Clinical Decision Support Systems in the Care of Hospitalised Patients with Diabetes

By

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Chapter 2

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Chapter 3

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Chapter 4

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Chapter 5

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Chapter 5

Nirantharakumar K, Hemming K, Narendran P, Marshall T, Coleman JJ. A prediction model to identify hospitalised patients with diabetes who may have an adverse outcome. *Diabetes Care.2013. DOI: 10.2337/dc13-0452. (In press).*

(more details in last appendix)

Abstract

Hospital admissions of patients with diabetes have been increasing steeply in parallel with the increasing prevalence of known diabetes in the general population. Furthermore patients with diabetes have poor clinical outcomes during their hospital stay. There are major implications for secondary care: 1) increasing demand placed on hospital staff and diabetes specialist teams may impact on the quality of care provided to patients with diabetes; and 2) financial strains will result due to the greater cost associated with in-hospital care of patients with diabetes.

Health informatics solutions including clinical decision support systems have been implicated as tools that may improve effectiveness, efficiency and quality of services provided to hospitalised patients. In this thesis I have explored the role of health informatics, in particular clinical decision support systems, in the care of hospitalised patients with diabetes through a systematic review and by analysing data from University Hospital Birmingham captured by two electronic patient information systems: 1) electronic prescribing, information and communication system; and 2) electronic patient administration system.

Findings from the thesis: 1) highlight the potential role of computerised physician order entry system in improving guideline based anti-diabetic medication prescription in particular insulin prescription, and their effectiveness in contributing to better glycaemic control (chapter 2); 2) quantify the occurrence of missed discharge diagnostic codes for diabetes using electronic prescription data and suggests 60% of this could be potentially reduced using an algorithm that could be introduced as part of the information system (chapter 3); 3) add evidence to the poor clinical outcomes

of diabetic patients with hypoglycaemia whom were found to have higher in-hospital mortality rates and longer length of stay (chapter 4); 4) quantify the hypoglycaemia rates in non-diabetic patients and proposes one method of establishing a surveillance system to identify non diabetic hypoglycaemic patients (chapter 4); 5) describe metrics that may be useful in monitoring institutional blood glucose control (chapter 4); 6) add evidence to the factors including foot disease, that may explain the excess inpatient mortality and length of stay in admissions with diabetes (chapter 5); and 7) introduce a prediction model that may be useful to identify patients with diabetes at risk of poor clinical outcomes during their hospital stay (chapter 5).

Generally the findings support the important contributions health informatics could make in improving care for hospitalised patients with diabetes. To maximise the impact of the research findings in this thesis it is essential when implementing the recommendations they are evaluated to high standards. This will help to continuously improve the performance of the tools suggested and at the same time will maximise the generalisability of tools to other settings other than University Hospital Birmingham.

Acknowledgements and Statement of Contributions

The work arising from this thesis is part of the theme 9 of the National Institute for Health Research (NIHR) funded Collaborations for Leadership in Applied Health care (CLAHRC) for Birmingham and Black Country. Theme 9 is titled improving patient safety: studying an evolving IT system. I was awarded a studentship after submitting the proposal titled “active case finding of hospitalised patients with diabetes at risk of poor clinical outcomes”. The work in this thesis arises from this proposal.

Chapter 1 – This introductory chapter is my own work. Valuable comments were received from both of my supervisors.

Chapter 2 – The systematic review was carried out at the request of Dr. Jamie Coleman (JJC) and I am thankful for his guidance in completing the review and guiding me in preparing the manuscript that was accepted in Diabetic Medicine journal. I developed the research question and search strategy and then carried out the search with guidance from the librarians at the Health Service Management Centre (HSMC) at University of Birmingham. Study selection was done by me and my supervisor (JJC) acted as the second reviewer. Data extraction was carried out by me with JJC and another colleague (Yen Fu Chen / YFC) checking on the accuracy of the data extracted. YFC checked the accuracy of my quality assessment of the studies. Jonathan Webber, consultant diabetologist gave specialist input. Narrative synthesis of the data was carried out by me and the manuscript submitted to the journal was drafted by me and received valuable comment from all authors.

Chapter 3 – The research idea to use electronic prescription data and the statistical method of capture recapture to estimate missed discharge diagnostic codes for diabetes was conceived by me and all work were carried out by me. Valuable statistical supervision was provided by Dr Karla Hemming (KH) (Senior Lecturer in Medical Statistics) and the statistical formula for capture recapture technique was developed in an excel format by James Hodson (JH), a statistician at the University Hospital Birmingham. Data extraction from the health information system was carried out by David Westwood, Sarah Wang and Jo Cook. Clinical insight was provided by Dr. Parth Narendran (PN), a consultant diabetologist. I presented the findings in the Diabetes UK conference (2012) and published the article in the Diabetic Medicine journal. Both my supervisors (JJC and Tom Marshall (TM)) gave valuable comments to improve the intellectual content and the presentation of my work.

Chapter 4 – The study exploring the association between hypoglycaemia and inpatient mortality (section 4.2) was my own work. I conceived the idea and carried out all the necessary work with statistical supervision from KH and clinical insight from PN. JJC and TM gave valuable comments for the work. The work was published in the Diabetic Medicine journal. The study question addressed in section 4.3 on non-diabetic hypoglycaemia arose from a collaborative work with Prof. Robin Ferner (RF). After the initial question was developed I carried out all the work with statistical supervision from Prof Jon Deeks. JH checked all my statistical work to ensure they were accurate. The work was presented in the International Conference for Endocrinology (2012) and published in the PLoS One journal. The draft for the manuscript was prepared by me and I am extremely thankful to RF for his input in improving the presentation of the paper. All authors of the article gave valuable comments. PN provided valuable clinical insight. The section on Glucometrics is my

own work based on the tool developed by Yale Centre for Medical Informatics, Boston.

Chapter 5 – The idea for the foot disease section (5.2) and the active case finding model (section 5.3) was conceived by me and all work was carried out by me. For the foot disease paper valuable clinical insight was provided by Saeed Mujahid (SM), consultant diabetologist and Ian Wilson (IW), Head of Podiatry, University Hospital Birmingham. I am thankful to KH for her patience in educating me with the skills in developing high quality statistical model. Both my supervisors gave valuable support and comments to improve on the work. Both the work has been submitted for publication.

Chapter 6 – Is my own work summarising the thesis findings and their implications.

I am particularly grateful to my supervisor Dr. Jamie Coleman for placing his trust in me to take on this project, awarding a studentship to carry out this project and his recommendation for my current position as a senior research fellow. I would also like to thank Prof KK Cheng and Dr Tom Marshall for their guidance throughout the time I have spent at the University of Birmingham.

Last but not the least I would like to thank my family (my wife Vaani and my children Abhinash and Yuvanash) whom have supported me with my career and put up with all my degree and membership exams and finally with the MD and writing up of this thesis.

Contents

List of Tables and Figures

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Abbreviations

ADA	American Diabetes Association
AHRQ	American Healthcare Research and Quality
AIC	Akaike Information Criteria
AMIA	American Medical Informatics Association
AUC	Area Under the Curve
BIC	Bayesian Information Criteria
BMI	Body mass Index
CCS	Clinical Classification System
CDSS	Clinical Decision Support System
CI	Confidence Interval
CPOE	Computerised Physician Order Entry
CRD	Centre for Review and Dissemination
CRP	C-Reactive Protein
DKA	Diabetic Keto-Acidosis
EBHI	Evidence Based Health Informatics
EBM	Evidence Based Medicine
eGFR	estimated Glomerular Filtration Rate
FFA	Free Fatty Acids
GCS	Glasgow Coma Scale
GEE	Generalised Estimated Equations
HbA1c	Haemoglobin A 1c
HES	Hospital Episode Statistics
HLA	Human Leucocyte Antigen
HONK	Hyper-Osmolar hyperglycaemic Non-Ketotic coma
HRG	Healthcare Resource Group
HSE	Health Survey for England
ICD10	International Classification of Diseases version 10
ICU	Intensive Care Units
IMD	Indices of Multiple Deprivation
IQR	Inter-Quartile Range
LOS	Length Of Stay
NaDIA	National Diabetes Inpatient Audit
NDA	National Diabetes Audit
NHMRC	Australian National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute of health and Clinical Excellence
OGTT	Oral Glucose Tolerance Test
OPCS4	Office of Population, Censuses and Surveys Classification of surgical operations and procedures version 4
OR	Odds Ratio
PAS	Patient Administration System
PICS	Prescribing Information and Communication System
POC BG	Point Of Care Blood Glucose

RCT	Randomised Controlled Trial
ROC	Receiver Operating Curve
RR	Relative Risk
SD	Standard Deviation
UHB	University Hospital Birmingham
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
YHPHO	Yorkshire and Humberland Public Health Observatory

CHAPTER 1

Introduction

1 Introduction

In this chapter I will first highlight the burden of diabetes mellitus (which will be referred to as diabetes throughout the thesis) giving particular attention to inpatient care and inpatient outcome. Then I will summarise the current guidelines for inpatient management of patients with diabetes. Thereafter I will draw attention to health informatics and the role of clinical decision support systems in health care. Finally I will lay out the aims and objectives of this thesis.

1.1 Diabetes Mellitus

Diabetes has emerged as one of the biggest global health challenges in the last few decades. Estimates suggest the global prevalence has risen from 8.3% to 9.8% in men and 7.5% to 9.2% in women from 1980 to 2008 [1]. In numbers this is an increase from 150 million to 350 million individuals with diabetes during this period globally [1]. These estimations underscore the need for the global health community to implement effective preventative methods. In addition health care facilities should identify means to efficiently use resources in detecting and treating people with diabetes to limit disease progression. Control of disease progression is important as diabetes has serious long term consequences such as cardiovascular disease, blindness, chronic renal disease and amputations.

