patients with AKI may present with symptoms or signs relating to reduced kidney function - such as haematuria, oedema or oligoanuria - prompting diagnosis. For many, however, a diagnosis of AKI is asymptomic and not associated with indicative clinical signs. For this reason, a drop in kidney function may not be recognized until serum creatinine is measured, often in a routine timescale. Creatinine itself is an imperfect biomarker of renal injury for a number of reasons. It is released from muscle and excreted in urine; as such, creatinine concentration reflects both muscle mass and renal excretory capacity, both of which vary considerably between patients. In addition, rises in creatinine concentration are dependent on accumulation. As a result, concentration rises slowly with respect to changes in filtration; a single creatinine is therefore not a reliable indicator of renal function outside the steady state[49]. Furthermore, a raised creatinine is a non-specific marker of renal injury, telling clinicians nothing about the pathogenesis or ongoing severity of injury. A number of at-risk groups will not experience an early rise in creatinine to above the upper limit of the normal range, due to low muscle mass e.g. patients with malnutrition or liver disease. Lastly, the relationship between SCr and GFR is non-linear, with early SCr rises indicating a significant reduction in GFR.

According to current diagnostic criteria (Table 1.1), sustained oliguria is also diagnostic of AKI[49]. It may be beneficial to monitor urine output in high risk patients, although such measurement is not routine for most hospital inpatients. Furthermore, errors in the estimation of urinary volumes from visual inspection of conventional urometers may exceed 25%[50].

In summary, clinicians should seek to understand both the risk factors their patients are exposed to and their baseline renal function, monitor their SCr and urine output, and be alert to early changes which might signify significant losses of kidney function and provide an opportunity for effective clinical intervention.

Clinical assessment and investigation

In the past, causes of AKI were classified according to gross anatomical site affected (i.e. prerenal, intrinsic or postrenal). However, many disease states cross such boundaries; in

practice, AKI represents a heterogeneous group of conditions encompassing impairments in kidney structure and function. In addition, multiple mechanisms may exist in parallel (e.g. where ischaemia, sepsis and nephrotoxicity co-exist) which may complicate both recognition and management. It therefore makes more sense to approach patients with a diagnosis of AKI using an organised framework of specific diagnoses in mind. One such approach will now be outlined.

Hypovolaemia and sepsis

AKI frequently occurs in hypovolaemia e.g. following haemorrhage or diarrhoea. Renal perfusion may also decrease in states of reduced effective circulating arterial volume e.g. in hepatorenal syndrome. In the context of sepsis, hypoperfusion likely plays only a part in renal dysfunction, where AKI can occur in the setting of normal or increased renal blood flow[51]. Optimal treatment for patients with sepsis-associated AKI relies upon prompt delivery of treatment, where delays in the administration of antibiotics may put patients at a significantly higher risk of developing renal dysfunction[52].

Hypovolaemia may be suggested by the presence of postural hypotension or tachycardia. In ventilated patients, hypovolaemia may be implied by the presence of variation in arterial pulse pressure or Inferior Vena Cava diameter[53]. The aim of fluid therapy in hypovolaemic patients is to restore mean arterial pressure, but routinely measured haemodynamic parameters may be poorly predictive of renal blood flow for many. Acute illnesses (including sepsis), comorbid diseases and some medications may alter the response to any fluids prescribed. Furthermore, aggressive resuscitation risks fluid overload. Hypervolaemia itself can be injurious to kidney function; intra-abdominal hypertension and venous congestion can lower renal blood flow and GFR[54,55], and several studies have found a relationship between positive fluid balance and adverse outcomes in AKI, independent of confounding effects such as haemodynamic instability or illness severity[56,57]. Unnecessary fluid administration in patients with hypotension unresponsive to initial fluid resuscitation may be limited by early admission to intensive care for invasive monitoring[34]. Goal-directed fluid therapy may decrease the incidence of AKI in the peri-operative period[58], and in patients with sepsis[59].

Renal injury can also arise in the context of dysfunction in other organs. Hepatorenal syndrome is characterised by deteriorating renal function in the setting of cirrhosis. This may be characterized as being either a rapidly progressive AKI in <2 weeks (type I), or slower in both onset and progression (type 2)[60]. Cardiorenal syndrome is defined as primary dysfunction of either the heart or kidney, resulting in secondary dysfunction to the other organ. It is classified into 5 types, depending on whether acute heart failure leads to AKI (type 1); chronic cardiac dysfunction leads to progressive CKD (type 2); AKI leads to acute cardiac dysfunction (type 3); primary CKD contributes to cardiac dysfunction (type 4); or simultaneous cardiac and renal dysfunction occurs secondary to a systemic condition affecting both organs such as cirrhosis or sepsis (type 5)[61].

Nephrotoxins and obstruction

The use of nephrotoxic drugs may be a contributing factor in up to a quarter of cases of AKI[62]. The most commonly implicated classes of drugs are those acting on the cardiovascular system (such as diuretics or angiotensin converting enzyme inhibitors), antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs)[63]. Nephrotoxins may work in different ways e.g. NSAIDs affect renal autoregulation, whereas crystalline nephropathy (associated with the use of acyclovir) affects the interstitium. A number of drugs (e.g. trimethoprim) can increase SCr without decreasing GFR by competitively inhibiting the tubular secretion of creatinine[63].

Obstruction may occur at any point in the urinary tract, and is commonly caused by stones, and external urethral compression by the prostate, enlarged lymph nodes, tumours, or retroperitoneal fibrosis[64]. Irreversible tubulointerstitial fibrosis will occur if obstruction is not treated. Several factors might contribute to the chance of full renal recovery (such as the presence or absence of infection and the site of obstruction), but the most important factor appears to be time to relief[65]. As a result, national best practice guidance recommends that stenting or a nephrostomy is used to treat obstruction of the upper tract within 12 hours of diagnosis[66]. Subsequent massive diuresis can follow, to which activation of natriuretic factors after volume expansion and an impaired ability to concentrate urine due to tubular damage may contribute. As a result, careful haemodynamic monitoring may be necessary in this period[67].

Intrinsic renal disease

A wide variety of diseases affect the kidney directly, which may be divided anatomically. Diseases affecting the renal vasculature include small vessel vasculitides (e.g. Thrombotic Thrombocytopaenia Purpura and Haemolytic-Uraemic Syndrome) and diseases affecting larger vessels (e.g. systemic thromboembolism or acute renal vein thrombosis)[68,69]. Diseases affecting the glomeruli are commonly separated into two distinct groups: (i) those causing a *nephritic* pattern (e.g. proliferative glomerulonephritis), with active urinary sediment with dysmorphic red blood cells/ cellular casts, and (ii) those causing a *nephrotic* pattern, which presents with a spectrum of proteinuria, from subnephrotic (1-3g/day) to the full nephrotic syndrome, (>3.5g/day, with marked oedema and hyperlipidaemia)[70]. Causes of AKI in this category include primary renal disease (e.g. minimal change disease, idiopathic membranous nephropathy), and a range of systemic disorders that affect the kidneys (e.g. amyloid, Human Immunodeficiency Syndrome). Lastly, a number of diseases affect the tubules or interstitium (e.g. drug-induced interstitial nephritis, Tumour Lysis Syndrome).

A patient's systemic presentation may suggest the underlying cause of AKI e.g. haematuria following a respiratory tract infection might suggest an immune-complex-mediated glomerulonephritis. The correct approach, therefore, is to take a thorough history and perform a thorough examination. Urine dipstick and microscopy, and screening blood tests (e.g. serum free light chains, immunoglobulins, anti-glomerular basement membrane antibody etc.) are useful. In the presence of a urine dipstick positive for blood or protein, or where a primary renal injury is likely or suspected, an urgent review by nephrology should be arranged[71].

Complications and Renal Replacement Therapy

AKI may result with fluid overload, uraemia and metabolic derangements such as hyperkalaemia or acidosis[71]. Patients with AKI should be monitored for complications[66]. Medical treatments can be used to temporize in this setting; urgent supportive RRT may be indicated where these treatments fail pending recovery of renal function. In a proportion of non-recovering AKI survivors, it may be required longterm[72]. There are a number of options available for providing RRT in the acute setting; in the main, these may be convective (*haemofiltration*), diffusive (*haemodialysis*), or rely on both (*haemodiafiltration*). In addition,

therapies may be continuous or intermittent. The use of peritoneal dialysis in acute rather than chronic renal disease is generally limited to paediatric patients and resource-limited settings[9]. The optimal modality, intensity and timing of initiation have been the subject of considerable investigation.

Initiation of RRT prior to the development of complications does not appear to be of benefit. Whilst the ELAIN trial found that delayed RRT was associated with increased 90-day mortality[73], in the AKIKI study, almost half of the patients in the delayed group did not commence RRT at all, suggesting benefits to holding off initiation[74]. In certain clinical situations, the use of one modality may be preferred; factors influencing this decision therefore include the primary goal of therapy (removal of solute, fluid, or both), and practical issues relating to the patient. The use of continuous therapy may provide a theoretical advantage for the management of hypervolaemia[75,76], and minimize haemodynamic instability[77]. However, a recent retrospective study suggested that rates of renal recovery were marginally lower with intermittent than continuous RRT[78]. As regards intensity, higher intensity RRT does not appear to affect mortality, but may delay renal recovery[79].

In some clinical scenarios, the use of one modality may be preferable. Factors influencing this decision will include the primary goal of therapy (i.e. removal of fluid, solute, or both), practical issues relating to the individual patient (e.g. need for ongoing rehabilitation activities) and local expertise. RRT should be continued until kidney function begins to improve. This may be manifested by an increase in urine output in patients with oliguria; a progressive decline in serum creatinine may also be seen. Although specific measurement of creatinine clearance can give a clearer picture of renal recovery, there is no universally accepted indicator for the discontinuation of RRT.

Referrals

For patients with AKI, there is evidence that delayed nephrology review results in poorer outcomes[80]; this is also true for patients in high dependency settings[81]. National guidelines[66] suggest that the management of a patient with AKI should be discussed with local nephrology services where one of the following conditions are met:

- Stage 3 AKI
- AKI with complications e.g. hyperkalaemia

- AKI with no clear cause, or where there has been an inadequate response to treatment
- AKI in a patient with severe pre-existing CKD
- AKI in a transplant recipient
- Where the underlying diagnosis may need specialist management e.g. suspected vasculitis or glomerulonephritis

In addition, urgent referral to local urological and/or radiology services is warranted for those with renal obstruction[66].

The impacts of AKI

AKI is strongly associated with a substantially increased risk of death[4,82–84]. The relationship between AKI, critical illness and comorbidities is complex. The mechanisms through which AKI increases the risk of adverse outcomes is incompletely understood; as AKI is often seen in the course of other systemic diseases, separating out cause and effect can be difficult[85]. Animal models involving injury or the removal of the kidneys have suggested pathways by which effects on distant organs might be mediated. Complex cross-talk involving dysfunctional inflammatory cascades, pro-apoptotic pathways and oxidative stress have been shown to have effects on the lung[86,87], heart[88], liver[89], and brain[90] after AKI. Mortality risk persists up to 90 days following discharge and varies with stage of disease[91]; among patients requiring RRT, is as high as 50-60%[92,93]. Mortality risk appears to exhibit some seasonal variation (being worse in winter)[94], but there is no evidence of a “weekend effect”[95]. It is not clear why small reductions in renal function are associated with an increased risk of death. This may be non-causative i.e. AKI might serve as a marker of severity of concurrent illnesses; the renal medulla and tubulointerstitium are vulnerable due to low oxygenation levels and high metabolic demands[19] and therefore might act as a sensitive marker to general illness.

AKI is also associated with a host of further adverse outcomes including prolonged hospitalisation[83], requirement for RRT[96], a need for high dependency/ intensive care[92], and the development of CKD[97]. A single AKI episode is associated with an 8-fold lifetime increase in the risk of CKD[98]. The risk of CKD at 1-year is over 10%, and 1% of patients will

require dialysis at this time[99]. Risk factors for progression to CKD in such patients include old age, male sex, and the presence of sepsis[100]. Associated excess costs to the National Health Service (NHS) in England - through increased length of stay, critical care utilisation and need for RRT - may exceed £1 billion per annum.[13]

Increasing awareness of the clinical and economic impact of this condition has led to local, regional, national and global initiatives to try to prevent AKI occurring, and to encourage timely and appropriate interventions to prevent progression and deliver more rapid recovery. Thus NHS England has a national campaign to improve AKI outcomes ("*Think Kidneys*"[101]), whilst AKI was identified as a priority area in the strategic plan for the NHS in England (the "*Five Year Forward View*"[102]) leading to the implementation of a National Commissioning for Quality and Innovation (CQUIN) target[103] relating to documentation of AKI recognition and action.

The quality of AKI management

As outlined above, effective management of AKI involves four key elements: (i) timely recognition, (ii) general supportive care, (iii) therapy directed at the underlying cause of AKI, and (iv) the management of complications[71]. The goals of such intervention are thus to prevent disease progression and the occurrence of complications, whilst treating any such complications and promoting more rapid AKI resolution[71]. Given the heterogeneous nature of causative disease states, such treatment may involve the coordination of hospital pathology and radiology services, as well as contributions from multiple specialty teams. Whilst as yet unquantified in scale, timely recognition of, and early intervention for AKI are thought likely to improve outcome[104].

However, local and national audits have revealed substantial deficits in all key processes of AKI care including recognition, early therapy, escalation to specialist or critical care services and follow-up[105]. In part, this is due to the complexity of the patient care pathway. In secondary care, AKI is particularly prevalent in emergency admission pathways but may arise in diverse locations and specialities across the hospital system[106]. It is often managed by teams without expert renal knowledge, who are responsible for AKI detection (by review of blood test data), for diagnosis of its cause, for instituting early treatment, and for

escalating care to other specialists as appropriate. Such functions are often performed by junior staff, who must also manage the deployment and coordination of a number of diagnostic services including biochemistry, microbiology and radiology, and of other relevant clinical teams, such as those involved in acute medicine, critical care, nephrology and primary care.

The Royal Free Hospital (RFH) site of the Royal Free London NHS Foundation Trust (RFLFT) serves as a useful exemplar. It deploys an historic AKI detection algorithm that identifies (by 'flagging' of results in the electronic record) 1.5-fold rises in SCr to define cases of AKI. Duty biochemists report some cases by telephone to the clinical area in which the AKI patient is located. In the main, however, AKI cases are identified by clinicians through the viewing of pathology results in an unprompted fashion, usually in batched form and often at the end of the working day, several hours after the result is available. If responsible clinicians recognise the presence of AKI (it may be missed) they may/may not formulate and/or enact an appropriate and complete management plan which may/may not include seeking senior, more experienced or expert help. Help from renal or critical care services is thus commissioned ad hoc, usually through phone-calls, hospital pager or email systems, and referral thresholds may vary considerably.

This early part of the AKI pathway is therefore administered by (albeit supervised) trainee doctors operating within non-specialist teams. They may manage this clinical problem infrequently and do not always follow accepted best practice. At the RFH Emergency Department, an audit conducted in November 2015 showed that:

- AKI was not recognised at all in 20% of cases
- the median time to recognition of AKI was over 3 hours after arrival
- where treatment involved simple fluid therapy or antibiotics, this was delivered to patients within 4 hours of arrival in only 55% of cases

RFLFT continues to report serious adverse events relating to care and service delivery problems relating to the management of AKI; these have resulted in avoidable harm and death. Improving the care of patients with AKI has therefore been identified as a Trust priority within the corporate Patient Safety Programme, launched in October 2014.

Improving care for patients with AKI

E-alerts and AKI

Historical perspective

Electronic medical records may be used to store and present clinical data digitally. Such systems also support the use of auxiliary functions, such as electronic prescribing. There is therefore considerable international interest in the use of electronic medical records for improving safety and the quality of care[107]. Electronic medical records have been used to drive improved decision-making by clinicians. Simple algorithms embedded within Information Management Systems can be used to analyse data about an individual patient and generate patient-specific recommendations, which are then communicated directly to clinicians via an electronic alert ('e-alert')[108], E-alerts have been reported in a number of clinical scenarios (e.g. preventing venous thrombosis[109], flagging abnormal diagnostic imaging test results[110], notification of accidental prescribing errors[111]). In current practice, clinicians will only identify high risk blood test results in one of their patients when notified by biochemistry, or at the point of manual results viewing (which may occur in a 'routine' timescale, towards the end of the working day). E-alerts can be used to automate this process.

E-alert systems for AKI are based on two separate processes[112]:

- **diagnosis**: where an algorithm compares SCr concentration to a baseline reference value, and
- **notification**: where the outputs of this analysis are communicated to a relevant clinician.

In 2012, NHS Kidney Care (now part of NHS England) issued a survey to all NHS Trusts in England on their use of e-alerts for AKI[113]. Of those who responded, 52% had no plan to implement an AKI e-alert system at all. In those who did, considerable differences were noted in the application of existing diagnostic criteria:

- four utilized e-alerts that were generated in real-time without the need for authorisation by a clinical biochemist
- three Trusts employed systems that required authorisation of automatically-generated alerts
- the remaining two produced e-alerts that required a manual search of all creatinine results.

Respondents' perceived barriers to the implementation of e-alerts were as follows:

- existing software e.g. an inability to add flags or alerts to pathology results in the current system and a perceived lack of interest in clinicians to create the system
- lack of technical expertise
- lack of clinical expertise in AKI among clinicians
- increased workload for biochemistry department
- cost
- lack of expert Information Technology (IT) personnel

It was also noted that variations in accuracy occur when trying to establish the "optimum" baseline creatinine to use, or where a baseline is not known[114–116]. Aiming to address such barriers, a UK-wide consensus conference was hosted by the Royal College of Physicians of Edinburgh in November 2012, to discuss the role of e-alerts in AKI. The conference statement concluded that:

> *"A National group should be established to develop agreed standards for e-alert systems … including an agreed definition of AKI based on the KDIGO classification and a standardised methodology for the derivation of baseline serum creatinine."*[117]

Such a group convened in July 2013, and included biochemists, nephrologists and representatives from companies producing Laboratory Information Management Systems (LIMS).[118] A new algorithm for the diagnosis of AKI based on changes in serum creatinine was produced. This new diagnostic algorithm was endorsed by the joint UK Renal Registry and NHS England National AKI Programme, subsequently branded "*Think Kidneys*"[101]. In recognition of the importance of AKI detection to patient safety, NHS England issued a

directive (level 3) Patient Safety Alert: *"Standardising the Early Identification of AKI"*[11] mandating:

- the installation of a detection algorithm in LIMS
- that AKI detection is recorded in the patient's clinical record, and
- that these results also populate a national registry.

However, the scope of this project extended only as far as the generation of a diagnostic "flag" to identify cases of AKI within hospital LIMS; the group did not focus on the alerting arm of the e-alert process, or clinical implementation, hoping to encourage innovation and the development of sophisticated alerting processes[11]. Best practice guidance on clinical utilisation of the detection messages generated by the algorithm was subsequently provided by "*Think Kidneys*"[119]. Clinical practice guidelines for the management of AKI have also been developed[66].

E-alerts and the NHS algorithm

Electronic alerting systems that utilize the national diagnostic algorithm have been described[84]. However, alerts issued via hospital LIMS may be ignored by clinicians[120]. Some systems have issued alerts in an 'interruptive' fashion, where clinicians are presented with alerts when accessing a patient record but prevented from leaving the alert screen without acknowledging receipt of the relevant result[121]. However, such alerts are only flagged for review when clinicians log in to review blood tests.

Increasing the impact of AKI e-alerts

The first published *mobile* AKI alert system was developed by Colpaert et al, who sent patient-specific AKI alerts via Digital Enhanced Cordless Technology phones. This was found to be acceptable to clinicians, and was associated with a significant increase in the number and timeliness of clinical interventions for patients developing AKI in Intensive Care[122]. In the first randomised trial of an AKI e-alerting system, Wilson et al issued text alerts via pagers, in a batched fashion once per hour. No change in physician behaviour or patient outcomes was noted when compared to controls[123]. How representative this trial was to English practice is unclear: it took place in an American healthcare organisation in which

baseline mortality rates were lower, and doctor to patient ratios higher, than in recent studies based in England[16,124]. However, several reasons might account for why this 'simple alert' failed to improve outcome: it did not offer any associated data which might provide clinical context, and was deployed without a protocolised or structured intervention. Nor did it prompt engagement of experts/ those more experienced where needed.

More recently, AKI alerts have been linked to bundles of care and education programmes. A number of centres have reported improved outcomes for patients and reduced lengths of stay[125,126]. A paper by Kolhe et al reported that the introduction of an interruptive e-alert led to a 10-fold increase in the rate of completion of a bundle of care, with completion being associated with improved mortality and length of stay[127].

Alerts have also been used to encourage communication with specialist services. In one centre, a team of nephrologists and nurses would perform telephone outreach for all cases, providing a non-significant improvement in mortality[128]. The use of alerts flagging cases of AKI to nephrologists within the hospital LIMS has been described by Hill et al[129]. However, the effectiveness of deploying specialist responders earlier in the care pathway is currently unknown: the "Research Recommendations" of the National Institute for Clinical Evidence (NICE) guideline on AKI suggest that the benefit and value associated with such a 'rapid referral' nephrology service in moderate to severe AKI be assessed as a matter of national importance[66].

The formation of a differential diagnosis and planning of immediate investigations and treatments depend on the aggregation of an array of clinical data[130]. Additionally, viewing historical graphs of creatinine may play an important role in ruling out "false positive alerts" e.g. where a spuriously low baseline has been selected, or where a change in creatinine represents normal variation in patients with CKD[131]. However, integrating complex decision support tools within existing LIMS has been a significant challenge in the past[115].

Summary

AKI is a common condition which is associated with poorer patient outcomes and with substantial increases in care costs - an association which may be causal in nature. Despite this, cross-pathway deficiencies in care exist at both local and national levels. Systems to enhance the early recognition of AKI are now mandated - although the use of 'simple alerts' appears to be of limited impact in improving patient outcomes. Whilst a number of centres have reported different strategies to improve AKI care, the best process to achieve these goals, and the scale of the resulting impact are not clear. Furthermore, the benefits of deploying specialist resource early in the course of AKI remain unknown.

New pathways of care should rapidly and reliably alert clinicians to the presence and severity of AKI, provide patient-specific recommendations that allow clinicians to determine the likely cause of AKI at the point of care, include a structured 'best practice' response and improve early access to specialist expertise. Such systems should be integrated into existing infrastructure and patterns of work, and be designed with the needs of end-users in mind. Such a digitally enabled, enhanced care pathway might (i) have utility in improving AKI outcome, and (ii) produce net healthcare cost savings.

Hypothesis

I hypothesised that the introduction of a digitally-enabled care pathway would lead to (i) faster recognition of AKI, and (ii) more rapid and appropriate interventions for such cases, which would (iii) improve patient outcomes.

Aims and Objectives

I aimed to test this hypothesis by (i) developing such a pathway, comprising a technology platform, a specialist response team, and a standardized care protocol.

I then (ii) oversaw testing and implementation of this pathway at a single hospital site, seeking to discover and address barriers to successful implementation and record any unintended consequences of use.

Finally, I (iii) led a service evaluation of the pathway at a single hospital site (RFH), utilising mixed methodologies. Data derived from the evaluation served two purposes:

1. To allow the evaluation of impact respect to processes of care, clinical outcome and NHS costs, and
2. To assess the experience of end-users and the wider clinical community.

Thesis outline

In this thesis, I will initially describe the development of each component part of the new digitally-enabled care pathway, the testing of the care pathway and the training of response team members (***Chapter 2***). I will then describe the design and planning of the mixed-methods evaluation (***Chapter 3***), before describing the initial deployment of the care pathway, and detail the changes made to the pathway as a result (***Chapter 4***). I will next describe the quantitative analyses of the care pathway, comprising analyses of processes of care, clinical outcome, and costs to the NHS (***Chapter 5***), and the qualitative analysis of semi-structured interviews carried out with clinicians (***Chapter 6***). Finally, I will summarize the results of the evaluation and outline its possible impacts on future research, clinical practice and the formation of health policy (***Chapter 7***).

Chapter 2: Development of a new AKI care pathway

Introduction

As outlined in the previous chapter, AKI is common and associated with a range of adverse clinical outcomes and substantially increased cost of care provision[13,82–84]. Despite this, local and national audits have found significant cross-pathway deficiencies in care, relating to both recognition and management of AKI, as well as delayed access to specialty services[105]. Whilst a number of centres have reported a range of strategies aiming to drive improvements in care[125,126,132], the best process to achieve these goals and the scale of any resulting impact are not clear.

New pathways of care should include the automated diagnosis of AKI, using a standardized algorithm (such as that developed by NHS England). To accelerate the provision of treatment, clinicians should be notified of the presence of AKI in real-time, and actions which follow should be part of a structured and standardised best-practice response. However, in this respect, a number of technical challenges remain unanswered.

The use of 'simple alerts' in the form of a text message to hospital pagers appears to be of limited impact[123]; given the wide variety of diseases known to cause AKI and its high incidence among multimorbid patients, clinicians should have mobile access to a wide variety of clinical data at to allow them to determine the most likely cause at the point of diagnosis. Any new technologies used in a novel care pathway should be designed with the needs of end-users in mind, such that they integrate with established patterns of work[133,134] and existing hospital infrastructure.

Furthermore, whilst determining the clinical impact of deploying specialist resource early in the course of AKI is of significant national interest[66], it is unclear *how* such a resource should best be deployed. Alerting systems that automate specialist referral might be expected to have significant social and professional implications, for both clinicians receiving such referrals and other clinicians looking after patients with AKI.

The deployment of any new clinical pathway should be expected to have unintended consequences. These may be related to a broad number of domains e.g. the thought processes, habits of behavior, and capabilities of key stakeholders, and the complex environment in which they are deployed[135]. As a result, such consequences should be specifically sought. More broadly, an evaluation of the impacts of the pathway should be carried out; this should be broad in scope, seeking to understand both positive and negative impacts on processes of care, clinical outcomes, the cost of care provision, and the workflows of clinicians.

I sought to address these questions through the design and deployment of a novel digitally-enabled care pathway for patients with AKI. I hypothesised that the introduction of this pathway would lead to faster AKI recognition, would reduce the time-frame in which key treatments were delivered, and would thus drive improvements in patient and economic outcomes. In this chapter, I will discuss the development of the care pathway.

The Digitally-enabled Care Pathway

The digitally-enabled care pathway was deployed at RFLFT and is comprised of three components: a technology platform, a specialist response team, and a standardized care protocol. These will now be discussed in turn.

The Streams app

Streams (DeepMind Technologies Ltd, London, UK) is a mobile application ("app") that is deployed on iPhone Operating System (iOS)-enabled smartphones (Apple, Inc., Cupertino, California, USA), the mobile devices most commonly utilised by healthcare professionals[136]. It processes relevant routinely-collected clinical and demographic data through secure integration with hospitals' existing information systems. The Streams app is the result of a strategic partnership between DeepMind Health (DMH) - a UK-based health technology company - and RFLFT, with input from academic clinicians of University College London (UCL). Streams was first registered with the Medicines and Healthcare Products Regulatory

Agency as a Class I, non-measuring, non-sterile medical device under the EU Medical Device Directive (1993) on 30/08/2016.

Technical architecture

The Streams app is fully integrated with the existing RFH information systems. Due to the need for real-time event-driven data, Health Level Seven (HL7) v2 feeds were used for integration with the Laboratory Information Management System (LIMS) and Electronic Health Record (EHR). Data security is ensured through the use of on-disk (AES256) and in-flight encryption (TLS v1.2) for all app data in compliance with NHS Digital information security guidelines[137]. The Trust's full approval was obtained for DeepMind Health to process these data for direct patient care purposes, and DeepMind was shown to be fully compliant with all systems necessary for secure transmission and storage of NHS data.

Using these secure pipelines, patient data (such as blood test results) are transmitted as soon as they are released to a secure server compliant with NHS security standards, allowing rapid, real-time analytics to be performed. The outcomes of these analyses are then transmitted to a secure smartphone app via the hospital's Wi-Fi network in real-time. I worked with DeepMind Health (being embedded there for a part of each week during the early phase of my PhD) to develop the functionality of Streams with regard to AKI detection and presentation of relevant patient data. This involved liaising with a team of designers, engineers and the Clinical Safety Officer to ensure the design of the Streams app was safe to use and met the needs of clinician users at RFH. The functionality of the app will now be discussed.

The Streams AKI alert

When Streams identifies a potential AKI case (as defined by the NHS England AKI algorithm), a patient-specific notification is delivered directly to the clinician user's iPhone. In current clinical practice, clinicians must distinguish patients with clinically relevant changes in creatinine from those without, through graphical review of current and historical blood tests, or elements of past medical history that indicate disease causality, complications or pre-existing risk. As part of this process, Streams flags high risk blood tests within each alert where specific results are outside the Trust laboratory's 'normal range' (potassium, urea,

calcium, phosphate, lactate and C-reactive protein). The app also provides clinicians with demographic information and past medical history from coded Hospital Episode Statistics (HES) data. These data are displayed in-app alongside the AKI alert to facilitate interpretation and clinical decision making. These functions are displayed in Figure 2.1, below.

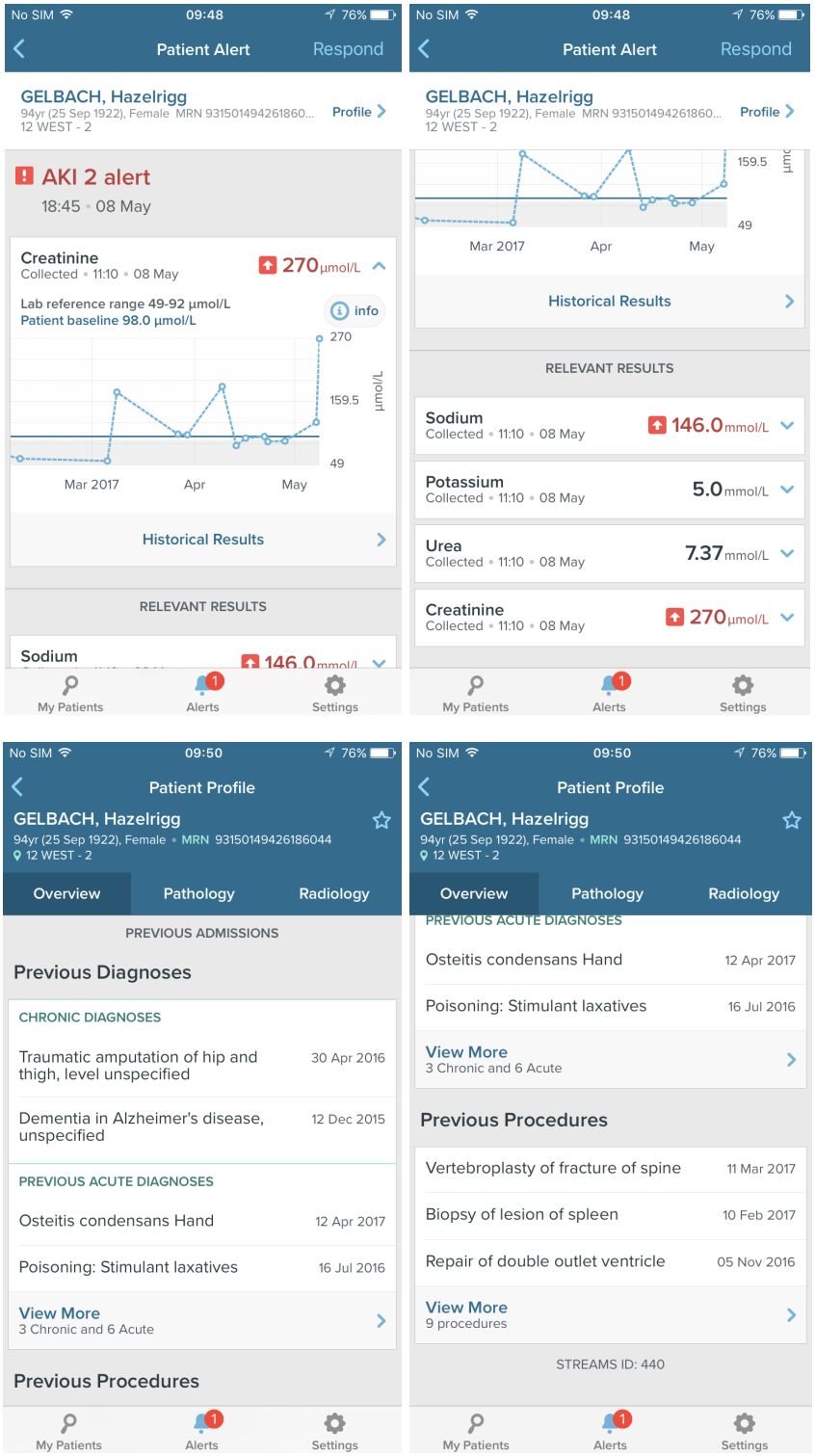

Figure 2.1: The Streams AKI alert (using fictitious patient data). After users select an AKI alert from the menu screen, they arrive at the alert landing screen. Historical creatinine results are displayed graphically; a horizontal line on the graph represents the baseline calculated by the NHS algorithm. Alerts also display the most recent set of bloods sent for the patient, previously coded diagnoses and procedures for each patient.

Filtering of AKI alerts

The sensitivity of the NHS algorithm (i.e. the proportion of AKI patients correctly identified as such) is determined by the algorithm itself. Through comparison with coded diagnoses, this has previously been demonstrated to be >90% on a population level[131]. The specificity (i.e. proportion of cases without AKI correctly identified as such) of the algorithm has not been described. Nonetheless, false positive alerts may be generated in patients with end-stage kidney disease undergoing RRT e.g. where large swings in SCr concentrations occur with dialysis[106]. I thus sought a technical solution to exclude dialysis patients from alert generation. Patients receiving RRT at RFLFT are managed using a separate EHR software system (VitalData, VitalPulse Ltd, Great Dunmow, Essex, UK). I ensured that this EHR sent a feed to the Streams server every evening, using this patient list to suppress AKI alerts where any patient is known to be receiving RRT.

In addition, I decided to filter any alerts for patients admitted to clinical areas where the deployment of the AKI response team would not be expected to improve the care currently being delivered (i.e. the Trust's Acute Kidney Injury or Intensive Treatment Units).

Finally, the NHS algorithm calculates baseline creatinine as the lower of either (i) the lowest value from the last seven days, or (ii) the median value measured between 7 and 365 days ago. It is therefore possible to generate repeated alerts for the same AKI episode, even when creatinine is falling. In order to lessen the 'alert burden' on clinicians, I therefore decided to filter any repeat alert that was generated for an individual patient within forty eight hours, unless the AKI stage had increased or where a new complication of AKI (e.g. hyperkalaemia, acidosis, uraemia) was detected by Streams. As a result, repeated alerts for the same AKI episode would only be sent where the AKI severity is worsening, or where it has not resolved. The impact of such filtering is discussed in more detail below.

Triage of AKI alerts

As part of the 'Best Practice Guidance' published by NHS England, it was acknowledged that AKI alerts may be generated for patients without AKI[119]. I therefore developed a triage tool within Streams, allowing clinicians to triage AKI alerts through review of current and

historical blood tests in-app. This allows the separation of patients with clinically-relevant changes in creatinine from those without. This may occur in a variety of settings:

- Spuriously low baseline selected by algorithm
- Normal variation in creatinine in the context of CKD
- Haemodialysis patient not coded as such
- Repeat alerts for patients in whom creatinine is significantly improved

Streams allows responders to record the results of this triage process, alongside any free text they wish to record. This is displayed in-app (Figure 2.2), allowing clinicians to quickly check which patients they planned to review. A second block of free text may be appended to an alert, allowing users to record the result of any subsequent patient review.