Diabetes is a state of persistent high blood sugar as a result of deficiency in insulin production from the pancreas or due to poor utilisation of insulin (insulin resistance) by peripheral tissues [2]. Type 1 diabetes is a where there is absolute deficiency of insulin production and therefore patients are dependent on lifelong exogenous insulin treatment [2]. Type 2 diabetes is often a combination of insulin deficiency and insulin resistance and patients are treated with lifestyle modification, oral hypoglycaemic agents and/or insulin [2]. The aetiology of type 1 diabetes suggests

autoimmune mediated destruction of β-cells in the pancreas and strong links with specific Human Leucocyte Antigen (HLA) genes, whereas in type 2 diabetes obesity, aging, genetic predisposition and physical inactivity are the key risk factors that lead to insulin resistance and relative insulin deficiency [2].

The World Health Organisation (WHO) defines diabetes as either a fasting plasma glucose of ≥7.0 mmol/l or random plasma glucose of ≥11.1mmol/l on two occasions or once if symptoms are indicative of diabetes [3]. These symptoms include polyuria, polydipsia and unexpected weight loss. Alternatively post prandial blood glucose of ≥11.1mmol/l after 2 hours of an Oral Glucose Tolerance Test (OGTT) is diagnostic of diabetes [3]. WHO in a recent document [4], following the American Diabetes Association (ADA) directive to use Haemoglobin A1c (HbA1c) as a diagnostic test [5], have accepted a cut point of ≥ 6.5% (≥ 48 mmol/mol) for HbA1c as diagnostic of diabetes. These criteria have been accepted and are in use in United Kingdom (UK) [6,7].

1.1.1 Diabetes in England, UK

United Kingdom has a population of 63 million based on the latest census carried out in 2011 [8]. Fifty three million are from England and the rest from Scotland, Northern Ireland and Wales [8]. In England, based on National Diabetes Audit (NDA) the prevalence of diabetes was 4.57% in 2010-11 [9]. This means in total approximately 2.5 million individuals have diabetes in England. Around 9% of them had type 1 diabetes and the rest had type 2 diabetes [9]. The NDA identified gaps in care processes in primary care and noted that only 63% had good glycaemic control (HbA1c ≤7.5% / 58mmol/mol) and only 36% had blood pressure within target range (<140/80mmHg for those without and <130/80mmHg for those with end organ damage) [9].

In the Health Survey for England (HSE) [10], prevalence of adults (≥16 years) was higher in the aged population (example; 2.6% of men aged ≤45 years rising gradually to 25.7% in ≥85 years), in males (7.0% men vs. 4.9% women) and in those from low income households (lowest quintile men 11.0% and women 5.9% vs. 4.7% in men and 3.7% women from highest quintile). The survey also demonstrated the relationship between obesity and diabetes, for example in females with a Body Mass Index (BMI) ≥30kg/m^2 the prevalence was 9.9%; 4.3% in BMI 25-30kgm^2; and 1.5% in BMI <25kg/m^2 [10]. A recent study demonstrated high incidence in Indian Asian and African Caribbean population and suggested this is likely linked to their greater insulin resistance and truncal obesity [11]. Similar observations have been noted in the British Pakistani population as well [12].

The NDA in its second part of the report for 2011compared hospital admissions with complications for people with diabetes to those of the general population from England [13]. They found a 48% increase in myocardial infarction admissions in diabetic patients when compared to the general population. The risk of admission for Heart failure was 65% higher; 25% higher for stroke; 144% higher for renal replacement therapy; 329% higher for minor amputation (below the ankle); and 186% higher for major amputation (above the ankle).

In the last 4 years there have been annual audits of diabetic care in hospitals (National Diabetes Inpatient Audit or NaDIA) in England and Wales. Audits for the year 2009, 2010 and 2011 are available. These audits provide a comprehensive picture of inpatient care and highlight areas for improvement. Key results from 2010 and 2011 for England are listed below and the findings will be reiterated in the sections below where a detailed discussion of the consequences of diabetes in hospitalised patients is given [14,15].

The burden of inpatient diabetes

- Around 15% of audited beds were occupied by patients with diabetes (2010/11)
- Patients with diabetes were likely to be older than those without diabetes (median age 75 years Vs. 65 years in 2011)
- Median length of stay is 8 days in patients with diabetes vs. 5 days in non-diabetics (2010/11)
- Only 9% are admitted for diabetes specific disease management, almost a half of these were related to active foot disease (2010 /11)
- Nearly 40% are treated with insulin while in hospital (2010 /11)

Provision of diabetes care

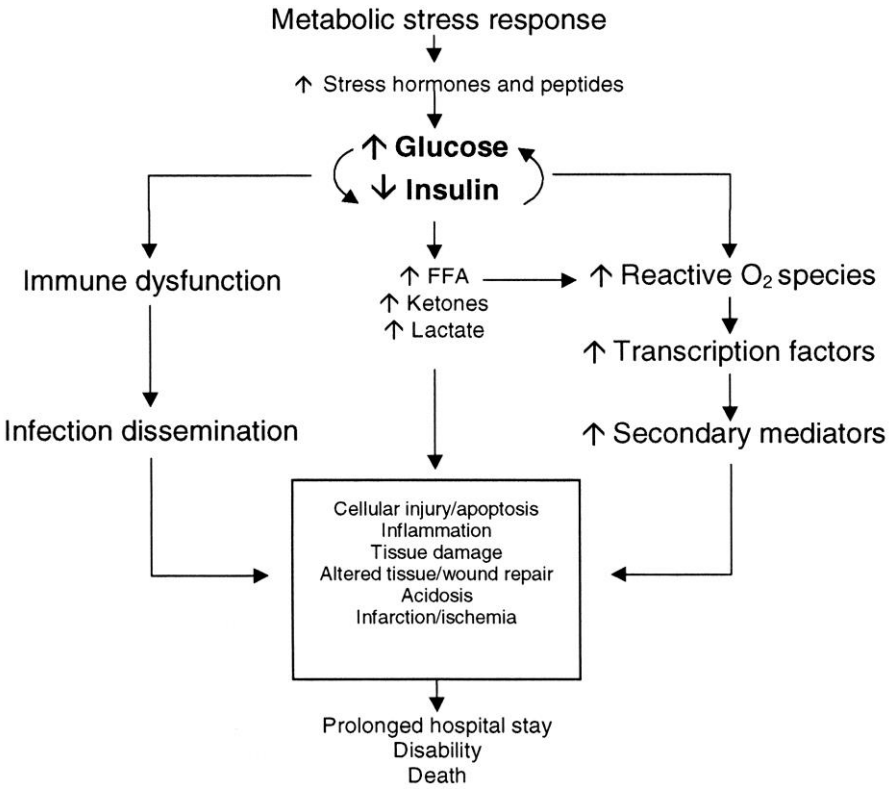
- 37% of patients with diabetes had at least one medication error in 2010 although this dropped to 32% in 2011, it is still very high
- Those with medication error were twice likely to have a severe hypoglycaemic episode than those without a medication error (2011)
- 8% of insulin infusions were considered to be in place for longer than necessary (2011)
- In the 2011 audit, on average 58% of patient days had “good glycaemic control” (defined as patient days with blood glucose no more than once ≥11mmol/l and no single measure below 4mmol/l)
- 69% of hospitals did not provide specialist dietetic services for people with diabetes (2011)
- 31% of hospitals had no inpatient podiatry services (2011)
- Only 27% of patients with diabetes had foot examination documented during their stay (2010 /11)

1.1.2 Consequences of diabetes in hospitalised patients

Patients with diabetes admitted to hospital or those with hyperglycaemia during inpatient stay have a range of poor clinical outcomes [16-31]. They include excess mortality [17-21,24,25,31-33], higher complication rates, in particular infection [25,27,30,34], and increased length of stay [14,27,31,35]. These outcomes are often linked in these studies to hyperglycaemia. In fact it has been shown that those with hyperglycaemia detected for the first time during their hospital stays have similar or worse clinical outcomes than those with known diabetes having hyperglycaemia [31]. In addition to these poor clinical outcomes, antidiabetic medication prescription errors, especially insulin, have resulted in harm to inpatients [36]. Furthermore, patients with diabetes complain of poor management of their diabetes while in hospital [37,38].

The underlying mechanism on how hyperglycaemia results in poor clinical outcomes is unclear but it is proposed as a response to metabolic stress there is a rise in stress hormones and peptides, which in turn alters the glucose metabolism resulting in increased metabolites such as Free Fatty Acids (FFA), ketones and lactate [39,40]. Along with this there is immune dysfunction giving rise to infection. Moreover, reactive oxidative stress leads to changes that raise secondary mediators. In combination all these changes induce cellular injury, inflammation, tissue damage and altered tissue wound repair. A process that ends with complications, prolonged length of stay and death [40] (Figure 1.1).

Figure 1.1: Underlying patho-physiological changes that may explain poor hospital outcomes in people with diabetes



Source: Clement S et al. Diabetes Care. 2004; 27:553-591[40] (reproduced with permission)

In a recent report titled “Mortality among inpatients with diabetes” for England [33], Diabetes Health Intelligence, a unit at the Yorkshire and Humberland Public Health Observatory (YHPHO) found that diabetes patients were 10% more likely to die in hospital than those without diabetes. In particular there was wider variation across hospitals after adjustment for co-morbidities, with 24 hospitals being identified as outliers; one hospital with a higher mortality rate was University Hospital of Birmingham. The methods used to analyse the data have limitations, as no methodology can give an accurate picture of the case-mix. Nevertheless it indicates the need to identify possible reasons for excess mortality and emphasises the need to implement interventions to reduce adverse outcomes including excess mortality.

Kerr [41] in her national report titled “Inpatient care for people with diabetes: the economic case for change”, highlighted the economic cost of diabetes. She reported that 11% of total NHS expenditure on in-hospital care was spent on people with diabetes, totalling around 2.5 billion pounds for the year 2009/10. Furthermore, of the above cost a sum of around 600 million pounds is excess expenditure compared to a similar population without diabetes. It was also found patients with diabetes had higher rates of admission and were likely to stay on average 3 days more than non diabetic patients, a finding that corroborates with previous studies [14,35,42].

Patient surveys and qualitative studies using validated questionnaires [37,38,43,44] have highlighted issues around incorrect medications, disempowerment, poor meal timing and choice, and inadequate specialist team input in their care. This is further exacerbated by numerous errors in prescriptions for people with diabetes [36]. In particular Insulin is considered as one of world’s top ten dangerous drugs [45] and has been even used with malicious intent by health care workers as a murder weapon [46]. A national guideline exists to improve error free prescription of insulin and key recommendations include electronic prescriptions [47].

1.1.3 Current evidence based guidelines in caring for hospitalised patients with diabetes

There are numerous guidelines addressing management of diabetes. In this section I will summarise the key messages from national documents produced in England addressing inpatient management. These national documents are:

1) Safe and effective use of insulin in hospitalised patients [47]
2) Hospital management of hypoglycaemia in adults with diabetes mellitus [48]
3) Inpatient management of diabetic foot problems: NICE guideline [49]

4) The management of diabetic ketoacidosis in adults [50]
5) Self management of diabetes in hospital [51]

1.1.3.1 Safe and effective use of insulin in hospitalised patients [47]

Earlier I discussed the undesirable effect of hospitalised patients with diabetes which have been mainly shown to be associated with hyperglycaemia. In the early part of the last decade Van Den Berghe et al [52] demonstrated that tight glycaemic control (<6.1mmol/l) could reduce adverse clinical outcomes including mortality for patients with hyperglycaemia in critical care setting. However recent studies found harm in administering such a tight glucose control strategy in Intensive Care Units (ICU), showing that resulting hypoglycaemia was associated with increased mortality [53,54]. A meta-analysis involving these and other similar studies did not find any reduction in mortality in ICU [55]. Nevertheless good glucose control (<10mmol/l) remains as an important component of managing critical care patients [56]. In the non critical care setting a recent (2012) systematic review involving ten observational studies and nine randomised controlled trials showed good glycaemic control (varied targets but often close to current recommended target of <7.8mmol/l pre-meal and less than 10 mmol/l any other time), reduced infection rates (relative risk (RR) 0.41; with 95% confidence interval(95%CI) 0.21-0.77) but potentially increased the rate of hypoglycaemia (RR 1.58;95%CI 0.97-2.57)[57]. No benefit or harm in terms of mortality or occurrence of co-morbidities such as myocardial infarction or stroke was noted, though the trend was towards reduction of these outcomes. However the studies included in the systematic review mostly reflected surgical units and were often of poor quality. Therefore the review supported the urgent need for a large well conducted randomised controlled trial to determine the value of good glycaemic control in non critical care setting. Until this is carried out there is consensus among

the endocrinology community to take an approach that will limit hyperglycaemia as well as hypoglycaemia. This guideline outlines the recommendation on glucose control targets and safe use of insulin to achieve this.

The document draws attention to the importance of recording diabetes status of patients clearly, the benefits of using electronic information system for record keeping and the utility of electronic prescriptions to prevent insulin prescription errors. Guideline based insulin administration and the necessity to avoid sliding scale insulin is also highlighted. The recommended target for blood glucose control set out in the guideline are 5 to 7.8 mmol/l pre-meal and <10mmol/l at any random time point or post meal. Additional information includes general training of doctors and other health professionals towards safer prescription of insulin and the functions of a diabetes team in promoting good glycaemic control across the institution.

1.1.3.2 Hospital management of hypoglycaemia in adults with diabetes mellitus [48]

Hypoglycaemia, like hyperglycaemia, is associated with poor clinical outcomes in the non critical care setting (chapter 4) [58,59]. Therefore it is important to avoid extremes of blood glucose control. The document aims to give guidance on how to detect hypoglycaemic episodes and treat them appropriately. It emphasises the need for early detection, involvement of the diabetes team where it is recurrent or severe, immediate availability of treatments in a “Hypo Box” and training of staff in optimum management of hypoglycaemia.

1.1.3.3 Inpatient management of diabetic foot problems [49]

Diabetic foot problems refers to any inflammation or swelling of the foot, break in skin or blisters, ulcers, unexplained pain in the foot, fracture or dislocation of any part of the foot without any preceding significant injury or gangrene of the foot [60].

Diabetic foot disease leads to long term sequelae such as poor quality of life, amputation and mortality [61-65]. In-hospital outcomes include longer length of stay and high economic cost [66]. Evidence on association between foot disease and inpatient mortality is demonstrated in chapter 5. This guideline tries to address the inpatient management of foot disease to avoid such poor clinical outcomes.

The guideline highlights the need for a multidisciplinary foot care team which may have a positive impact on reducing these poor clinical outcomes. The guideline describes the composition of the team, which should include a diabetologist with an interest in diabetic foot disease, podiatrist, vascular surgeon, diabetes nurse specialist and tissue viability nurse. It also emphasises the need for foot assessment of every patient with diabetes within the first 24 hours of admission. Furthermore it states the need for the multidisciplinary team to review patients referred to them at least within 24 hours of being informed. Additional aspects address clinical assessment and management of diabetic foot disease.

1.1.3.4 The management of diabetic ketoacidosis in adults [50]

Diabetic Keto-Acidosis (DKA) indicates a state of hyperglycaemia and metabolic acidosis (due to increased ketones in blood). The guideline gives detailed management of these patients and is mostly aimed at clinical practitioners to guide appropriate treatment. The relevant message for this thesis is that it recommends that diabetes specialist teams should be involved in the management of all DKA patients.

1.1.3.5 Self management of diabetes in hospital [51]

Earlier I identified how patient surveys have underscored the importance of empowering patients to be involved in their care of diabetes during hospital stay. The guideline recommends, where exclusion criteria do not apply, that patients should be

given the option of self managing their medication with the aim to lessen prescription errors, reduce length of stay and improve patient satisfaction. The document lays out the process of safely implementing the self management initiative.

1.2 Health Informatics and Computerised Clinical Decision Support Systems

Terminologies used in health informatics, also often described as medical informatics [67] have considerable overlap. Wyatt et al produced a glossary to define most of the terms used in medical informatics [67]. I will first define key terms mainly based on this glossary and then discuss in detail clinical decision support systems, their usefulness and the challenges they pose.

1.2.1 Health informatics

Previously health informatics and medical informatics were recognised as the same discipline and were defined as:

“Medical informatics is the study and application of methods to improve the management of patient data, clinical knowledge, population data, and other information relevant to patient care and community health” [67]

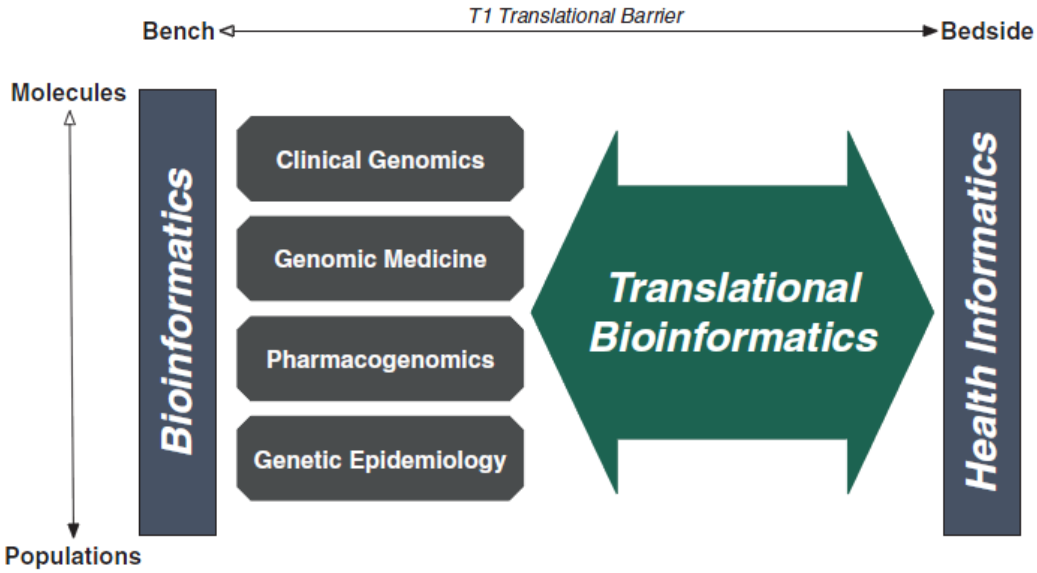
Or

"Medical Informatics comprises the theoretical and practical aspects of information processing and communication, based on knowledge and experience derived from processes in medicine and health care." [68]

Both definitions acknowledge the spectrum of issues medical/health informatics cover, from coding of specific conditions and medical terminologies in a meaningful way, to that of using computers to support decision making at an individual patient and population level. Even though Wyatt et al [67] described bioinformatics

(molecular biology), clinical informatics (individual patient care), consumer health informatics (information technology supporting the pubic to access health information and make decision) and public health informatics (population health intelligence and surveillance) as branches of medical / health informatics, recent definitions see bioinformatics and health informatics as two different disciplines of a spectrum known as biomedical informatics, interlinked by what is called translational bioinformatics [69]. The American Medical Informatics Association (AMIA) defines biomedical informatics as the "*interdisciplinary field that studies and pursues the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving and decision making, motivated by efforts to improve human health*" [70]. Translational bioinformatics is described as, "*a system theory approach to bridge the biological and clinical divide through a combination of innovations and resource across the entire spectrum of biomedical informatics*" [69] (Figure 1.2).