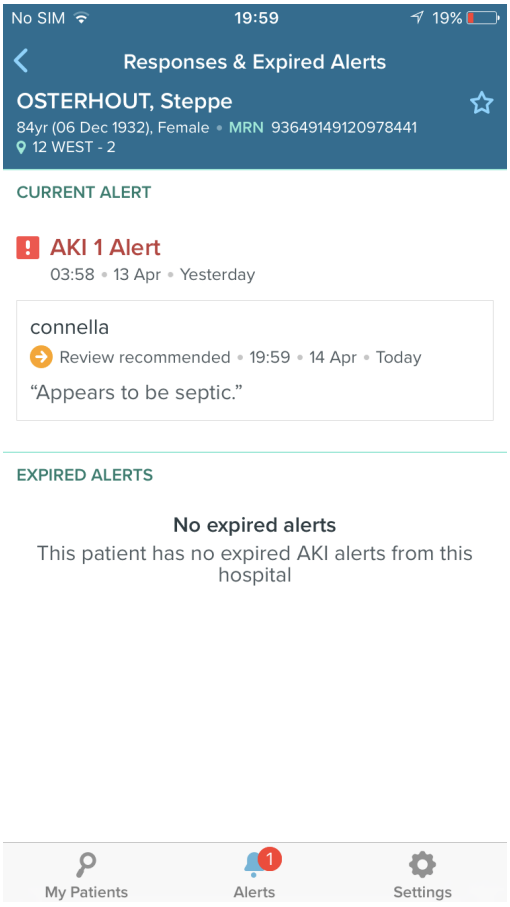

Figure 2.2: Triage of the Streams AKI alert (using fictitious patient data).

Optimising the user interface

I worked alongside a team of designers at DeepMind Health to organise user experience testing. In total, 50 individual 30-minute sessions were run, with both doctors and nurses working in a variety of acute care subspecialties. Attendees were given specific tasks to complete in-app e.g. looking up specific blood test results or triaging an AKI alert, and encouraged to verbalise their thoughts as they moved through the user interface. This feedback was used by the design team to drive iterative improvements to ensure that user interactions with the app became rapid and intuitive. Such development paid heed to the factors which promote uptake and dissemination, referred to above:

- **Compatibility**: Streams was developed to apply the mandated NHS algorithm, and the expressed needs of its intended users, which were explored in detail.
- **Complexity**: Both Streams and it's associated care bundle were designed to be clear and easy to understand.
- **Trialability**: Streams is designed to be deliverable within current hospital resources, and to be open to evaluation
- **Relative advantage**: I engaged to develop the product such as to be superior to existing care pathways in user experience and value to clinicians. I now sought to test its clinical and economic benefit, and qualitative measures of clinician satisfaction.
- **Observability**: Evaluation would allow accrual of data which, if supportive, could be widely disseminated (via scientific journals, national and international meetings/ conferences).

Trust technologies

At the RFLFT, Streams was first installed on six Trust-owned iPhones in December 2016. As well as Streams, I installed and configured the following apps to each:

- **London AKI** (Health Creatives, London, UK). An educational app developed by the London AKI Network. Contains guidelines and care pathways for preventing and managing AKI

- **Sepsis 6** (Health Creatives, London, UK). Lists criteria for the diagnosis of sepsis and details the Sepsis 6 interventions
- **CliniCalc** (Medicon Apps, Copenhagen, Denmark). Contains a list of clinical scoring systems (e.g. Glasgow Coma Score) and calculators (e.g. fractional excretion of sodium)
- **Microguide** (Horizon Strategic Partners Ltd, Leeds, UK). Hosts the Trust's microbiology guidelines
- **NICE BNF** (National Institute for Health and Care Excellence, London, UK). Hosts the British National Formulary
- **Contacts** (Apple Inc., Cupertino, California, USA). Apple's proprietary address book application. Contains contact details for all other members of the response team and technical support phone lines
- **Induction** (Podmedics Ltd., Northwood, UK). A complete list of the Trust phone and bleep numbers
- **Hangouts** (Google Inc., Mountain View, California, USA). An encrypted messaging application. Contains a chat group for messaging all other members of the response team at once
- **Calculator** (Apple Inc., Cupertino, California, USA). Apple's proprietary calculator application
- **Safari** (Apple Inc., Cupertino, California, USA). Apple's proprietary internet browser application

The transmission of AKI alerts to RFLFT-owned iPhones occurs via Trust Wi-Fi. Prior to implementation, it was therefore essential for me to ensure that all clinical areas had adequate Wi-Fi reception. In December 2016 I undertook a review of Wi-Fi connectivity, using a Trust iPhone to connect to the internet in each clinical area. Wi-Fi signal was absent or weak in 2 wards; these were flagged to the Trust Information Management and Technology lead, who installed new routers to boost reception.

The AKI response team

The proposed care pathway included automated referral to specialist clinicians. I therefore created a specialist *AKI response team* comprising RFLFT's existing 'patient-at-risk and

resuscitation' (PARRT) and nephrology teams. The PARRT team (Clinical Nurse Specialists who review at-risk or deteriorating inpatients) received alerts on all patients with AKI stages 2 and 3, and are on-site twenty-four hours a day. The nephrology team comprises a renal consultant and a speciality registrar, both of whom received all AKI notifications. The registrar is on-site twenty-four hours per day and was typically the first responder. The consultant could triage alerts through secure, remote access if off-site, providing clinical supervision and subsequent patient review where needed. Following in-app review of alerts, all patients determined to be suffering from clinically-relevant AKI received a prompt bedside review by a nephrologist, who administered a standardized care protocol (outlined below). The critical care outreach nurse on call received alerts relating to more severe (stage 2 and 3) cases and assisted with the most severely unwell cases according to clinical judgement of patient risk.

All interventions and future care requirements were communicated to responsible clinicians verbally and through a standard written proforma entered into the patient record (outlined below). Where necessary, the clinical response team arranged a further review within 24 hours. The Streams app issued a further alert to the team if the patient's AKI stage subsequently worsened, and also alerted after 48 hours if a patient was still suffering from AKI, as determined by the national AKI algorithm. The team responded to such follow-up alerts according to best practice and clinical judgement.

The AKI care protocol

I used existing best practice guidance[66] to create a list of actions to be completed by members of the response team at bedside review following receipt of an AKI alert:

1. General clinical assessment
2. Assessment and optimisation of circulatory status
3. Assessment, screening and therapy of acute infection
4. Optimisation of current drug therapies (cessation of potentially nephrotoxic drugs, and adjustment of those renally excreted)
5. Ordering of supplemental diagnostic tests
6. Documentation of likely diagnosis (if available)

7. Escalation of care to inpatient nephrology or critical care services
8. Instigation of a monitoring plan
9. Arrangement for a 24 hour follow-up review if necessary

It was advised that the outcome of this assessment, including suggested interventions and future care requirements, should be communicated to a patient's responsible clinicians. I therefore produced a standard written proforma for entry into the patient record that mapped to the above points (see Appendix 1).

Training of Response Team members

I formulated a series of training sessions to be delivered to members of the clinical response team prior to implementation in three parts:

- At two nephrology departmental meetings, I presented the digitally-enabled care pathway to both nephrology and critical care outreach nursing teams
- I recorded a video outlining the Streams app and outlining a standard operating procedure, and circulated it to all response team members
- In the week before they were due to begin a shift with Streams, I planned a final 'face-to-face' induction session, comprising:
    - A detailed review of the app
    - Introduction to the devices being used to host the app (RFLFT-owned iPhones)
    - Review of the standardised digitally-enabled AKI care protocol

The digitally-enabled care pathway was therefore made up of three main parts: (i) real-time diagnosis and mobile notification of AKI (via the Streams app), (ii) the specialist AKI response team, and (iii) the AKI care protocol. Following the development of the care pathway, I then moved to test the functioning of these individual parts prior to implementation.

Testing of Streams and the AKI care protocol

After the development process described above was completed, I oversaw a raft of technical and clinical tests. These tests aimed to discover any technical barriers to implementation, and to ensure the the AKI care protocol was deliverable using available clinical resources. Testing was divided into (i) validation of Streams' AKI detection capabilities, and (ii) trialling the clinical response. These will be discussed in turn.

Validation of AKI detection capabilities

Materials and methods

As part of their best practice guidance, NHS England published a "test script" to allow Trusts to demonstrate that their local implementation of the AKI detection algorithm (Figure 3.1) was functioning correctly[119].

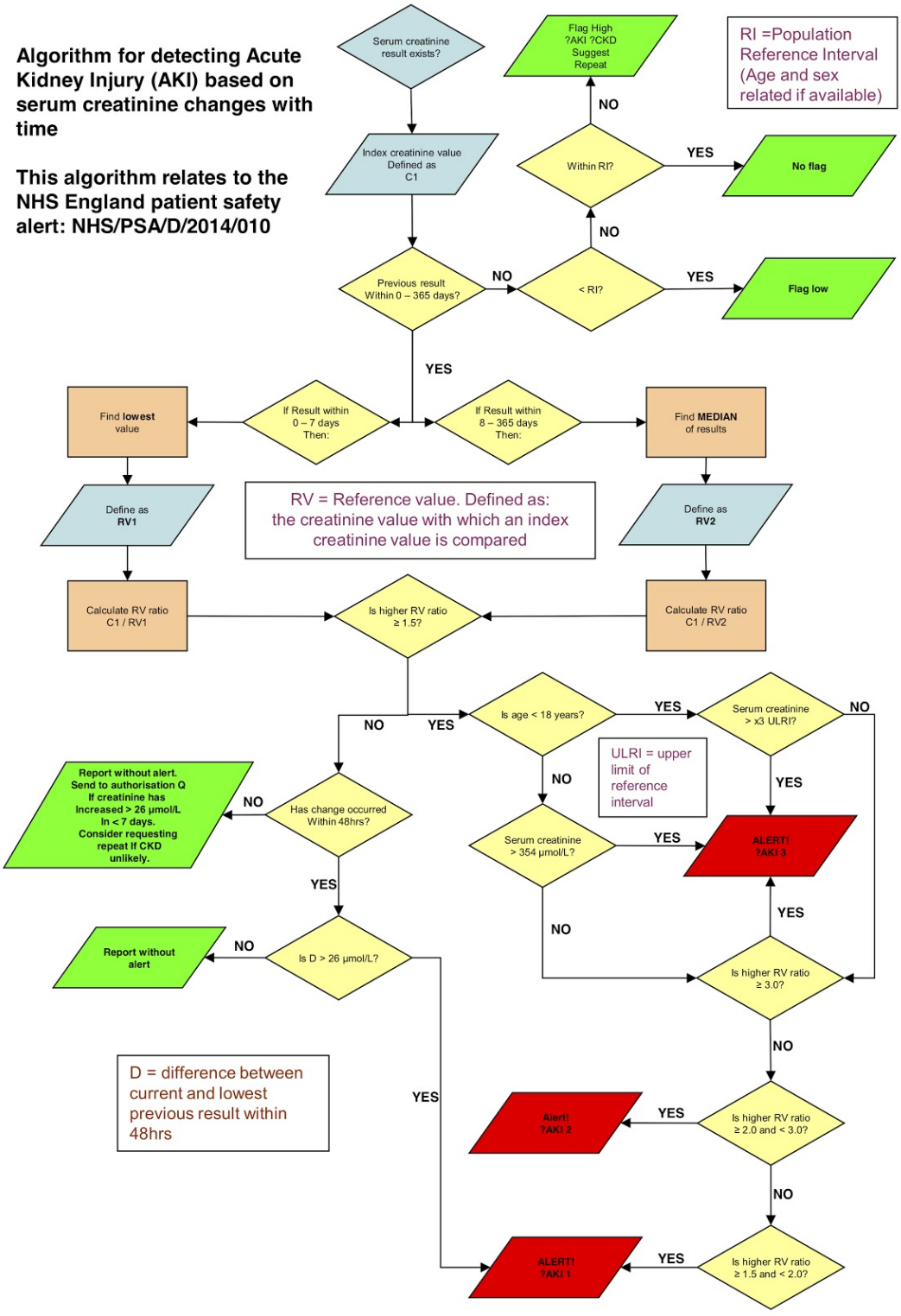

Figure 2.3: **The NHS AKI algorithm**

This test script includes a set of 21 patients, each with a unique set of historical and current creatinine results; individual patients test a separate limb of the algorithm. In order to validate the functions of Streams, I amended this test script in the following ways:

1. Basic AKI detection. Historical and current creatinines from each of the 21 patients in the original test script were not amended.

2. Alert filtering. I added patients to the test database to include patients that met the alerting rules for Streams (outlined in the previous chapter):

- a patient not admitted as an inpatient to RFH
- a patient admitted to clinical areas where the clinical response team would not be deployed (i.e. the Trust's Acute Kidney Injury or Intensive Treatment Units)
- a patient listed on the Trust renal EHR software (VitalData) as receiving haemodialysis

3. Decision support data. As the NHS England test script patients had only SCr results, I added extra results for some of the test script patients to determine whether the presence of the following AKI complications would be flagged in-app at the point of alert:

- a patient with hyperkalaemia
- a patient with uraemia
- a patient with hypercalcaemia
- a patient with hyperphosphataemia

4. Re-alerting rules. For a subset of patients who were expected to generate an AKI alert, I added a further set of SCr results to assess whether the re-alerting rules outlined above functioned as expected.

- A patient with a result consistent with the same AKI stage within 48 hours of the initial alert (who was therefore not expected to generate a second alert)
- Three further patients who were expected to generate a second alert in Streams:
    - A patient with a result consistent with a worsening AKI stage within 48 hours
    - A patient with a result consistent with AKI and a new complication (hyperkalaemia) within 48 hours

    - A patient with a result consistent with non-recovery of AKI 48 hours after the first alert was produced

I led a team of staff from both RFLFT (Biochemistry, Nephrology, Information Management and Technology departments) and DeepMind Health to oversee the testing process. Including the NHS England test script and the patients necessary to test both the alerting functions specific to Streams outlined above, a total of 28 patient scenarios were necessary. With the supervision of the Trust's Lead Biochemist, I created 28 test patients in the Trust LIMS, *WinPath* (CliniSys, Chertsey, Surrey, UK). For each, I inputted all historical creatinine results, before authorizing them and posting them to the Trust EHR software, Cerner (Cerner Corporation, Kansas City, Missouri, USA). This process matched the current RFLFT system architecture and processes used in the reporting of pathology results. Historical creatinine results were backdated in order to exactly match those from the patient scenarios described above.

On 3 consecutive testing days, the following testing procedure was carried out:

- using Cerner, test patients were admitted to the hospital. The mode (i.e. inpatient vs. outpatient) and location (i.e. specific ward) of admission were defined by the patient scenarios
- pathology results (as defined by the patient scenarios) were added to WinPath and authorized
- pathology results for each patient were viewed in Cerner to ensure they had been passed to the EHR successfully
- any AKI alerts generated in Streams were viewed with an engineer from DeepMind Health and a clinician from RFH to ensure each was generated and presented in-app, and that any additional functions of Streams (e.g. highlighting of AKI complications) occurred as expected
- any deviation from these behaviours was recorded in a testing log

Results

For all patients, historical creatinine results were added to Cerner successfully. Alerts were generated and represented in-app as expected for 26 of the 28 scenarios. After working with

engineers from DMH and clinicians from the biochemistry department, I uncovered the reasons for this variance were as follows:

- in one scenario, a test patient was not successfully added to the list of patients receiving haemodialysis in VitalData before this list was sent to the Streams server the night before
- in one scenario, a high calcium result that was included to test the surfacing of high risk blood tests was so high (4.0mmol/L) that it was above a critical threshold requiring special authorization by a consultant biochemist prior to being released to Cerner. As a consequence no results from the same sample (including the creatinine that would have resulted in an AKI alert being generated) were authorized.

In both instances, a repeat test of the scenario in question resulted in the expected alert behaviour. The initial failure of these two scenarios related to operator error (in the case of the haemodialysis patient), and a behaviour of the Trust LIMS that I was not aware of at the time of scenario design. It is of course proper that blood tests that are extremely out of range (and might therefore indicate an error in collection or analysis) are authorized by a senior clinician before being released to the EHR software.

Overall, the tests confirmed that Streams had successfully embedded the NHS diagnostic algorithm, and that the clinical decision support functions of the app worked as expected. Importantly, the filtering of patients not admitted to the hospital and receiving haemodialysis was found to be effective. How this filtering affects the overall number of alerts will be reviewed in subsequent chapters.

Trialling the clinical response

Materials and methods

To establish whether the proposed clinical review, completion of AKI proforma, and a brief clinical handover could be done in a reasonable time-frame, I organized a testing session in the RFLFT Medical Simulation Centre in August 2016 with four trainee nephrologists (Specialist Trainee level 3 and above). I recruited this cohort from the group of registrars who would be staffing the AKI response team. I designed three mock patient scenarios (see Appendix 2) which used the Trust's *SimMan* patient simulator (Laerdal, Stavanger, Norway)

and to which the registrars had to respond. Scenarios were designed to reflect a range of clinical presentations (severe sepsis, obstruction, and heart failure) and patient locations (Emergency Department, surgical and medical wards).

The session began with an explanation of the new care pathway, incorporating the use of Streams and AKI response team. Copies of the AKI care protocol were distributed. This was then discussed by the group in an unstructured fashion, gathering general feedback points. Individual nephrologists then took it in turns to complete the prepared simulation scenarios, rotating through different roles (reviewing nephrologist, responsible clinician, staff nurse). After each scenario was complete, the group reconvened to discuss which parts of the clinical review and proforma worked well, and where they might be improved.

Results

Including handover, each scenario lasted between fifteen and twenty minutes in total. At the end of the session, the group reconvened to discuss how they felt the AKI proforma might be improved. Gathered feedback broadly related to the following two points:

- that the protocol was too long
    - several members of the group highlighted that, at 10 pages, it resembled the Trust's medical patient clerking proforma, and that it was too structured
- that the scope of the proforma was too specific and not generalizable
    - clinicians pointed out that the nature of response might be different when reviewing patients in different locations or clinical settings. As such, they might waste time reading and filling out sections of the proforma that were not relevant, or end up repeating data that another clinician had already recorded in the clinical record.

To incorporate these feedback points, I edited the proforma to make it significantly shorter (from 7 pages to 3 pages, see Appendices 1 and 3). In doing so, the amended proforma focused on key clinical findings (e.g. the presence or absence of life threatening complications), and the likely cause(s) of AKI. To account for the expected variation in patients reviewed, I included an expanded free text area for clinicians to record their overall

impression and suggested management plan. These amendments were discussed with and presented to both the Trust lead for the AKI, and the project implementation team.

Summary

The digitally-enabled care pathway was designed to specifically address the principal deficiencies identified in the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) AKI report[105]: failures in AKI recognition, the delivery of early therapy, and escalation to specialist or critical care services. Each component was also designed with the specific needs of users (i.e. response team members) in mind.

As outlined above, I tested the function of each constituent part of the care pathway individually prior to rollout of the broader pathway. In advance of the implementation of the entire care pathway (which occurred in January 2017), I then moved to plan the conduct of an evaluation of its effectiveness. This will be discussed in the next chapter.

Chapter 3: Planning an evaluation of the pathway

Introduction

Whilst technology products and services have transformed everyday life[138], technological change in healthcare has been variable. In many settings, the use of paper and pre-millennial technologies such as pagers continues to be the norm, despite concerns about the impact of their use on productivity and happiness at work[139,140].

There is, however, light at the end of the tunnel. In Finland, the use of emails to communicate between clinicians and patients has been routine for almost 15 years[141]. In the United States (US), several large health providers offer patient portals that are used for online access to clinicians and routine telephone consultations[142]. In the UK, telephone and website services designed to provide patients with a 'non-emergency' point of entry to the healthcare system[143] have recently been enhanced by the launch of the NHS app[144], and the use of fax machines in the transmission of patient data is to be phased out[145]. Technology holds much promise in the health sector[146], and substantial thought has gone into preparing the workforce to deliver on this promise[147]. It is now commonplace for practicing clinicians to be involved in the design, manufacture and dissemination of technology in health[148].

However, the rapid pace of development of such digital tools should not be at the expense of providing evidence of benefit. In a landmark editorial discussing this issue - described as "digital exceptionalism" - The Lancet described, "a failure to agree on what constitutes appropriate evaluation before widespread roll-out" as a common problem[149]. Evaluation of digital interventions is important for a number of reasons. Firstly, evaluations of safety and cost-effectiveness ensure technology delivers real value to a health system, and does not entrench existing biases and health inequalities[150]. Secondly, innovations do not exist in isolation, but become part of a complex socio-technical healthcare system[151]; the replacement of existing technologies and practices with digital products might therefore reasonably be expected to have unexpected consequences, which should be specifically sought and quantified[152]. Failing to robustly evaluate digital health interventions therefore presents a significant risk for both patients and broader health systems[149].

I sought to understand the impact of the digitally-enabled care pathway on patients, clinicians, and the health system it was embedded in. In order to do so, I led the design and conduct of an evaluation that used a mixture of quantitative and qualitative methods. This chapter will discuss each of the methods proposed in turn.

Sites

I oversaw implementation of the digitally-enabled care pathway at a single hospital site within the RFLFT: the RFH, an 800-bed teaching hospital which also provides diverse specialist and tertiary services, including a dialysis unit and 34-bed intensive care unit with RRT onsite. I decided to compare clinical outcome data for patients admitted to the RFH before and after implementation. However, this approach would now allow me to control for any secular trend change in clinical outcomes not related to implementation. I therefore decided to collect further control data from a second hospital that is part of the RFLFT, and in which the digitally-enabled care pathway was not implemented. Barnet General Hospital (BGH) is a 450-bed district general hospital providing acute care including onsite RRT, a 12-bed ITU and on-site nephrology services. BGH had similar arrangements for the care of AKI patients to that at the RFH prior to the implementation of the digitally-enabled care pathway.

The Pre-implementation care pathway

Prior to the deployment of the care pathway outlined above, AKI at both RFLFT hospital sites was commonly managed in its early stages by general acute care and various specialty teams. An historic AKI detection algorithm in the RFH LIMS (which predated the NHS England algorithm) identified potential AKI cases and presented a message for clinicians in the EHR. This message also flagged the availability of clinical guidance and education (via the London AKI Network website[153]). In the historic care pathway, such results were normally batch-reviewed by non-specialists at the end of the day and may only have been seen several hours after the results first became available. Clinicians may have opted to review results earlier, but this process relied upon repeated accessing of the results systems, as clinicians had no way of knowing when results were ready. Where blood tests suggested

AKI, this may have been communicated by telephone to the clinical teams responsible for the patient by the biochemistry laboratory. However, this process was cumbersome and may have been unreliable.

Specialist nephrology review of kidney function blood tests or of patients with AKI only occurred if requested by the patient's responsible clinical team. This required the responsible team to assess kidney function results, assess the patient, decide to option a specialist review, contact the renal team via phone or pager systems and await a response. The renal team would then receive verbal referral information or would manually access results and other clinical data to prioritise the referral, managing information relating to multiple referrals with paper-based processes. The hospital's critical care outreach team previously received no automated referrals and were entirely reliant on being contacted by pager systems when ward staff were concerned that a patient was deteriorating. The RFLFT had deployed clinical guidelines and had an active AKI education programme to support clinical teams, but as outlined in Chapter 1, local audit showed that performance in managing AKI at RFH varied, and had not always consistently met national standards.

Figure 3.1 outlines the principal components of both the pre-implementation and digitally-enabled care pathways.

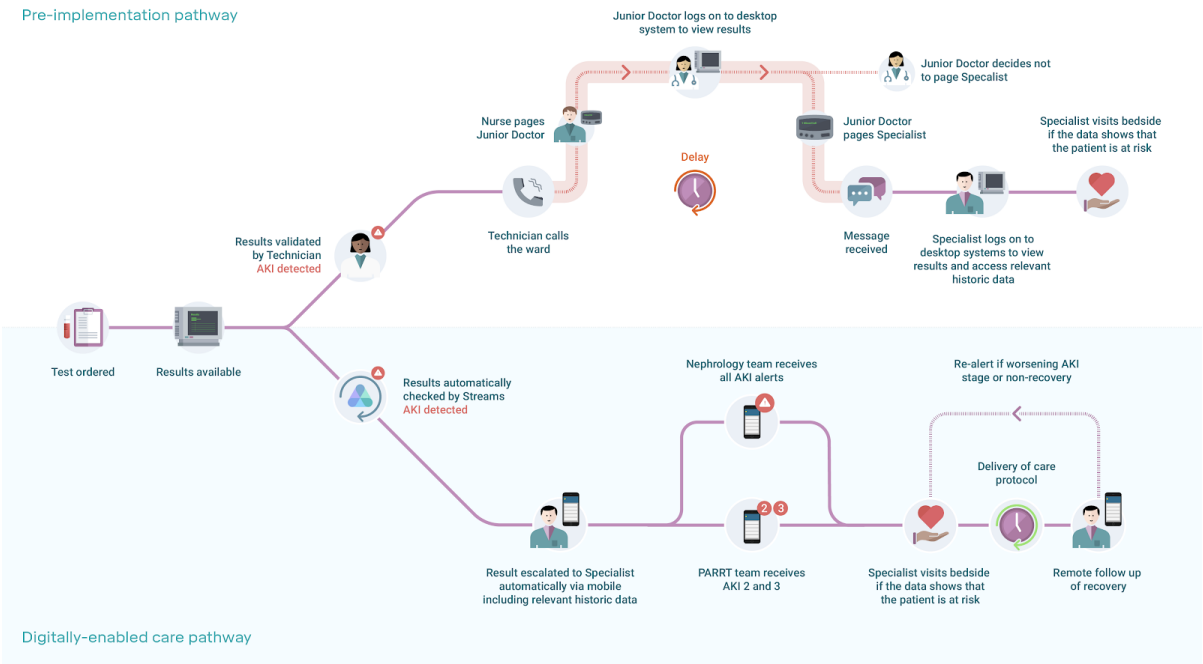

Figure 3.1: Pre- and post-implementation care pathways

As Figure 3.1 demonstrates, the principal aims of the digitally-enabled care pathway were to reduce the time-frame in which AKI was diagnosed and the time-frame in which a specialist was notified of the presence of AKI, so as to accelerate the provision of effective treatments and supportive care. To understand the nature and scale of the impact this care pathway had on the RFH, I designed an evaluation that included quantitative and qualitative elements. Each will be discussed in turn.

Outcome framework

Quantitative evaluation

I selected recovery of renal function as the primary outcome of the evaluation, which I defined as a return to a creatinine level to within 120% of the baseline specified by the National AKI algorithm (Figure 2.3) prior to discharge from hospital, as per the Renal Association Clinical Practice Guidelines on AKI[154]. I convened a meeting with my supervisors to discuss the selection of secondary outcome measures to more fully

understand the impacts of the care pathway. In keeping with existing literature[132,155–157] and with the most recent ADQI consensus statement on electronic alerting for AKI[158], we selected a range of secondary clinical (e.g. mortality; requirement for RRT) and operational (e.g. length of stay; readmission to hospital) outcomes (Table 3.1). Each was selected to reflect the known sequelae of AKI. To understand how any modifications in these sequelae related to changes in the time-frames in which key treatments were delivered, I selected a range of process outcomes (Table 3.2). I also hypothesized that the implementation of the care pathway would lead to a reduction in the cost of care provision. To this end, I planned an analysis of economic Payment Level Information and Costing System (PLICS) data, and local/ Payment by Results tariffs at the RFLFT. Outcomes were therefore categorised into four areas: processes of care, clinical outcomes, Trust-wide metrics, and NHS costs.

Outcome measure	Definition	Source of data
Recovery of renal function	Return to <120% index creatinine (as defined by NHS diagnostic algorithm) by the time of hospital discharge	HL7 data aggregated within the Streams data processor
Time to recovery of renal function	The time from AKI alert to recovery of renal function (<120% index creatinine)	HL7 data aggregated within the Streams data processor
Progression of AKI stage	Movement between AKI severity classes following AKI alert and prior to hospital discharge	HL7 data aggregated within the Streams data processor
Cardiac arrest rate	Number of cardiac arrests (on wards where alerts are active) per 1000 bed days	Trust critical care outreach team logs
Mortality	Death in 30 days following AKI alert	HL7 data aggregated within the Streams data processor
Length of stay	Time from AKI alert to hospital discharge	HL7 data aggregated within the Streams data processor
Admission to high acuity or specialist renal inpatient bed	Admission to Acute Kidney Unit (AKU), High Dependency Unit (HDU) or Intensive Treatment Unit (ITU)	HL7 data aggregated within the Streams data processor
Length of stay in high acuity bed	Length of stay on AKU/ HDU/ ITU	HL7 data aggregated within the Streams data processor
Requirement long-term RRT	Use of RRT in 30 days following hospital discharge date	Trust Nephrology Information Management System (VitalData) and Health Episode Statistics Admitted Patient Care database.
Readmission to hospital	Re-admission to hospital in 30 days following index admission discharge date	HL7 data aggregated within the Streams data processor

Table 3.1: Definitions and data sources for clinical outcomes. *Health Level 7 (HL7) messages are used to transfer information between different healthcare IT systems

Outcome measure	Definition	Source of data
Recognition of AKI	Time of documentation of recognition of AKI in written notes	Electronic/ paper note review, data aggregated within the Streams data processor
Time to treatment	Time of documentation of: - Delivery of antibiotics for sepsis - Delivery of fluid for hypovolaemia - Relief of obstruction - Withdrawal/adjudication of nephrotoxins - Definitive treatment for parenchymal kidney disease	Electronic/ paper note review

Table 3.2: Definitions and data sources for process of care outcomes

Participants

As outlined in the previous chapter, the Streams app automatically filtered alerts for selected patient groups. The inclusion and exclusion criteria I specified for the evaluation are as follows:

Included were

- Inpatients aged 18 or over triggering an AKI alert as defined by the NHS AKI detection algorithm

Excluded were

- Inpatients on the Acute Kidney or Dialysis Unit or ITU, where the care of patients developing AKI was expected to derive no additional benefit from protocolised review
- Patients with active diagnostic codes for end-stage renal failure

The NHS algorithm can produce false positive alerts[131]. As outlined in the previous chapter, this can happen in a number of specific clinical scenarios in the absence of any clinically-relevant change in kidney function e.g. where the algorithm selects a spuriously low “baseline” creatinine. I therefore decided to include only clinician-confirmed episodes of AKI in the analysis. For patients at RFH after the implementation period, I decided to use the results of alert triage performed by members of the AKI response team. However, AKI alerts produced during historical control time periods and at BGH would need to be triaged.

Furthermore, I determined that such triage should take place using the same clinical data that were available to clinicians using Streams in the live clinical environment. As a result, I worked with engineers at DMH to produce a version of the app that processed historical data and produced AKI alerts for all control time periods at both RFH and BGH. Alerts produced in this app removed all personally identifiable information about patients and their admission details. Using this app, I planned to triage all control AKI alerts, with the assistance of a consultant nephrologist (Dr. Chris Laing, see *Personnel*, below).

Sample size and power calculation

I discussed various analysis options with my supervisors. A randomized controlled trial might have been subject to considerable contamination bias. Furthermore, the digitally-enabled care pathway was to become the new standard of care at RFH; as such, RFLFT may have found it ethically and operationally unacceptable for this pathway to have been active for only a portion of the patients admitted. I also considered stepped wedge cluster randomization. However, having discussed these plans with the UCL Joint Research Office, I determined that such a design would require the randomization of a large number of individual clinical areas and would therefore be impractical. After discussion with my supervisors, I planned to use an interrupted time series segmented regression analysis to analyse the data collected.

For the interrupted time series segmented regression analysis, each dependent variable was measured as a weekly proportion, and modelled using a generalized linear model assuming a binomial distribution and using a logit link, allowing me to test for a change in level and/or regression slope following the implementation of the intervention. This modelling approach ensured that predicted values yielded from the model could not fall outside of the valid (i.e. 0-100%) range. I planned to check for autocorrelation in the model, which can be an issue with time series data.

At the beginning of my PhD, there were no published sample size calculations available for determining the number of timepoints needed for an interrupted time series design. However, I used a simulation study approach, implementing the SIMSAM command in *Stata* (StataCorp LLC, College Station, Texas, USA) to establish the sample size needed, with the

help of Dr. Claire Nightingale (see *Personnel*, below). We produced simulated data for the four years prior to the intervention (i.e. where the intervention occurred at 208 weeks). The average baseline recovery rate was assumed to be 0.51 (standard deviation 0.08) which was determined using one year of pre-intervention data from the RFH. One hundred observations (patients) or more per time point are encouraged[159]; the historical data collected confirmed that this was a viable assumption based on historical data. We generated a normally distributed random variable with mean of zero and standard deviation of 0.08 to simulate the variation in recovery rate. The pre-intervention regression slope, the change in the effect of the intervention over time following the intervention were all assumed to have an odds ratio of one. The recovery rate was generated as a function of these effects, the average baseline alert rate and the random variable.

The number of timepoints needed to detect an odds ratio of 1.15 for the intervention effect with 90% power assuming a significance level of 5%, determined by simulation, was 11 weeks in total. This number of post-intervention timepoints increased to 32 weeks if the effect to be detected is an odds ratio of 1.1 i.e. a 10% increase in the odds of recovery. The number of timepoints needed to detect an odds ratio of 1.1 for the intervention effect with 80% power assuming a significance level of 5%, determined by simulation was 20 weeks in total.

Timelines

As the analysis of data employed an interrupted time series, the implementation period was split into two distinct phases. Firstly, a 12 week *formative phase*, during which the intervention was embedded. No clinical outcome data were collected from this period. Following this, an 18 week *summative phase* began, during which clinical outcome data were accrued. For comparative analysis, I collected data from the intervention and control sites relating to three time periods:

- One year before deployment (May to September 2016)
- Immediately before deployment (September 2016 to January 2017)
- During deployment (May to September 2017)

Figure 3.3 outlines the timeframe for each phase of the service evaluation as described above.

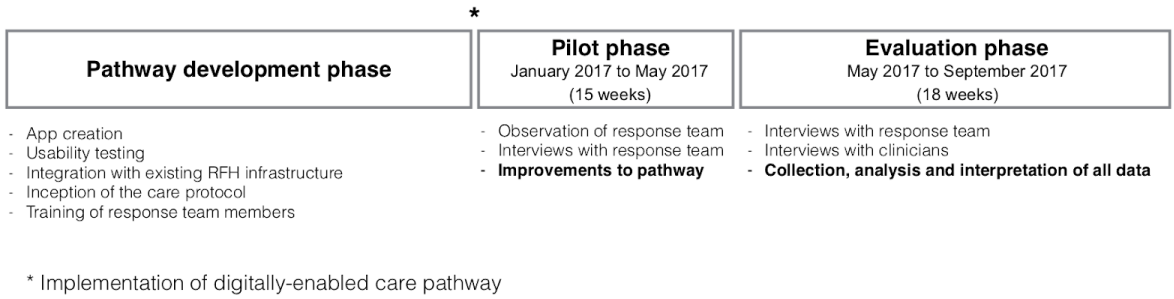

Figure 3.2: Phases of the service evaluation

Qualitative evaluation

In order to evaluate barriers to service provision, and the acceptability of use for end users, I planned a series of semi-structured interviews; this technique allowed me to divert from a set of questions to more thoroughly explore themes of interest during an interview. Interviews were carried out throughout the deployment period. In order to determine the impacts of the care pathway on the broader health system, I carried out interviews with a selection of AKI response team members (including nephrology consultants and specialty registrars, and critical care outreach nurses) and clinicians responsible for patients who had been reviewed by the AKI response team during the evaluation. I employed purposive sampling, following a key informant strategy[160], which identified individuals with important roles in the study environment who had expert knowledge to share impartially. I aimed to carry out twenty interviews (a sample size typical for a case study such as this, and in line with both international consensus guidance and common practice in qualitative research[161,162]), seeking a diverse range of clinical experience and level of comfort with mobile technologies.

I developed an interview guide with the broader research team, which included physicians with extensive experience in clinical Nephrology and Intensive Care Medicine, and experts in Health Services Research. The interviews explored whether the clinical response team members found that the new care pathway helped them provide better quality care for patients, which aspects of the digitally-enabled pathway worked well or where they might be

improved, whether they experienced any adverse consequences of app use, and whether they noted any unexpected indirect beneficial or adverse effects (see Appendix 4).