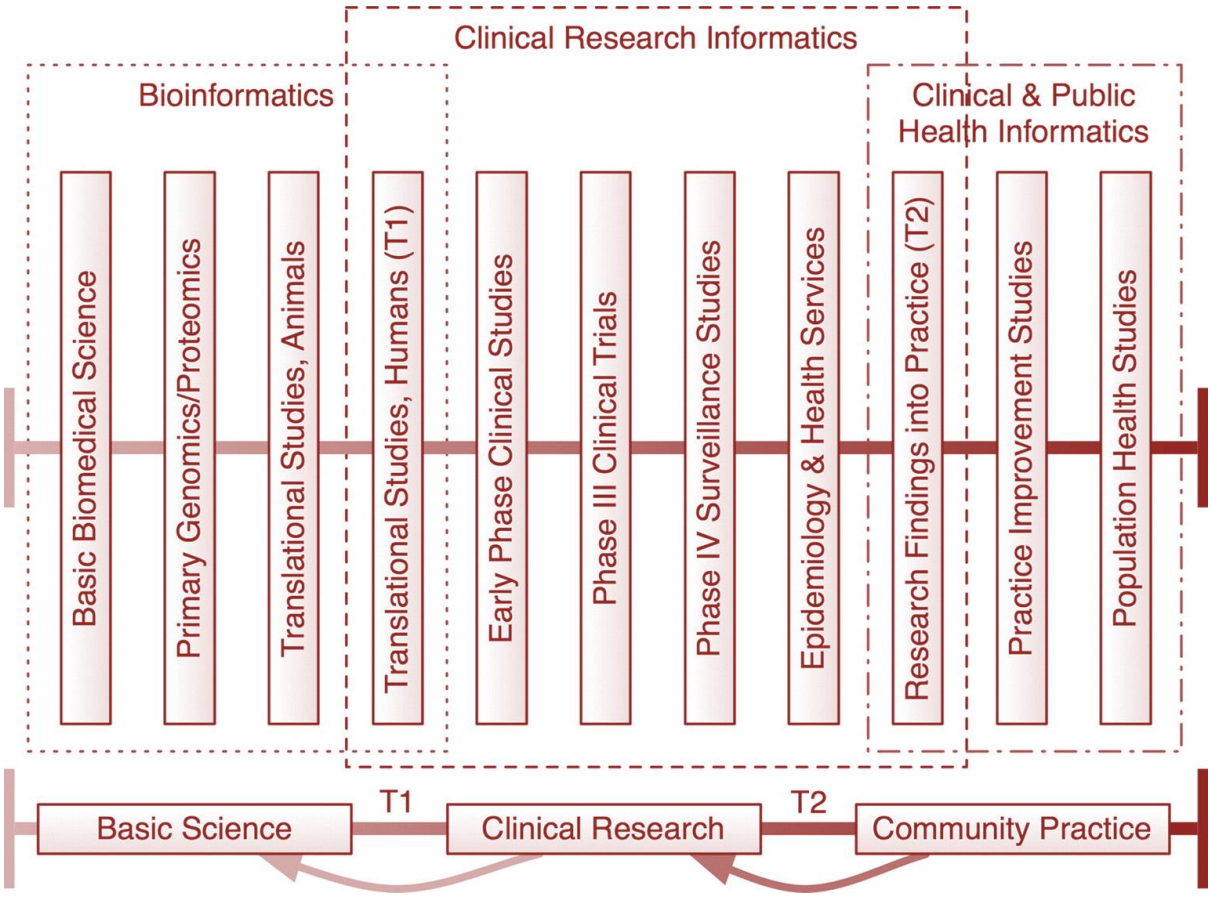
Figure 1.2: Translational bioinformatics



Source: Sarkar et al. J Am Med Inform Assoc 2011; 18(4): 354-357. (reproduced with permission)

Another much more complex but informative spectrum is shown in figure 1.3. Current proposed definitions by AMIA in 2012 recognise the combination of clinical and public health informatics as health informatics [70]. They see medical informatics (physician orientated), nursing informatics (nursing orientated) and dental informatics (dental practitioner orientated) as branches of clinical informatics [70]. For the purpose of this thesis the focus is on health informatics (clinical and public health informatics) tools, in particular Computerised Clinical Decision Support System (CDSS), in improving the care of hospitalised patients with diabetes.

Figure 1.3: Detailed spectrum of biomedical informatics



Source: Enbi et al. J Am Med Inform Assoc 2009; 16:316-327. (reproduced with permission)

1.2.2 Computerised Clinical Decision Support Systems (CDSS)

CDSS has been defined as: *"A computer system that uses two or more patient data to generate case specific or encounter specific advice" [67].* However this implies CDSS helps to make decisions for individual patients, though similar tools can be used to make decisions for populations. For example a physician may use a risk tool such as the Framingham cardiovascular risk engine [71] in a computer to decide the need for lipid lowering therapy in an individual patient. At the same time the same physician can use the computer with an inbuilt decision support system to identify all patients whom may fulfil the criteria for the need for lipid lowering therapy using Framingham risk tool. Here a decision can be made to invite all these patients to assess suitability of lipid lowering therapy, a decision at the population level. CDSS are therefore best loosely described as information systems designed to assist and improve clinical decision making [72]. In this thesis assisting decision making could be both at an individual level and at times at population level.

1.2.2.1 Types of clinical decision support systems

There are different types of clinical decision support system. I will describe them individually.

Alerts or reminders

These are the commonly used computerised decision support tool. For example if a patient is allergic to a medication but the physician unintentionally prescribes the medication to the patient, then the computer will alert the physician of the potential hazard. Similarly where a patient is due for a routine check-up a reminder will be generated to the physician as an alert when he logs into the computer or in the form of an email. There are population level reminders that are often used to generate a list of patients whom for example are due for annual influenza vaccine or diabetes

review. Other common alerts include abnormal blood results and observations both in primary care and secondary care.

Electronic triggers are a specific type of alert where they may identify potential harm that might have occurred to patients. For example naloxone medication can be a trigger of opioid overdose, similarly high INR can be a trigger of higher than needed dose of Warfarin prescription [73].

Diagnostic system

Here when patient symptoms and sign are recorded the system can generate a set of differential diagnosis that needs to be considered. The first such attempt was in the diagnosis of acute abdominal pain presenting in accident and emergency department, to diagnose acute appendicitis [74,75]. Since then many complex tools have been developed such as the Isabel clinical decision support tool which generates differential diagnoses when presented with symptoms and signs [76].

Electronic guidelines

These are tools that encourage use of evidence based decisions in the management of patients. For example if a physician were to deter from the guideline then the CDSS will alert or warn him. The physician then can override the warning on clinical grounds or change practice and adhere to the guideline.

Computerised Physician Order Entry (CPOE)

CPOE are systems which enable ordering of prescriptions, laboratory tests, referrals, imaging and even meals in hospitals through a computer based system. CPOE on its own are often not termed as part of CDSS but in recent history almost always have features that support decisions. For example they may highlight duplication of blood

test requests, give guidance on prescription by suggesting medication doses and automate referrals if the patient meets certain clinical criteria.

Prognostic risk engines

Many prognostic risk scores have been developed over the last two decades such as the Framingham [71] and Q-risk [77] for cardiovascular disease, UKPDS risk score [78] for cardiovascular risk in type 2 diabetes patients, Q-fracture [79] for detecting patients with high risk of fragility fracture, Patient At Risk for Readmission (PARR) algorithm [80] for identifying patients at high risk of hospitalisation and many more. These are gradually being implemented as part of electronic health records and are used at individual patient level to detect disease, discuss prognosis and provide treatment (lipid lowering medication for those with a cardiovascular risk of greater than 20% in the next ten years) [81] and at population level to invite a list of patients, assess their risk of developing disease and to drive prevention programmes in these patients [82].

1.2.2.2 Benefits and challenges of computerised clinical decision support systems

Many reviews have identified the benefits of CDSS, in particular CPOE systems [83-88]. CDSS as part of CPOE have been found to reduce medication errors and adverse drug events [83,84,87,88]. They also have shown to improve physician performance, these include correct dosing, adherence to guidelines and to an extent efficient use of time [85,86,89]. CDSS have a role in prevention at outpatient clinics and primary care, for example by alerting physicians of the need for routine blood pressure checking, to offer influenza vaccination and to recommend cervical screening [86]. Other individual studies have also shown better communication between primary and secondary care [90] and improved documentation of problem

lists for patients [91]. For example if a patient is prescribed levothyroxine then the system could alert the physician to add hypothyroidism to the patient's diagnosis list. This approach using medications to identify diagnoses is used in chapter three to study under reporting of diabetes diagnosis, where a prescription for diabetes exists but a diagnosis of diabetes is not entered in the discharge summary [92].

However there are challenges in using CDSS and many studies have questioned the above advantages. Ash et al [93] categorised the unintended consequences of information technology on health care as those that occur during entering and retrieving information, and those that occur in the communication and process co-ordination the system is expected to support [93]. Most of the unintended errors the author described are relevant to CDSS.

In the first category the errors she describes include: 1) the interface between the computer and the practitioner may not be suitable in an environment where one needs to multitask; 2) physicians often complain about the crowded nature of the options available on the screen which may result in choosing the wrong option unintentionally; 3) some systems ask for elaborate information which could be time consuming; 4) the need to switch between screens to assimilate information may fragment the overall view of the patient; and 5) at times too much information could be difficult to go through in busy clinics. In the second category of possible errors Ash et al [93] first discusses about the inability of the CDSS to have options that will fulfil every single patient's needs. This can lead to what is known as automation bias [94,95]. The bias occurs when a practitioner makes an error by carrying out the recommendations of the CDSS without duly considering the individual patient need (by commission) or by not following the recommendations of the CDSS when it would have benefited the patient (by omission) [95]. Secondly the system may be

inflexible, for example in providing medication during an urgent need. Thirdly an order in the system (physician ordering the medication) does not mean it has been communicated to the individual carrying out the order (nurse who administers it). Such an assumption by the physician can result in miscommunication. Lastly decision support overload with too many alerts is a common problem encountered. This can lead to health professionals ignoring essential warnings that potentially could lead to harm. A term often used to describe this is alert fatigue [96]. Most of these errors described by Ash et al were identified in subsequent published studies and reviews using both quantitative and qualitative methods [97-99]. One study queried a possible rise in mortality in a paediatric hospital after implementation of a CPOE system, though this observational before and after study had several limitations [100].