Ethical considerations

Approvals

Plans for the evaluation of the digitally-enabled care pathway were independently reviewed by the UCL Joint Research Office. They directed that this project fell under the remit of service evaluation, as per guidance from the NHS Health Research Authority[163]. As such, the service evaluation was registered locally with the RFLFT Audit Lead and Medical Director. The service evaluation was approved by the RFLFT Executive, RFLFT Board and Sub-Board Patient Safety Committee (which included patient governor representatives, a non-Executive Chair and an RFLFT Board Member).

Use of patient data

RFLFT used Streams as part of its provision of care for patients. To support this service, DeepMind Health processes Patient Identifiable Data. This is in line with the governance arrangements for all other clinical software applications and this arrangement forms part of a data processing agreement with the Trust, which they published on their website. The digitally-enabled care pathway was a new standard clinical service at RFH and under NHS guidance there were therefore no consent requirements for patients for the processing of their personally identifiable data for direct patient care functions.

Pseudonymisation, confidentiality and data storage

I organized access to space in UCL's Data Safe Haven and organized the signing of a new data sharing agreement between the University and RFLFT such that clinical outcome data could be transferred securely and legally. Each patient was allocated a unique identifier code at the point of data extraction. Data were stored in a Relational Database Management System (MySQL, Oracle Corporation, Redwood City, USA). Patients' personal data (e.g. hospital ID number, postcode) was not recorded next to any clinical data.

Personnel and oversight

Core research team

I formulated and directed my PhD plans under supervision. In so doing, I relied upon the support and education of several key individuals who have complementary skills. Three (HM, RR and PM, below) also acted as my formal PhD supervisors.

Hugh Montgomery (HM), Professor of Intensive Care and Director of the Institute of Human Health and Performance, UCL. Hugh has extensive experience in the assessment of AKI in 'outreach' roles, and in its ward- and ICU-based management and has published over 300 papers. Prior to the inception of the digitally-enabled care pathway, he had been working with Dr. Laing on a data analytics project relating to AKI for over three years, which initiated the development of the current app. He provided oversight on the design of the evaluation, as well as the analysis and interpretation of results, and was my primary PhD supervisor.

Rosalind Raine (RR), Professor of Health Care Evaluation, Head of Department of Applied Health Research at UCL and Director of NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames is a public health doctor and mixed (quantitative/qualitative) applied health researcher who has extensive expertise in the evaluation of health care innovations using experimental and observational research methods. She provided oversight on the design of the evaluation, as well as the analysis and interpretation of results. She was one of my secondary PhD supervisors.

Peter Martin (PM) is a Lecturer in applied statistics at the UCL Institute of Epidemiology and Health. He provided oversight of the analysis and interpretation of results. He was one of my secondary PhD supervisors.

Chris Laing (CL), consultant nephrologist at RFH and University College London Hospitals. He is the founder of the London AKI Network, sits on the national AKI programme board, and leads a large scale AKI improvement programme with UCL Partners Academic Health Science Network. With Prof. Montgomery, he was responsible for the inception and

development of the Streams project to date. He oversaw the implementation of the care pathway at the RFH.

Steve Morris (SM), Chair in Health Economics, Institute of Epidemiology and Health, UCL, was responsible for overseeing the economic evaluation of the care pathway.

Claire Nightingale (CN), Lecturer in Medical Statistics, Queen Mary University of London, oversaw the statistical planning at the project's inception.

Implementation team

I convened an implementation team at RFH. I selected the members of the team to reflect the different stakeholders involved, recruiting the clinical leads from the two teams making up the AKI response team (i.e. PARRT and nephrology), as well as a nephrology registrar (who was also part of the AKI response team), a program manager from DMH, and two members of the RFH Patient Safety Team. In the months leading up to implementation (and for 2 months after implementation), we met on a weekly basis. These meetings sought to uncover barriers to the smooth running of the new service, and to help drive iterative improvements in the care pathway.

Steering committee

A project steering committee was convened at RFH. They reviewed the project and evaluation plans, as well as reviewing the results of all interim and final analyses on behalf of RFLFT. As it was important that this group operated independently of the core research group, this committee included an independent chair with no relationship to the project, a patient member, a member of the Royal Free Kidney Patients Association, and a nephrologist from a different NHS Trust.

Patient and public involvement

I presented the Streams project to the CLAHRC North Thames Patient and Public Involvement Panel in 2016. In advance of the meeting, members of the panel had the

opportunity to read a lay summary of the project plan. My presentation was followed by a question and answer session. The project was subsequently mentioned in their newsletter and the CLAHRC annual report. The project had the full support of the Royal Free Kidney Patients Association, and was the subject of an article in their bi-monthly newsletter in January 2017.

Peer review

I wrote and published a protocol outlining plans for the mixed-methods service evaluation in an open access, open peer-review scientific publishing platform (F1000)[164].

Summary

New technologies and pathways of care might offer hope at a time when resources in the NHS are being stretched to their limits[165]. However, it is vital that such pathways are subject to robust and broad-ranging evaluations of safety and cost-effectiveness[150]. I planned the evaluation outlined above, with clinical and academic oversight from my PhD supervisors, before writing-up and publishing these plans. As discussed in the Introduction to this chapter, the replacement of existing technologies and practices with digital products should be expected to have unexpected consequences[152]. The interrupted time series analysis planned allowed for a 15 week pilot phase after implementation, during which time such consequences could be sought and addressed - these will be detailed and discussed in the following chapter.

Chapter 4: Observations from implementation

Introduction

As outlined in the previous chapter, the design for the evaluation of the digitally-enabled care pathway - an interrupted time series analysis - allowed a period following implementation from which no clinical outcome data would be collected, and during which the care pathway could be optimized. I therefore set out to use this time to seek and address any barriers to implementation. This chapter details how I approached this problem and how the barriers encountered were addressed.

Alert numbers

During the first 28 days of implementation, a total of 25,252 serum creatinine results were processed by the RFH laboratory. This generated a total of 578 AKI alerts, a mean of 20.6 per day (standard deviation 5.7). Filtering for patients receiving haemodialysis and outpatients was found to be effective; for the same time period, 1638 alerts would have been produced without filtering in place.

Although the majority of alerts were for patients in the ED, they were generated from a wide variety of inpatient ward locations, as shown in Figure 4.1.

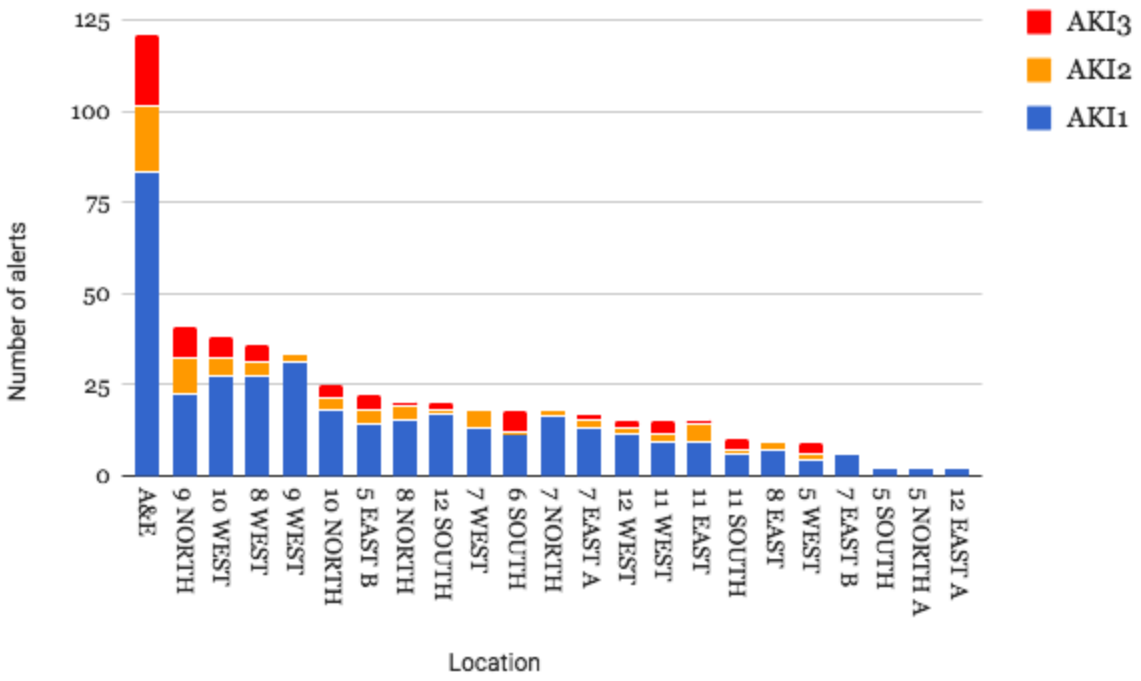

Figure 4.1: Distribution of AKI alerts for the first 28 days of implementation. A&E: Emergency Department; 9 North = Hepatology; 10 West = Cardiology; 8 West = Health Services for Elderly People; 9 West = Hepatobiliary; 10 North = Health Services for Elderly People; 5 East B = Renal Cancer; 8 North = Medical Acute Admissions; 12 South = Private Patient Unit; 7 west = General Surgery; 6 South = Stroke & Neurology; 7 North = Plastic Surgery and Gynaecology; 7 East A = Trauma and Orthopaedics; 12 West = Private Patient Unit; 11 West = HIV and Infectious Diseases; 11 East = Oncology; 11 South = Haematology; 8 East = Respiratory; 5 West = Labour Ward; 7 East B = Orthopaedics; 5 South = Postnatal Care; 5 North A = General Surgery; 12 East A = Oncology

Alert triage data

During this time period, alerts were reviewed by a member of the clinical response team within a median of 14 (interquartile range 1 - 60.5) minutes after it was generated. Of the 578 alerts generated, 153 were triaged as having a clinically relevant change in creatinine and marked for review by at least one member of the response team. This equated to a mean of 5.5 patient reviews per 24 hours (standard deviation 2.9).

Addressing barriers to service provision

During observation of team members, a number of barriers to service provision and some unexpected consequences of app use were uncovered.

Materials and methods

During the implementation of the digitally-enabled care pathway, I gathered feedback from members of the response team in three distinct ways:

- **Direct observation of response team members**
    - During the first four weeks of implementation, I shadowed individual members of the response team, observing user behaviour in the ED and on inpatient wards during day and evening shifts, using extensive note taking to document users' interaction with the Streams app and impacts on working practices and inter-professional relationships.
- **Weekly implementation team meetings**
    - Members of the implementation team met weekly to discuss improvements that would contribute to the smooth running of the new clinical service.
- **Semi-structured interviews**
    - As outlined in the previous chapter, I carried out interviews with members of the response team. These took place throughout the pilot and evaluation phases, and were specifically intended to help me understand which aspects of the digitally-enabled pathway worked well and where it might be improved, adverse experiences or consequences of app use, and any unexpected indirect beneficial or adverse effects. Any points from interviews carried out in the pilot phase that related to barriers to service provision or unexpected consequences of app use were used to drive improvements in the service.

Results

Barriers uncovered related to both the Streams app and the broader care pathway.

The Streams app

Early in the implementation of Streams, users reported that the loading of data in-app was occasionally delayed by about 5 seconds. In frustration at not being able to see relevant data quickly whilst busy, some users reported that they would often put down their phones and carry on with other clinical tasks before returning to the alert in question much later in their shift. This was fed back to engineers at DMH who instituted a minor change to the app, which stopped this from happening. Many users also reported frustration that they could not tell when an alert had been viewed or triaged by other team members. This might have led to duplication of work (where the same alert was triaged by several different users). In addition, users wanted to be able to mark in-app which patients had received a clinical review, and to be able to communicate the outcome of such reviews to other team members. With these points in mind, I worked with designers at DMH to produce a larger update to Streams.

Following this update, the outcome of alert triage was shared with all other members of the team instantly. As in the previous version of the app, users were also able to enter free text, such as the reason why an AKI alert was dismissed or the outcome of clinical review. Each response was stored and displayed against the AKI alert, allowing clinicians to quickly and intuitively prioritise patients for review based on clinical need and the behavior of other team members. These functions are outlined in Figure 4.2.

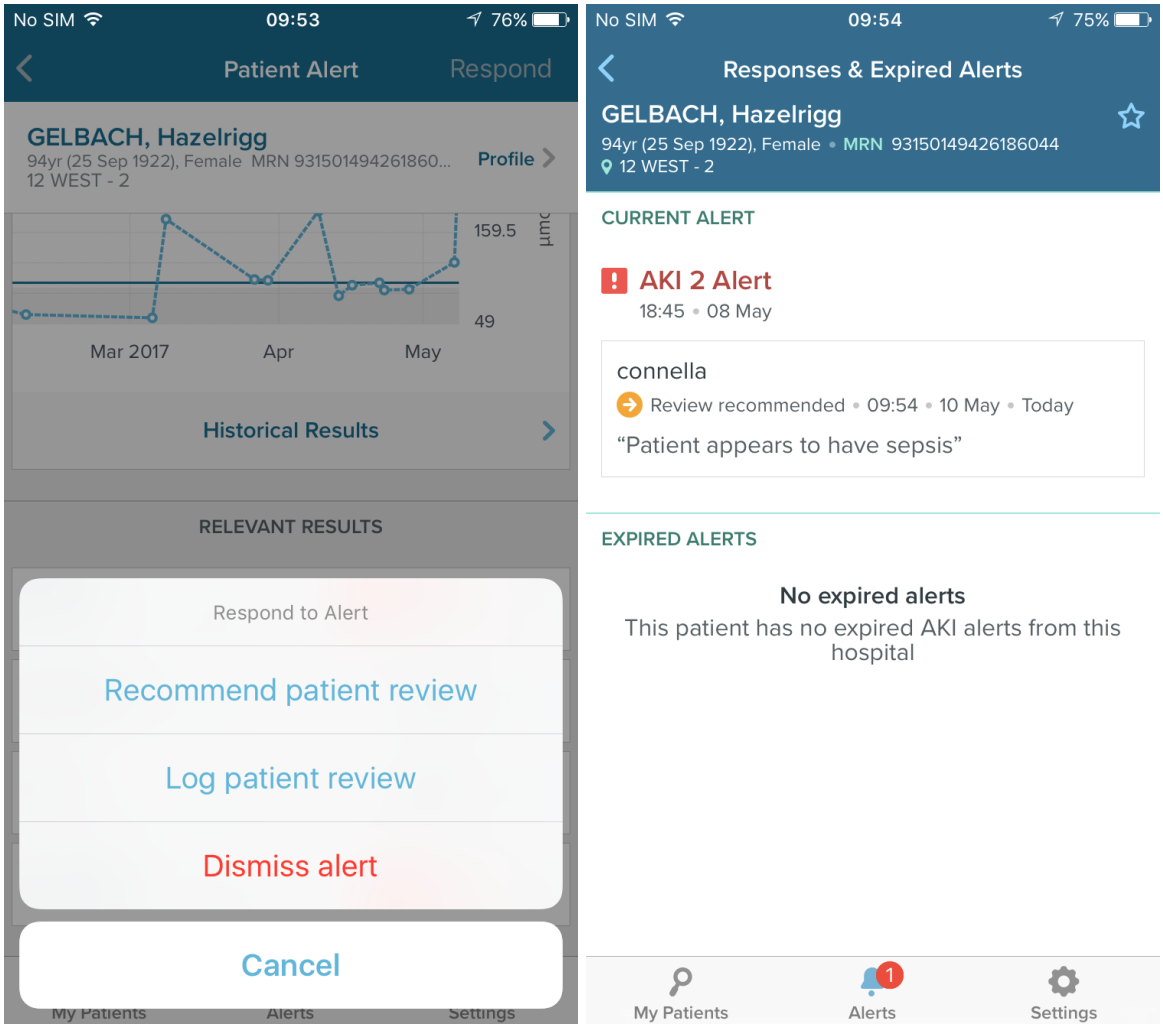

Figure 4.2: Alert triage and recording the clinical response in Streams (app version 1.2) using fictitious patient data. When triaging an alert or logging a patient review, users could now input a message as free text. In addition, alert responses were instantly visible to all other users.

The broader care pathway

Alert times

As outlined above, the AKI response team would deploy to review between 5 and 10 patients per 24 hours. Several clinicians reported that the majority of alerts would arrive over a relatively short period of time in the afternoon, and that their arrival coincided with a time of day where clinicians might be busy with other clinical commitments (e.g. reviewing patients in the ED). They may also struggle to order appropriate diagnostic investigations at this late stage in the working day. As the timing of alerts is a function of when blood test results are

released by the laboratory, I sought to establish if there were any avoidable delays in the process of blood tests being taken and analysed.

Figure 5.3 displays the time of day that creatinine results were released by the laboratory during the first 28 days of implementation.

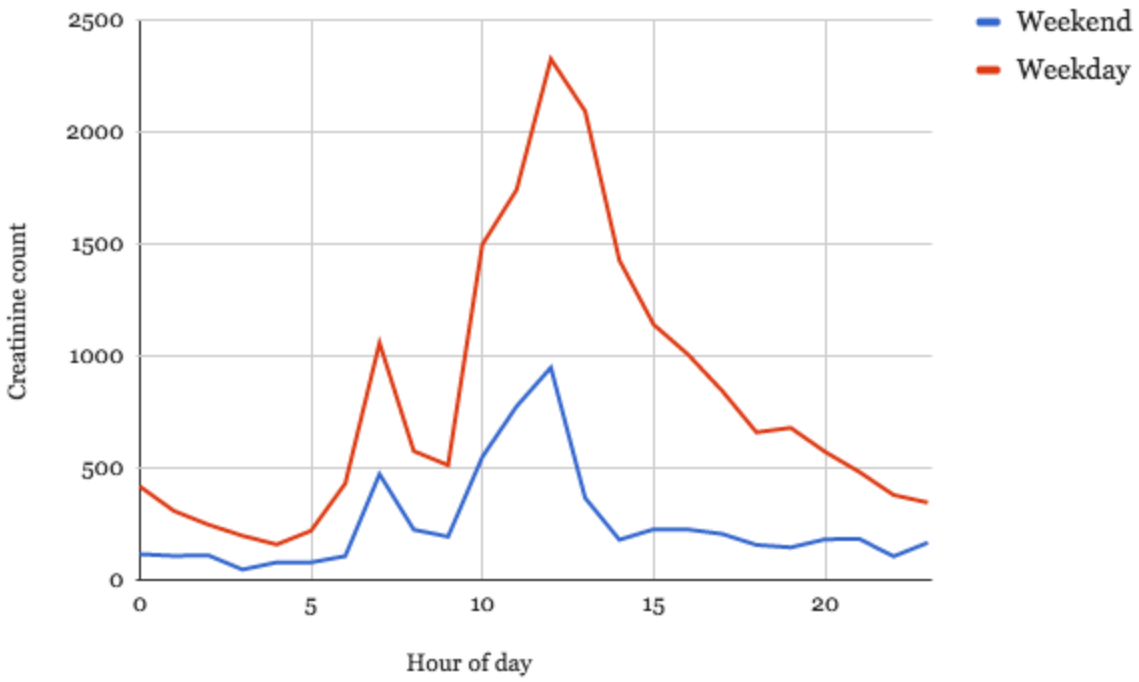

Figure 4.3: Number of inpatient serum creatinine results at RFH as a function of the time of day

I chaired a meeting with one of the phlebotomists and the hospital's operations manager. As part of efforts to meet the '4 hour wait' Commissioning for Quality and Innovation (CQUIN) target, the Trust had already fully optimised the phlebotomy process for admissions to ED. Blood tests are taken at the point of triage and sent straight to the laboratory in specially coloured bags, where they are prioritised for analysis. For the majority of inpatients, blood tests are taken by one of seven RFH phlebotomists who begin their working day at 8am. Each phlebotomist followed a preordained order. On each ward, they picked up orders that were made and printed by junior doctors the previous night. After taking the bloods, they were sent to the laboratory in canisters using a pneumatic tube transport system, each

canister being able to hold 3-5 sets of blood tests. However, each phlebotomist had only one canister. As a result, they would often send blood tests only when all the blood samples had been taken from a given ward, and thus some time after they had been taken - and then stand by the pneumatic tube transporter.

I aimed to optimize this service, such that patients at high risk of deterioration had their bloods taken and processed as early as possible. Two important constraints to this optimization process were that the Trust would not provide any extra phlebotomists, and that their working day could not begin earlier than 8am.

However, I did make two changes to the phlebotomy pathway. Firstly, given the process outlined above, I asked the RFH Patient Safety team to apply for funding to pay for more blood transport canisters so that phlebotomists could send blood tests to the lab as they were taken. Secondly, in order to prioritize areas of the hospital with patients at risk of deterioration, I aimed to optimize the ward order in which each phlebotomist went about their rounds. Using an historical database, I mapped the number of AKI alerts for 2016 to inpatient ward locations. These were compared to Trust cardiac arrest audit data and the ward location of referrals to the Trust critical care outreach nursing team. The individual phlebotomists' ward review order was reconfigured so that wards that had a high number of AKI alerts, cardiac arrests and outreach team referrals were prioritised. This was discussed and agreed with Trust service leads.

To analyse whether these measures had any impact, I analysed the timeframes in which AKI alerts were generated for all inpatient wards between Monday and Friday, both immediately before (September 2016 to January 2017) and after (May 2017 to September 2017) the changes described above were implemented. These data are displayed in Figure 4.4 and Table 4.1.

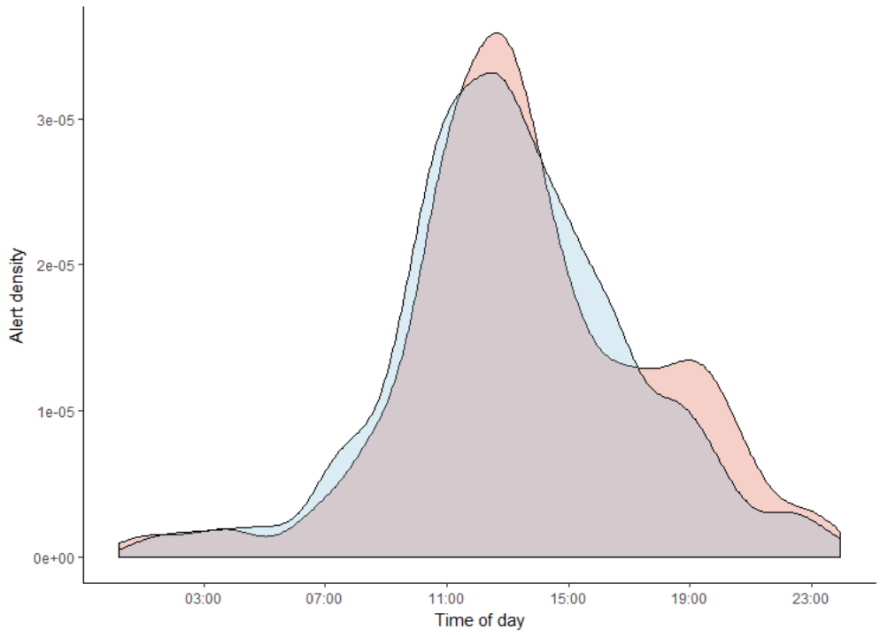

Figure 4.4: Density plot of alerts before and after pathway improvements. Pink = before pathway improvements (September 2016 to January 2017), blue = after pathway improvements (May 2017 to September 2017).

	1st quartile	median	3rd quartile
Before	11:13	13:06	16:08
After	10:51	12:53	15:28

Table 4.1: Quartile distribution of alerts in time before and after pathway improvements. Before = September 2016 to January 2017. After = May 2017 to September 2017.

I used a two-sided Kolmogorov–Smirnov test to confirm that the distribution of alerts in the two time periods was significantly different ($p = 0.003$).

The care proforma

Although the care proforma was tested with end-users prior to implementation (a process described in Chapter 2), a number of users complained that it took too long to fill in. In addition, they worried that it risked being lost among other sheets of paper in patients' notes.

I therefore revised the protocol to make it easier to fill in, and edited it using *Adobe Indesign* (Adobe Systems, Mountainview, California, USA) so that it would fit on one A4 page. Instead of being added as a loose sheet to the notes, I printed it onto a sticker to be placed in the existing care record. I distributed the new proforma stickers to all ward locations where patients with AKI were found. The final version is displayed in Figure 4.5, below.

Royal Free London NHS
NHS Foundation Trust

affix patient sticker here

This patient has generated an AKI alert on the Streams application.
The AKI response team are here to support and advise.
Ongoing management remains the responsibility of the home team unless otherwise agreed.

We recommend the following actions to STOP-AKI:

Management of life threatening complications of AKI	**Critically ill:** Call PARRT (2525) or ITU (1030)	☐
	Hyperkalaemia or acidosis: commence medical therapy as per guidelines	☐
	Fluid overload: Commence diuretics, nitrates/oxygen (if necessary), fluid restriction	☐
Sepsis and hypoperfusion	**Sepsis:** complete Sepsis 6 care bundle	☐
	Has an infection causing AKI: send cultures, commence or escalate antibiotics	☐
	Hypovolaemic: Start bolus fluid protocol. Give 500mls crystalloid and reassess, repeat as necessary. Escalate to senior review after 2 litres bolus therapy	☐
	Commence maintenance IV fluids	☐
Toxicity	**Drug cessation or adjustment required**	☐
Obstruction	**Obstruction is possible and patient needs same day diagnostic renal USS** Please call Matteo Rossi for bedside USS on 07443101848. If out of hours then discuss with radiology (1462). If obstruction present please contact urology registrar on 1487 or on x39536	☐
Primary Renal Disease	**Perform urine dipstick**	☐
	If urine dip clear: order 'AKI diagnostic set (basic)' on Cerner	☐
	If blood or protein present: order 'AKI diagnostic set (glomerular)' on Cerner	☐
General advice If in doubt, contact the AKI registrar on 07950860822 (day) or 07950843257 (night) For guidelines and education, visit londonaki.net or download the London AKI app:		
	- Take 4 hourly observations & ensure an escalation plan is in place - Commence a fluid balance chart, measure weights daily and set a daily fluid balance target - Daily bloods: use 'AKI follow up' order set on Cerner and follow up to renal recovery - Avoid contrast if possible. Consider prophylaxis where contrast absolutely necessary - If renal function does not return to baseline at discharge, contact AKI registrar for advice	
Follow up	We will only see if contacted by you or re-alerted in Streams due to worsening AKI	☐
	We will schedule a further review	☐
	We will take over care of patient	☐

TIME SEEN:_____:_____ DATE: _____/_____/_____ SIGNED:_____

Grade: Registrar ☐ Consultant ☐ NAME:_____

Figure 4.5: The updated AKI response team proforma

Spillover effects

As well as displaying AKI alerts, Streams allows users to check blood tests for any patient under their care. Members of the response team reported that this functionality dramatically reduced the time it took them to review blood tests when compared to the existing IT infrastructure. As a result, I amended the interview schedule for the semi-structured interviews to include questions on behaviours relating to general results viewing before and after Streams was implemented (see Appendix 5).

Discussion

The design and implementation of Streams occurred as the result of a strategic partnership between DMH and RFLFT. Both organizations have a genuine commitment to improving patient care. This commitment has been key in both the speed with which the app was built and implemented, and the process of continual improvement described above. Since implementation, it has also become clear that in order to leverage maximum value from such partnerships, it is vital to seek and address barriers to successful implementation. Marshall describes the use of 'Knowledge mobilisation' to increase the impact of health services research on service improvement. This strategy includes the "co-production of knowledge" between academic researchers and key stakeholders; knowledge gathered *in context* from interactions with practitioners, managers, and service users may provide valuable insights in this regard[166]. One way to promote knowledge co-production is through an 'embedded researcher', where a researcher is affiliated to both an academic institution and an organisation outside of academia in which they develop a relationship with staff and is seen as part of the team[167]. I assumed such a role, and found it to be both key to the wider project, and intellectually stimulating.

As described, I used feedback from clinicians (incorporating direct observation and semi-structured interviews) to uncover barriers to service provision. These included problems with the design of the app and care proforma, and an unforeseen barrier to the efficient running of the Trust's phlebotomy service. I also observed an interesting spillover effect, where clinicians reported that use of the Streams for results viewing saved them considerable amounts of time during the working day. This is consistent with findings

detailed in a recent report by the King's Fund, in which it was acknowledged that the use of existing IT systems engendered significant delays to efficient patient care[168].

Having used these data to fully optimize the digitally-enabled care pathway, it was ready to be evaluated. The following chapter details the impact of the pathway on processes of care, clinical outcomes, and the cost of care provision.

Chapter 5: Quantitative analyses of the care pathway

Introduction

The digitally-enabled care pathway was implemented at RFH in January 2017. The activities outlined in Chapter 5 that related to optimization of the pathway ended in April; the formal evaluation period commenced in May, and ended in September. As discussed in Chapter 4, the qualitative evaluation aimed to establish the impact of the care pathway on three domains: (i) processes of care, (ii) clinical outcomes, and (iii) economic outcomes. These will be discussed in turn. However, first I will discuss the results of two analyses of alert triage that I performed.

Alert triage: live vs. historical cohorts

As detailed in Chapter 3, the evaluation of clinical outcomes would be restricted to patients triaged for review. To this end, I originally decided to use triage results from two sources. For alerts produced during the implementation period at RFH, I would use the results of alert triage performed by members of the AKI response team. For alerts produced in all other time periods and sites, I decided to use the results of alert triage which I performed with Dr. Chris Laing, using a version of the app that processed historical data and produced AKI alerts.

Twelve weeks after the evaluation period began, it became clear that the raw proportions of alerts triaged for review from these two sources appeared to be different. However, the alerts being triaged by Dr Laing and me were from the control time periods. Without direct comparison of triage data from the same alerts, it was not possible to conclude that the triage decisions by clinicians in the AKI response team were different. I decided to

investigate this further by directly comparing the triage decisions made by both groups, using all alerts that had been produced in the first 12 weeks of implementation.

Materials and methods

For the purposes of historical alert triage, alerts were randomly allocated to either Dr. Laing or me. Triage for this group of alerts took place using the custom version of the Streams app described in the Chapter 4. Triage decisions from the live clinical environment by the AKI response team took place in the Streams app. For this exercise, the triage decision made by the most senior member of the response team was used for any alerts triaged in the live clinical environment more than once (ranked nephrology consultant, nephrology registrar, PARRT nurse, respectively).

Alert triage data were extracted from the database supporting Streams using MySQL Workbench (Oracle Corporation, Redwood City, California, USA). I then used Cohen's Kappa to determine the inter-rater agreement between the two groups using RStudio, running R version 3.4.3 (RStudio Incorporated, Boston, USA).

Results

In the first 12 weeks of the evaluation period, 1435 alerts were produced at RFH. Of these, 72 alerts (5.0%) were not triaged by any member of the AKI response team; as outlined above, these were included in the group of alerts not triaged for review.

		Historical triage	
		No	Yes
Live triage	No	397	445
	Yes	59	534

Table 5.1: **Comparison between decisions made by different triage groups**. The two groups included in this analysis relate to decisions taken by the AKI response team (live triage), and by Dr. Chris Laing and me (historical triage). Alerts are further separated into two groups - one in which the alert was triaged for clinical review ("Yes"), and one in which the alert was marked as a false positive ("No").

As can be seen in Table 5.1, 979 alerts (68.2%) were triaged for review using historical triage, compared to 593 alerts (41.3%) from triage performed by clinicians in the AKI response team. Cohen's Kappa coefficient between live and historical triage was 0.34 (95% confidence interval 0.30-0.38), suggesting poor agreement between live and historical triage decisions[169], and confirming my hypothesis that the triage decisions being taken in the live clinical environment appeared to be different to those being taken by Dr. Laing and me. Data from the semi-structured interviews I carried out suggested a reason for this; as the AKI response team comprised existing clinical resources at RFH, clinicians performing alert triage in the live clinical environment did so alongside their usual clinical duties. Clinicians therefore had to decide whether or not to review patients producing an AKI alert in the context of their existing workload, and prioritise such reviews accordingly. In contrast, triage performed by Dr. Laing and me using the historical triage app took place in a different context; we purely had to decide whether the alert suggested the patient had a significant change in kidney function.

I discussed these results with my PhD supervisory group. We decided that the evaluation should include all patients who were judged to have had a clinically relevant change in their kidney function as determined by Dr. Laing and me using the historical alert triage app. One implication of this decision was that a significant proportion of such patients from the

intervention period would not have been reviewed by the AKI response team. The final analysis would therefore be akin to an intention-to-treat analysis, where all patients judged to have suffered a clinically relevant change in creatinine were included, regardless of whether they were reviewed by the AKI response team or not. However, I judged this to be a fair test of the impact of the intervention; if I used the triage results from the AKI response team for the intervention period at RFH as originally planned, the (proportionally smaller) group of patients they triaged for review might reflect the cohort of patients that was judged to be the highest risk.

Alert triage: assessment of inter- and intra-operator variability

As discussed above, the triage of evaluation alerts was carried out jointly by Dr. Laing and me using the historical alert triage app. I decided to validate the alert triage process by testing inter- and intra-operator agreement.

Materials and methods

After all alerts had been triaged once, a random selection of 250 from each operator were validated again by both, allowing me to assess inter- and intra-operator agreement. As before, alert triage data were extracted from the database supporting Streams using MySQL Workbench (Oracle Corporation, Redwood City, California, USA). I then used Cohen's Kappa to determine the inter-rater agreement between the two groups using RStudio, running R version 3.4.3 (RStudio Incorporated, Boston, USA).

Results

Table 5.2 outlines the results of the inter- and intra-operator agreement analyses.

	Operator 1	Operator 2
Operator 1	κ = 0.83 (0.76 - 0.90)	
Operator 2	κ = 0.75 (0.65 - 0.84)	κ = 0.79 (0.71 - 0.87)

Table 5.2: **Results of inter- and intra-operator agreement analyses**. Operator 1 = Alistair Connell. Operator 2 = Chris Laing. For each comparison pair, Cohen's kappa coefficient was calculated to establish inter- and intra-operator variability. 95% confidence intervals are shown in brackets.

These results confirm that both Dr. Laing (Kappa coefficient = 0.79) and I (Kappa coefficient = 0.83) had excellent intra-operator agreement. The agreement between operators (Kappa coefficient = 0.75) was also excellent[169]. Having validated the alert triage process, I then proceeded to analyse the impact of the care pathway on processes of care.

Evaluation of care processes

Materials and methods

Participants

All process of care data were collected as part of an existing RFH project in which paper notes for a random selection of patients known to have been diagnosed with AKI in the ED were reviewed by a team of junior doctors in order to explore processes of care. I extended the project so that it covered the data collection periods outlined below. The original plan for data collection outlined in Chapter 4 included patients diagnosed with AKI in the course of an admission to an inpatient ward location. However, patient notes at RFH are scanned and archived in the Trust Electronic Document and Record Management system. It thus became clear that collecting data relating to process of care for inpatients would be impractical, as locating the relevant sections of the scanned patient record often took several hours per case. As a result, I decided to collect and report data just for patients in ED.

Data collection

Data were collected over the two 9-month periods before and after the introduction of the new care pathway (January to September 2016 and 2017, respectively). Each month, 30 clinically-validated AKI alerts were selected at random, split evenly across the three stages of AKI severity. Patient record reviews were carried out by a team of RFH junior doctors.

Times for hospital arrival, AKI recognition (where recognition occurred) and treatment of each principal AKI cause were entered into an Excel (Microsoft Corporation, Redmond, Washington, USA) spreadsheet. Recognition was defined as the time at which AKI presence was documented in the patient's notes by a clinician. The time at which nephrotoxicity was addressed was defined as the time at which a physician documented the decision to withhold or adjust the dose of nephrotoxic medication. Times for the treatment of sepsis, hypovolaemia, obstruction and primary renal disease were defined as those recorded in drug chart or procedural documentation. The time recorded was the time at which definitive treatment was delivered (e.g. relief of obstruction via nephrostomy, or drug treatment given). Discrepancies or queries about the cases or data collection methods raised by data collectors were adjudicated by a nephrology registrar who helped lead data collection. The same registrar reviewed every collected process of care data-point. I used a chi-squared test to determine the effect of the digitally-enabled care pathway on the number of AKI cases that were not recognized by any clinician. As a portion of AKI went unrecognized, I used a survival analysis to determine the effect of the digitally-enabled care pathway on the time to recognition. The time to delivery of each treatment was analysed using the Wilcoxon rank-sum test. To determine whether any improvements in the time to AKI recognition related to changes in the ED admission pathway at RFH, I compared the times between hospital admission and AKI alert generation for patients in ED at RFH during the calendar-matched time periods using the Wilcoxon rank-sum test. All analyses were performed using RStudio, running R version 3.4.3 (RStudio Incorporated, Boston, USA).

Results

Clinical notes for 540 episodes of clinician-confirmed AKI were reviewed. I removed 32 episodes from the final analysis due to incomplete data collection, leaving 266 and 242 episodes in the pre- and post-implementation periods respectively. After the introduction of

the care pathway, the number of unrecognised AKI cases (i.e. those not clinically recorded in patient documentation) reduced significantly from 33 to 8 (12.4% to 3.3%, p<0.001). Following pathway implementation, the time from ED registration to AKI recognition also reduced significantly (log-rank test p<0.001, Figure 5.1).

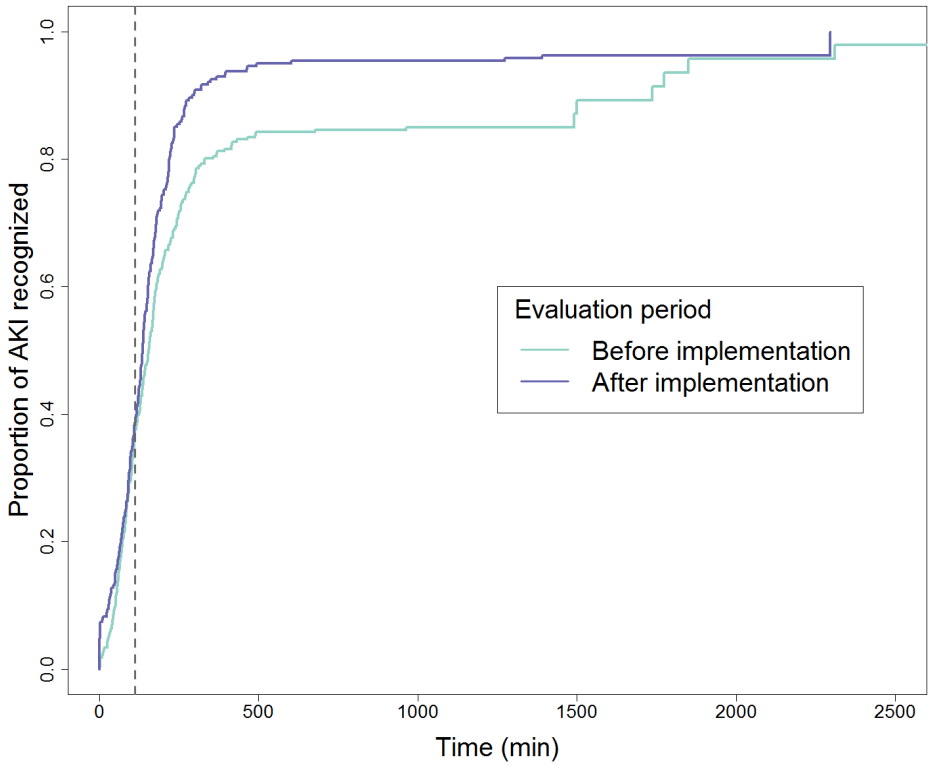

Figure 5.1: Time from admission to recognition of AKI. Kaplan-Meier curves for recognition of AKI after entry to the ED, before and after the implementation of the care pathway. The vertical dashed line represents the median time of creatinine result release across both time periods.

I found no significant difference in the time between entry to ED and the release of creatinine tests by the hospital laboratory; the median (interquartile range [IQR]) times were 113.5 (81.3-155.2) and 107.3 (77.3-141.4) minutes before and after the introduction of the intervention respectively (p=0.26). These data suggest that improvement in the recognition of AKI related to results viewing in-app, interpretation and timely documentation.

For alerts produced relating to patients in the ED, the median (IQR) time from alert generation to alert review by a specialist was 11.50 (IQR 1.00-58.25) minutes. Timeframes from hospital admission to the treatment of each of the main causes of AKI are detailed in Table 5.3. Implementation of the care pathway was associated with a significant reduction in the time to treatment of nephrotoxins (median time to treatment 207.5 vs 145.0 minutes, p=0.047). Implementation was associated with faster treatment in patients admitted with sepsis-related AKI and those with obstruction (median times to treatment 114.0 vs 100.0 minutes, p=0.29, and 268.0 vs 224.0 minutes, p=0.50, respectively), although in both cases the differences were not statistically significant.

	Time period	Number of patients treated	Median (IQR) time to treatment (mins)	p value
Sepsis, infection and hypovolaemia	Before implementation	223	114.0 (50.0 - 216.5)	0.29
	After implementation	196	100.0 (45.0 - 195.2)	
Nephrotoxicity	Before implementation	28	207.5 (145.8 - 313.5)	0.047
	After implementation	43	145.0 (105.5 - 224.5)	
Obstruction	Before implementation	27	268.0 (186.5 - 632.5)	0.50
	After implementation	31	224.0 (114.5 - 875.5)	
Primary renal disease	Before implementation	8	515.5 (203.8 - 1295.5)	0.35
	After implementation	6	1087.0 (537.0 - 1602.0)	

Table 5.3: Timeframes from admission to the delivery of treatment of AKI.

Evaluation of clinical end points

Materials and methods

Participants

As outlined in Chapter 3, I compared sociodemographic and clinical outcome data from the intervention period (May-September 2017) to data from the pre-deployment phase (May 2016-January 2017). A number of publications have noted differences in characteristics and outcomes among patients presenting with AKI on admission (community-acquired AKI), and

among those developing AKI in the course of admission[170–173]. I decided to report and publish results for these two patient groups independently. I used patient location at the time of alert to differentiate between these two groups.

Outcome framework

The primary outcome I specified was recovery of renal function, defined as a return to within 120% of the baseline creatinine specified by the NHS England AKI algorithm, as per the Renal Association Clinical Practice Guidelines on AKI[154]. I specified five secondary outcome measures: mortality within 30 days of alert; progression of AKI stage; transfer to Renal Unit /ITU during admission; readmission within 30 days of discharge; and dependence on RRT 30 days after discharge.

Data collection, linkage and storage

I gathered demographic and outcome data from the Streams data processor at DMH using MySQL Workbench (Oracle Corporation, Redwood City, California, USA). I derived Indices of Multiple Deprivation (IMD) - a measure combining seven domains (income/ employment/ living environment/ education, skills and training/ health, deprivation and disability/ barriers to housing and services/ crime) into a single deprivation score for a small area - by cross-referencing patient postcodes with the UK Government's Indices of Deprivation 2015 dataset[174], allowing me to sort patients into quintiles of deprivation (i.e. where quintile 1 was least deprived and quintile 5 most deprived). I uploaded all data to the UCL Safe Haven via secure portal, where data linkage occurred using a unique pseudo-identifier for each patient and AKI alert. I then derived overall patient-specific Charlson comorbidity index scores (which categorizes comorbidities based on the International Classification of Diseases (ICD) diagnosis codes in administrative data) as per Thygesen *et al*[175]. The impact of the care pathway on cardiac arrests rate was measured on a hospital level as it was not possible to ascertain which cardiac arrests occurred among patients with AKI. I gathered monthly cardiac arrest data from the intervention and comparator sites from existing RFLFT logs. These logs (compiled by the RFLFT PARRT) automatically excluded patients with cardiac arrests occurring in either hospitals' ED, cardiac catheterization lab, ICU, Coronary Care Unit or in patients who had a formal 'not for resuscitation' order signed.

Analysis

I used Wilcoxon rank-sum and chi-squared tests to analyse sociodemographic variables, and segmented regression analysis to estimate the effect of the intervention on the clinical outcomes specified above. I measured all outcomes as weekly proportions and used binomial regression models with a logit link. The variable “intervention” was coded 1 for the time period after the intervention (May-September 2017) and 0 for the pre-intervention time period (May 2016-January 2017). The intervention and comparator sites were coded 1 and 0 respectively. The variable “time” denoted the week number, with 1 denoting the first week of the intervention period, and weeks in the pre-intervention period being denoted by negative numbers. The statistical model I used was:

$$logit(y) = \beta_0 + \beta_1 int + \beta_2 time + \beta_3 site + \beta_4 int \times time + \beta_5 int \times site + \beta_6 time \times site + \beta_7 int \times time \times site$$

where *y* denoted the proportion of interest, *int*, *time* and *site* denoted the variables intervention, time and site respectively (as defined above), and β_0, …, β_7 were the coefficients to be estimated. My analysis focused on four effects of interest. Two coefficients evaluate the evidence for a step change in each outcome: the coefficient *intervention* estimates the step change in outcome at the start of the intervention period at RFH. The interaction term *site×intervention* estimates the difference-in-difference in the step change between the intervention and comparator sites. Two further effects of interest relate to temporal trends in each outcome: the interaction term *time×intervention* estimates of the difference in outcome trend over time between the pre-intervention period and intervention period at RFH; the three-way interaction term *time×site×intervention* estimates the difference-in-difference in this trend between the intervention and comparator sites.

I checked all models for autocorrelation by inspecting the autocorrelation function up to lag 15. At the planning stage of my PhD, I did not anticipate that I would be able to collect patient-level data relating to sociodemographics and co-morbid diseases. To examine the robustness of the primary outcome analysis I originally specified, I performed a sensitivity analysis using binary logistic regression that used the same model and interaction terms as above, but where the outcome was defined at the patient level, and patient-level

characteristics were included as covariates. Covariates used for this model were age, sex, ethnicity category, index of multiple deprivation, AKI alert level, the presence of complications at the time of alert, and the presence of individual Charlson Score comorbidities. The addition of these covariates allowed me to adjust for any differences in casemix between sites, and within sites over time.

I used a Poisson regression model with a log link and an offset variable adjusting for the number of admissions per month to estimate the intervention effect on hospital-wide cardiac arrests. As these data were collected monthly, there was a relative paucity of post-intervention data points. As a result, estimating the effect of the intervention on outcome trend was not possible. The statistical model I used was:

$$log(number\ of\ cardiac\ arrests) = \beta_0 + \beta_1 int + \beta_3 site + \beta_5 int \times site + log(number\ of\ admissions)$$

I analysed the time to renal recovery (where this occurred by hospital discharge) using the Wilcoxon rank-sum test. To allow for the effects of in-hospital death on length of stay, I used a competing risk analysis[176]. All analyses were performed using RStudio, running R version 3.4.3 (RStudio Incorporated, Boston, USA).

Results

At the intervention site (RFH), clinical validation of the 4392 and 2254 AKI alerts during pre-deployment (May 2016-January 2017) and post-deployment (May-September 2017) phases respectively yielded 1760 and 919 AKI episodes in each phase, with 755 (42.9%) and 439 (47.8%) located in the ED. In the pre-deployment and post-deployment phases at BGH, clinical validation of the 2866 and 1364 alerts respectively yielded 1669 and 772 AKI episodes, with 1015 (60.8%) and 422 (54.7%) being located in the ED (figure 5.2).

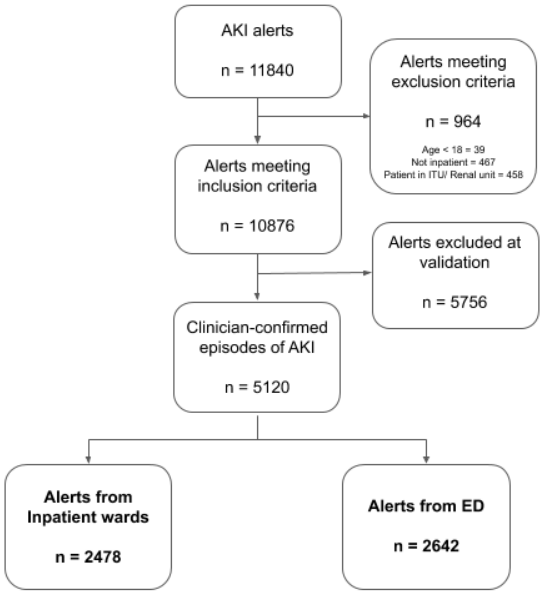

Figure 5.2: Defining the final evaluation sample

Community-acquired AKI

Table 5.4 summarises the sociodemographic and clinical characteristics of patients producing AKI alerts in the ED at both evaluation sites and time periods. RFH AKI patients were younger (median 71 vs 78 years, p<0.001) and less likely to be white (65.6% vs. 78.6%, p<0.001) than at BGH. RFH patients had significantly more comorbidity (median and interquartile range (IQR) Charlson comorbidity score 4.5 (IQR 3.0-7.0) vs. 4.0 (IQR 3.0-6.0), p<0.001) and significantly more severe AKI (p<0.001). The proportion of patients with pre-existing renal disease was also higher (34.1% vs. 19.8%, p<0.001).

Comparing the pre- and post- intervention cohorts, I also found some significant differences within each evaluation site over time. In the post-intervention period at RFH, patients were younger (median age 72 vs 69 years, p=0.003). At BGH, patients in the post-intervention period were less likely to be white (80.8% vs. 73.2%, p=0.030), and had a significantly higher burden of comorbid disease (p<0.001). At both RFH and BGH, patients in the post-intervention period had a higher burden of pre-existing renal disease (37.8% vs. 32.0%, p=0.047 and 23.2% vs. 18.4%, p=0.045, respectively)

Variable		Hospital site / time period				p value		
		RFH pre	RFH post	BGH pre	BGH post	RFH pre vs RFH post	BGH pre vs BGH post	All RFH vs all BGH
No. of AKI alerts		766	439	1015	422			
Alert severity	AKI1	455 (59.4%)	272 (62.0%)	658 (64.8%)	289 (68.5%)	0.68	0.32	<0.001
	AKI2	161 (21.0%)	86 (19.6%)	210 (20.7%)	83 (19.7%)			
	AKI3	150 (19.6%)	81 (18.5%)	147 (14.5%)	50 (11.8%)			
Male		417 (54.4%)	244 (55.6%)	521 (51.3%)	219 (51.9%)	0.75	0.89	0.09
Median age in years (IQR)		72.00 (59.00-83.50)	69.00 (55.00-82.00)	78.00 (64.00-87.00)	78.00 (67.00-86.00)	0.003	0.79	<0.001
Ethnicity	White	509 (66.4%)	280 (63.8%)	820 (80.8%)	309 (73.2%)	0.74	0.03	<0.001
	Black or Black British	68 (8.9%)	46 (10.5%)	31 (3.1%)	19 (4.5%)			
	Asian or Asian British	79 (10.3%)	53 (12.1%)	75 (7.4%)	46 (10.9%)			
	Mixed	10 (1.3%)	6 (1.4%)	4 (0.4%)	3 (0.7%)			
	Other	100 (13.1%)	54 (12.3%)	85 (8.4%)	45 (10.7%)			
Index of Multiple Deprivation	Quintile 1	180 (23.5%)	95 (21.6%)	76 (7.5%)	39 (9.2%)	<0.001	0.90	<0.001
	Quintile 2	191 (24.9%)	100 (22.8%)	212 (20.9%)	88 (20.9%)			
	Quintile 3	183 (23.9%)	96 (21.9%)	315 (31.0%)	122 (28.9%)			
	Quintile 4	169 (22.1%)	112 (25.5%)	305 (30.0%)	112 (26.5%)			
	Quintile 5	38 (5.0%)	28 (6.4%)	102 (10.0%)	58 (13.7%)			
	Unknown	5 (0.7%)	8 (1.82%)	5 (0.5%)	3 (0.7%)			
Charlson score	0	48 (6.3%)	45 (10.3%)	78 (7.7%)	16 (3.8%)	0.62	<0.001	<0.001
	1	45 (5.9%)	21 (4.78%)	73 (7.2%)	19 (4.5%)			
	2	77 (10.1%)	36 (8.2%)	84 (8.3%)	44 (10.4%)			
	3	93 (12.1%)	43 (9.79%)	137 (13.5%)	57 (13.5%)			
	4	130 (17.0%)	60 (13.7%)	307 (30.2%)	91 (21.6%)			
	≥5	373 (48.7%)	234 (53.3%)	336 (33.1%)	195 (46.2%)			
Pre-existing renal disease present		245 (32.0%)	166 (37.8%)	187 (18.4%)	98 (23.2%)	0.047	0.045	<0.001

Table 5.4: Sociodemographic and clinical characteristics of patients producing AKI alerts in the ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. pre = May 2016 to January 2017, post = May 2017 to September 2017.

I found no evidence for a step change in renal recovery rate following the intervention at RFH. The estimated odds ratio (OR) for the intervention step change was 1.03 (95% Confidence Interval (95%CI): 0.56-1.87), which was not significantly different from 1 (p=0.93). I found no evidence for a difference in step change of recovery rate between RFH and BGH (estimated OR=1.10, 95%CI: 0.48-2.53, p=0.83). The model estimated a statistically significant change in the trend of renal recovery rates at RFH (estimated OR=1.04, 95%CI:1.00-1.08, p=0.038), indicating that the trend in the intervention period at RFH was stronger in the direction of higher recovery rates, compared to the pre-intervention period i.e. there may have been a trend towards decreasing recovery rates at RFH in the pre-intervention period, which may have been reversed in the intervention period. However, I found no significant difference in the trend change between sites (estimated OR=0.95, 95%CI:0.90-1.00, p=0.053). The data and model predictions are illustrated in Figure 5.3, and estimates from the segmented regression analysis of weekly renal recovery rate which relate to the research hypothesis are shown in Table 5.5.

Model estimates for the four effects of interest from the sensitivity analysis controlling for differences in casemix are not statistically significant and do not differ substantially from the primary analysis model estimates (Table 5.6).

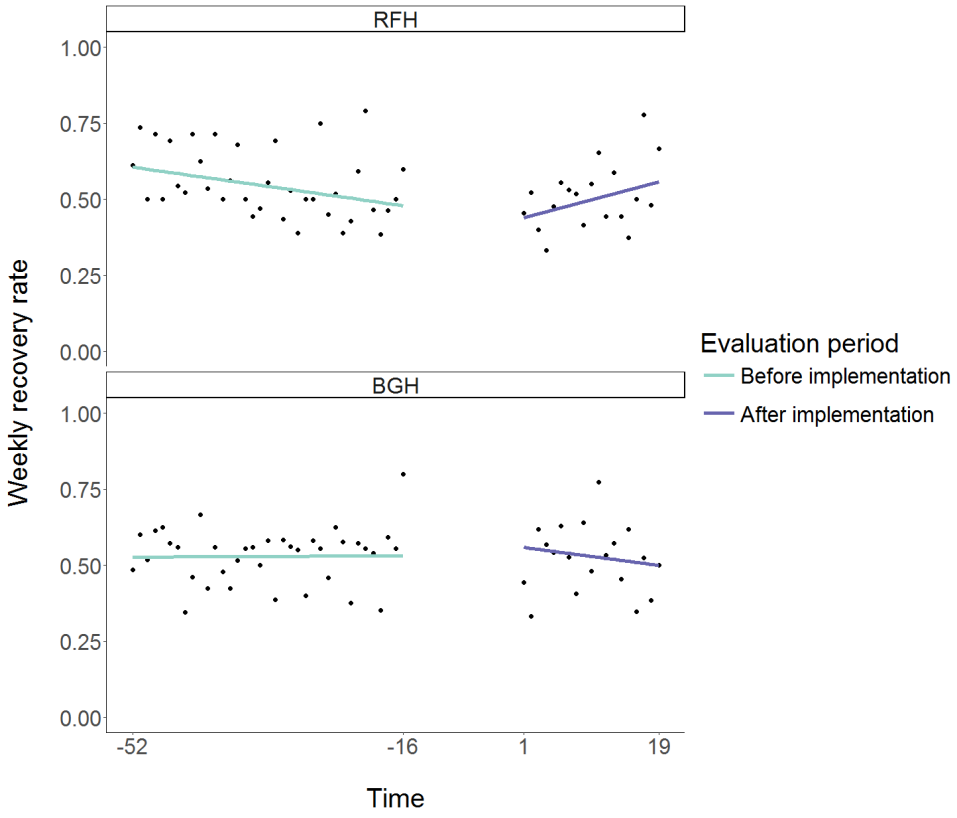

Figure 5.3: Weekly recovery rate at RFH and BGH before and after implementation of the care pathway for patients in ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of recovery for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

	Renal recovery				Mortality			
	β	p value	OR	95% CI	β	p value	OR	95% CI
intervention	0.03	0.93	1.03	(0.56-1.87)	-0.82	0.055	0.44	(0.19-1.01)
site×intervention	0.09	0.83	1.10	(0.48-2.53)	-0.66	0.27	0.52	(0.16-1.67)
time×intervention	0.04	0.038	1.04	(1.00-1.08)	-0.05	0.10	0.95	(0.90-1.01)
time×site×intervention	-0.05	0.053	0.95	(0.90-1.00)	0.04	0.38	1.04	(0.95-1.13)

	Progression of AKI stage				Admission to ITU/Renal Unit			
	β	p value	OR	95% CI	β	p value	OR	95% CI
intervention	0.19	0.78	1.22	(0.30-4.89)	0.23	0.57	1.26	(0.57-2.79)
site×intervention	-0.52	0.60	0.59	(0.08-4.08)	0.33	0.60	1.40	(0.40-4.81)
time×intervention	-0.07	0.16	0.93	(0.83-1.03)	-0.05	0.044	0.95	(0.90-1.00)
time×site×intervention	0.05	0.47	1.05	(0.92-1.22)	0.06	0.14	1.06	(0.98-1.16)

	Readmission at 30d				RRT use at 30d			
	β	p value	OR	95% CI	β	p value	OR	95% CI
intervention	0.47	0.20	1.59	(0.78-3.28)	-0.68	0.41	0.51	(0.10-2.50)
site×intervention	-0.54	0.33	0.58	(0.19-1.73)	-17.24	1.00	0.00	(0.00-Inf)
time×intervention	0.03	0.20	1.03	(0.99-1.08)	-0.11	0.057	0.90	(0.80-1.00)
time×site×intervention	0.02	0.55	1.02	(0.95-1.10)	0.07	1.00	1.07	(0.00-476.75)

Table 5.5: Results of segmented regression analyses for patients in ED. The coefficient *intervention* provides an estimate of the difference in outcome between the intervention period and the pre-intervention period at RFH. The two-way interaction *site×intervention* provides an estimate of the difference-in-difference between the two hospital sites. The two-way interaction *time×intervention* provides an estimate of the difference in outcome trend over time in the intervention period compared to the pre-intervention period at RFH. The three-way interaction *time×site×intervention* provides an estimate of the difference-in-difference in the trend between the sites.

	Renal recovery			
	β	p value	OR	95% CI
intervention	0.10	0.75	1.11	0.60 - 2.03
site×intervention	-0.03	0.94	0.97	0.42 - 2.25
time×intervention	0.03	0.14	1.03	0.99 - 1.07
time×site×intervention	-0.04	0.14	0.96	0.90 - 1.01

Table 5.6: Results from binary logistic regression (sensitivity analysis) for patients in ED. Renal recovery was defined at the patient level and patient-level characteristics were included as covariates. Covariates used for this model were age, sex, ethnicity category, index of multiple deprivation, AKI alert level, the presence of complications at the time of alert, and the presence of individual Charlson Score comorbidities. The coefficient *intervention* provides an estimate of the difference in outcome between the intervention period and the pre-intervention period at RFH. The two-way interaction site×intervention provides an estimate of the difference-in-difference between the two hospital sites. The two-way interaction time×intervention provides an estimate of the difference in outcome trend over time in the intervention period compared to the pre-intervention period at RFH. The three-way interaction time×site×intervention provides an estimate of the difference-in-difference in the trend between the sites.

Estimates of interest from the segmented regression analyses of secondary outcomes are shown in Table 5.5. Of the 20 coefficients of interest, 11 had estimated odds ratios suggesting a beneficial effect of the intervention. The only statistically significant finding was the estimate for the effect of the intervention on the trend change in admission to ITU or Renal Units during RFH admission (estimated OR:0.95, 95%CI:0.90-1.00, p=0.044). However, I found no significant difference in the trend change between sites (OR=1.06, 95%CI:0.98-1.16, p=0.14). I found no significant autocorrelation in any of the models. The data and model predictions are shown in Figures 5.5 to 5.9.

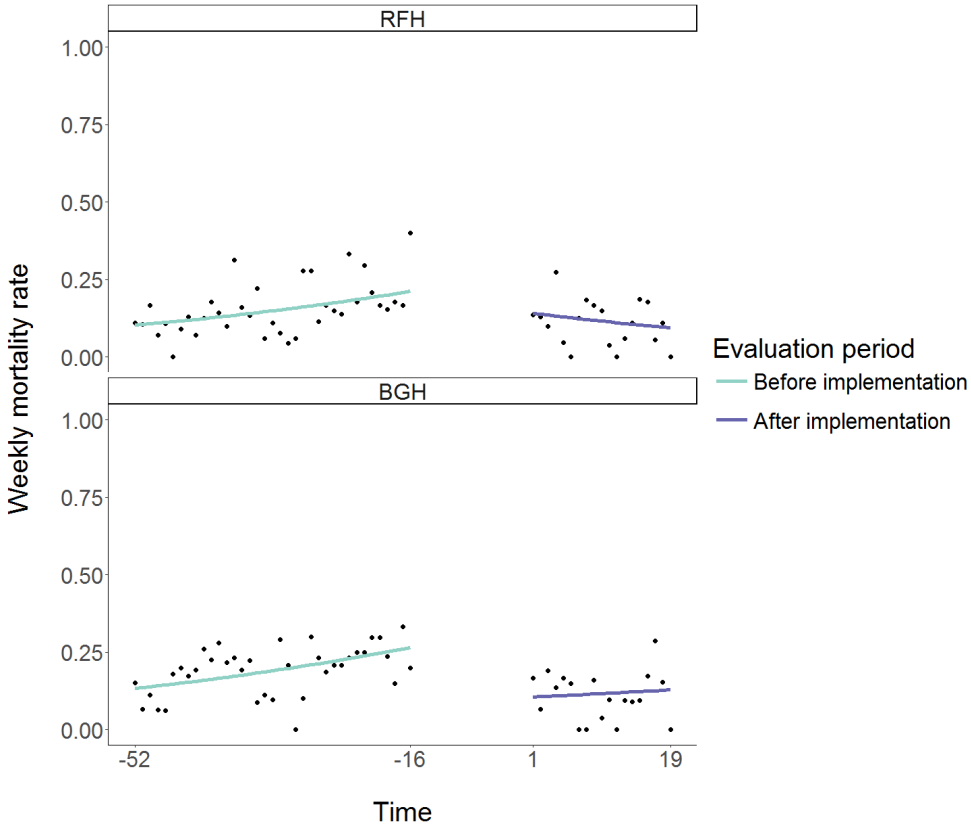

Figure 5.4: Weekly rates of mortality at RFH and BGH before and after implementation of the care pathway for patients in ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

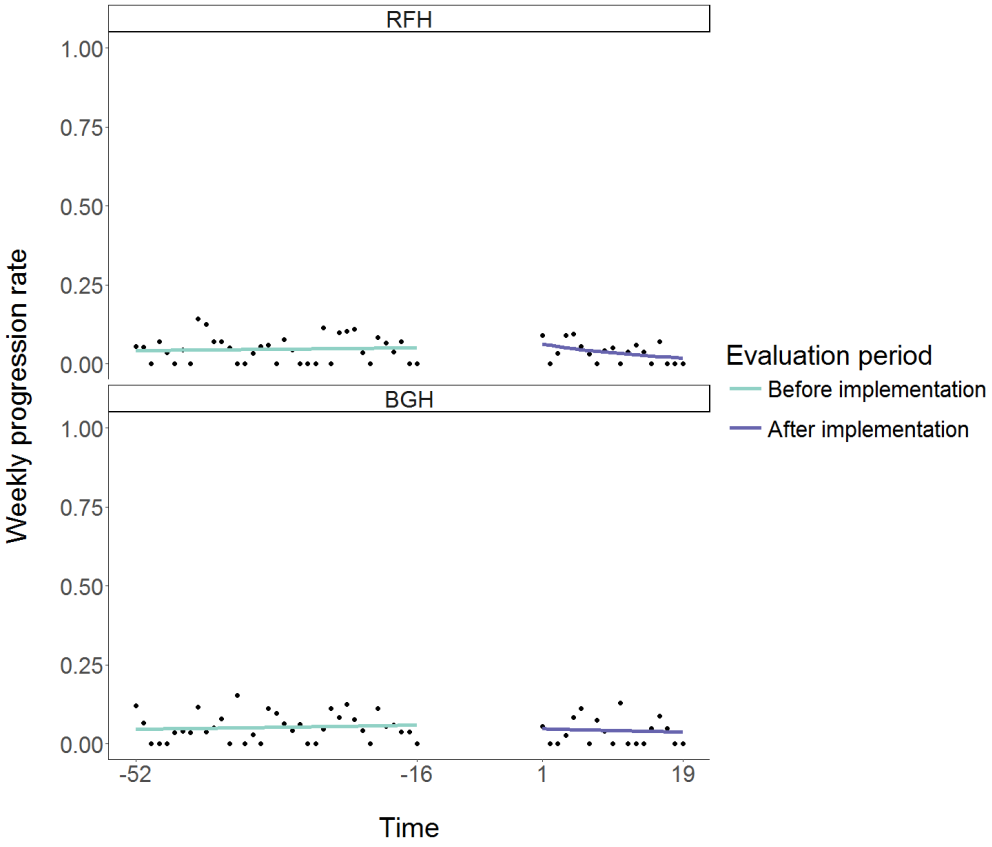

Figure 5.5: Weekly rates of AKI progression at RFH and BGH before and after implementation of the care pathway for patients in ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

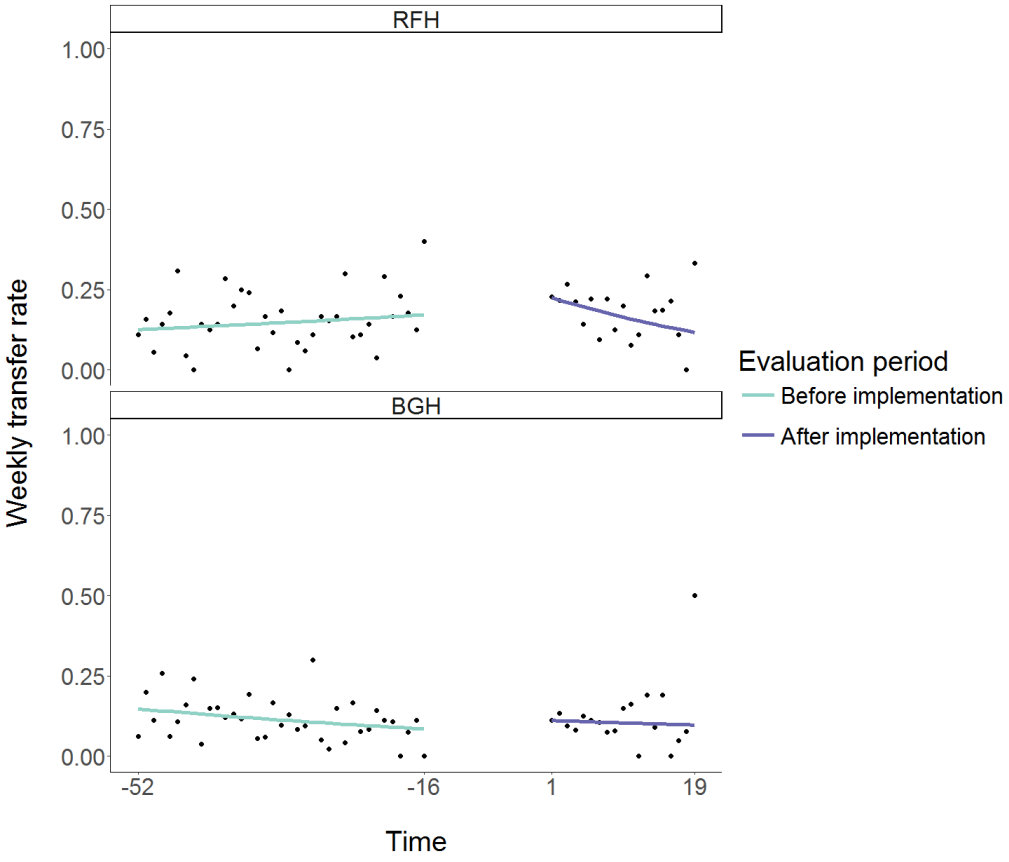

Figure 5.6: Weekly rates of transfer to ITU/ renal unit at RFH and BGH before and after implementation of the care pathway for patients in ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

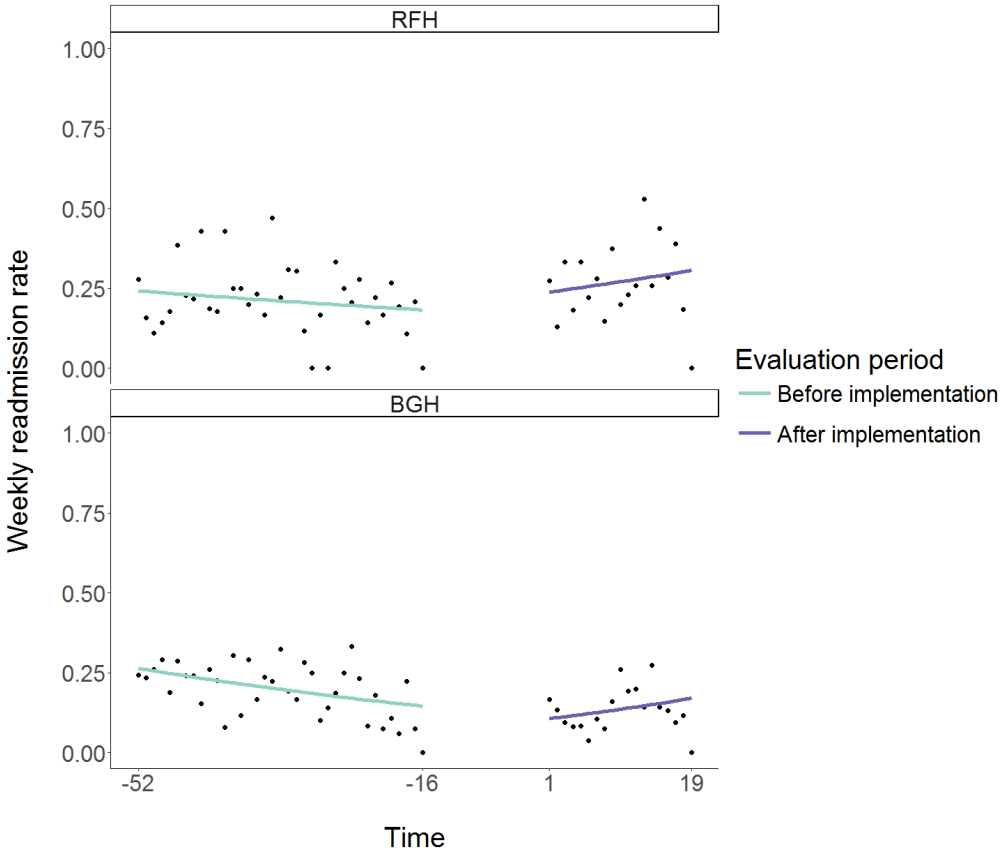

Figure 5.7: Weekly rates of readmission at RFH and BGH before and after implementation of the care pathway for patients in ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

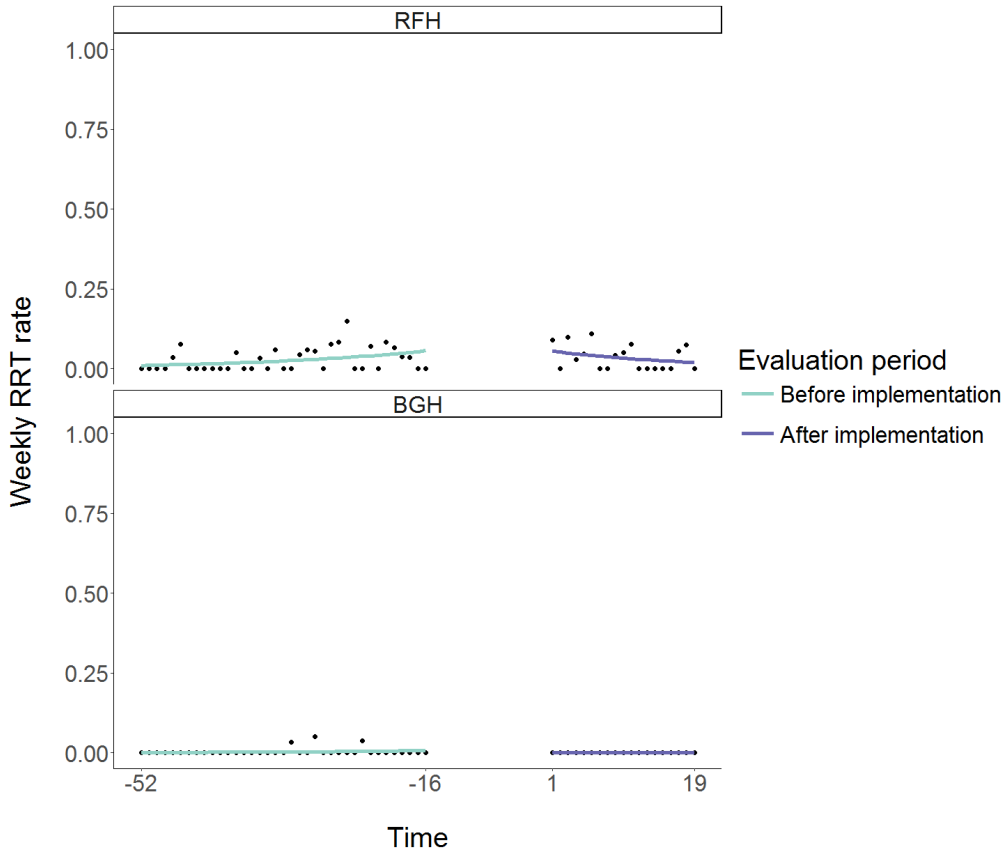

Figure 5.8: Weekly rates of 30-day dependence on renal replacement therapy at RFH and BGH before and after implementation of the care pathway for patients in ED. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

At RFH the median (and IQR) time to renal recovery was 2.00 days (IQR 1.00-12.00 days) before the introduction of the digitally-enabled care pathway, and 3.00 days (IQR 1.00-13.25 days) after introduction ($p = 0.128$). At BGH the median (IQR) time to renal recovery was 2.00 days (1.00-9.00 days) before and 2.00 days (1.00-5.00 days) after the intervention respectively ($p<0.001$).