1.2.3 Planning and development of computerised clinical decision support systems

In order to develop CDSS that are beneficial, at the same time have the ability to overcome the challenges described above, careful planning is essential. It is important to know what features lead to success so that effective evidence based solutions can be developed.

A review addressing the question about what components make a good clinical decision support tool found that computerised clinical decision support systems were much superior to that of manual decision support tools [101]. They also found decision support tools that are available at the point of decision making, that provide recommendations rather than assessment (example instead of displaying the cardiovascular risk for a patient if it recommends what medication should be given based on the risk score) and integrated within clinician workflow were more likely to

succeed [101]. This systematic review also considered additional features such as local user involvement and justification of decision support, by provision of reasoning (example stating why a reminder for HbA1c testing is recommended). Though these were not found to be significant, the authors concluded that they have a role in enhancing the acceptance of the CDSS among health care professionals [101].

Initially the problem should be defined [102], such as the high incidence of hypoglycaemia in hospitalised patients with diabetes and associated poor clinical outcomes (chapter 4). The identified need should have effective solutions that could be enhanced by CDSS. For example, in the case of hypoglycaemia if the electronic observation were to show severe or recurrent hypoglycaemia, I will explore the possibility of alerting diabetes specialist team. Similarly at a population level I will explore if it is feasible to have quality assurance at hospital or ward levels on how well they are preventing or managing hypoglycaemia. In addition one should consider if such approaches are likely to be successful in terms of effectiveness when measuring clinical outcomes and efficiency when measuring institutional outcomes. If previous studies haven't demonstrated effectiveness or efficiency then evaluation methods should be in place to assess them.

Once the problem and the need for CDSS are determined, the type of CDSS should be determined. This may be an alert based on simple logical sequence, or could involve set of rule based system or algorithm as often used in electronic guidelines or complex regression prediction models to identify those with poor clinical outcomes (chapter 5).

1.3 Main aims and objectives of the thesis

The overarching aim of the study is to determine the role of health informatics, in particular CDSS in the care of hospitalised patients with diabetes. This will be

explored : 1) using existing literature; 2) through analysing data from a locally developed Prescribing Information and Communication System (PICS) to identify problems; 3) by emphasising need for health informatics (CDSS) as a potential solution; and 4) by examining or developing potential CDSS tools that could improve care for the patients with diabetes.

Specific objectives are to:

- Examine the current evidence on the role of computerised clinical decision support systems in the care of hospitalised patients with diabetes (Chapter 2)
- Determine the frequency of underreporting of diabetes as a discharge diagnosis using electronic prescription data in University Hospital Birmingham (Chapter 3)
- Study the association between hypoglycaemia and mortality / length of stay in admissions with diabetes in University Hospital Birmingham (Chapter 4)
- Determine the frequency of non diabetic hypoglycaemia in University Hospital Birmingham (Chapter 4)
- Describe indicators of inpatient “glucose control” using electronic observations of point of care blood glucose in admissions at University Hospital Birmingham (Chapter 4)
- Study the association between foot disease in admissions with diabetes and length of stay / mortality (Chapter 5)
- Develop a model to predict admissions with diabetes that result in excessive length of stay or death using data from patient administration system and electronic prescribing system (Chapter 5)

CHAPTER 2

Computerised clinical decision support systems in the Care of Hospitalised Patients with Diabetes: Systematic Review

2 Computerised clinical decision support systems in the Care of Hospitalised Patients with Diabetes: Systematic Review

2.1 Background

In the introduction the rising number of hospital beds occupied by patients with diabetes [14,15,103] and their poor clinical outcomes were discussed [16-31]. Current guidelines published by the ADA [104] and NHS Diabetes [47] have recognised the above issues and have put forward key actions that need to be incorporated into inpatient care for patients with diabetes. These actions are to ensure (1) better control of blood glucose without increasing the risk of hypoglycaemia, (2) safe and effective use of insulin and (3) improved quality indicators in caring for hospitalised patients with diabetes. The use of electronic health records and prescriptions has been cited as key strategies to provide an efficient inpatient diabetes management programme in these guidelines.

As stated in the introduction for this review CDSS are described as information systems designed to assist and improve clinical decision making [72]. I also stated CDSS have been shown to reduce prescription errors, increase adherence to guidelines, improve physician performance and enhance surveillance and monitoring of patients across a wide variety of patient conditions [72,85,87,105,106]. However a review into these systems in improving care for hospitalised patients with diabetes has not been conducted to support implementing them efficiently.

To assist diabetes teams and service commissioners putting into practice CDSS the available evidence was systematically reviewed to determine the role and effectiveness of CDSS in improving care of hospitalised patients with diabetes in the non critical care setting.

2.2 Methods

A systematic review aims to adhere to an explicit and stated method to minimise bias by critically appraising and synthesising the evidence for a clearly defined question [107,108]. Once the research question is defined the key steps defined by Centre for Review and Dissemination (CRD) [109] which I have followed in conducting this systematic review are:

- A clear search strategy
- Inclusion and exclusion criteria
- Data extraction
- Quality assessment
- Synthesis of the data

2.2.1 Search strategy

I searched for CDSS interventions in secondary care for patients with diabetes or hyperglycaemia in MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO) and the Cochrane Library (Wiley). Keywords and free text search were conducted in all these databases. Search terms for CDSS are often poorly defined [110]. Further health informatics tools that are beneficial for inpatient care but that may not fulfil the exact definition of CDSS may be missed. Therefore multiple terms that may identify the interventions under interest were used. These included ‘informatics’, ‘computers’, ‘decision support’ and ‘computerised physician order entry system’ (a detailed search strategy is given in appendix 2.1). I did not set search limits based on study design, study outcome, language or peer reviewed journals. The search was limited from 1970 to 2010 (EMBASE, CINAHL and Cochrane August 2010 and MEDLINE December 2010). My secondary search strategy included searching bibliographies of

all included studies and a search in selected journals in the fields of diabetes and health informatics using available search engines in their respective websites.

2.2.2 Inclusion criteria

Inclusion criteria were defined based on population, intervention, comparator and outcome. The population were hospital patients with diabetes or hyperglycaemia. This review did not exclude children with diabetes, pregnant women with gestational diabetes or patients diagnosed during admission. The setting was limited to in-patient non critical care. The decision to exclude intensive care settings was taken on the basis they differ in their goals in treating hyperglycaemic patients and that almost all interventions are related to computerised / computer based protocol driven continuous insulin infusions. A review into these types of devices in this care setting already exists [111].

Interventions were defined based on the description of CDSS [72] stated in the background. Even though the comparator was set to that of no CDSS I included surveys that were valuable for planning diabetic care where both reviewers agreed. Outcomes were either beneficial or harmful effect in relation to glucose control, use of insulin, patient satisfaction, length of stay and quality of diabetic care.

Studies that reported preliminary data of another included study were excluded. Case reports or case series with fewer than 5 patients, studies specific for outpatient setting, and inpatient experiments used for the sole basis of a controlled environment were also excluded. The inclusion criteria checklist is given in appendix 2.2.

2.2.3 Data extraction and assessment of study quality

Titles and abstracts of all studies identified were reviewed by two independent members of the research team (the author and JJC). Papers identified as relevant or

of uncertain relevance based on the abstracts were further independently evaluated by both the researchers. Any discrepancies between the two reviewers were resolved by discussion. Reasons for exclusion were documented.

The data extraction and quality assessment of the studies were done by author and individually checked by JJC and YFC for accuracy and to identify any missing information. The data extraction form used was a modified version of the template from the CRD guidance for systematic reviews and included quality criteria according to its guidelines [109]. Many studies were based on before and after analyses, either as retrospective observational studies or as prospective interventional studies. The most useful classification system to grade such studies was the one produced by the Australian National Health and Medical Research Council (NHMRC) [112]. The data extraction form used is given in appendix 2.3.

2.2.4 Data synthesis

A meta-analysis was not carried out due to the variety of different outcome measures, poor quality of the studies and due to the heterogeneous nature of the interventions. Therefore I did a narrative synthesis by tabulation based on the interventions, textual description clustered on the basis of outcome and by developing the theory on how the interventions work.

2.3 Results

In the primary database search a total of 2,057 references were identified. After duplicates were excluded there were 1,110 articles for which titles and abstracts were screened by author and JJC. After discussion between author and JJC, 63 articles were identified for possible inclusion. After review of all 63 full texts by author and JJC, 11 studies meeting the full inclusion criteria were identified [113-123].

Another 3 articles meeting the inclusion criteria were identified through the secondary searches [124-126] (Figure 2.1). Eleven studies were from United States, two from Germany and another from Israel.

2.3.1 Quality of studies

Two of the studies were cluster Randomised Controlled Trials (RCT) [115,124]. Another 8 studies were before and after analysis [114,116,119,120,122,123,125,126] however only one of them was a planned interventional study [116] and another a prospective analysis of observational data [126] while all others were retrospective analysis of observational data. Of the remaining studies one was a case series [117] and the other 3 observational descriptive studies [113,118,121]. Both the RCT evaluated computerised provider order entry (CPOE) as an individual component where as all the before and after analytical studies had the CDSS as one component of a complex intervention and were also prone to change in secular trends and regression to the mean (table 2.1). One RCT looked at a computerised insulin ordering template alone [124] whereas the other had a CPOE with built-in components on prescription, investigations and diet orders, referral indication, and discharge orders [115].

Figure 2.1: Study selection flow chart

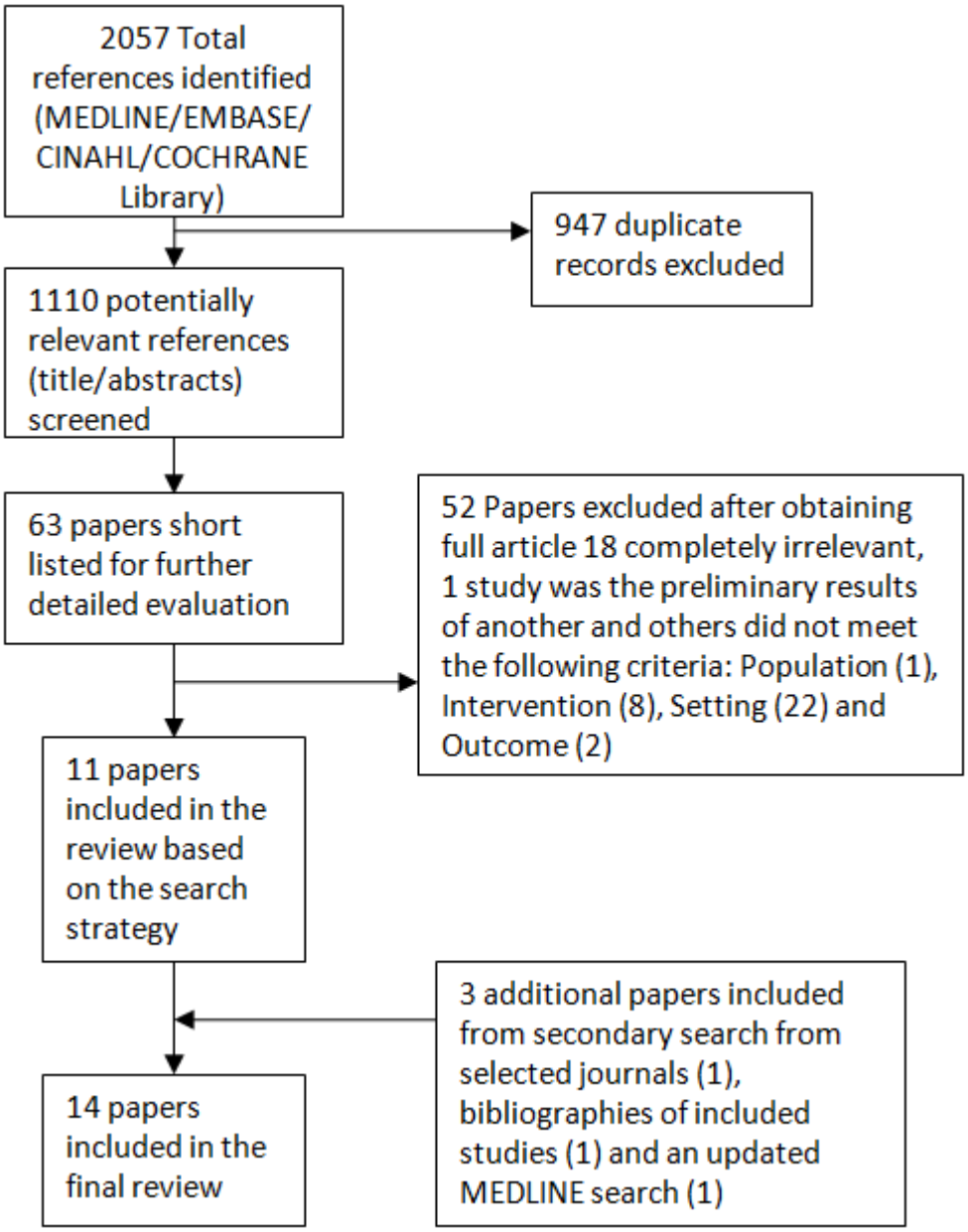


Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design #	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
Wexler, 2010 [124]	Cluster RCT	II	Electronic Insulin Order Template	**Inclusion criteria –** Patients prescribed insulin by 7 internal medicine team between a period of 30th Apr 2009 to 27th May 2009. Exclusion criteria - Patients with type 1 diabetes (n=11) and type 2 diabetes with blood glucose between 60 and 180mg/dL (because the order set was designed to apply to hyperglycaemia in patients with type 2 diabetes without other risks for hypoglycaemia (i.e.liver or renal failure)). **Random allocation of clusters –** Using a computerized coin toss, 7 teams were assigned either to have the option to use the order template (Intervention) or to use the usual insulin ordering (control). **Allocations of participants to cluster –** Participant were not randomised to the clusters. Usual admission protocol to the teams. **Blinding -** The providers prone to know who were in the intervention arm. Not clear if the patients or the data analysts were aware of this.	No	**Type of analysis** (Intention to treat analysis or protocol based analysis) – Not reported **Power calculation** - Done	**Period of Study**- One month with each patient followed till discharge. **Outcome measurement** - Similar but depend on the number of glucose measurement taken in each patient. **Drop out or withdrawals –** Non reported	**Effect of differences at baseline** - No differences **Effect of co-intervention** - Both arms were given the same educational session **Factors not included in the study** - Given the short period of the study unlikely any other factors could have affected	Patients selected are those who had a prescription of Insulin. There is possibility patients in need of insulin but not given would be left out. This would have introduced selection bias. Also likely those in the control group being aware of the intervention might have prescribed better than in usual circumstances reducing effect size of the outcome.
Guerra 2010, [123]	Observational retrospective study	III-3	Computerised Physician Order Entry Based Hyperglycaemic Inpatient Protocol (CPOE-HIP) - 3 main elements: 1. Modification of CPOE to comply with ADA guidelines 2. In service training of all nursing personnel on the details of CPOE-HIP 3. Hospital wide online availability of the HIP	**Inclusion criteria –** Patients with a previous diagnosis of type 1 or 2 diabetes. Exclusion criteria - Patients transferred from ITU and those identified as hyperglycaemic without previous diagnosis of diabetes Only a sample of the population before and after the intervention analysed. Variability in the admission patterns in the months specified could lead to bias. (Before -15 March 2006 to 11 April 2006 (1325 patient days) compared with: After - patients admitted between 3 October 2007 and 30th October 2007 (1490 patient days)).	Age (1.6 years) No information on co-morbidities	**Type of analysis and Power Calculation** - Not reported	**Outcome measurement** – Number of glucose samples per patient day similar. Also the metric used are the currently widely accepted measures for glucose control.	**Effect of differences at baseline** - No adjustment made for age but agree that clinically the difference unlikely to be important. Also note no information on co-morbidity **Effect of co-intervention** In service training of nursing staff could have affected the outcome. **Factors not included in the study** Given the data is more than year apart other changes especially national initiatives could have led to the improved changes.	The analysis is before and after and therefore subject to regression to the mean and secular trend changes.
Schnipper 2010, [115]	Cluster RCT	II	Computerised order set with components on insulin prescriptions, POC testing, HbA1c testing,	**Inclusion criteria –** Consecutive patients admitted to the general medical service (GMS) teams 1 through 4 with either known diabetes mellitus or inpatient hyperglycaemia (1 lab glucose value	No	Intention to treat analysis.	**Period of Study**- 79 days with each patient followed till discharge	**Effect of differences at baseline** Even though the co-morbidity index was not significant between the group there were a	The study was conducted in one institute with only four teams being

I (Systematic review of level II studies), II(Randomised controlled trial), III-1(A pseudorandomised controlled trial), III-2 (Comparative study with concurrent controls), III-3 (Comparative study without concurrent controls), IV (Case series with either post-test or pre-test/post-test outcomes)

Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design #	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
			hypoglycaemic orders, discharge orders and indication for endocrine consultation	>180mg/dL) Exclusion criteria - pregnant, presented with HONK, DKA, receiving parenteral nutrition, other indication for insulin, receiving palliative care or had zero POC glucose determinants **Random allocation of clusters** –Method of random allocation not reported **Allocation of participants to cluster** – Not randomised to the teams likely followed usual admission protocol. **Blinding** - The providers prone to know who were in the intervention arm. Not clear if the patients or the data analysts were aware of this.		Power calculation done.	**Outcome measurement –** Measurement of the glucose values could have been varied between patients and lead to bias in outcome measurement **Drop out or withdrawals –** None reported	higher percentage in the control group with an index of 4 or above (54%) compared to that of the intervention group (36%). When adjusting for the primary outcome this was not included. **Effect of co-intervention** Additional training and protocol for management provided for both arms equally. **Factors not included in the study** None identified	involved in the randomisation process. Method of randomisation not described. Since it is impossible to blind and because all wards were situated in the same floor with likely interaction between the staff contamination is likely to have occured.
Schnipper, 2009 [116]	Before and after study	III-2	The study intervention consisted of three components, initiated in January 2006: 1. Glycaemic management protocol 2. Diabetes education 3. Order Set: an order set, built into the proprietary computer provider order entry (CPOE) system	**Inclusion criteria –** Inclusion - Eligible subjects were patients scheduled for admission to the hospital Physician Assistant/Clinician Educator (PACE) service with either a known diagnosis of type 2 diabetes mellitus or inpatient hyperglycemia (at least 1 random laboratory glucose >180 mg/dL) Exclusion Criteria - Type 1 DM, Hyperosmolar hyperglycaemic non ketotic coma, Diabetic ketoacidosis, Total parental nutrition and patients receiving palliative care. Prospective recruitment of patients meeting eligible criteria for the study.	Case mix index was not different but difference in Charlson index was statistically significant	Intention to treat analysis Power calculation done.	**Study period and follow up-** 5 month before and after with patients followed up till discharge **Outcome measurement** – A complex primary outcome rather than the preferred patient day weighted blood glucose. The reported outcome depends on the number of measurement carried out. **Drop out or withdrawals –** None reported	**Effect of differences at baseline** Adjustment made for baseline characteristics that determine glucose control but not for the co-morbidity index (Charlson Score). **Effect of co-intervention** Impossible to separate the effect of the other two components. **Factors not included in the study** Considering this is before and after study cannot exclude initiatives that took place during the same time period would not have contributed to the findings.	Regression to the mean and secular trend change is possible considering it is a before and after study.
Maynard , 2009 [126]	Observational retrospective study	III-3	Interventions evaluated had three components: 1. Structured subcutaneous Insulin	**Inclusion criteria** Adult inpatients on non-critical care units with electronically reported point of care (POC) glucose testing from November 2002 through December 2005.	Difference noted in Case-mix index score and % with	**Type of analysis and Power Calculati**	**Baseline period** – Nov 2002 to Oct 2003 **After structured order set period** – Nov 2003	**Effect of differences at baseline** Not adjusted for case mix index however the statistical significance of the outcomes are	Regression to the mean and secular trend change is possible considering it is a before and