A significant reduction in length of stay was demonstrated at both RFH ($p=0.024$) and at BGH ($p<0.001$) after the RFH implementation period using competing risk analyses, (Figures 5.10 and 5.11, below).

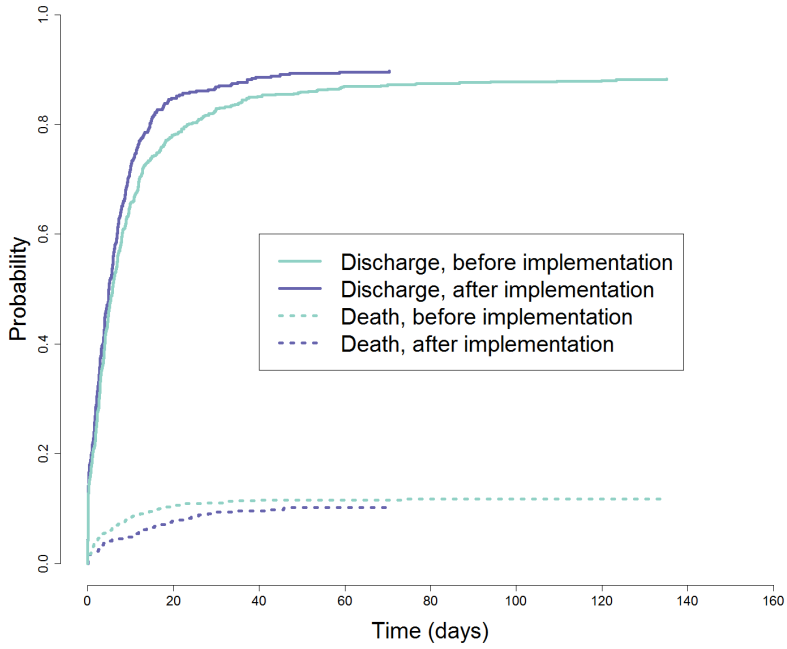

Figure 5.9: Plot of competing risk analysis for mortality and hospital discharge at RFH for patients who had AKI in ED

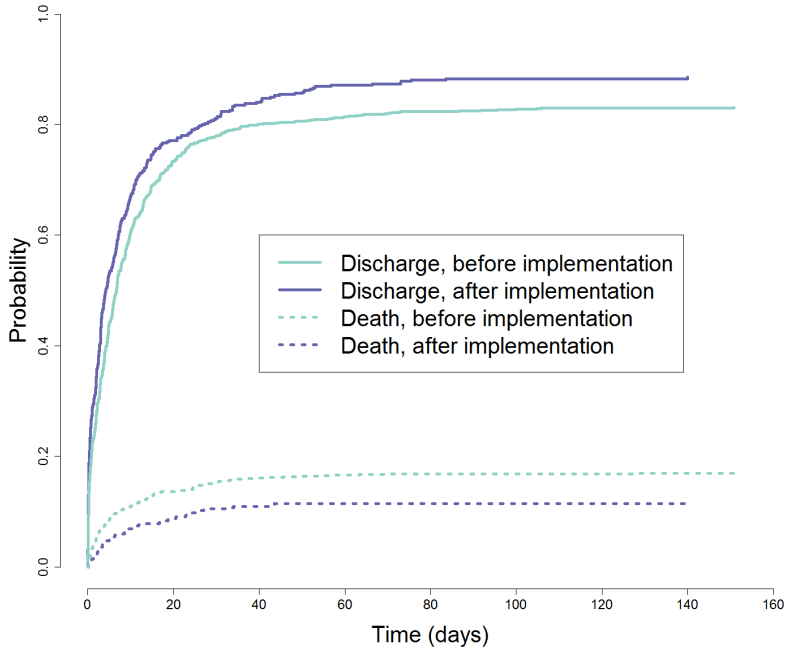

Figure 5.10: Plot of competing risk analysis for mortality and hospital discharge at BGH for patients who had AKI in ED

AKI presenting in hospitalized inpatients

Table 5.7 summarises the sociodemographic and clinical characteristics of patients producing AKI alerts after hospital admission at both sites and time periods. RFH inpatients were younger (median 72 vs 82 years, $p<0.001$) and less deprived ($p<0.001$) than at BGH. RFH patients had significantly less comorbidity (Charlson score 5.0 (IQR 3.0-8.0) vs. 5.0 (IQR 4.0-8.0), $p<0.001$). The proportion of patients with pre-existing renal disease was also lower at RFH than at BGH (31.5% vs. 37.2%, $p<0.001$). In addition, there were some significant differences within BGH comparing the pre- and post-intervention cohorts. At BGH, patients in the post-intervention period had significantly more severe AKI ($p=0.01$), and a higher burden of renal disease (45.1% vs. 32.9%, $p<0.001$) and co-morbidities ($p<0.001$) than in the pre-intervention period.

Variable		Hospital site / time period				p value		
		RFH pre	RFH post	BGH pre	BGH post	RFH pre vs RFH post	BGH pre vs BGH post	All RFH vs all BGH
No. of AKI alerts		994	480	654	350			
Alert severity	AKI1	809 (81.4%)	411 (85.6%)	571 (87.3%)	281 (80.3%)	0.10	0.01	0.32
	AKI2	127 (12.8%)	44 (9.2%)	60 (9.2%)	47 (13.4%)			
	AKI3	58 (5.8%)	25 (5.2%)	23 (3.5%)	22 (6.3%)			
Male		541 (54.4%)	257 (53.5%)	331 (50.6%)	186 (53.1%)	0.74	0.48	0.30
Median age in years (IQR)		73.00 (58.00-84.00)	70.00 (57.00-83.00)	82.00 (73.00-88.00)	82.00 (73.25-88.75)	0.14	0.81	<0.001
Ethnicity	White	625 (62.9%)	281 (58.5%)	512 (78.3%)	274 (78.3%)	0.09	0.32	<0.001
	Black or Black British	76 (7.7%)	34 (7.1%)	29 (4.4%)	12 (3.4%)			
	Asian or Asian British	110 (11.1%)	52 (10.8%)	60 (9.2%)	25 (7.1%)			
	Mixed	10 (1.0%)	2 (0.42%)	3 (0.5%)	4 (1.1%)			
	Other	173 (17.4%)	111 (23.1%)	50 (7.7%)	35 (10.0%)			
Index of Multiple Deprivation	Quintile 1	184 (18.5%)	84 (17.5%)	42 (6.42%)	25 (7.1%)	0.87	0.83	<0.001
	Quintile 2	216 (21.7%)	130 (27.1%)	132 (20.2%)	60 (17.1%)			
	Quintile 3	233 (23.4%)	89 (18.5%)	183 (28.%)	111 (31.7%)			
	Quintile 4	224 (22.5%)	111 (23.1%)	186 (28.4%)	99 (28.3%)			
	Quintile 5	97 (9.8%)	46 (9.6%)	108 (16.5%)	53 (15.1%)			
	Unknown	40 (4.0%)	20 (4.2%)	3 (0.5%)	2 (0.6%)			
Charlson score	0	114 (11.5%)	49 (10.2%)	10 (1.5%)	7 (2.0%)	0.49	<0.001	<0.001
	1	51 (5.13%)	11 (2.3%)	25 (3.8%)	9 (2.6%)			
	2	63 (6.3%)	54 (11.2%)	29 (4.4%)	13 (3.7%)			
	3	107 (10.8%)	43 (9.0%)	78 (11.9%)	21 (6.0%)			
	4	169 (17.0%)	63 (13.1%)	150 (22.9%)	59 (16.9%)			
	≥5	490 (49.3%)	260 (54.2%)	362 (55.4%)	241 (68.9%)			
Pre-existing renal disease present		303 (30.5%)	162 (33.8%)	215 (32.9%)	158 (45.1%)	0.23	<0.001	<0.001

Table 5.7: Sociodemographic and clinical characteristics of patients producing AKI alerts on inpatient wards. RFH = Royal Free Hospital, BGH = Barnet General Hospital. pre = May 2016 to January 2017, post = May 2017 to September 2017.

I found no evidence for a significant change in renal recovery rate following the intervention at RFH. The estimated OR for the intervention step change was 1.00 (95% 95%CI: 0.58-1.71). There was also no evidence for a significant difference in step change in recovery rate between RFH and BGH (estimated OR= 1.24, 95%CI:0.53-2.92, p=0.62). In addition, the model did not estimate a statistically significant change in the trend of renal recovery rates at RFH (estimated OR=0.99, 95%CI:0.96-1.03, p=0.61), and there was no significant difference in the trend change between sites (estimated OR=0.97, 95%CI:0.92-1.03, p=0.29, Table 5.8). The data and model predictions are illustrated in Figure 5.12. Model estimates from the sensitivity analysis controlling for differences in casemix did not differ substantially from the primary analysis model estimates, and none of the four examined estimated odds ratios were statistically significantly significant (Table 5.9).

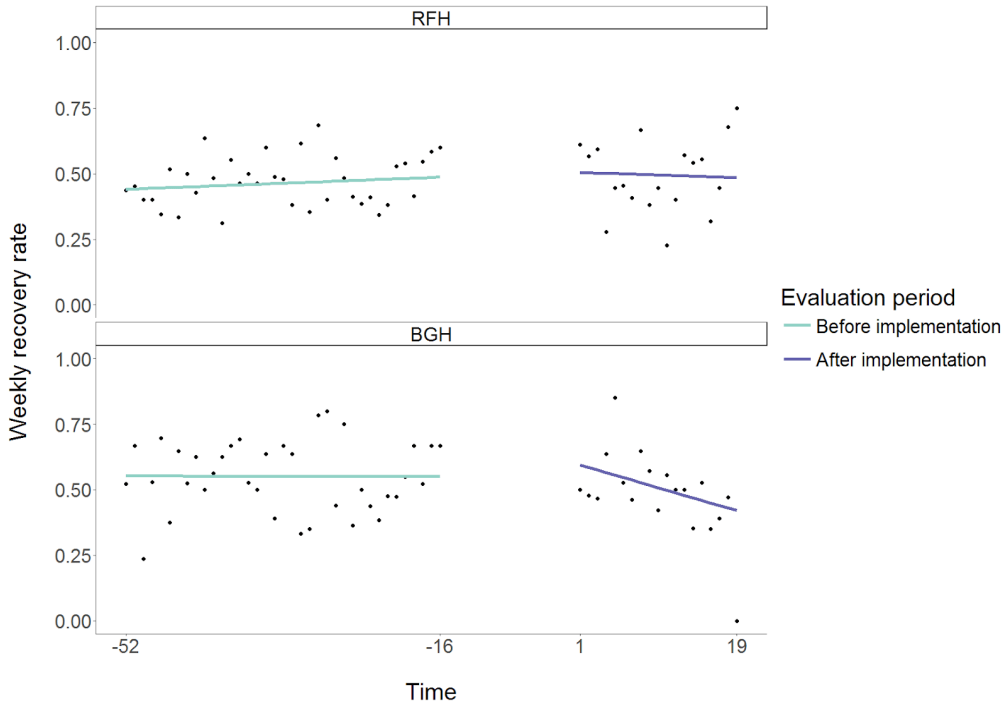

Figure 5.11: Weekly recovery rate at RFH and BGH before and after implementation of the care pathway for hospital inpatients. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

	Renal recovery				Mortality			
	β	p value	OR	95% CI	β	p value	OR	95% CI
intervention	0.00	0.99	1.00	(0.58-1.71)	0.17	0.67	1.18	(0.55-2.52)
site×intervention	0.22	0.62	1.24	(0.53-2.92)	0.06	0.91	1.07	(0.36-3.15)
time×intervention	-0.01	0.61	0.99	(0.96-1.03)	0.00	0.89	1.00	(0.96-1.05)
time×site×intervention	-0.03	0.29	0.97	(0.92-1.03)	-0.03	0.44	0.97	(0.91-1.04)

	Progression of AKI stage				Admission to ITU/Renal Unit			
	β	p value	OR	95% CI	β	p value	OR	95% CI
intervention	0.67	0.11	1.96	(0.86-4.47)	0.40	0.42	1.50	(0.57-4.00)
site×intervention	-0.71	0.27	0.49	(0.14-1.71)	-1.18	0.18	0.31	(0.05-1.68)
time×intervention	-0.01	0.60	0.99	(0.93-1.04)	0.02	0.55	1.02	(0.96-1.08)
time×site×intervention	0.04	0.32	1.04	(0.96-1.13)	0.07	0.19	1.08	(0.97-1.20)

	Readmission at 30d				RRT use at 30d			
	β	p value	OR	95% CI	β	p value	OR	95% CI
intervention	0.20	0.54	1.22	(0.65-2.29)	-3.32	0.03	0.04	(0.00-0.62)
site×intervention	-0.16	0.77	0.86	(0.31-2.39)	-1.04	0.99	0.35	(0-Inf)
time×intervention	-0.03	0.23	0.97	(0.93-1.02)	0.00	0.98	1.00	(0.83-1.23)
time×site×intervention	0.01	0.84	1.01	(0.94-1.08)	-17.62	0.99	0.00	(0-Inf)

	Cardiac arrest			
	β	p value	OR	95% CI
intervention	-0.60	<0.001	0.55	(0.38-0.76)
site×intervention	0.12	0.69	1.13	(0.63-1.99)

Table 5.8: Results of segmented regression analyses for hospital inpatients. The coefficient *intervention* provides an estimate of the difference in outcome between the intervention period and the pre-intervention period at RFH. The two-way interaction *site×intervention* provides an estimate of the difference-in-difference between the two hospital sites. The two-way interaction *time×intervention* provides an estimate of the difference in outcome trend over time in the intervention period compared to the pre-intervention period at RFH. The three-way interaction *time×site×intervention* provides an estimate of the difference-in-difference in the trend between the sites.

	Renal recovery			
	β	p value	OR	95% CI
intervention	-0.10	0.73	0.91	(0.52-1.58)
site×intervention	0.32	0.47	1.38	(0.58-3.26)
time×intervention	-0.02	0.40	0.98	(0.94-1.02)
time×site×intervention	-0.02	0.42	0.98	0.92-1.03

Table 5.9: Results from binary logistic regression (sensitivity analysis) for hospital inpatients. The coefficient *intervention* provides an estimate of the difference in outcome between the intervention period and the pre-intervention period at RFH. The two-way interaction *site×intervention* provides an estimate of the difference-in-difference between the two hospital sites. The two-way interaction *time×intervention* provides an estimate of the difference in outcome trend over time in the intervention period compared to the pre-intervention period at RFH. The three-way interaction *time×site×intervention* provides an estimate of the difference-in-difference in the trend between the sites.

Estimates from the models predicting secondary clinical outcomes are reported in Table 5.8. I found evidence for a step reduction in the rate of cardiac arrest following the intervention at RFH (estimated OR=0.55, 95%CI:0.38-0.76, p<0.001). However, there was no statistically significant difference in the step change between sites (OR=1.13, 95%CI:0.63-1.99, p=0.69, Table 5.8). The data and model predictions are shown in Figure 5.12.

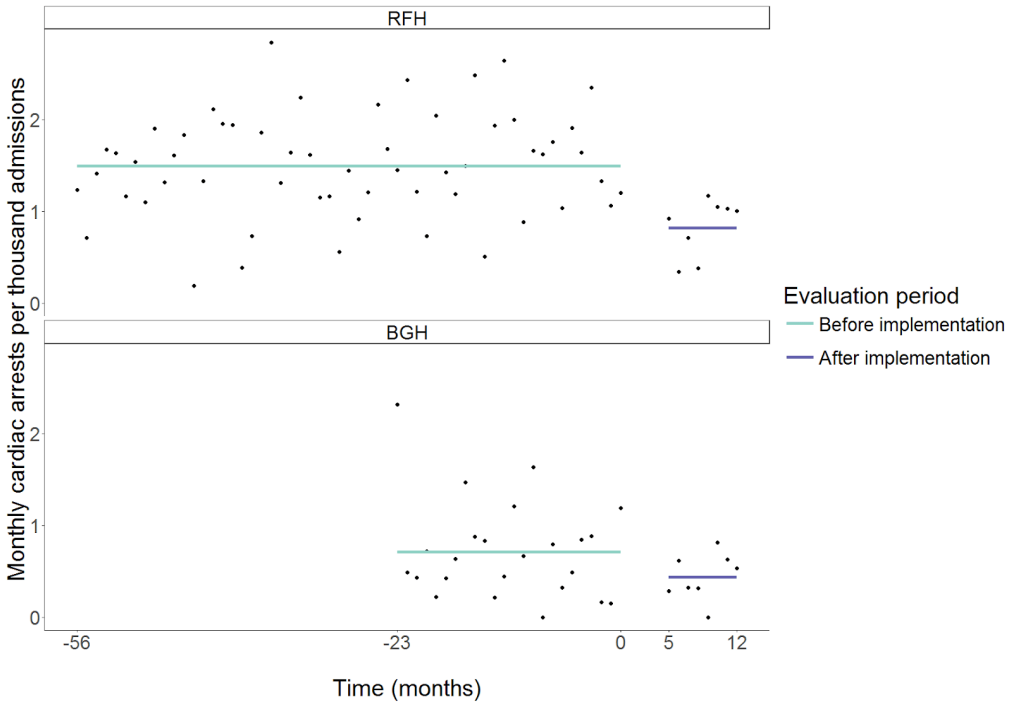

Figure 5.12: Cardiac arrests at RFH and BGH. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of cardiac arrest per thousand admissions for a single month. Solid lines indicate fitted values from the modelling functions. Time is noted in months from the implementation of the care pathway.

I also found evidence for a step reduction in the rates of RRT at 30 days at RFH (estimated OR=0.04, 95%CI:0.00-0.62, p=0.04). However, estimates for this outcome were not reliable (see estimates and confidence intervals listed in Table 5.8); this is likely because RRT was a rare event (Figure 5.18). For all other secondary outcomes, models did not provide statistically significant evidence for an impact of the intervention. I found no significant autocorrelation in any of the models. The data and model predictions are shown in Figures 5.13 to 5.17.

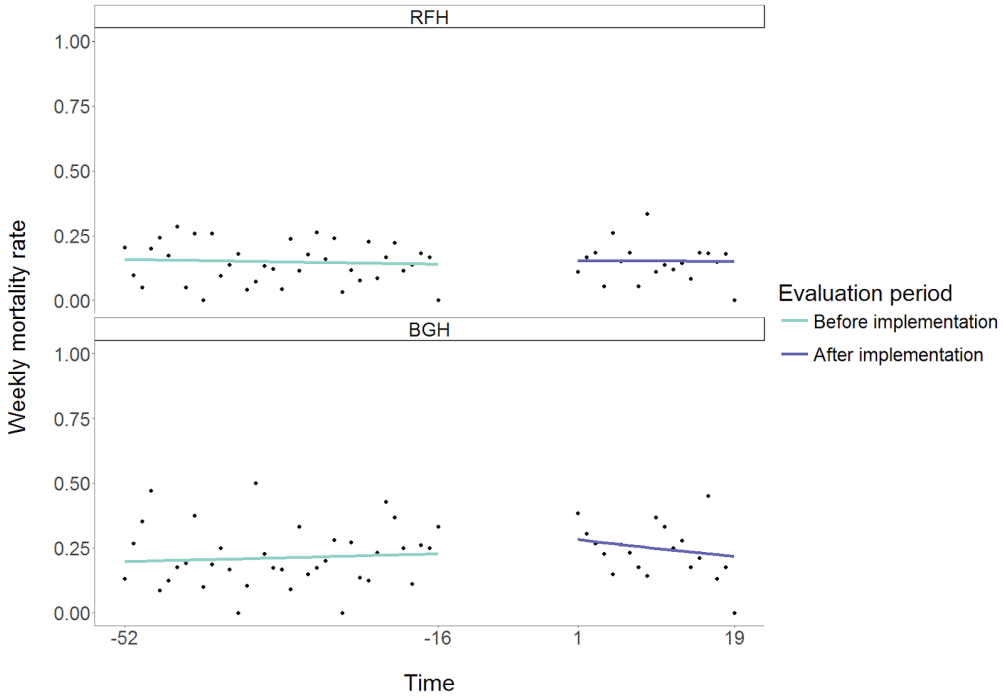

Figure 5.13: Weekly rates of mortality at RFH and BGH before and after implementation of the care pathway for hospital inpatients. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

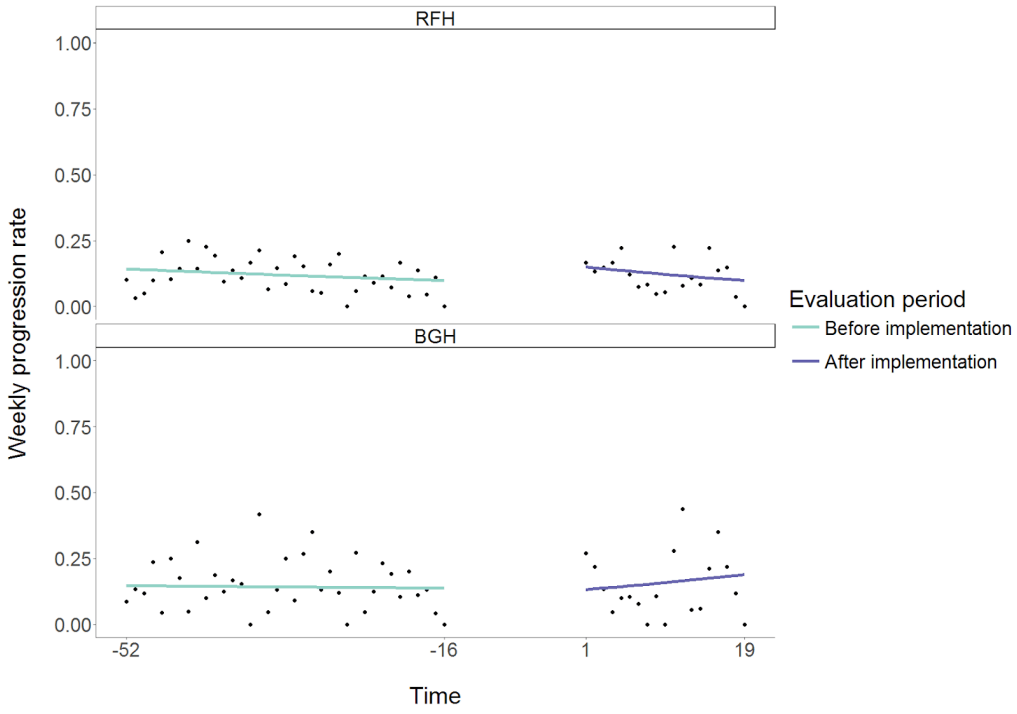

Figure 5.14: Weekly rates of AKI progression at RFH and BGH before and after implementation of the care pathway for hospital inpatients. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

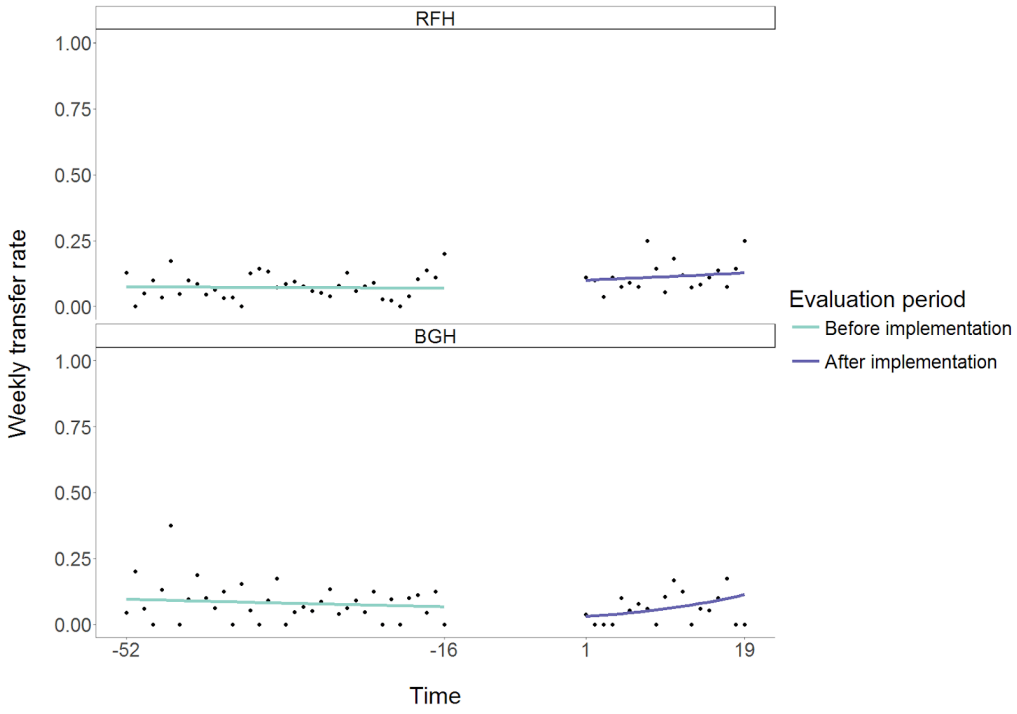

Figure 5.15: Weekly rates of transfer to ITU/ renal unit at RFH and BGH before and after implementation of the care pathway for hospital inpatients. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

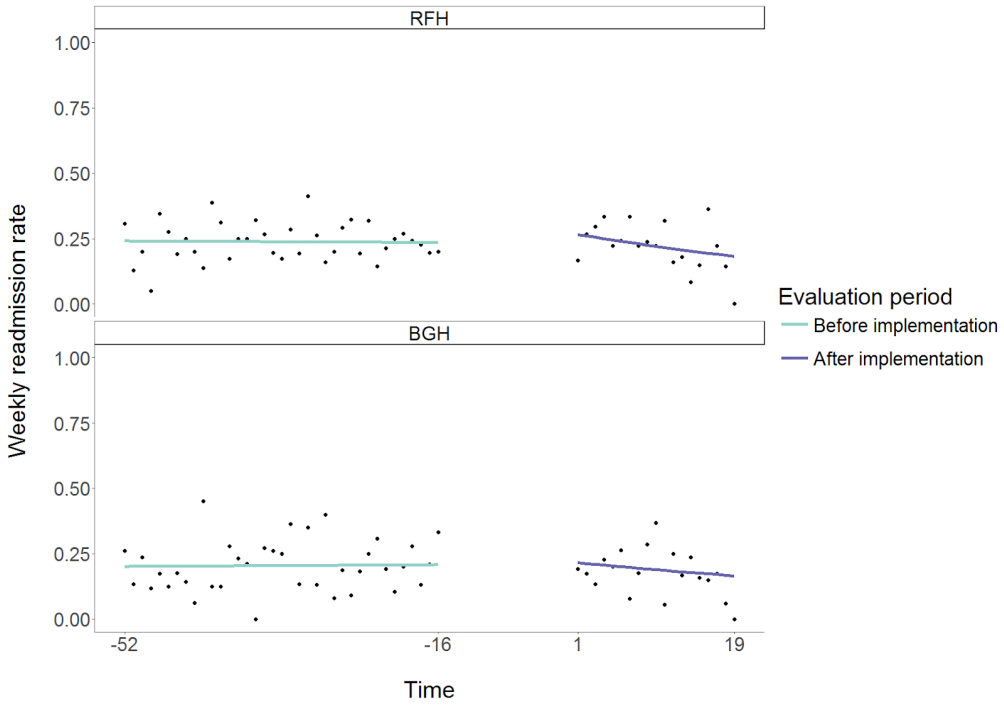

Figure 5.16: Weekly rates of readmission at RFH and BGH before and after implementation of the care pathway for hospital inpatients. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

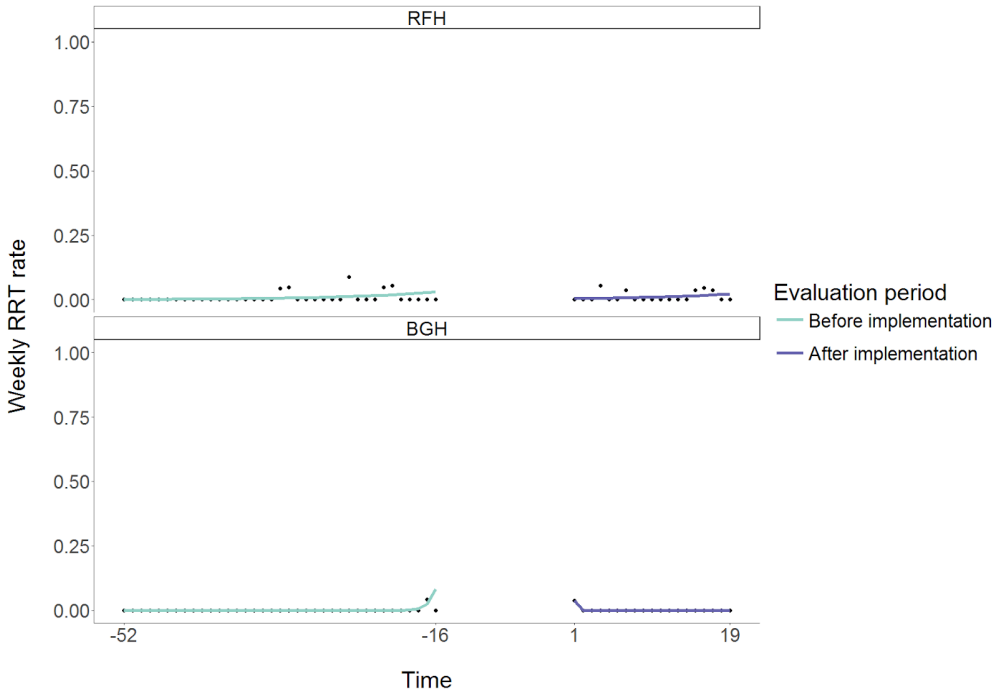

Figure 5.17: Weekly rates of 30-day dependence on RRT at RFH and BGH before and after implementation of the care pathway for hospital inpatients. RFH = Royal Free Hospital, BGH = Barnet General Hospital. Individual data points reflect the rate of each outcome for a single week. Solid lines indicate fitted values from the modelling functions. Time is noted in weeks, relative to the beginning of the Evaluation phase.

I found no evidence for an effect of the intervention on the time to renal recovery; at RFH the median (IQR) time to renal recovery was 3.00 days (1.00-15.00 days) before and 4.00 days (1.00-12.00 days) after the introduction of the intervention respectively (p=0.14). At BGH the median (IQR) time to renal recovery was 3.00 (1.00-13.00) and 3.00 (1.00-7.00) days respectively (p=0.100).

I found a significant increase in length of stay at both RFH (p=0.046) and at BGH (p=0.03) after the introduction of the intervention using competing risk analyses (Figures 5.19 and 5.20, below).

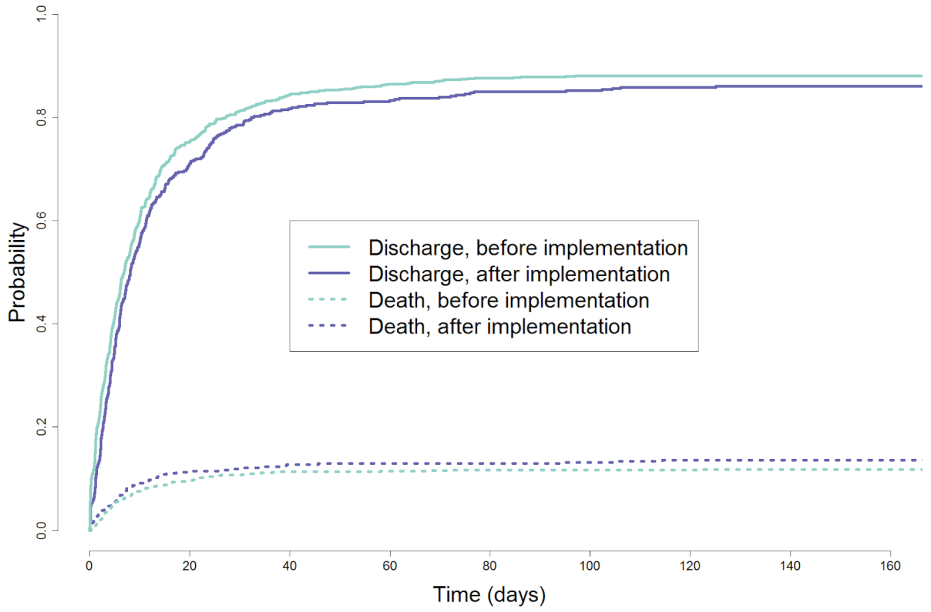

Figure 5.18: Plot of competing risk analysis for mortality and hospital discharge at RFH for hospital inpatients. Significant increase in LoS after implementation (p=0.046). No significant difference in mortality after implementation (p=0.32)

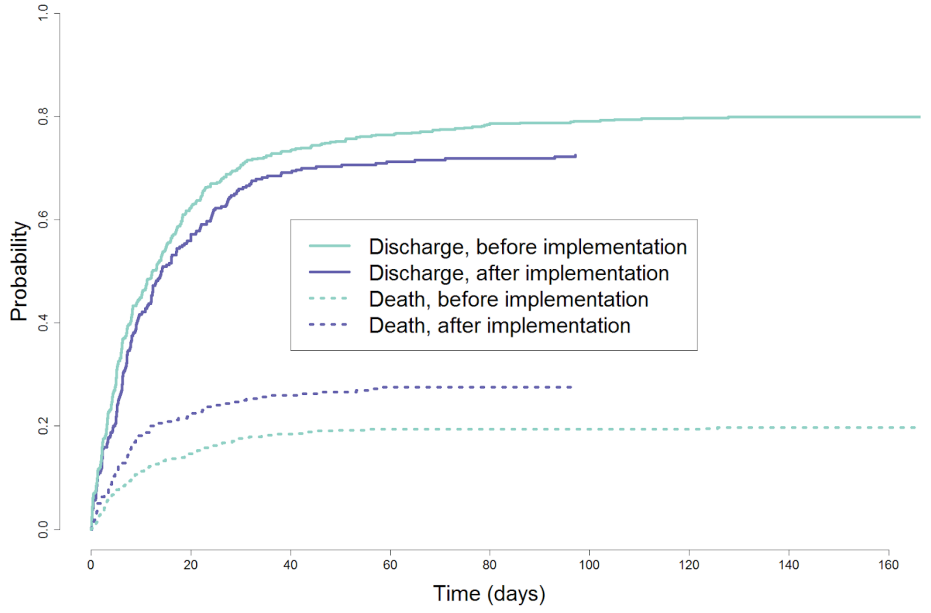

Figure 5.19: Plot of competing risk analysis for mortality and hospital discharge at BGH for hospital inpatients. Significant increase in LoS after implementation (p=0.033). Significant increase in mortality after implementation (p=0.003). NB: the model estimated odds ratio (OR) for the effects of the intervention on 30-day mortality was not significant (OR=2.08 (95%CI 0.90 - 4.79, p=0.09).

Evaluation of economic impact

The evaluation of economic impact was carried out by Prof. Steve Morris at the UCL Centre for Applied Health Research. I oversaw data collection and linkage, and assisted in data analysis and the interpretation of results.

Materials and methods

Participants

The economic analysis included all participants with a clinician-verified episode of AKI during any stage of their admission (Figure 5.2).

Data collection, linkage and storage

Working with a RFLFT data analyst, I joined the pseudonymised dataset used for the analysis of clinical outcomes to data from the Trust's Patient Level Information and Coding System (PLICS). PLICS is a clinical costing system mandated for use across the NHS, where costs are derived for each patient spell (i.e. admission) by tracing resources used by an individual patient in diagnosis and treatment, and calculating the expenditure on those resources using the actual costs incurred by the provider, including staffing costs and infrastructure absorbed costs[177].

The PLICS data I gathered also included data on the costs associated with selected individual components of a spell, which we analysed separately (i.e. length of stay, pathology and radiology examinations, theatre total time and theatre cutting time). However, individual cost components were based on tariffs and not fully absorbed costs. In addition, we could not obtain individual costs of inpatient dialysis. The final dataset used in the economic analysis was therefore comprised of total and component-specific spell-level costs at RFH and BGH, before and after the digitally-enabled care pathway was introduced at RFH.

Outcome framework

The economic analyses used generalized linear models to estimate difference-in-differences between the implementation and comparator sites. Costs were defined at the spell level and patient-level characteristics (age, sex, ethnicity category, Index of Multiple Deprivation [IMD], the presence of complications at the time of alert, and the presence of individual Charlson Score comorbidities) were included as covariates to allow adjustment for any differences in case-mix between sites, and within sites over time. We adjusted for clustering at the patient level to account for the possibility that patients may have had multiple spells.

A Generalized Linear Model (GLM) was specified using a gamma family and log link to account for data skewness. The model used was:

$$log(cost) = \beta_0 + \beta_1 age + \beta_2 sex + \beta_3 ethnicity + \beta_4 imd + \beta_5 comp + \beta_6 CharlsonScore + \beta_7 time + \beta_8 site + \beta_9 time \times site$$

where *time* was defined in relation to the intervention. For robustness checks, we also carried out a secondary analysis, where May-September 2016 was considered pre-intervention (t_1), and May-September 2017 was considered post-intervention (t_3). The coefficient β_9 is the coefficient of highest interest, measuring the between-site difference-in-differences, comparing the change over time at RFH to the change over time at BGH.

Results

Table 5.10 provides descriptive statistics of total costs per spell at each site before and after the intervention. Figure 5.20 shows the positively skewed distribution of these costs.

Total Cost	RFH		BGH	
	pre	post	pre	post
Mean	£12,015.24	£10,154.92	£7,391.16	£7,108.88
Standard deviation	£22,732.78	£19,582.30	£14,346.27	£11,512.95
Median	£5,640.50	£4,954.00	£3,712.50	£3,774.00
1st centile	£166.00	£207.00	£160.00	£199.00
25th centile	£2,391.50	£2,079.00	£1,424.00	£1,153.50
75th centile	£13,208.50	£10,567.00	£8,466.00	£8,897.00
99th centile	£111,245.00	£90,138.00	£51,991.00	£45,614.00

Table 5.10: Descriptive statistics of total cost per spell producing AKI alerts. RFH = Royal Free Hospital, BGH = Barnet General Hospital. pre = May 2016 to January 2017, post = May 2017 to September 2017

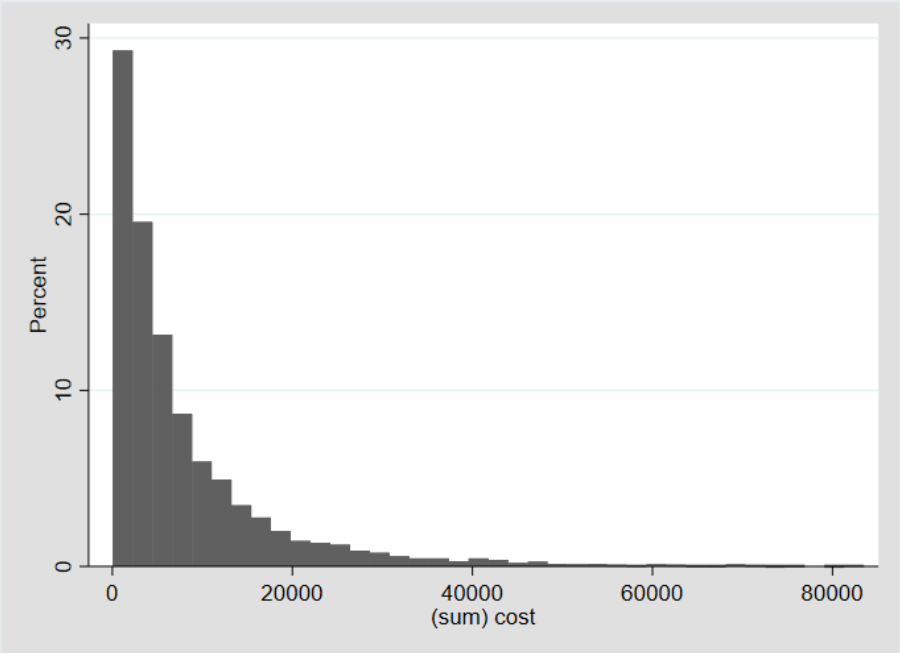

Figure 5.20: Distribution of cost per spell, across both sites and all time periods. Cost is shown in pounds.

There was a significant reduction in adjusted mean costs per spell over time at RFH but not at BGH (Table 5.11). There was a significant reduction in mean costs per spell at the RFH in the post-implementation period compared with the pre-intervention period over and above

the (non-significant) change seen at BGH: the difference-in-differences was -£1,631 per spell (95%CI=-£3,218;-£44 p=0.044). For the specified secondary analysis, the difference-in-differences was -£2,123 per spell (95%CI=-£4,024;-£222, p=0.029).

	RFH									
Total Cost	Pre-intervention			Post-intervention			Difference			
	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p value
All periods	£11,772.63	£10,936.03	£12,609.23	£9,761.59	£8,755.45	£10,767.72	-£2,011.05	-£3,283.53	-£738.56	<0.01
Periods t1&t3 only	£12,176.52	£10,996.53	£13,356.50	£9,853.37	£8,840.91	£10,865.82	-£2,323.15	-£3,843.90	-£802.41	<0.01

	BGH									
Total Cost	Pre-intervention			Post-intervention			Difference			
	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p value
All periods	£7,623.76	£7,007.67	£8,239.86	£7,243.58	£6,413.81	£8,073.35	-£380.19	-£1,358.56	£598.19	0.45
Periods t1&t3 only	£7,507.88	£6,589.77	£8,425.99	£7,307.27	£6,461.82	£8,152.71	-£200.62	-£1,370.27	£969.04	0.74

Difference-in-difference				
Total Cost	Mean	Lower CI	Upper CI	p value
All periods	-£1,630.86	-£3,217.50	-£44.22	0.04
Periods t1&t3 only	-£2,122.54	-£4,023.37	-£221.70	0.03

Table 5.11: Results of economic analyses. RFH = Royal Free Hospital, BGH = Barnet General Hospital. CI = Confidence Interval. t1 = May to September 2016; t3 = May to September 2017.

Cost component analyses for RFH and BGH are shown in Table 5.12 and Table 5.13, respectively. No significant change in costs were noted in the difference-in-difference analyses of the cost components (Table 5.14).

RFH											
Component	Time period	Pre-intervention			Post-intervention			Difference			
		Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p value
Radiology exams	All periods	£241.78	£225.89	£257.66	£215.37	£194.43	£236.30	-£26.41	-£52.10	-£0.72	0.04
	Periods t1&t3 only	£251.75	£228.98	£274.53	£219.32	£197.88	£240.76	-£32.44	-£63.03	-£1.84	0.04
Pathology exams	All periods	£507.40	£475.87	£538.93	£434.31	£395.92	£472.69	-£73.09	-£121.53	-£24.65	0.003
	Periods t1&t3 only	£534.45	£489.32	£579.58	£441.41	£402.10	£480.71	-£93.04	-£151.76	-£34.32	0.002
Theatre cutting time	All periods	£1,106.97	£957.68	£1,256.26	£978.47	£792.31	£1,164.64	-£128.50	-£363.54	£106.54	0.28
	Periods t1&t3 only	£1,209.78	£982.57	£1,436.99	£949.20	£773.18	£1,125.23	-£260.58	-£543.91	£22.75	0.07
Theatre total time	All periods	£841.46	£745.99	£936.93	£798.94	£661.84	£936.04	-£42.52	-£209.88	£124.83	0.62
	Periods t1&t3 only	£901.27	£762.38	£1,040.16	£781.36	£651.20	£911.53	-£119.90	-£310.60	£70.79	0.22
Length of stay	All periods	£6,312.34	£5,782.31	£6,842.37	£5,023.42	£4,464.65	£5,582.18	-£1,288.92	-£2,018.84	-£559.01	0.001
	Periods t1&t3 only	£6,412.47	£5,725.75	£7,099.20	£5,047.79	£4,490.96	£5,604.63	-£1,364.68	-£2,227.27	-£502.10	0.002

Table 5.12: Cost components analysis at RFH. t1 = May to September 2016; t3 = May to September 2017.

BGH											
Component	Time period	Pre-intervention			Post-intervention			Difference			
		Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p value
Radiology exams	All periods	£172.87	£161.22	£184.52	£157.81	£141.77	£173.85	-£15.06	-£34.26	£4.13	0.12
	Periods t1&t3 only	£171.15	£154.52	£187.79	£157.83	£141.69	£173.96	-£13.33	-£35.80	£9.15	0.25
Pathology exams	All periods	£628.75	£579.91	£677.59	£536.59	£478.41	£594.78	-£92.16	-£164.98	-£19.33	0.01
	Periods t1&t3 only	£618.41	£541.85	£694.97	£542.90	£483.49	£602.31	-£75.52	-£168.77	£17.74	0.11
Theatre cutting time	All periods	£570.91	£427.01	£714.81	£356.34	£229.38	£483.29	-£214.57	-£401.39	-£27.76	0.02
	Periods t1&t3 only	£717.52	£470.48	£964.55	£363.76	£239.74	£487.78	-£353.75	-£615.93	-£91.57	0.008
Theatre total time	All periods	£383.51	£305.42	£461.60	£292.34	£202.01	£382.66	-£91.18	-£211.39	£29.04	0.14
	Periods t1&t3 only	£455.45	£330.19	£580.72	£292.41	£206.12	£378.71	-£163.04	-£312.04	-£14.04	0.03
Length of stay	All periods	£5,644.89	£5,099.14	£6,190.64	£4,511.97	£3,965.38	£5,058.56	-£1,132.92	-£1,866.18	-£399.66	0.002
	Periods t1&t3 only	£5,469.91	£4,619.59	£6,320.22	£4,559.53	£3,991.79	£5,127.27	-£910.38	-£1,872.28	£51.53	0.06

Table 5.13: Cost components analysis at BGH. t1 = May to September 2016; t3 = May to September 2017.

Difference-in-difference					
Component	Time period	Mean	Lower CI	Upper CI	p value
Radiology exams	All periods	-£11.35	-£42.97	£20.27	0.48
	Periods t1&t3 only	-£19.11	-£56.35	£18.12	0.31
Pathology exams	All periods	£19.07	-£67.80	£105.94	0.67
	Periods t1&t3 only	-£17.53	-£127.13	£92.08	0.75
Theatre cutting time	All periods	£86.08	-£217.09	£389.25	0.58
	Periods t1&t3 only	£93.18	-£289.96	£476.31	0.63
Theatre total time	All periods	£48.65	-£158.95	£256.25	0.65
	Periods t1&t3 only	£43.13	-£196.92	£283.19	0.72
Length of stay	All periods	-£156.00	-£1,170.46	£858.45	0.76
	Periods t1&t3 only	-£454.31	-£1,736.82	£828.21	0.49

Table 5.14: Cost components difference-in-difference analysis. CI = Confidence Interval. t1 = May to September 2016; t3 = May to September 2017.

Discussion

Introduction of the digitally-enabled care pathway was associated with a significant improvement in outcome trend of renal recovery at the intervention site among patients with AKI at presentation to ED, although this trend change was not statistically significantly different from that observed at the comparator site. No other significant impacts on the primary outcome of renal recovery were noted. There are several possible explanations for the lack of impact on renal recovery. First, this may reflect existing high standards of AKI care prior to implementation: 30-day mortality for pre-intervention patients at RFH was 14.9% compared with 18.1% nationally[178]. It is possible that our intervention may have delivered more benefit in hospitals with worse baseline outcomes. Secondly, AKI detection using the NHS algorithm depends on an elevation of serum creatinine, the detection of which may lag many hours or even days after the time of renal insult[49]. For ED patient

cohorts, both insult and renal injury may also have been established some considerable time before admission. In consequence renal injury may be less modifiable by this stage, even using a rapid system of detection such as that described. Thirdly, demonstrable process improvement may have been insufficiently impactful on the outcomes considered here. Finally, benefit may have been limited to specific patient groups (e.g. patients with severe AKI, or with specific causative diagnoses). It is possible that the Streams app may have had greater impact were it to have been implemented as part of a different care pathway - perhaps one which involved general physicians as well as specialty care.

I noted a significant reduction in cardiac arrest rate at RFH. However, this finding needs to be viewed with caution; this was a hospital-wide measure so may have been influenced by other, concurrently implemented initiatives. Furthermore, cardiac arrest rates also reduced at the comparator site. BGH had an active quality improvement initiative for patients with sepsis at the time of the evaluation; it is possible that both the RFH digital pathway and the BGH quality improvement initiative were effective to some extent, via different mechanisms. However, an explanation for the possible effect of the intervention on rates of cardiac arrest emerged from qualitative data (which will be discussed in the next chapter). Here, users suggested the care pathway not only enhanced early access to specialist care for deteriorating patients, but also informed treatment escalation plans; the latter included institution of ceilings of care and ‘do not resuscitate’ orders with patients and relatives. Both would be expected to contribute to a reduction in the recorded unexpected cardiac arrest rate.

Among process measures, pathway implementation was associated with significant improvement in the reliability of AKI recognition, a reduction in the timeframe in which recognition occurred, and a reduction in the timeframe in which adjustment of potentially nephrotoxic medications occurred for patients in ED. The improvements in the time to treatment for sepsis and renal tract obstruction I observed were not statistically significant.

Pathway implementation was associated with a significant reduction in adjusted mean costs per patient admission. However, it is not possible to judge whether or not it would be cost saving overall, as we did not include the costs of providing the technology or any additional costs incurred in implementation. However, my results suggest that the digitally-enabled

care pathway would be cost saving provided implementation costs were less than around £1600 per patient spell. The source of the cost savings are unclear; although the most important cost component contributing to this reduction was length of stay, the causes are likely to be multifactorial, and further research to investigate these would be useful.

My data are consistent with recent reports of the benefits of e-alerting systems for AKI for patients and the wider health system. A large multicentre sequential period analysis of an alerting system warning clinicians of the possible presence of AKI next to the display of serum creatinine results, resulted in a small but sustained decrease in in-hospital mortality, dialysis use and length of stay[179]. That this might improve outcomes is supported by a Korean study which reported the impacts of an e-alert system which facilitated nephrology consultation. AKI detection improved, nephrology consultations within three days increased, and the odds of AKI recovery increased[180]. More ambitious implementations also appear to be of benefit; two recent single-site quality improvement projects combining AKI alerts with care bundles and targeted staff education also improved recognition of AKI and the quality of inpatient care[181,182]. However, it is unclear which components of these pathways influenced these outcomes. A number of mixed-methods analyses of e-alerting systems for AKI are still underway; results from the qualitative segments of the AKORDD[183] and TACKLING[184] studies are awaited.

In conclusion, implementation of the digitally-enabled care pathway significantly improved some processes of care and clinical outcomes for some patient populations. It also significantly reduced the cost of care delivery. The results presented in this chapter have now been published in two manuscripts[185,186]. In the next chapter I will present a qualitative evaluation of the experiences of users and other healthcare professionals whose work was affected by implementation. We sought to characterise the impacts on staff of such automated alerting, mobile results viewing and ready communication, with particular focus on their working practices and interprofessional relationships.

Chapter 6: Qualitative evaluation of user experience

Introduction

Many modern health systems struggle to meet the health needs of an ageing demographic of hospital patients with a greater need for diverse investigations and treatments. Although modern care pathways are increasingly reliant on clinicians having expedient access to diverse data about their patients and timely communication between individuals and multidisciplinary teams[187], there have been fewer developments in the way in which clinical data are accessed and presented, and the way in which healthcare teams communicate. Worldwide, the most widely used hospital communication system continues to be the pager[188], whilst data are still commonly accessed from paper records. Systems that have supported the digitisation of health records often result in the concomitant use of a range of disparate and disconnected electronic data repositories. In addition, working with such tools may be injurious to the wellbeing of clinicians[139]. Care and the clinician experience might be readily improved were it possible to readily access data in a form which integrated with clinical workflows, and were communication tools improved.

The introduction of digital technologies offers one potential solution, and the embedding of digital technologies into healthcare is now a priority in the United Kingdom[189] and internationally[190]. I thus created a digital care pathway for the management of patients with AKI. I have previously described the impact of this pathway on clinical and economic outcomes (see Chapter 5). However, the impacts of the adoption of such technologies on users and the broader health system should be thoroughly assessed; the 2016 ADQI consensus statement on assessments of the impact of electronic alerting for AKI emphasized the importance of including an evaluation of user experience[158]. In this chapter, I present an analysis of semi-structured interviews carried out with users and other healthcare professionals whose work was affected by implementation of the digitally-enabled care pathway.

Materials and methods

As outlined in Chapter 3, I sought to characterise the impacts on staff of automated alerting, mobile results viewing and ready communication, with particular focus on their working practices and inter-professional relationships. I collected data using non-participant field observations and in-depth semi-structured interviews.

I developed the semi-structured interview guides with the broader research team, which included physicians (with extensive experience in clinical Nephrology and Intensive Care Medicine) and experts in Health Services Research. Interviews explored the impacts of the care pathway on staff members and on the care delivered to patients, with particular focus on working practices and inter-professional relationships. As outlined in Chapter 4, I amended this interview guide following observations I made in the pilot phase of implementation so as to more fully explore the impact of the pathway on clinician experience (see Appendices 4 and 5).

Interviews began one month after the start of the pilot phase of implementation, and were spaced throughout a 16 month period of implementation and evaluation (February 2017 to May 2018). I employed purposive sampling, following a key informant strategy[160], in which individuals with important roles in the environment under study who had expert knowledge were identified. The total number of users involved in providing the care pathway was small, which necessarily restricted the number of interviews that could be carried out. I aimed to carry out twenty interviews, a sample size typical for a case study such as this, and in line with both international consensus guidance and common practice in qualitative research[161,162]. I drew up a list of potential respondents to ensure representation from both groups in the AKI response team (i.e. nephrology and PARRT teams), and from clinicians from the wider hospital community affected by the care pathway. In drawing up this list, I also sought a diverse range of clinical experience and level of comfort with mobile technologies. Twenty respondents were approached, and nineteen consented to interview. Eight PARRT nurses (five Band seven, three Band eight or above) and eight Nephrologists (four Registrars, four Consultants) were interviewed from the AKI response team. Three respondents (two Consultant Physicians and one Medical Registrar) from the wider hospital community were selected as a result of their frequent interactions with the AKI response

team. Each respondent was interviewed once. I carried out all interviews, which were audio-taped using an Olympus VN-741 dictaphone (Olympus Corporation, Tokyo, Japan). Recordings were transferred to the Data Safe Haven at UCL before being transcribed verbatim. Transcribed data were identifiable by the participant's unique study ID only and any identifiable data were not included in the transcripts.

In collaboration with a qualitative researcher from the UCL Department of Applied Health Research (Dr. Georgia Black), I analysed the interview data using a combination of inductive and deductive thematic analysis techniques[191]. Quotes from each interview were arranged into a matrix, in which rows represented individual respondents and columns represented categories, each of which aligned to the basic principles of the intervention pathway (e.g. the triage of AKI alerts). Dr. Black and I analysed data independently; however, we met regularly to critique and challenge each other's matrix allocations. I then reviewed the matrix allocations with one of my supervisors (Professor Rosalind Raine), a process that enabled us to identify discordant views.

We then synthesised new descriptive codes based on emergent themes in the matrix e.g. the impact of real-time information availability. Together, we assigned the extracted quotes to the new themes, routinely seeking and discussing any quotes that challenged these themes. In doing so, we employed the principle of 'keyness' in our analysis[192]; instead of focussing on issues specific to AKI or the RFH, we aimed to enumerate novel issues that might be generalisable and relevant more broadly to the adoption of digital health products in clinical practice (for example, how mobile working tools impact established clinical workflows).

Results

As outlined above, interviews sought to characterise the impacts of automated alerting and mobile results viewing on clinicians, with particular focus on their working practices and interprofessional relationships. Three central themes emerged.

Theme 1: The impact of real-time information availability

The first theme relates to respondents' experiences of real-time access to patient data. As outlined in Chapter 2, the Streams app provided automated AKI alerts and gave staff mobile access to current and historic patient data. Some participants in both teams reported that these dual functions saved time:

> *"Being able to look up the blood results for anyone in the hospital wherever you are is unparalleled. [...] it feels almost archaic these days, to go and see a patient and then go and sit down in front of a computer 15 minutes later. As a doctor you have to integrate what you know about them at the time of seeing them. So if you could literally have this phone, look at the results, go and see them… Or even look at it while you are seeing them. [...] It must save at least - I don't know if you could analyse it - but it must save at least a couple of hours in a day."* Respondent 3: Nephrology Team

These functions expedited intervention for deteriorating patients, regardless of where they were situated in the hospital:

> *"The speed at which it happened was impressive. [...] I happened to be in A&E and got the alert of someone with severe kidney injury. [...] The patient was admitted to [...] a specialist renal ward [...] within 2 or 3 hours, which I don't think would have happened without the app. [...] I think it streamlines care, and speeds up the time in which they get a specialist renal review."* Respondent 9: Nephrology team

> *"I personally have noticed [...] patients who have flagged up on the app that the clinical management has been poor up to that point. When we get involved, or the renal team get involved, that management changes [...] It has definitely saved people's lives."* Respondent 14: PARRT

> *"Being able to access all the bloods for the patients in the hospital and to be able to be alerted to the sick ones and already know about them before we usually do… Sometimes you know about them before the crash bleep comes through. You turn up and you think, 'That was actually the alert I was coming to see'"* Respondent 10: PARRT

Participants in both teams suggested AKI alerts were particularly valuable for patients under the care of surgical consultants:

> *"The most value came from patients under [...] surgical patients, for whom the list of priorities for their clinicians are very different from what [physicians] look for when they are looking after a patient. For those [patients], getting a rapid alert about deranged renal function is very valuable."* Respondent 6: Nephrology team

However, real-time clinical alerts and the introduction of team communication via mobile phones introduced workload for clinicians in a new modality. There was a discrepancy in clinicians' ability to integrate AKI alerts into their existing workload. Overall, experienced clinicians more easily discriminated between cases of high and low risk, and used this information to adjust their priorities:

> *"I would intermittently [...] check it, like I would [...] check emails, [...] check it every hour or so, something like that. And within 5 minutes or so I could easily flick through the alerts and [...] identify which ones I needed to see. [...] I felt it was very easy to use, I think some people when they were trying to use it would try and respond immediately to every alert. I wouldn't personally, I didn't think that was the best way to do it. Intermittently checking it throughout the day, I managed to keep on top of things."* Respondent 9: Nephrology team

In contrast, some junior clinicians in both teams suggested that clinical review might not be deliverable to all patients as the pathway created additional workload:

> *"It does increase our work. Some days [...] we can have eight or nine referrals. But there is obviously a huge issue about workload for many people. But if we need to increase the size of our team because of this then that's a good thing. And also it highlights […] the acuity of our patients in our hospital. These patients are not straightforward."* Respondent 19: PARRT

Other clinicians suggested that the volume of "false positive" alerts produced by the NHS AKI algorithm added to the extra workload perceived:

> *"...if the noise of the system could be reduced it would be a lot better. If [we were] able to get rid of all the nonsense alerts, that would be fantastic."* Respondent 1: Nephrology team

Some respondents from the Nephrology team balanced the perceived benefits of real-time information availability with anxiety perceived as a result of uncertainty relating to who was primarily responsible for delivering timely care. Again, the expansion of the workforce responding to AKI alerts was suggested as a way to mitigate this stress:

> *"...as Renal [Registrars], [...] you are always now, in the back of your head, thinking "I've got this other job to do". And I think it does create… not anxiety that keeps you up at night… But it's another anxiety when you already have enough anxiety! So I think even if it was available in the hands of more people, or we were a bit clearer that during times of people being unwell who are your own patients, you shouldn't prioritise Streams people because they are under another team, then that's fine. That's one way of dealing with it."* Respondent 3: Nephrology team

In summary, the care pathway was valued by clinicians for allowing efficient access to patient information and facilitating better care. However, some respondents reported increased workload and anxiety.

Theme 2: The implications of early detection

The second theme relates to the implications of early detection of AKI. As outlined in Chapter 2, the digitally-enabled care pathway was designed to expedite identification of AKI and communication of such identification to specialist clinicians at the earliest possible point in time. Respondents in both teams pointed out that the AKI algorithm identified deteriorating patients at an earlier stage than was possible through other means:

> *"It's a good thing from the point of view that I know there are patients that are potentially sick out there. [...] You could have an AKI and look relatively well initially. But [...] nobody would have known about those patients."* Respondent 8: PARRT

As a result of early identification, staff who more typically review critically unwell patients would now also attend to patients perceived to be at lower risk. Members of the AKI response team diverged in their opinion about the utility of such an approach. Some respondents emphasised the benefits of early recognition in terms of its impact on reducing the complexity of interventions required:

> *"I think it does a good job. We pick up patients that would maybe sit for another day or so before we pick them up. It's certainly beneficial. It is more work, but we might be saving ourselves work in a couple of days, we might have to do more stuff to catch up."* Respondent 15: PARRT

However, some respondents in the Nephrology team did not see value in being alerted to a group of patients perceived to be low in risk:

> *"...you get a lot of AKI stage 1s. They build up. Looking through those and dismissing them each time is time consuming. The AKI stage 2 and 3 [alerts] are more helpful for me to look at, so I tend to just look at those and dismiss the stage 1s."* Respondent 18: Nephrology Team

In addition, for some members of the nephrology team, early identification could not necessarily be aligned to early intervention because of uncertainty as regards the optimal management strategy for some patient groups:

> *"The patients you definitely need to see are the patients that have acute renal failure with a creatinine of 300 or 400 and it's going up - patients you'd normally want to see [...] The other patients [...] that have a rising creatinine, but the creatinine is not very high - it doesn't mean that they don't need to be seen necessarily. We are not trained as doctors to look after those sort of patients."* Respondent 1: Nephrology Team

In summary, the shift towards earlier detection engendered by the implementation of the care pathway highlighted the need to consider both the resources and training needed to enable clinicians to effectively intervene at an earlier stage.

Theme 3: Behavioural effects of the care pathway

The final theme relates to the impact of real-time data provision on the relationship between users of intervention and the broader health system, and how these related to beliefs, behaviours and care delivery. These impacts are best described in three subcategories. First, the care pathway affected behaviours *within* clinical teams. Members of both teams described beneficial effects relating to the use of mobile phones for team communication:

> *"I've found the [mobile phone] really useful because I've been able to message my team when I'm out seeing a patient, rather than finding a phone and to bleep them with and waiting for them to answer"* Respondent 5: PARRT

However, as junior members of the nephrology team (i.e. House Officers) do not currently use the Streams app (and therefore accessed patient data through traditional means such as desktop computers), a disadvantage was also identified. Occasionally, the different modes of access to patient data reversed the usual direction of communication of information from junior doctor to consultant. Some nephrology consultants suggested that this impacted on the learning opportunities that such communication engenders:

> *"I think it's important for [Junior Doctors] to understand what the decisions about their patients are. They have to be across the data. And that's why I prefer getting information from them" [...] "We were in the position where I was telling the Juniors what the blood results were. It makes me uncomfortable and it makes them uncomfortable."* Respondent 6: Nephrology team

As outlined in Chapter 4, users specifically requested the ability to view each other's triage decisions to aid communication and avoid the duplication of work. However, the communication of these decisions revealed previously unrecognised variations in professional judgements, which caused confusion for some:

> *"I was quite surprised about how other people triaged initially. I felt we'd be much more similar in our thinking, because when we talk about other things we do think similarly about other stuff. [...] I felt like - probably naively - that everyone would do what I did. And they didn't at all."* Respondent 11: PARRT

Secondly, the digital pathway had an impact on relationships *between* clinical teams. Several members of the Nephrology team suggested that they were unhappy providing an opinion about a patients' care when not specifically invited to by colleagues.

> *"So you might [...] call the team and say "we suggest you give some fluid", but I don't think it's ethical to prescribe it yourself. After all, they might say, 'Listen he has heart failure'. So you can't intrude."* Respondent 2: Nephrology team

However, several members of the PARRT team suggested that this concern might be specifically limited to established patterns of communication and behaviour among doctors:

> *"I think the doctors have found it more difficult because in medicine there is this real model of, "[...] I don't see this patient unless I'm asked to see them". There's this formality. [...] Nurses don't think like that, people are used to us showing up. So it's been easier for us to think of every patient that we see as our patient, our problem, our sick patients. I think that's been easier for this team to absorb and deal with."* Respondent 11: PARRT

This is relevant, because the digitally-enabled care pathway also changed patterns of communication for this group:

> *"[I will] always [speak to] the nursing staff, because you are on their ward. It's only polite and also you will generally be recommending frequencies of obs;*

> *they need to know what's going on. And someone from the medical team. I would say the app is making me speak to more senior doctors more. [...] I'd be more likely to seek out a consultant and say "by the way, this person has alerted" and show them the app."* Respondent 5: PARRT

Lastly, the care pathway had an impact on the relationship between clinicians and their patients. As outlined above, several respondents described that the care pathway enabled the identification of deteriorating patients at an earlier stage than was possible through established pathways and behaviours (e.g. monitoring of vital signs). This led to an unexpected role for some members of the team; several respondents described how the care pathway facilitated earlier discussions relating to ceilings of treatment, enabling them to help patients make informed decisions surrounding end-of-life care.

> *"Why do we have to talk about end of life just as I'm about to die? [...] We could plan. Every single person we've been referred today has a terminal disease. [...] Trying to move the decision making back, in a more timely way. [...] We are getting an alert before they have even triggered [via vital signs], so we can probably have a sensible conversation with a patient with capacity."* Respondent 4: PARRT

This finding is particularly relevant, given the impact of the digitally-enabled care pathway on hospital-wide rates of cardiac arrest described in Chapter 5.

Discussion

The qualitative analysis I performed suggested that the ability to integrate mobile results viewing into existing clinical workflows might increase efficiency for some clinicians. In addition, the real-time identification of patients at an early stage in deterioration might offer opportunities for more constructive end-of-life planning. However, these benefits came at a price, particularly for some junior staff, in terms of anxiety associated with increasing numbers of 'priority' patients and information overload. These factors were in part exacerbated by false positive alerts produced by the NHS England AKI algorithm. Finding the most appropriate balance between sensitivity and specificity for clinical alerts can be

difficult to achieve; whilst it is recognised that the NHS England AKI algorithm produces false positives, some argue that this is a necessary trade-off for enhanced sensitivity[193]. Such factors were also exacerbated by perceived differences in the staffing of the AKI response team and the workload it engendered. Furthermore, I highlighted an unmet training need that related to the provision of early care. Training will be vital if we are to optimise the value of digital innovations aiming to promote early intervention. These findings suggest that the true effectiveness of innovations cannot be assessed until the balance between early intervention and increased workload is ascertained.

My qualitative evaluation had a number of strengths. Firstly, it benefited from the diversity of the respondent sample (i.e. the clinicians interviewed). I interviewed a range of specialists, of diverse age and familiarity with digital technology. This allowed me to present multiple perspectives on the intervention. Secondly, the research team was diverse, including personnel from medical, public health and psychology backgrounds. This encouraged debate and multidisciplinary interpretation of results, and reduced the risk of bias in our interpretation of the results. Lastly, the robust analysis process described above uncovered issues which are likely to be generalisable to the implementation of other digital technologies in healthcare.

The evaluation had a number of limitations. Firstly, I initiated interviews during the pilot period, in order that I might gather insights that would improve the pathway. However, at this early stage, interviewees might not have been used to their new roles and might have been more likely to include negative feedback as a result. In addition, the relatively short period of time in which interviews were carried out did not allow me to assess whether perceptions of the digitally-enabled care pathway changed over time. In retrospect, I might have been as well to repeat this process once the system was fully operational and embedded. Secondly, by necessity, the interviews I carried out were all in a single clinical setting. Although I specifically aimed to identify findings generalisable to health systems situated elsewhere, their generalisability might vary according to the attitudes of clinicians and the digital maturity of the healthcare environment, among other factors. Finally, the early deployment of specialist resources may have an impact on other clinical teams and patients; I could have carried out more interviews with these groups.

Few qualitative studies of AKI alerting systems have been previously described. An evaluation of a clinical decision support system for AKI by Bevan *et al* found that alerts were unpopular due to their interruption to established workflows[194]. I was able to avoid this problem through the separation of alerts from the hospital's EHR. Mobile working might better allow clinicians to integrate alert reviews into their working practice and established workflows. This is an important finding; junior medical staff currently spend up to half their working day using desktop computers[195].