I (Systematic review of level II studies), II(Randomised controlled trial), III-1(A pseudorandomised controlled trial), III-2 (Comparative study with concurrent controls), III-3 (Comparative study without concurrent controls), IV (Case series with either post-test or pre-test/post-test outcomes)

Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design #	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
			Order Set (Order set introduced as paper based in Oct 2003 and then as computer based from Jan 2004 to Sep 2004). 2. Inpatient insulin management algorithm 3. Background educational programme	**Exclusion criteria** • Patients who did not have either a discharge diagnosis of Diabetes (ICD 9 codes 250-251.XX) or demonstrated hyperglycemias (fasting POC glucose >130 mg/dL, or a random value of >180 mg/dL) • Women admitted to Obstetrics To assess insulin usage insulin orders were audited. Monthly 70-90 orders were audited	any intensive care unit days.	**on** - Not reported	to Apr 2005 **After structured order set and protocol period** – May 2005 to Dec 2005 **Outcome measurement** – Primary analysis for hyperglycaemia and hypoglycaemia included most data available. A secondary analysis has also been conducted to validate the findings using data obtained from those with 8 or more POC BG.	highly significant. **Effect of co-intervention** The inpatient management protocol could explain the difference seen after its implementation. Equally there was likely background educational programme going on throughout which may explain some of the improvement that took place with the introduction of the order set alone. Beside the order set initially was paper based and therefore it is not possible to attribute the effect to computer based order set on its own.	after study
Murphy 2009 [125]	Observational Retrospective study	Not applicable	**Multi-component interventions included:** **1.** Education regarding basal bolus concept and release of Non-Intensive Care Unit (ICU) hyperglycaemia management protocol **2. Insulin order sets in electronic medical records** **3.** Guideline for inpatients on continuous tube feed	**Inclusion criteria** Analysis was carried out on patients with any code on their hospital bill for diabetes as coded by the medical record department. **Exclusion criteria** Patients with hyperglycaemia not coded as diabetes, glucose readings <40 and >400mg/dL, patients younger than 18 years and observation cases were not included in the analysis	Differences were not reported.	**Type of analysis and Power Calculation** - Not reported	**Period of data analysis** Stepwise introduction of intervention component from 2004 to 2005. Data analysis period 2003-2007 **Outcome Measurement Bias** Not clear why median was chosen as the outcome when there were large number of BG values available.	**Effect of differences at baseline** Possibly multiple considering characteristics of patients before and after are not described. **Effect of co-intervention** Many interventions reported and therefore results can be interpreted with electronic insulin order as a component of multiple interventions. **Factors not included in the study** –awareness about the inpatient glycaemic management was increased nationally during the same period	Regression to the mean and secular trend change is possible considering it is a before and after study
Achtmeyer, 2002	Observational retrospec	III-3	Modification of CPOE to prescribe insulin sliding scale according to best	**Inclusion criteria** – Insulin orders using computerised order entry. Excluded orders written by surgical providers, one time orders to	Differences were not reported.	**Type of analysis and**	**Period of study-** 34 weeks before intervention and 16	**Effect of differences at baseline** Possibly multiple considering	The intervention was poorly designed with alteration done

I (Systematic review of level II studies), II(Randomised controlled trial), III-1(A pseudorandomised controlled trial), III-2 (Comparative study with concurrent controls), III-3 (Comparative study without concurrent controls), IV (Case series with either post-test or pre-test/post-test outcomes)

Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design #	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
[119]	tive study		practice	supplement regular insulin and any orders written on wards not using full-computerised order entry. Extracted data on all electronic prescriptions for hospitalised patients (1 st Dec 1998 - 16th November 1999). Intervention 26th July 1999.		**Power Calculation** - Not reported	weeks after intervention. Shorter follow-up data after the intervention. **Outcome measurement** - There is a chance for misclassification when classifying orders before the intervention into the two categories (Traditional sliding scale orders as opposed to minimal intervention orders).	characteristics of patients before and after are not described. **Effect of co-intervention** No co-intervention reported **Factors not included in the study** - Other than the baseline characteristics it is possible any teaching, junior doctors training that might have taken place during the time could have led to the improvement reported.	later on due to physician request.
Cook, 2009 [113]	Descriptive observational study	Not applicable	Connective software to automatically transfer and analyse POC BG	**Inclusion criteria** – Adult inpatient data on POC BG from January to December 2007 were collected. Exclusion Criteria: Out-of-range values of ''LO'' (<10 mg/ dL) and ''HI'' (>600 mg/dL) were discarded. The number of HI/LO values totaled less than 0.4% of the measurements. Repeat measures, largely performed to verify hypoglycemia were found to be present for <3% of the measures and were retained in the analyses.	Not reported	Not applicable	Period of data described – 1 year **Outcome measurement –** Description is based on the acceptable glucometrics published.	Not applicable since it is purely descriptive of data show how data capture can be useful in describing outcomes.	The study only describes the ability to capture POC-BG data from multiple sites in a hospital and between hospitals. The outcomes are therefore process orientated (abilty to connect all portals and produce measures of glucose control) and not a measure of end point in achieving better glycaemic control in hospitals. However considering this is important this study has been incluced in this review.

Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design #	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
Boaz, 2009 [114]	Observational retrospective study	III-3	Program for the Treatment of the Hospitalised Diabetic Patient (PTHDP) with the Institutional Blood Glucose Monitoring System (IGMS) as an integral component	**Inclusion criteria** – Included in the study were data from all internal medicine and surgical departments and intensive care units. Data from pediatric, obstetrics, and emergency care departments were not included. Data reported are those from the 15th day of each month, starting from August 2007 to October 2008. Included were the results of any blood glucose test measured using the time stamped from 12:01 through 23:59 on the 15th day of a given month.	Not reported	**Type of analysis and Power Calculation** - Not reported	**Period of study data -** 14 months **Outcome measurement -** Bias could have been introduced depending on the frequency of measurement of BG values of each patient and difference in measurement frequency throughout the period. It also has to be noted only the 15th day of the month values were used to assess trend over time.	**Effect of differences at baseline-** Multiple considering characteristics of patients before and after are not described.. **Effect of co-intervention and Factors not included in the study -** The glucose monitoring system which is a connectivity tool to monitor blood glucose in institutions has been used for measurement of outcome and does not consist as part of the main intervention. Therefore the change cannot be attributed to the connectivity tool alone. Also due to the before and after analysis many reasons could explain the change other than the connectivity tool and the glucose control program.	Subject to Regression to the mean as well.
Thompson, 2009 [120]	Observational retrospective study	III-3	Multiple components implemented in stages over a period of 3 years. Multidisciplinary committee (Early 2003) established to develop glucose control program. The program consisted of 1) subcutaneous insulin order form (May 2004) 2) **Out of range glucose report derived electronically (Feb 2006),** and 3) Clinical Intervention team (Aug 2006)	**Inclusion criteria** – All patients hospitalised in non-critical care wards - (medical, surgical, and psychiatric). They were categorised as dysglycaemic if they 1) received subcutaneous insulin or oral diabetic medication and had any single glucose level outside the normal range of >125 mg/dL or <60 mg/dL.. All others categorised as euglycaemic.	Described difference between dysglycaemic patients and euglycaemic patients. However most outcomes (except Length Of Stay) are based on the trend in dysglycaemic patients over four years. Difference between	**Type of analysis and Power Calculation** - Not reported	**Period of data reported**- Looked at trend in prescribing and glucose control over four years. **Outcome measurement –**. There could have been many measurement error in the outcomes reported. It is not clear if all patients had blood glucose measurements done systematically. There are likely to be variation in the number of blood glucose recorded per patient and therefore the reported values	**Effect of co-intervention and factors not included in the study** As noted during the same time period there was a greater emphasis for tigher glycaemic control and appropriate insulin usage which could explain most of the changes occurred.	

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Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design #	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
					patients in each year has not been described.		will not reflect the true picture. As in any trend analysis there is a chance for Regression to the mean. The subset selected for analyses of short acting insulin is fewer in number and therefore lacks the power to detect important reductions in sliding scale insulins. The reporting for hypoglycaemic episode is inappropriate. Trend analysis has been performed to the data available after the intervention only. The author defends the increase in 2004-2005 to that of the global drive for intensive blood glucose control in in-patients.		
O'Neill, 2006 [118]	Observational Descriptive study	Not applicable	Real time data displayed in a Diabetic Dashboard, which alerts the clinician to abnormal blood glucose values for hospitalised patients	**Inclusion criteria** – Not reported. The findings reported are part of a report and poorly presented.	Not reported	**Type of analysis and Power Calculation** - Not reported	**Period of follow up-** 11 months **Outcome measurement -** The findings are reported as part of an article in the use of clinical informatic tools. No information on methods were provided.	**Effect of co-intervention and factors not included in the study** Trend could have been due to chance and many other interventions not described in this paper.	The paper was included to give a breadth of CDSS interventions that are in place. The causal relationship between the outcome and the interventions cannot be assessed due to inadequate reporting of methods used in the study.