Kanagasundam *et al* examined the effects of an interruptive AKI clinical decision support system through a series of semi-structured interviews with clinicians[196]. Some of their findings were similar to those enumerated by the existing clinical decision support literature e.g. alert fatigue. The authors suggested that a major reason for dismissing alerts was users' need to review a comprehensive clinical dataset at the point of alert, underlining the importance of the contextual data that Streams provides. In common with my findings, Kanagasundam also reported that some clinicians' impression of the system's utility was limited by their belief that the alert system prioritised sensitivity over specificity. A number of mixed-methods analyses of e-alerting systems for AKI are awaited (e.g. AKORDD[183] and TACKLING[184]) .

A manuscript describing the qualitative evaluation presented in this chapter has now been published[197]. My results are relevant to the design and evaluation of care pathways involving mobile technologies, the automated provision of clinical alerts, or the early deployment of specialist care. Such findings will be important the digital maturity of health systems improves and novel innovations supporting early diagnosis and disease prediction (such as machine learning[25,198]) emerge. My findings suggest that these systems will succeed only if clinicians believe in an intervention's effectiveness, feel able and equipped to take part, and understand what their responsibilities are. Lastly, my results suggest that training in prioritisation of information may be required, so that clinicians feel better able to balance the possible benefits of real-time access to patient data with the cognitive load this might produce. Future evaluations should seek to further explore these issues more fully.

Chapter 7: Summary and discussion

Overview of results

I have described the successful design and implementation of a digitally-enabled care pathway that enables a team of clinicians to (i) be alerted to potential changes in hospitalized patients' kidney function in real-time, (ii) rapidly review relevant contextual data, (iii) intervene proactively, and (iv) remotely monitor cases.

I have shown that, through this care pathway, in-application specialist review of AKI cases can take place within minutes. For patients with AKI on presentation to the hospital ED, implementation of the care pathway improved the timeliness and reliability of AKI recognition, and of the delivery of some AKI therapies. In this cohort, trends for creatinine recovery rates and admission to renal units or to ITU improved significantly at the intervention site. However, difference-in-difference analyses between this and the non-intervention comparator site for both outcome metrics were not significant. For patients developing AKI during the course of hospital admission, there was no evidence for impact on the primary outcome (recovery of renal function) or on any of the secondary clinical outcome measures. However, there was evidence of possible impact on the broader health system. The hospital-wide cardiac arrest rate fell significantly at the intervention site following implementation of the care pathway (although difference-in-differences analysis with the comparator site was not significant), and the mean healthcare costs per patient admission were reduced by £1,630 per admission spell (not including costs of providing the technology). My analysis of semi-structured interviews carried out with caregivers suggested the pathway improved access to patient information and expedited early specialist care, and may have enabled more constructive planning of end-of-life care for some patients. However, the shift towards earlier detection also highlighted resource constraints at the deployment site, and some clinical uncertainty about the value of intervening at such an early stage.

Overall, my evaluation suggests that the implementation of alerting systems may have positive impacts on the quality of care delivered to AKI patients, and on selected clinical and

economic outcomes. It also helps to clarify why e-alerting alone might fail to improve outcomes[157]; I demonstrated the need to consider the organisational as well as the technical aspects of digital interventions by coupling the alerting system to specific management pathways. My qualitative research emphasized the importance of engaging with end-users in the design and implementation of digital technologies; alerting systems aiming to encourage early or preventive action will only achieve maximum impact if users believe in the clinical effectiveness of the intervention, understand clearly what their responsibilities are, and feel empowered to act. Lastly, I also demonstrated the importance of maintaining vigilance for unexpected barriers to implementation, and for unintended consequences of implementation. The inevitable introduction of digital technology to healthcare is more likely to improve both working practices and patient outcomes if such introduction is aligned with a commitment to proactively identify and address concomitant and sometimes unexpected sequelae.

Strengths and limitations of the project

A strength of my evaluation was the use of a comparator site: this follows best practice[199], and is the first study of its kind to do so. The inclusion of this comparator site ensured transparency in the drawing of conclusions about the 'active' components of the intervention and highlighted and the necessity of comparator data to avoid erroneous conclusions about intervention effectiveness. In addition, I triaged all alerts prior to analysis, to account for the high number of false positive alerts produced by the NHS England AKI algorithm. I validated this triage process, showing that it had high inter- and intra-rater reliability. This was (to my knowledge) the first study to define the economic impact of implementing a digital innovation for AKI on health systems. Strengths of the qualitative evaluation I carried out included the diversity of the respondent sample, allowing multiple perspectives on the intervention based on cultural differences between different professionals and teams to be elucidated. The research team itself was similarly diverse in experience, generating a robust analysis which uncovered issues likely to be generalisable to the implementation of other digital technologies in healthcare. I believe the implementation of novel technologies in health systems should be subject to rigorous and broad evaluation. This is not always the case; whilst over half of respondents in a survey of US trainee doctors by the Accreditation

Council for Graduate Medical Education reported using smartphone apps in their clinical practice[200], relatively few studies of the impact of such use exist. My study defined the impact of the digitally-enabled care pathway in diverse but complementary domains, including patient and economic outcomes, and user experience.

My evaluation had several limitations. Firstly, longer timeframes and the inclusion of multiple intervention and comparator sites would have allowed me to investigate the impact of the care pathway on different health systems and on specific patient subgroups. It is possible, for instance, that early disease is far more responsive to intervention than established severe AKI. Longer timeframes would also have allowed me to control for any seasonal changes in outcome, which are known to occur: in a study of AKI alerts in the Welsh Health Service, ninety-day mortality was 28.5% October-March vs. 25.5% in April-September[94]. This approach would also have better allowed me to better adjust for annual and seasonal changes in case-mix, and for the impacts of separate quality improvement initiatives being initiated at 'control' sites (and which could not ethically be prevented). Secondly, the time series models I used do not adjust for differences in patient-level variables between sites and time periods. Populations at the intervention and comparator hospitals differed significantly in some baseline patient characteristics; this probably related to the complex nature of care provided at RFH, which includes regional renal, liver, respiratory, cardiac and rheumatology services. Although the sensitivity analysis I performed controlled for the effects of some potential confounders on renal recovery and found similar results to our primary analysis, I cannot rule out that unmeasured confounders may have influenced my findings. Furthermore, impact at the implementation site may have been limited by high standards of AKI care prior to implementation: 30-day mortality for pre-intervention patients at RFH was 14.9% compared with 18.1% nationally[178]. The intervention may have delivered more benefit in hospitals with worse outcomes. Impact may also have been limited by the use of serum creatinine as biomarker for renal injury, increases of which may lag many hours or even days after the time of renal insult[49], by which time intervention may be less effective. Although the economic analysis found a significant impact on the cost of care provision, it was not possible to collect data relating to the cost of providing the innovation the intervention site, which should be included in future cost-benefit analyses.

As outlined in Chapter 5, there was poor agreement between the triage decisions taken by Dr. Laing and me, and those taken by clinicians using the care pathway in the real world. The qualitative evaluation I carried out suggested that the additional workload engendered by providing the new care pathway on top of regular clinical duties resulted in patients at highest risk being prioritised. Whilst this is of course appropriate, it will have resulted in the inclusion of some patients in the final evaluation sample that did not receive any clinical review by the AKI response team. Ultimately, I may have been able to provide more patient benefit if the staffing of the intervention had been differently configured or resourced. Finally, the initial evaluation plan did not account for the effect of alert validation on case numbers; weekly case numbers were lower than anticipated at the time I published the evaluation protocol.

Implications for research

My evaluation delineated the impact of the digitally-enabled care pathway in a single hospital site. Multi-site evaluation, over longer periods, would be required to comprehensively assess the performance and impact of the pathway on AKI outcomes in different healthcare organisations.

Clinical pathways that include the use of novel digital technologies should be expected to be more commonplace in the coming years, as the digital maturity of the NHS improves. Digital innovations should not be exempt from robust evaluation[149], and requirements for evaluating such novel pathways might be different to existing paradigms[201,202]. Furthermore, my research suggests that implementation of novel technology should be expected to have unintended consequences on the broader health system. As such, future research projects evaluating digital interventions should proactively seek to delineate such consequences, and be subject to multi-method evaluation of clinical, organisational, behavioural and technical impacts.

My evaluation suggests that the impact of novel treatment pathways for patients with AKI may be limited by the use of serum creatinine as a marker of renal injury. Future research should focus on moving the diagnosis of AKI closer to the time of renal injury. Whilst novel biomarkers to predict the development of AKI have been widely researched, experience of

using biomarkers to predict clinical course in other clinical contexts has shown this approach to have limitations. Biomarkers do not outperform diagnostic scores such as CURB-65 in predicting mortality in community-acquired pneumonia[26]. Likewise, urinary, plasma and serum biomarkers for the prediction of AKI also perform modestly[27]. Although several trials have shown the use of a novel biomarker for the prediction of AKI to be associated with a reduced incidence and severity of AKI in conjunction with structured clinical interventions among critically ill cohorts[23,24], the optimal use of biomarkers in more diverse clinical settings remains to be seen; more widespread implementation would require routine measurement and considerable expense to health systems. Machine learning may offer significant promise in this regard[198,203]. Such predictions could use data which are already collected (and cost-neutral) in routine clinical practice across all clinical settings, allowing continuous AKI prediction to occur - not just when clinical suspicion is high. Furthermore, the sensitivity and specificity of predictions could be changed to suit the clinical environment. Should the performance of algorithms prove to be clinically applicable in multisite, prospective studies, they might be operationalized through technology platforms such as Streams.

Finally, my work might have impact on the conduct of future research. Given the high rate of false positive alerts produced by existing AKI algorithms, future interventional studies could aim to measure impact on validated cases of AKI, as I did. Furthermore, technology platforms similar to Streams that process patient data in real-time might support case selection and enable the delivery and evaluation of novel interventions.

Implications for practice

My research suggests that deriving maximum benefit from novel pathways of care such as that described that seek to deploy clinical resource early in the course of patient decline (or indeed technologies that seek to predict decline, as outlined above) will also depend on adequately training clinicians to provide such services.

As outlined in Chapter 4, embedding new technologies in health systems is often challenging from a technical and operational point of view. However, the qualitative research I carried out emphasized that equal attention should be placed on seeking to understand the possible cultural barriers to implementation. In deploying novel technologies, practitioners should therefore seek to understand the impact of technologies in the context in which they

are deployed. Significant engagement with a diverse range of stakeholders is often required. Failing to understand the complexity of this task might be a reason why such technologies fail to scale and spread[204]. However, the results of my mixed-methods evaluation are encouraging. In particular, the qualitative evaluation suggested the use of mobile devices to securely access patient-specific data anywhere in the hospital might save clinicians several hours per day. Understanding how best to realize this value for the health workforce at large at RFLFT will remain a challenge; at the point of submitting my thesis, they are disseminating the Streams app to a larger cohort of clinicians in a second hospital site. Imperial College Healthcare NHS Trust has also started piloting Streams as a mobile results look-up tool.

Implications for policy

As outlined in Chapter 2, the development and deployment of Streams and it's associated care pathway was the result of a strategic partnership between RFLFT and DMH. This partnership was subject to an investigation by the Information Commissioner's Office. RFLFT has since published an audit completed to comply with undertakings following this investigation[205]. Maximising the value that partnerships between providers and consumers of technology might deliver to the broader health service will be a substantial challenge for policymakers. Ultimately, data security and privacy must not be sacrificed at the expense of innovation, and care should be taken to ensure that all stakeholders involved derive value from such partnerships.

Lastly, policymakers involved in the regulation of innovation will face similar challenges. Policy and law relating to the regulation of medical devices will be updated in the coming years[206]. As outlined above, technology platforms and advanced analytical techniques (such as machine learning) could deliver substantial value to health systems. The regulation of such platforms will be a substantial challenge, where the pace of change and improvements in performance might be more rapid than traditional cycles of regulatory oversight[207]. In the future, policymakers must balance the vital requirement that such systems are safe for clinical care without stifling innovation.

References

1. McMahon, A. P. Development of the Mammalian Kidney. *Curr. Top. Dev. Biol.* **117**, 31–64 (2016).
2. Hoenig, M. P. & Zeidel, M. L. Homeostasis, the milieu intérieur, and the wisdom of the nephron. *Clin. J. Am. Soc. Nephrol.* **9**, 1272–1281 (2014).
3. Beall, D., Bywaters, E. G., Belsey, R. H. & Miles, J. A. Crush Injury with Renal Failure. *BMJ* **1**, 432–434 (1941).
4. Hoste, E. A. J. & Kellum, J. A. Incidence, classification, and outcomes of acute kidney injury. *Contrib. Nephrol.* **156**, 32–38 (2007).
5. Lameire, N. H. *et al.* Acute kidney injury: an increasing global concern. *Lancet* **382**, 170–179 (2013).
6. Skrypnyk, N. I., Siskind, L. J., Faubel, S. & de Caestecker, M. P. Bridging translation for acute kidney injury with better preclinical modeling of human disease. *Am. J. Physiol. Renal Physiol.* **310**, F972–84 (2016).
7. Bellomo, R. *et al.* Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **8**, R204–12 (2004).
8. Mehta, R. L. *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **11**, R31 (2007).
9. KDIGO Clinical practice guidelines for acute kidney injury. *Kidney Int. Suppl.* **2**, 1–138 (2012).
10. Feehally J. *et al.* RCPE UK consensus conference statement management of acute

kidney injury: The role of fluids, e-alerts and biomarkers. *J. R. Coll. Physicians Edinb.* **43**, 37–38 (2013).

11. Selby, N. M., Hill, R., Fluck, R. J. & NHS England 'Think Kidneys' AKI Programme. Standardizing the Early Identification of Acute Kidney Injury: The NHS England National Patient Safety Alert. *Nephron* **131**, 113–117 (2015).
12. Lewington, A. J. P., Cerdá, J. & Mehta, R. L. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int.* **84**, 457–467 (2013).
13. Kerr, M., Bedford, M., Matthews, B. & O'donoghue, D. The economic impact of acute kidney injury in England. *Nephrol. Dial. Transplant.* **29**, 1362–1368 (2014).
14. Xue, J. L. *et al.* Incidence and Mortality of Acute Renal Failure in Medicare Beneficiaries, 1992 to 2001. *J. Am. Soc. Nephrol.* **17**, 1135–1142 (2006).
15. Finlay, S. *et al.* Identification of risk factors associated with acute kidney injury in patients admitted to acute medical units. *Clin. Med.* **13**, 233–238 (2013).
16. Selby N.M. *et al.* Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. *Clin. J. Am. Soc. Nephrol.* **7**, 533–540 (2012).
17. Fernandes, A. R. *et al.* Outcomes of acute kidney injury in a nephrology ward. *Int. Urol. Nephrol.* **49**, 2185–2193 (2017).
18. Prowle, J., Bagshaw, S. M. & Bellomo, R. Renal blood flow, fractional excretion of sodium and acute kidney injury. *Curr Opin Crit Care.* **18**, 585–592 (2012).
19. Aksu, U., Demirci, C. & Ince, C. The Pathogenesis of Acute Kidney Injury and the Toxic Triangle of Oxygen, Reactive Oxygen Species and Nitric Oxide. *Contrib Nephrol.* 119–128 (2011). doi:10.1159/000329249
20. Molitoris, B. A. Therapeutic translation in acute kidney injury: the epithelial/endothelial axis. *J Clin. Invest.* **124**, 2355–2363 (2014).

21. Gomez, H. *et al.* A Unified Theory of Sepsis-Induced Acute Kidney Injury. *Shock* **41**, 3–11 (2014).
22. Ortiz, A. *et al.* Translational value of animal models of kidney failure. *Eur. J. Pharmacol.* **759**, 205–220 (2015).
23. Ftouh, S., Lewington, A. & Acute Kidney Injury Guideline Development Group. Prevention, detection and management of acute kidney injury: concise guideline. *Clin. Med.* **14**, 61–65 (2014).
24. Vanmassenhove, J., Kielstein, J., Jörres, A. & Van Biesen, W. Management of patients at risk of acute kidney injury. *Lancet* **389**, 2139–2151 (2017).
25. Koyner, J. L., Carey, K. A., Edelson, D. P. & Churpek, M. M. The Development of a Machine Learning Inpatient Acute Kidney Injury Prediction Model. *Crit. Care Med.* **46**, 1070–1077 (2018).
26. Viasus, D. *et al.* Biomarkers for predicting short-term mortality in community-acquired pneumonia: A systematic review and meta-analysis. *J. Infect.* **72**, 273–282 (2016).
27. Ho, J. *et al.* Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. *Am. J. Kidney Dis.* **66**, 993–1005 (2015).
28. Lin, X., Yuan, J., Zhao, Y. & Zha, Y. Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. *J. Nephrol.* **28**, 7–16 (2015).
29. Kim, S. *et al.* Is plasma neutrophil gelatinase-associated lipocalin a predictive biomarker for acute kidney injury in sepsis patients? A systematic review and meta-analysis. *J. Crit. Care* **33**, 213–223 (2016).
30. Nakhjavan-Shahraki, B. *et al.* Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and

meta-analysis. *BMC Nephrol.* **18**, 120 (2017).

31. Bihorac, A. *et al.* Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. *Am. J. Respir. Crit. Care Med.* **189**, 932–939 (2014).
32. Biernawska, J. *et al.* Cardiac surgery related cardio-renal syndrome assessed by conventional and novel biomarkers - under or overestimated diagnosis? *Arch. Med. Sci.* **13**, 1111–1120 (2017).
33. Zhang, L., Chen, Z., Diao, Y., Yang, Y. & Fu, P. Associations of fluid overload with mortality and kidney recovery in patients with acute kidney injury: A systematic review and meta-analysis. *J. Crit. Care* **30**, 860.e7–13 (2015).
34. Prowle, J. R., Kirwan, C. J. & Bellomo, R. Fluid management for the prevention and attenuation of acute kidney injury. *Nat. Rev. Nephrol.* **10**, 37–47 (2014).
35. Rivers, E. *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N. Engl. J. Med.* **345**, 1368–1377 (2001).
36. ProCESS Investigators *et al.* A randomized trial of protocol-based care for early septic shock. *N. Engl. J. Med.* **370**, 1683–1693 (2014).
37. ARISE Investigators *et al.* Goal-directed resuscitation for patients with early septic shock. *N. Engl. J. Med.* **371**, 1496–1506 (2014).
38. Finfer, S. *et al.* A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N. Engl. J. Med.* **350**, 2247–2256 (2004).
39. Yunos, N. M. *et al.* Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* **308**, 1566–1572 (2012).
40. Serpa Neto, A. *et al.* Balanced versus isotonic saline resuscitation-a systematic review and meta-analysis of randomized controlled trials in operation rooms and intensive care

units. *Ann Transl Med* **5**, 323 (2017).

41. Self, W. H. *et al.* Balanced Crystalloids versus Saline in Noncritically Ill Adults. *N. Engl. J. Med* **378**, 819–828 (2018).
42. Semler, M. W. *et al.* Balanced Crystalloids versus Saline in Critically Ill Adults. *N. Engl. J. Med.* **378**, 829–839 (2018).
43. Do, C. Intravenous Contrast: Friend or Foe? A Review on Contrast-Induced Nephropathy. *Adv. Chronic Kidney Dis.* **24**, 147–149 (2017).
44. Weisbord, S. D. & Palevsky, P. M. Prevention Strategies for Contrast-Induced Nephropathy. *Ann. Intern. Med.* **164**, 511 (2016).
45. Stacul, F. *et al.* Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur. Radiol.* **21**, 2527–2541 (2011).
46. Zapata-Chica, C. A. *et al.* Sodium bicarbonate versus isotonic saline solution to prevent contrast-induced nephropathy : a systematic review and meta-analysis. *Colomb. Med.* **46**, 90–103 (2015).
47. Ortega, L. M., Harmouch, I. & Nayer, A. Contrast-induced nephropathy: pathogenesis and new therapeutic options for prevention. *Am. J. Ther.* **22**, 469–476 (2015).
48. Ehrmann, S., Aronson, D. & Hinson, J. S. Contrast-associated acute kidney injury is a myth: Yes. *Intensive Care Med.* **44**, 104–106 (2018).
49. Thomas, M. E. *et al.* The definition of acute kidney injury and its use in practice. *Kidney Int.* **87**, 62–73 (2015).
50. Hersch, M., Einav, S. & Izbicki, G. Accuracy and ease of use of a novel electronic urine output monitoring device compared with standard manual urinometer in the intensive care unit. *J. Crit. Care* **24**, 629.e13–7 (2009).
51. Langenberg, C. *et al.* Renal blood flow in sepsis. *Crit. Care* **9**, R363–74 (2005).

52. Bagshaw, S. M. *et al.* Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med.* **35**, 871–881 (2009).
53. Van der Mullen, J., Wise, R., Vermeulen, G., Moonen, P.-J. & Malbrain, M. L. N. G. Assessment of hypovolaemia in the critically ill. *Anaesthesiol. Intensive Ther.* **50**, 141–149 (2018).
54. Firth, J. D., Raine, A. E. & Ledingham, J. G. Raised venous pressure: a direct cause of renal sodium retention in oedema? *Lancet* **1**, 1033–1035 (1988).
55. Mohmand, H. & Goldfarb, S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. *J. Am. Soc. Nephrol.* **22**, 615–621 (2011).
56. Basu, R. K. *et al.* Acute kidney injury based on corrected serum creatinine is associated with increased morbidity in children following the arterial switch operation. *Pediatr. Crit. Care Med.* **14**, e218–24 (2013).
57. Fülöp, T. *et al.* Volume-related weight gain and subsequent mortality in acute renal failure patients treated with continuous renal replacement therapy. *ASAIO J.* **56**, 333–337 (2010).
58. Schortgen, F. Hydroxyethyl starches in the intensive care unit. *Reanim. Organes Artif.* **23**, 159–166 (2014).
59. Lin, S.-M. *et al.* A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. *Shock* **26**, 551–557 (2006).
60. Acevedo, J. G. & Cramp, M. E. Hepatorenal syndrome: Update on diagnosis and therapy. *World J. Hepatol.* **9**, 293–299 (2017).

61. Kotecha, A., Vallabhajosyula, S., Coville, H. H. & Kashani, K. Cardiorenal syndrome in sepsis: A narrative review. *J. Crit. Care* **43**, 122–127 (2018).
62. Bentley, M. L., Corwin, H. L. & Dasta, J. Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies. *Crit. Care Med.* **38**, S169–74 (2010).
63. Goldstein, S. L. Medication-induced acute kidney injury. *Curr. Opin. Crit. Care* **22**, 542–545 (2016).
64. Faubel, S., Patel, N. U., Lockhart, M. E. & Cadnapaphornchai, M. A. Renal relevant radiology: use of ultrasonography in patients with AKI. *Clin. J. Am. Soc. Nephrol.* **9**, 382–394 (2014).
65. Lucarelli, G. *et al.* Delayed relief of ureteral obstruction is implicated in the long-term development of renal damage and arterial hypertension in patients with unilateral ureteral injury. *J. Urol.* **189**, 960–965 (2013).
66. Acute Kidney Injury: Prevention, Detection and Management. *NICE* (2013). Available at: https://www.nice.org.uk/guidance/cg169.
67. Hamdi, A. *et al.* Severe post-renal acute kidney injury, post-obstructive diuresis and renal recovery. *BJU Int.* **110**, E1027–34 (2012).
68. Jennette, J. C. & Nachman, P. H. ANCA Glomerulonephritis and Vasculitis. *Clin. J. Am. Soc. Nephrol.* **12**, 1680–1691 (2017).
69. Maritati, F., Iannuzzella, F., Pavia, M. P., Pasquali, S. & Vaglio, A. Kidney involvement in medium- and large-vessel vasculitis. *J. Nephrol.* **29**, 495–505 (2016).
70. Khanna, R. Clinical presentation & management of glomerular diseases: hematuria, nephritic & nephrotic syndrome. *Mo. Med.* **108**, 33–36 (2011).
71. Connell, A. & Laing, C. Acute kidney injury. *Clin. Med.* **15**, 581–584 (2015).
72. Doyle, J. F. & Forni, L. G. Acute kidney injury: short-term and long-term effects. *Crit.*

Care **20**, 188 (2016).

73. Zarbock, A. *et al.* Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *JAMA* **315**, 2190–2199 (2016).
74. Gaudry, S. *et al.* Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N. Engl. J. Med.* **375**, 122–133 (2016).
75. Bouchard, J. *et al.* Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* **76**, 422–427 (2009).
76. Bouchard, J. & Mehta, R. L. Volume management in continuous renal replacement therapy. *Semin. Dial.* **22**, 146–150 (2009).
77. Conger, J. D. Does Hemodialysis Delay Recovery from Acute Renal Failure? *Semin. Dial.* **3**, 146–148 (1990).
78. Bonnassieux, M. *et al.* Renal Replacement Therapy Modality in the ICU and Renal Recovery at Hospital Discharge. *Crit. Care Med.* **46**, e102–e110 (2018).
79. Wang, Y. *et al.* Renal replacement therapy intensity for acute kidney injury and recovery to dialysis independence: a systematic review and individual patient data meta-analysis. *Nephrol. Dial. Transplant.* **33**, 1017–1024 (2018).
80. Meier, P., Bonfils, R. M., Vogt, B., Burnand, B. & Burnier, M. Referral patterns and outcomes in noncritically ill patients with hospital-acquired acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **6**, 2215–2225 (2011).
81. Costa e Silva, V. T. *et al.* Nephrology referral and outcomes in critically ill acute kidney injury patients. *PLoS One* **8**, e70482 (2013).
82. Wang, H. E., Muntner, P., Chertow, G. M. & Warnock, D. G. Acute kidney injury and mortality in hospitalized patients. *Am. J. Nephrol.* **35**, 349–355 (2012).

83. Aitken, E. *et al.* Acute kidney injury: Outcomes and quality of care. *QJM* **106**, 323–332 (2013).

84. Khandaker M., Taha L., Fairclough C. & Ahmed S. Incidence and mortality of patients with acute kidney injury in hospitalised patients using the NHS England AKI algorithm. *Nephrol. Dial. Transplant.* **31**, i18–i19 (2016).

85. Grams, M. E. & Rabb, H. The distant organ effects of acute kidney injury. *Kidney Int.* **81**, 942–948 (2012).

86. Klein, C. L. *et al.* Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. *Kidney Int.* **74**, 901–909 (2008).

87. Kim, D. J. *et al.* Comparison of experimental lung injury from acute renal failure with injury due to sepsis. *Respiration* **73**, 815–824 (2006).

88. Kelly, K. J. Distant effects of experimental renal ischemia/reperfusion injury. *J. Am. Soc. Nephrol.* **14**, 1549–1558 (2003).

89. Miyazawa, S., Watanabe, H., Miyaji, C., Hotta, O. & Abo, T. Leukocyte accumulation and changes in extra-renal organs during renal ischemia reperfusion in mice. *J. Lab. Clin. Med.* **139**, 269–278 (2002).

90. Liu, M. *et al.* Acute kidney injury leads to inflammation and functional changes in the brain. *J. Am. Soc. Nephrol.* **19**, 1360–1370 (2008).

91. Jurawan, N. *et al.* Hospital acquired Acute Kidney Injury is associated with increased mortality but not increased readmission rates in a UK acute hospital. *BMC Nephrol.* **18**, 317 (2017).

92. Uchino, S. *et al.* Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* **294**, 813–818 (2005).

93. Wald, R. *et al.* Chronic dialysis and death among survivors of acute kidney injury

requiring dialysis. *JAMA* **302**, 1179–1185 (2009).

94. Phillips, D. *et al.* Seasonal pattern of incidence and outcome of Acute Kidney Injury: A national study of Welsh AKI electronic alerts. *Int. J. Clin. Pract.* **71**, (2017).
95. Kolhe, N. V., Fluck, R. J. & Taal, M. W. Effect of weekend admission on mortality associated with severe acute kidney injury in England: A propensity score matched, population-based study. *PLOS ONE* **12**, e0186048 (2017).
96. Metcalfe, W. *et al.* Acute renal failure requiring renal replacement therapy: incidence and outcome. *QJM* **95**, 579–583 (2002).
97. Chawla, L. S., Amdur, R. L., Amodeo, S., Kimmel, P. L. & Palant, C. E. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int.* **79**, 1361–1369 (2011).
98. Coca, S. G., Singanamala, S. & Parikh, C. R. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int.* **81**, 442–448 (2012).
99. Hsu, R. K. & Hsu, C.-Y. The Role of Acute Kidney Injury in Chronic Kidney Disease. *Semin. Nephrol.* **36**, 283–292 (2016).
100. Pereira, B. J. *et al.* Risk factors for the progression of chronic kidney disease after acute kidney injury. *J. Bras. Nefrol.* **39**, 239–245 (2017).
101. Acute Kidney Injury. *Think Kidneys* Available at: https://www.thinkkidneys.nhs.uk/.
102. 5 Year Forward View. *NHS England* (2014). Available at: http://www.england.nhs.uk/wp-content/uploads/2014/12/forward-view-plning.pdf.
103. AKI CQUIN. *NHS England* (2015). Available at: https://www.england.nhs.uk/wp-content/uploads/2015/03/9-cquin-guid-2015-16.pdf.
104. Keir, I. & Kellum, J. A. Acute kidney injury in severe sepsis: pathophysiology, diagnosis, and treatment recommendations. *J. Vet. Emerg. Crit. Care* **25**, 200–209 (2015).

105. Acute Kidney Injury: Adding Insult to Injury Report. *NCEPOD* (2009). Available at: http://www.ncepod.org.uk/2009aki.html.

106. Selby, N. M. *et al.* Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. *Clin. J. Am. Soc. Nephrol.* **7**, 533–540 (2012).

107. Black, A. D. *et al.* The impact of eHealth on the quality and safety of health care: a systematic overview. *PLoS Med.* **8**, e1000387 (2011).

108. Agno, C. F. & Guo, K. L. Electronic health systems: challenges faced by hospital-based providers. *Health Care Manag.* **32**, 246–252 (2013).

109. Kucher, N. *et al.* Electronic alerts to prevent venous thromboembolism among hospitalized patients. *N. Engl. J. Med.* **352**, 969–977 (2005).

110. Singh, H. *et al.* Timely follow-up of abnormal diagnostic imaging test results in an outpatient setting: are electronic medical records achieving their potential? *Arch. Intern. Med.* **169**, 1578–1586 (2009).

111. Niedrig, D. F. *et al.* Paracetamol overdosing in a tertiary care hospital: implementation and outcome analysis of a preventive alert programme. *J. Clin. Pharm. Ther.* **41**, 515–518 (2016).

112. Horne, K. L. & Selby, N. M. Recent developments in electronic alerts for acute kidney injury. *Curr. Opin. Crit. Care* **21**, 479–484 (2015).

113. Survey results. *NHS Kidney Care* (2012). Available at: http://www.nhsiq.nhs.uk/media/2388545/e_alerts_survey.pdf.

114. Kane-Gill, S. L. & Kellum, J. A. Advancing the Use of Clinical Decision Support to Prevent Drug-Associated AKI. *Nephron* **131**, 259–261 (2015).

115. Baron, J. M. *et al.* Enhanced creatinine and estimated glomerular filtration rate reporting to facilitate detection of acute kidney injury. *Am. J. Clin. Pathol.* **143**, 42–49 (2015).

116. Ahmed, S., Curtis, S., Hill, C. & Hine, T. Population-based estimated reference creatinine values: a novel method of a robust electronic acute kidney injury alert system. *Nephron Clin. Pract.* **128**, 166–170 (2014).

117. Feehally, J. *et al.* RCPE UK consensus conference statement: Management of acute kidney injury: the role of fluids, e-alerts and biomarkers. *J. R. Coll. Physicians Edinb.* **43**, 37–38 (2013).

118. ACB meeting statement: e-alerts for AKI. *Association of Clinical Biochemists* (2013). Available at: http://www.acb.org.uk/docs/E-Alerts_for_AKI_meeting_statement.

119. Acute Kidney Injury: Warning Algorithm Best Practice Guidance. (2016). Available at: https://www.thinkkidneys.nhs.uk/wp-content/uploads/2014/12/AKI-Warning-Algorithm-Best-Practice-Guidance-final-publication-0112141.pdf.

120. Elmamoun S., Wodeyar H., Goldsmith C., Abraham A. & Wootton A. The effectiveness of an e-alert warning in the management of patients with acute kidney injury. *Nephrol. Dial. Transplant.* **28**, i336 (2013).

121. Kolhe N. *et al.* A simple care bundle for use in acute kidney injury - a propensity score matched study. *Nephrol. Dial. Transplant.* **31**, i18 (2016).

122. Colpaert, K. *et al.* Implementation of a real-time electronic alert based on the RIFLE criteria for acute kidney injury in ICU patients. *Acta Clin. Belg.* **62 Suppl 2**, 322–325 (2007).

123. Wilson, F. P. *et al.* Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. *Lancet* **385**, 1966–1974 (2015).

124. Porter, C. J. *et al.* A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. *Nephrol. Dial. Transplant.* 1–6 (2014).

125. Master J., Hammad S., Chamberlain P., Chandrasekar T. & Wong C. Reduction in acute

kidney injury (AKI) mortality data with the development of a novel AKI management bundle. *Nephrol. Dial. Transplant.* **30**, 467 (2015).

126. Chandrasekar T., Sharma A., Chamberlain P. & Abraham A. Stop-AKI project: A streamlined approach to AKI management leads to reduction of in-hospital mortality, length of stay and AKI progression. *Nephrol. Dial. Transplant.* **31**, i70–i71 (2016).
127. Kolhe, N. V. *et al.* Impact of Compliance with a Care Bundle on Acute Kidney Injury Outcomes: A Prospective Observational Study. *PLoS One* **10**, e0132279 (2015).
128. Thomas, M. E., Sitch, A., Baharani, J. & Dowswell, G. Earlier intervention for acute kidney injury: evaluation of an outreach service and a long-term follow-up. *Nephrol. Dial. Transplant.* **30**, 239–244 (2015).
129. Hill L., Zacharia T., Hill C., Hine T. & Ahmed S. The usefullness of an electronic acute kidney injury (AKI) alert system for early diagnosis and intervention in hospitalised patients with AKI. *Nephrol. Dial. Transplant.* **30**, 451 (2015).
130. Goldstein, S. L. Automated/integrated real-time clinical decision support in acute kidney injury. *Curr. Opin. Crit. Care* **21**, 485–489 (2015).
131. Sawhney, S. *et al.* Acute kidney injury - How does automated detection perform? *Nephrol. Dial. Transplant.* **30**, 1853–1861 (2015).
132. Kolhe, N. V. *et al.* A simple care bundle for use in acute kidney injury: a propensity score-matched cohort study. *Nephrol. Dial. Transplant.* **31**, 1846–1854 (2016).
133. Horsky, J. *et al.* Interface design principles for usable decision support: A targeted review of best practices for clinical prescribing interventions. *J Biomed Inform.* **45**, 1202–1216 (2012).
134. Moja, L. *et al.* Effectiveness of Computerized Decision Support Systems Linked to Electronic Health Records: A Systematic Review and Meta-Analysis. *Am J Public*

Health. **104**, e12–e22 (2014).

135. Bloomrosen, M. *et al.* Anticipating and addressing the unintended consequences of health IT and policy: a report from the AMIA 2009 Health Policy Meeting. *J. Am. Med. Inform. Assoc.* **18**, 82–90 (2011).

136. Payne, K. F. B., Wharrad, H. & Watts, K. Smartphone and medical related App use among medical students and junior doctors in the United Kingdom (UK): a regional survey. *BMC Med. Inform. Decis. Mak.* **12**, 121 (2012).

137. Information Governance Toolkit. *NHS Digital* Available at: https://digital.nhs.uk/data-and-information/looking-after-information/data-security-and-information-governance/data-security-and-protection-toolkit. (Accessed: 12th May 2019)

138. A computer in your pocket: The rise of smartphones. *Science Museum* Available at: https://www.sciencemuseum.org.uk/objects-and-stories/computer-your-pocket-rise-smartphones. (Accessed: 9th April 2019)

139. Gardner, R. L. *et al.* Physician stress and burnout: the impact of health information technology. *J. Am. Med. Inform. Assoc.* **26**, 106–114 (2019).

140. Martin, G., Janardhanan, P., Withers, T. & Gupta, S. Mobile revolution: a requiem for bleeps? *Postgrad. Med. J.* **92**, 493–496 (2016).

141. Castrén, J., Niemi, M. & Virjo, I. Use of email for patient communication in student health care: a cross-sectional study. *BMC Med. Inform. Decis. Mak.* **5**, 2 (2005).

142. Pearl, R. Kaiser Permanente Northern California: current experiences with internet, mobile, and video technologies. *Health Aff.* **33**, 251–257 (2014).

143. Knowles, E., O'Cathain, A., Turner, J. & Nicholl, J. Awareness and use of a new urgent care telephone service, NHS 111: cross-sectional population survey. *J. Health Serv. Res. Policy* **19**, 224–230 (2014).

144. The NHS app. *NHS Digital* Available at: https://digital.nhs.uk/services/nhs-app. (Accessed: 9th April 2019)

145. Health and Social Care Secretary bans fax machines in NHS. *UK Department of Health and Social Care* (2018). Available at: https://www.gov.uk/government/news/health-and-social-care-secretary-bans-fax-machines-in-nhs. (Accessed: 9th April 2019)

146. Steinhubl, S. R., Muse, E. D. & Topol, E. J. Can mobile health technologies transform health care? *JAMA* **310**, 2395–2396 (2013).

147. The Topol Review. *Health Education England* Available at: https://topol.hee.nhs.uk/. (Accessed: 9th April 2019)

148. Gulland, A. Doctors developing apps to try to modernise the NHS. *BMJ* **360**, k685 (2018).

149. Is digital medicine different? [Editorial]. *Lancet* **392**, 95 (2018).

150. Topol, E. J. High-performance medicine: the convergence of human and artificial intelligence. *Nat. Med.* **25**, 44–56 (2019).

151. Coiera, E. Putting the technical back into socio-technical systems research. *Int. J. Med. Inform.* **76 Suppl 1**, S98–103 (2007).

152. Coiera, E., Ash, J. & Berg, M. The Unintended Consequences of Health Information Technology Revisited. *Yearb. Med. Inform.* 163–169 (2016).

153. Guidelines. *London AKI Network* Available at: http://www.londonaki.net/clinical/guidelines-pathways.html. (Accessed: 23rd July 2018)

154. Lewington, A. & Kanagasundaram, S. Renal Association Clinical Practice Guidelines on Acute Kidney Injury. *Nephron Clinical Practice* **118**, c349–c390 (2011).

155. Rind, D. M. *et al.* Effect of computer-based alerts on the treatment and outcomes of

hospitalized patients. *Arch. Intern. Med.* **154**, 1511–1517 (1994).

156. McCoy A.B. *et al.* A computerized provider order entry intervention for medication safety during acute kidney injury: A quality improvement report. *Am. J. Kidney Dis.* **56**, 832–841 (2010).

157. Wilson F.P. *et al.* Automated, electronic alerts for acute kidney injury: A single-blind, parallel-group, randomised controlled trial. *Lancet* **385**, 1966–1974 (2015).

158. Hoste, E. A. J. *et al.* Impact of Electronic-Alerting of Acute Kidney Injury: Workgroup Statements from the 15th ADQI Consensus Conference. *Can J Kidney Health Dis.* **3**, 101 (2016).

159. Wagner, A. K., Soumerai, S. B., Zhang, F. & Ross-Degnan, D. Segmented regression analysis of interrupted time series studies in medication use research. *J. Clin. Pharm. Ther.* **27**, 299–309 (2002).

160. Marshall, M. N. The key informant technique. *Fam. Pract.* **13**, 92–97 (1996).

161. Marshall, B., Cardon, P., Poddar, A. & Fontenot, R. Does Sample Size Matter in Qualitative Research?: A Review of Qualitative Interviews in is Research. *J Comput Inform Syst.* **54**, 11–22 (2013).

162. Vasileiou, K., Barnett, J., Thorpe, S. & Young, T. Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. *BMC Med. Res. Methodol.* **18**, 148 (2018).

163. Research Decision Tool. *NHS Health Research Authority* Available at: http://www.hra-decisiontools.org.uk/research/.

164. Connell, A. *et al.* Service evaluation of the implementation of a digitally-enabled care pathway for the recognition and management of acute kidney injury. *F1000Res.* **6**, 1033 (2017).

165. Is the NHS in crisis? *The King's Fund* Available at: https://www.kingsfund.org.uk/projects/nhs-in-crisis. (Accessed: 10th April 2019)

166. Marshall, M. N. Bridging the ivory towers and the swampy lowlands; increasing the impact of health services research on quality improvement. *Int. J. Qual. Health Care* **26**, 1–5 (2014).

167. Vindrola-Padros, C., Pape, T., Utley, M. & Fulop, N. J. The role of embedded research in quality improvement: a narrative review. *BMJ Qual. Saf.* **26**, 70–80 (2017).

168. Ham, C. & Berwick, D. *Organising care at the NHS front line: Who is responsible?* (The King's Fund, 2017).

169. Fleiss, J. L., Levin, B. & Paik, M. C. *Statistical Methods for Rates and Proportions*. (John Wiley & Sons, 2013).

170. Hsu, C.-N. *et al.* Incidence, Outcomes, and Risk Factors of Community-Acquired and Hospital-Acquired Acute Kidney Injury: A Retrospective Cohort Study. *Medicine* **95**, e3674 (2016).

171. Der Mesropian, P. J. *et al.* Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: a retrospective analysis. *Clin. Nephrol.* **81**, 174–184 (2014).

172. Wonnacott, A., Meran, S., Amphlett, B., Talabani, B. & Phillips, A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin. J. Am. Soc. Nephrol.* **9**, 1007–1014 (2014).

173. Inokuchi, R. *et al.* Differences in characteristics and outcomes between community- and hospital-acquired acute kidney injury: A systematic review and meta-analysis. *Clin. Nephrol.* **88**, 167–182 (2017).

174. English Indices of Deprivation. *UK Ministry of Housing, Communities & Local*

Government Available at: http://imd-by-postcode.opendatacommunities.org/. (Accessed: 23rd July 2018)

175. Thygesen, S. K., Christiansen, C. F., Christensen, S., Lash, T. L. & Sørensen, H. T. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med. Res. Methodol.* **11**, 83 (2011).
176. Brock, G. N., Barnes, C., Ramirez, J. A. & Myers, J. How to handle mortality when investigating length of hospital stay and time to clinical stability. *BMC Med. Res. Methodol.* **11**, 144 (2011).
177. Patient Level Information and Costing System (PLICS) Data Collections. *NHS Digital* Available at: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/patient-level-information-and-costing-system-plics-data-collections. (Accessed: 12th April 2019)
178. Reporting the rate of Acute Kidney Injury (AKI) within England – the current state of the NHS AKI Master Patient Index and Registry. *Think Kidneys* Available at: https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2018/03/Reporting-the-rate-of-AKI-January-2018.pdf. (Accessed: 30th March 2018)
179. Al-Jaghbeer, M., Dealmeida, D., Bilderback, A., Ambrosino, R. & Kellum, J. A. Clinical Decision Support for In-Hospital AKI. *J. Am. Soc. Nephrol.* **29**, 654–660 (2018).
180. Park, S. *et al.* Impact of Electronic Acute Kidney Injury (AKI) Alerts With Automated Nephrologist Consultation on Detection and Severity of AKI: A Quality Improvement Study. *Am. J. Kidney Dis.* (2017). doi:10.1053/j.ajkd.2017.06.008
181. Ebah, L. *et al.* A Multifaceted Quality Improvement Programme to Improve Acute Kidney Injury Care and Outcomes in a Large Teaching Hospital. *BMJ Qual Improv Rep* **6**, ii:

u219176.w7476 (2017).

182. Chandrasekar, T. *et al.* A Whole System Approach to Improving Mortality associated with Acute Kidney Injury. *QJM* (2017). doi:10.1093/qjmed/hcx101

183. Abdelaziz, T. S. *et al.* Acute Kidney Outreach to Reduce Deterioration and Death (AKORDD) trial: the protocol for a large pilot study. *BMJ Open* **6**, e012253 (2016).

184. Selby, N. M., Casula, A., Lamming, L., Mohammed, M. & Caskey, F. Design and Rationale of 'Tackling Acute Kidney Injury', a Multicentre Quality Improvement Study. *Nephron* (2016). doi:10.1159/000447675

185. Connell, A. *et al.* Implementation of a Digitally Enabled Care Pathway (Part 1): Impact on Clinical Outcomes and Associated Health Care Costs. *J. Med. Internet Res.* **21**, e13147 (2019).

186. Connell, A. *et al.* Evaluation of a digitally-enabled care pathway for acute kidney injury management in hospital emergency admissions. *npj Digital Medicine* **2**, 67 (2019).

187. Weller, J., Boyd, M. & Cumin, D. Teams, tribes and patient safety: overcoming barriers to effective teamwork in healthcare. *Postgrad. Med. J.* **90**, 149–154 (2014).

188. Smith, F. Who invented that bleeping thing? *BMJ* **327**, 719–719 (2003).

189. The future of healthcare: our vision for digital, data and technology in health and care. *UK Government* (2018). Available at: https://www.gov.uk/government/publications/the-future-of-healthcare-our-vision-for-digital-data-and-technology-in-health-and-care/the-future-of-healthcare-our-vision-for-digital-data-and-technology-in-health-and-care. (Accessed: 12th November 2018)

190. Transforming FDA's Approach to Digital Health. *US Food and Drug Administration* Available at: https://www.fda.gov/newsevents/speeches/ucm605697.htm. (Accessed: 14th November 2018)

191. Fereday, J. & Muir-Cochrane, E. Demonstrating Rigor Using Thematic Analysis: A Hybrid Approach of Inductive and Deductive Coding and Theme Development. *Int J Qual Methods.* **5**, 80–92 (2006).

192. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qual. Res. Psychol.* **3**, 77–101 (2006).

193. Sawhney, S. *et al.* Maximising Acute Kidney Injury Alerts - A Cross-Sectional Comparison with the Clinical Diagnosis. *PLoS One* **10**, e0131909 (2015).

194. Bevan M. *et al.* Electronic clinical decision support for the early recognition and management of acute kidney injury: Qualitative evaluation of end-user experience. *Nephrol. Dial. Transplant.* **30**, iii443 (2015).

195. Méan, M. *et al.* Computer usage and task-switching during resident's working day: Disruptive or not? *PLoS One* **12**, e0172878 (2017).

196. Kanagasundaram, N. S. *et al.* Computerized clinical decision support for the early recognition and management of acute kidney injury: a qualitative evaluation of end-user experience. *Clin. Kidney J.* **9**, 57–62 (2016).

197. Connell, A. *et al.* Implementation of a Digitally Enabled Care Pathway (Part 2): Qualitative Analysis of Experiences of Health Care Professionals. *J. Med. Internet Res.* **21**, e13143 (2019).

198. Mohamadlou, H. *et al.* Prediction of Acute Kidney Injury With a Machine Learning Algorithm Using Electronic Health Record Data. *Can J Kidney Health Dis* **5**, 2054358118776326 (2018).

199. Raine, R. *et al. Challenges, solutions and future directions in the evaluation of service innovations in health care and public health*. (NIHR Journals Library, 2016).

200. Franko, O. I. & Tirrell, T. F. Smartphone app use among medical providers in ACGME

training programs. *J. Med. Syst.* **36**, 3135–3139 (2012).

201. Jake-Schoffman, D. E. *et al.* Methods for Evaluating the Content, Usability, and Efficacy of Commercial Mobile Health Apps. *JMIR Mhealth Uhealth* **5**, e190 (2017).

202. Kaplan, B. Evaluating informatics applications - clinical decision support systems literature review. *Int. J. Med. Inform.* **64**, 15–37 (2001).

203. Cheng, P., Waitman, L. R., Hu, Y. & Liu, M. Predicting Inpatient Acute Kidney Injury over Different Time Horizons: How Early and Accurate? *AMIA Annu. Symp. Proc.* **2017**, 565–574 (2017).

204. Greenhalgh, T. How to improve success of technology projects in health and social care. *Public Health Res Pract* **28**, ii: 2831815 (2018).

205. Royal Free London publishes audit into Streams app. *Royal Free London Foundation Trust* Available at: https://www.royalfree.nhs.uk/news-media/news/royal-free-london-publishes-audit-into-streams-app/. (Accessed: 18th October 2018)

206. Regulatory framework - Internal Market, Industry, Entrepreneurship and SMEs. *European Commission* (2016). Available at: https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en. (Accessed: 14th April 2019)

207. Artificial Intelligence and Machine Learning in Software as a Medical Device. *US Food and Drug Administration* Available at: https://www.fda.gov/MedicalDevices/DigitalHealth/SoftwareasaMedicalDevice/ucm634612.htm. (Accessed: 14th April 2019)

Appendices

Appendix 1: AKI response team proforma draft 1.0

NAME:
MRN:
DOB:

AKI RESPONSE TEAM PROFORMA

WHY HAVE THE AKI RESPONSE TEAM ATTENDED THIS PATIENT?

AKI is a sudden loss of kidney function. It is associated with a substantially increased risk of death and the development of chronic kidney disease. Using an algorithm produced by NHS England, *Streams* monitors changes in serum creatinine and diagnoses possible episodes of AKI. **I have reviewed this patient's kidney function trends and think this patient is likely to have AKI.** The response team are here to support, advise and where necessary initiate emergency care. The patient and their AKI management remains the primary responsibility of the home team unless otherwise agreed.

I am responding to this AKI alert as part of:

AKI response team ☐ Patient at risk and resuscitation team ☐

Date :____/____/____ **Time** :_____:_____

RELEVANT CLINICAL HISTORY

RELEVANT INVESTIGATIONS

Renal imaging undertaken last 7 days: yes ☐ no ☐

Further details:

Urine dipstick: Blood_____ Protein_____ Leucocytes_____ Nitrites:_____

Other relevant investigations (ABG, bloods, imaging, urine etc):

INFECTION ASSESSMENT

Clinical signs of infection?: yes ☐ no ☐ CRP elevated: yes ☐ no ☐ WCC elevated: yes ☐ no ☐

Recent cultures: yes ☐ no ☐

Result:

Specify source of infection:

Criteria for sepsis: yes ☐ no ☐

FLUID STATUS

Urine volume last 24 hours: mL Balance last 24 hours: mL

I think this patient is: Hypovolaemic Euvolaemic Hypervolaemic

DIAGNOSIS

This patient has the following chronic conditions that put them at increased risk of AKI:

Age >65: yes no	CKD: yes no	Liver disease: yes no
Cardiac failure: yes no	Diabetes: yes no	Vascular disease: yes no
Background nephrotoxin: yes no		

The likely acute cause(s) of AKI are:

Sepsis and Hypoperfusion	**Primary renal disease**
Sepsis	Rapidly progressive glomerulonephritis
Infection but not sepsis	Tubulointerstitial nephritis
Hypovolaemia	Myeloma kidney
Cardiac failure	Rhabdomyolysis
Liver failure	Other
Renovascular compromise	
Toxicity	**Obstruction of the renal tract**
Radiological contrast	Specify:
Drugs	

This patient has developed the following complications of AKI:

Hyperkalaemia	Acidosis
Pulmonary oedema	Peripheral oedema
Uraemia	Hyperphosphataemia

AKI MANAGEMENT

	Time
Immediate escalation PARRT (bleep 2471) ☐ ITU (bleep 1030) ☐	
Oxygen therapy ☐ Specify:	
Treatment of infection Antibiotics ☐ Sepsis 6 pathway ☐	
Fluid bolus ☐	
Treatment of complications Hyperkalaemia: calcium gluconate for ECG changes ☐ Hyperkalaemia: insulin/dextrose (10 UNITS IN 50mls 50% dextrose 1/2hr) ☐ Acidosis: oral bicarbonate ☐ Acidosis: IV 1.26% bicarbonate ☐ Oedema: oral or IV diuretics ☐ Oedema: IV nitrates ☐ Oedema: CPAP ☐	
Cessation of nephrotoxins: ☐ Specify drugs stopped or amended: *For pharmacy advice please contact AKI pharmacist on 33118* or on bleep 1409	
AKI routine blood test panel ordered on Cerner ☐	
AKI diagnostic panel ordered on Cerner ☐ Order set includes immunology, myeloma, virology and urine protein	
Imaging pathway activated ☐ Phone Matteo Rosselli on 07443101848 or 2846 for immediate bedside USS If out-of-hours or not available contact imaging department on bleep 1462 or 39553	
Obstruction confirmed on USS - Urology AKI-obstruction pathway activated ☐ Contact urology registrar via switchboard **Specify details:**	
Therapy for primary renal disease	

Oral steroids Intravenous/pulsed steroids Rituximab Cyclophosphamide Forced diuresis or alkalinisation (rhabdomyolysis/tumour lysis) Hypercalcaemia therapy Plasma exchange Other Specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
Transfer Patient remains under home team Nephrology taking over care and arranging transfer to 10E Patient being transferred to ITU	 ☐ ☐ ☐	
Handover I have discussed this AKI case with the home team and we have agreed a plan I have discussed with patient and left a patient information sheet on AKI	 ☐ ☐	

FOLLOW UP BY AKI RESPONSE TEAM

I will schedule a proactive review of this patient ☐

I will only review this patient if called or re-alerted by the *Streams* app ☐

If this patients AKI stage worsens or is not recovering in 48 hours we will attend.

Please monitor kidney function to recovery.

CONTACT THE AKI RESPONSE TEAM FOR ANY FOLLOW UP ENQUIRIES ON 07908422116

SIGNED:_____

NAME: :_____GRADE:_____

DATE: _____/_____/_____ TIME OF COMPLETION:_____

EXAMINATION FINDINGS

B: Respiratory rate:____/min Saturations: _____% on _____L/min

Respiratory examination findings:

C: HR:_____/min BP:_____/_____mmHg JVP: elevated normal reduced

Peripheries warm: yes ☐ no ☐ Capillary refill time >2secs: yes ☐ no ☐

Skin turgor normal: yes ☐ no ☐ Sacral oedema: yes ☐ no ☐ Peripheral oedema: yes ☐ no ☐

Cardiovascular examination findings:

D: Alert and orientated: yes ☐ no ☐ GCS: Eyes: /4 Motor: /5 Speech: /6 Total: /15

E: Other relevant examination findings (including evidence of systemic disease):

GENERAL RECOMMENDATIONS FOR WARD NURSING STAFF

- Do daily weights
- Keep a fluid chart, document urine volumes and calculate 24 hour balance
- Do at least 4 hourly observations (more frequent if advised)
- Maintain fluid intake as per advised maintenance fluids - if unclear please clarify with ward doctor
- Ensure all drugs and fluids delivered on time
- Watch for signs of infection
- Maintain nutrition
- Please ensure patient has patient information sheet
- Watch for signs of deterioration - breathlessness, worsening swelling, tachycardia, high or low blood pressure, drowsiness or vomiting
- If concerned contact ward doctors and PARRT team (bleep 2471)

GENERAL RECOMMENDATIONS FOR WARD DOCTORS

- If fluid bolus protocol initiated for hypovolaemia continue until euvolaemic (see appendix)
- Once euvolaemic set a daily fluid target of maintenance fluids (may need restriction if oliguric)
- Examine daily - watch out for fluid overload, uraemia (drowsiness) or signs of infection
- Ensure any outstanding tests (imaging, AKI diagnostic blood or urine tests) are back - if unsure about any abnormalities discuss AKI response team.
- Check daily bloods until recovered, monitor renal function and look out for complications (hyperkalaemia, acidosis)
- If prescribing new drugs check dose appropriate for renal function - if in doubt contact renal pharmacist on 33118 or on bleep 1409
- Watch for signs of deterioration - breathlessness, worsening swelling, tachycardia, high or low blood pressure, drowsiness or vomiting
- If concerned contact PARRT team (2471), ITU team (1030), or AKI SpR (07908422116) for advice.

For up to date Trust guidance on AKI please visit www.londonaki.net/clinical or download LondonAKI mobile application for Android and iOS

A video on basic AKI care is available - to watch go on YouTube and search 'London AKI care bundle'

For other education on AKI visit www.londonaki.net/academy

For feedback please contact clinical lead Chris Laing on 07912147956 or chris.laing@nhs.net

Appendix 2: AKI response team training scenarios

Scenario 1: Patient in ED with sepsis

AKI alert: NPSA level 2 with CRP

Pathology results viewed in-app prior to arrival:
Cr 280 (baseline 70)
Ur 14.5
Na 134
K 4.8

Hb 102
Plt 235
WCC 18.8 (Nx 15)
CRP 128

LFTs NAD
Bone profile NAD

History (via A&E SHO)
82 year old female. NH resident. Presents to ED with a 4 day history of increasing confusion & intermittent agitation. Found on floor this morning; brought into hospital via ambulance.

Previous medical history: dementia; hypertension; ischaemic heart disease (1xMI 8 years ago- PCI with 2 stents)

Medication chart reviewed: from care home Aspirin 75mg OD; Bisoprolol 2.5mg OD; Ramipril 5mg OD; Furosemide 20mg OD; Donepezil 5mg OD

Allergies: Penicillin (rash)

Examination findings
A: Airway maintained

B: Spontaneous respiration. RR 24. Saturations on air 88%. Chest clear.

C: HR 110 BP 90/50. JVP not seen. Peripheries cool. Skin turgor normal. CRT 3 sec centrally. No sacral or peripheral oedema. Heart sounds normal.

D: Drowsy but rousable. Disoriented to time and place. E3M5V4. No uraemic flap

E: Very frail. Some bruising to left zygomatic arch.

G: abdomen diffusely tender (no peritonism or guarding). Worse over suprapubic area with some renal angle tenderness.

No other abnormal examination findings.

Relevant Investigations
No renal imaging
Urine dip:
Blood +
Pro +
Nit +
Leu ++
No urinary protein/ ur:cr results
No urine microscopy or culture results

Other relevant tests
ECG- sinus tachycardia
CXR- NAD

Infection assessment
Fever: t38.3
CRP elevated
WCC elevated
No recent cultures

Fluid status
No fluid output recorded

Scenario 2: patient on surgical ward with obstruction

AKI alert: NPSA Level 3 alert with hyperkalaemia

Pathology results viewed in-app prior to arrival:
SCr 290
Ur 20
Na 145
K6.7

Hb 14
WCC 14
CRP 120
Plt 301

Clotting normal
LFTs normal
Bone normal

History (from notes/ attending surgical SHO):
Male, 60 years old

Admitted 6 days ago having presented to ED feeling non-specifically unwell. Recent history of LUTS. Found to have AKI 3 (SCr 300) with a urea of 16. Potassium at this time was 4.5, no other abnormalities in bloods. No infection/ hypovolaemia. medical team arranged USS that evening Referred to surgical SHO, who arranged for him to have an ultrasound that evening. This found bilateral hydronephrosis and an obstructing bladder tumour. He underwent a bilateral nephrostomy on day 1 of his admission pending further surgical intervention by the urology team. This is scheduled for tomorrow.

Creatinine trend improving on days 2 and 3 (240-170).

Potassium trended upwards 4.6-4.9.

No further bloods done on days 4 and 5.

The patient was feeling much better, but is feeling “grotty” today. Complains of some diffuse abdominal pain.

Medication chart:
3 litres of normal saline prescribed over the first 3 days of admission.
Regular medications: omeprazole 40mg OD
PRNs: paracetamol; ibuprofen; dihydrocodeine; cyclizine; ondansetron, zopiclone.

Allergies: NKDA

Fluid balance chart:
UO from nephrostomies shows outputs of 2L from both drains yesterday and the day before
There is no input or output recorded over the last 24hrs.

Relevant Investigations
Renal imaging as described
Urine dip from admission:
Blood +
Pro -
Nit -
Leu -
No urinary protein/ ur:cr results
No urine microscopy or culture results

Other relevant tests
ECG- sinus tachycardia
CXR- NAD

Examination findings
A: Airway maintained

B: Spontaneous respiration. RR 12. Saturations on air 98%. Chest clear.

C: HR 100 BP 110/50. JVP not seen. Peripheries warm. Skin turgor normal. CRT <2 sec centrally. No sacral or peripheral oedema. Heart sounds normal.

D: Alert and orientated. E4M5V6. No uraemic flap

E: NAD

G: NAD

Nothing in either nephrostomy bag. On closer inspection you notice both drains are clamped.

No other abnormal examination findings.

Infection assessment
Fever: 37.4
CRP: up

WCC: up
No recent cultures

Fluid status
As above

Scenario 3: patient on cardiology ward with heart failure

AKI alert: NPSA level 1

Pathology results viewed in-app prior to arrival:

Cr 130 (baseline 95, less than 48 hrs before)
Ur 13.5
Na 132
K 3.9

Hb 103
Plt 158
WCC 6.4 (Nx 15)
CRP 2

LFTs NAD
Bone profile NAD

History (from notes):
Admitted via ED 2 days ago with shortness of breath. CXR and examination findings consistent with acute LVF; commenced on IV furosemide by ED SHO. Admitted to AAU under medical team. SCr on admission was normal (85). On PTWR was not deemed to be offloading sufficiently co commenced on furosemide infusion yesterday morning.

SCr yesterday was 95.

Examination findings:
A: Airway maintained

B: Spontaneous respiration. RR 14. Saturations on air 93%. Sats on 2L oxygen via NS 95%. Bibasal crackles

C: HR 95 BP 115/45. JVP 2cm. Peripheries warm. Skin turgor normal. CRT <2 sec centrally. Pitting peripheral oedema to above knees bilaterally. Heart sounds normal.

D: Alert and orientated.

E: NAD

G: NAD

No other abnormal examination findings.

Relevant Investigations:
Admission CXR from ED -> “Patient admitted with shortness of breath. Patchy shadowing in both lung fields consistent with pulmonary oedema.”

Other relevant tests:
ECG: voltage criteria for LVF; no other changes

Urine dip from admission:
Blood -
Pro -
Nit -
Leu -
No urinary protein/ ur:cr results
No urine microscopy or culture results

Infection assessment:
Fever: none
CRP: normal
WCC: normal
No recent cultures

Fluid status:
Fluid balance chart commenced by consultant yesterday on WR. In last 24hrs:
In 1.2L
Out (not catheterised) estimated to be 1.5L

Appendix 3: AKI response team proforma draft 1.1

Royal Free London NHS
NHS Foundation Trust

PATIENT STICKER

AKI RESPONSE TEAM 'SBAR' PROFORMA

Name of responder:

I am a renal consultant yes/no
I am a renal registrar yes/no

Time of attendance in ward ____:____ hrs Date of attendance ____/____/____

SITUATION

This patient has generated an AKI detection alert through the AKI clinical management software application called Streams. This application is running the NHS England mandated algorithm that detects possible AKI using changes in serum creatinine from blood tests. Following receipt of the AKI detection alert I have reviewed this patient's kidney function trends in-application and I think this patient is likely to have AKI. The response team are here to support, advise and where necessary initiate emergency care. The patient and their AKI management remains the primary responsibility of the home team unless otherwise agreed.

BACKGROUND (Relevant medical history)

This patient has the following *background* risk factors for AKI (circle)

>65 CKD Diabetes vascular disease cardiac failure liver failure background medication

---

ASSESSMENT

A Airway maintained: yes/no

B Respiratory rate:____min1 Saturations_____ %

C HR_____min BP_____mmHg Perfused? yes/no Oedema? yes/no Volume status: Hypo Normal Hyper

D (AVPU) circle one: Alert Responds to your voice Responds to pain Unresponsive Uraemic flap? yes/no

E Any other examination findings of note

Results *of note* (bloods, urine, imaging if available)

Urine dipstick result: Blood_____Protein_____Leucocytes_____

Is there evidence of infection? yes/no If there is infection is there evidence of severe sepsis? yes/no

Cause(s) of current AKI (STOP-AKI)		Specify exact cause where possible
Sepsis/infection and or hypoperfusion		
Toxicity (drugs or radiological contrast)		
Obstruction		
Primary renal disease		

The patient has the following complications of AKI (circle):

Hyperkalaemia acidosis symptomatic uraemia pulmonary oedema peripheral oedema

---

RECOMMENDATIONS AND ACTIONS	YES	NO
PARRT team called (bleep 2471)		
ITU team called (bleep 1030)		
Emergency therapy hyperkalaemia or acidosis commenced		
Home team advised to activate sepsis 6 pathway		
Bolus fluid protocol commenced and handed over - give 250mls-500mls crystalloid (Hartmanns or, if hyperkalaemic N saline) and reassess, giving further boluses as required until euvolaemic clinically		
Maintenance fluid plan started and handed over (specify):		
Diuresis or nitrates commenced		
Drug chart reviewed and following adjustments/cessations made if necessary (specify):		
Urgent USS requested (call Matteo Rossi on 07443101848, if unavailable/out of hours order within Cerner AKI diagnostic set and bleep radiology on 1462)		
AKI-obstruction pathway activated (call urology registrar on 39536) standard is same day decision and next morning relief of obstruction		
Renal disease therapy instituted (e.g. steroids). Specify:		
AKI diagnostic panel ordered Cerner (including glomerular screen - note some tests are 'opt-in')		
AKI diagnostic panel ordered Cerner (basic)		
AKI follow up panel ordered Cerner (mandatory all patients)		
Patient remains under 'home team'		
Patient taken over renal, accepted for transfer to renal and bed requested		

Patient transferring to ITU		
Patient information sheet given to patient/ward		
Full handover to home team (nurses and doctors)		
Home team discussion on escalation limits may be appropriate		

FOLLOW UP BY AKI RESPONSE TEAM (RENAL)

I will schedule a proactive review of this patient	
I will only review if called or if re-alerted by the streams application (we will be re-alerted if this patients AKI stage worsens or there is no recovery in 48 hours)	

GENERAL RECOMMENDATIONS FOR WARD NURSING STAFF

- Ensure patient gets prescribed fluids, keep a fluid chart, do daily weights and measure urine volumes
- Do at least 4 hourly observations (more frequent if advised)
- Maintain nutrition, for advice call ward dietician
- Please ensure patient has patient information sheet and condition explained
- Watch for signs of deterioration - breathlessness, worsening swelling, tachycardia, fever, high/low blood pressure, drowsiness or vomiting
- If concerned or triggering contact ward doctors and PARRT team (bleep 2471)

GENERAL RECOMMENDATIONS FOR WARD DOCTORS

- If fluid bolus protocol initiated for hypovolaemia continue 250-500ml boluses with reassessment until euvolaemic.
- Once euvolaemic set a daily fluid target of maintenance fluids (may need restriction if oliguric) and fluid assess daily.
- Ensure any outstanding tests (imaging, AKI diagnostic blood or urine tests) are back and discuss if necessary
- If prescribing new drugs check dose appropriate for renal function - if in doubt contact renal pharmacist on bleep 1409
- Watch for signs of deterioration - breathlessness, worsening swelling, tachycardia, high or low blood pressure, drowsiness, vomiting, signs of infection. If concerned contact PARRT team bleep 2471, ITU team 1030 or AKI response team (24/7) for advice.
- Monitor blood tests until recovered (Cerner AKI 5 day order set)

Supplemental advice may be provided in notes

If kidney function *has not* returned to baseline at discharge email chris.laing@nhs.net for AKI follow up

For follow up advice telephone AKI registrar: day (0900-2100) 07950860822 night (2100-0900): 07950843257

For up to date Trust guidance and training videos on AKI please visit www.londonaki.net or download LondonAKI mobile application for Android and iOS.

Appendix 4: Semi-structured interview schedule 1.0

1. **Basic details**
    a. Are you a nephrologist or member of the PARRT team?
    b. What grade are you?
    c. How long have you worked at RFH?

2. **Technology and you**
    a. Do you own a smartphone?
        i. What type?
        ii. Have you ever owned/used an iPhone?
    b. Do you use a smartphone at work?
        i. What do you use it for?
        ii. What apps (if any?) do you use for work?
        iii. How often do you use your phone to make decisions about patient care?

3. **Accessing patient data in the past:**
    a. How do you usually access patient results during the week[end]?
    b. When do you most commonly review blood test results during the week[end]?

4. **About Acute Kidney Injury (AKI):**
    a. How often do you encounter AKI in one of your patients?
    b. How were cases of AKI previously flagged to you (if at all)?
    c. In the past have you found the following useful?
        i. Interruptive alerts on the results management system
        ii. Checklists and/or guidelines
        iii. Consulting with the renal registrar or outreach

5. **Using Streams/ Trust iPhones:**
    a. What shift were you working when using Streams?
    b. Technical aspects
        i. Any problems logging in?
        ii. Any problems with the phones?
        iii. Good/bad points about the interface?
        iv. Any problems with the data?
        v. Any other technical issues?
    c. How did the phone change your working day?
        i. Good points?
        ii. Bad points?
    d. How long does it take to get used to the phone/care pathway?

6. **The care protocol**
    a. Did you use the care protocol?
    b. Did you find it useful?
    c. What would you keep?
    d. Would you add anything?
    e. What would you get rid of?

7. **The AKI response team**
    a. Did you contact other members of the response team during your shift?
        i. If so, how did this contact take place?
        ii. If not, why not?
    b. Did you find [interacting with] the other members of the response team useful?

8. **Other clinical teams**
    a. Did you interact with other clinical teams when reviewing patients with AKI on the wards?
    b. Were these encounters well received?
    c. Did you encounter any problems with these interactions?

9. **Considering the whole pathway**
    a. Would you want to use the intervention in the future as part of your routine?
        i. Why?
    b. What impact did this have from the patient POV?
    c. Any great “success stories”?
    d. Any unintended consequences?
    e. Any concerns?

10. **Any other comments?**

Appendix 5: Semi-structured interview schedule 1.1

1. **Basic details**
    a. Are you a nephrologist or member of the PARRT team?
    b. What grade are you?
    c. How long have you worked at RFH?

2. **Technology and you**
    a. Do you own a smartphone?
        i. What type?
        ii. Have you ever owned/used an iPhone?
    b. Do you use a smartphone at work?
        i. What do you use it for?
        ii. What apps (if any?) do you use for work?
        iii. How often do you use your phone to make decisions about patient care?

3. **If part of the Streams-AKI Clinical Response Team**
    a. With respect to Streams...
        i. App: how easy (or not) was it to use the app? e.g. was it intuitive; when did you become comfortable with its use? What was bad?
        ii. Alerts: How did you feel about receiving alerts? What was good about the alerts? What was bad?
        iii. Triage: when/how did you prefer to triage? What were the barriers to this? What happened if you disagreed with someone else's triage decision?
        iv. Did you use the Streams phone to look up blood test results? When/how did you do this? Was it useful?
        v. Did you use the Streams phone for anything else?
    b. With respect to the proforma...
        i. Did you use it? If not, why not?
        ii. Any specific good & bad points to highlight?
    c. With respect to other team members...
        i. Was it useful being part of a team?
        ii. Any frustrations with the way the team ran?
        iii. (How) did you contact other team members?
    d. What impact did the pathway have on you [good or bad]? Were there any unexpected effects?
    e. What impact did the pathway have from a patient point of view [good or bad]?
    f. What impact did the pathway have from the Trust point of view [good or bad]?
    g. Any other comments?

4. **If not part of the Streams-AKI Clinical Response Team (CRT)**
    a. With respect to the Streams-AKI CRT:
        i. Good and bad- tell me about what changed in terms of
            1. your interactions with professionals who were part of the team?
            2. your patients management
        ii. What were the implications of this?
    b. What impact did the pathway have on you personally [good or bad]? Were there any unexpected effects?
    c. What impact did the pathway have from a patient point of view [good or bad]?
    d. What impact did the pathway have from the Trust point of view [good or bad]?
    e. Would you want the CRT to keep using Streams? What would you change?
    f. Would you want to use Streams? What for?