I (Systematic review of level II studies), II(Randomised controlled trial), III-1(A pseudorandomised controlled trial), III-2 (Comparative study with concurrent controls), III-3 (Comparative study without concurrent controls), IV (Case series with either post-test or pre-test/post-test outcomes)

Table2.1 – Quality Assessment of Studies

Study	Design	Grading of study design [#]	Intervention	Recruitment of study participants	Differences at baseline	Analytical method	Follow up and measurement bias	Assessment of confounders	Additional notes
Roman, 1995 [122]	Observational retrospective study	III-3	Identification of patients with blood glucose <40 mg/dL or >450 mg/dL on two occasions or positive serum acetone >1+ through laboratory information system and reviewing documentation and management of these patients based on 4 continuous quality improvement indicators	**Inclusion criteria –** All patients with a blood glucose less than 40 mg/dL or greater than 450 mg/dL on two occasions or serum acetone >1+	Not applicable	**Type of analysis and Power Calculation** - Not reported	**Period of follow up**- 3 years **Outcome measurement** - Since the identification of patient is reliant on the laboratory system some hypo's could be missed if they are being measured on POC glucometers.	**Effect of co-intervention and factors not included in the study** Different population with no characteristics reported and muliple components in the intervention makes it difficult to decide which could have led to the improvement.	Given it is an anlysis over time without control it is subject to many bias.The trend could have been due to natural variation.
Piwernetz, 1990 [121]	Observational descriptive study	Not applicable	Clinical information system to store, retrieve and evaluate long term blood glucose monitoring data and to help identify type of diabetes patients. Three components of the information systems: **DIALIN** - Data bank designed for the use in hospitals or out clinics **CAMIT** - Diabetes management system for advanced evaluation of long-term blood glucose monitoring data. **DIACONS** - Expert system Which determines diabetes type and adequate initial therapy	**Inclusion criteria** – Not reported (Likely diabetes patients selected by a non random method to test components of the information system)	Not applicable (uncontrolled study)	**Type of analysis and Power Calculation** - Not reported	**Outcome measurement** - outcome measures were not clearly defined. Drop out or withdrawals – not applicable (not a longitudinal study)	Not applicable (the study did not evaluate clinical outcomes).	The methodology is hardly described
Schulz, 1985 [117]	Case series with pre and post test outcome	IV	Insulin dose adjustment program based on handheld computer	**Inclusion criteria** – Not reported. Included diabetes patients (primarily insulin dependant with C-peptide below 0.3 ng/ml and patients failing secondarily after oral antidiabetic therapy) admitted to the hospital for metabolic stabilisation	Not applicable (uncontrolled study)	**Type of analysis and Power Calculation** - Not reported	Methods of follow up and outcome measurement were not described.	Given the lack of a control group, regression to the mean could not be ruled out. Any changes in patient care that occurred during the study period other than the computer program could be confounding factors.	The methods of the study are poorly described.

I (Systematic review of level II studies), II(Randomised controlled trial), III-1(A pseudorandomised controlled trial), III-2 (Comparative study with concurrent controls), III-3 (Comparative study without concurrent controls), IV (Case series with either post-test or pre-test/post-test outcomes)

Results are described mainly based on outcomes as noted in glucose control and efficient insulin prescribing. Efficient insulin prescribing in this context refers to reduced errors in insulin prescription, increased use of basal insulin regimen and avoiding unnecessary sliding scale insulin. Summary of the individual study findings are categorised on the basis of types of interventions in table 2.2.

2.3.2 Glucose control

In assessing glucose control among inpatients, Point of Care Blood Glucose (POC BG) has been cited as more practical and therefore superior to that of venous sampling [127]. The ability to capture such information effectively using connectivity technology within and across hospitals was demonstrated by Cook et al [113]. Using recommended blood glucose measurement metrics [127] they were able to demonstrate difference in glucose control between Intensive Care Unit (ICU) and non-ICU settings and in between different hospitals. Boaz et al [114] in their analysis showed such an institutional blood glucose monitoring system as part of a glucose control program involving a multidisciplinary team and insulin treatment protocols can contribute to reduction in mean blood glucose and reduced hyperglycaemic events. Further description and discussion on the value of connective technology in capturing POC BG information is given in chapter 4 (section 4.4).

Both the cluster RCTs [115,124] and before and after analytic studies [116,123,125,126] commenting on the effect of CPOE involving either an insulin order template, or modification of CPOE by inserting alerts on efficient insulin prescription guidelines reported significant reduction in patient day weighted mean blood glucose concentration or similar alternative measures (mean/median blood glucose). Reported reduction in patient day weighted blood glucose ranged from 10.8 to 15.6 mg/dl (0.6 to 0.8mmol/l) from an initial/control value ranging from 158.3

to 179 mg/dL (8.8 to 9.9mmol/l). Wexler et al [124] in their Cluster RCT reported mean blood glucose (SD) reduction from 224 (57) to 194 (66) mg/dl (12.4 (3.2) to 10.8 (3.7)mmol/l). All but one [124] of these studies reported a statistically significant reduction in proportion of patients with hyperglycaemia. A case series using an insulin dose adjustment programme [117] and an active case finding approach using an information system [118] also reported reduction in mean blood glucose concentration.

One observational study reported an increase in proportion of patient days with hypoglycaemia after the intervention, however the frequency of severe hypoglycaemic episodes was not different between the before and after intervention groups in this study [123].Neither of the two cluster RCTs or any other studies reported increase in hypoglycaemic events. One study reported a significant reduction [126].

2.3.3 Effective use of insulin

Greater use of basal insulin regimens was noted in all of the four studies considering this outcome [115,116,120,124] but among the three studies reporting statistical significance only one was significant. Significant reduction in use of sliding scale or unnecessary use of supplementary short acting insulin was noted in 5 [115,116,119,123,126] out of 7 [115,116,119,120,123,124,126] studies reporting these outcomes. Sliding scale refers to stat bolus doses of subcutaneous insulin, given in response to the blood glucose level and not changes to the rate of an intravenous insulin infusion in relation to prevailing blood glucose [47]. Roman et al [122] used an active case finding approach to identify in-patients with extremes of blood glucose or with positive ketones and reviewed their management. He reported improvement in quality indicators with time in two domains; 1) documentation of

capillary blood glucose; and 2) implementation and documentation of intravenous insulin infusions in needful patients.

2.3.4 Miscellaneous outcomes

Two [115,123] out of three studies showed significant increased testing for HbA1c as per hospital guidelines after the introduction of the CPOE [115,116,123]. One study reported a significant reduction in length of stay [116] whereas the other studies that reported length of stay did not identify any significant changes [115,123,124,126]. One study reported positively the validity and acceptance of information system to store and analyse data of diabetes in-patients [121] .

Table 2.2: Summary of characteristics and findings of included studies (categorised according to type of intervention)

Study	County	Design	Intervention and Description	Number of Participants*	Mean Age (Yrs)	Duration of Study	Key Outcomes #
Computerised Physician Order Entry System (CPOE) based interventions							
Wexler, 2010 [124]	USA	Cluster RCT	**Electronic Insulin Order Template**	Control - 63 Intervention - 65	Control-70 Intervention -68	1 month	**Control / Intervention / P Value** **Glucose Control** **Mean BG (mg/dL)** 224 / 194 / 0.004 **Prolonged Hyperglycaemia%(3 consecutive BG>240mg/dL)** 38 / 26 / 0.2 **Hypoglycaemia at any time <60mg/dL%** 14 / 12 / 0.7 **Severe Hypoglycaemia at any time <40mg/dL%** 1 / 0 / 0.5 **Efficient Insulin Use** **Basal insulin prescribed day of admission%** 31 / 30 / 0.9 **Basal insulin prescribed any time%** 65 / 61 / 0.7 **Basal Insulin dose (Median Units)** 16 / 18 / 0.4 **% on sliding scale insulin alone** 35 / 38 / 0.7 **Length of stay (Median)** 5 / 6 / 0.6
Guerra, 2010 [123]	USA	Observational retrospective study	**Computerised Physician Order Entry based Hyperglycaemic Inpatient Protocol (CPOE-HIP)** 3 main elements: 1. Modification of CPOE to comply with ADA guidelines 2. In service training of all nursing personnel on the details of CPOE-HIP 3. Hospital wide online availability of the HIP	Before - 241 After - 197	Before - 60.7 After - 58.1	Before -1 month cross sectional data After -1month cross sectional data	**Before / After / P Value** **Glucose Control** **Patient day weighted mean POC BG (mg/dL)** 175.5 / 164.7 / <0.001 **Hyperglycaemic patient days%** 16.9 / 13.8 / <0.001 **Patient days on target for hyperglycaemia%** 41.1 / 46.1 / <0.001 **Hypoglycaemic patient days%** 9.1 / 11.7 / <0.05 **Severe hypoglycaemic patient days%** 0.95 / 1.27 / NS **Efficient Insulin Use** **% on Insulin** 46.9 / 63.9 / <0.001 **% in compliance with guidelines on insulin initiation and modification of dose** 36.4 / 50.7 / 0.067 **% on sliding scale insulin** 22.8 / 0.5 / <0.001 **Compliance with HbA1c testing%** 37.3 / 64.5 / <0.001 **Length of stay (Mean)** 5.1 / 5.2 / NS

Schnipper, 2010 [115]	USA	Cluster RCT	**Computerised order set** with components on: Ordering diet Insulin prescriptions POC testing HbA1c testing Hypoglycaemic orders Discharge orders Indication for endocrine consultation	Control -89 Intervention – 90	Control - 65.4 Intervention -64.8	2-3 months	**Glucose Control** **Mean % glucose readings 60-180mg/dL per patient** **Patient day weighted mean POC BG (mg/dL)** **Percent patient days with any glucose** **<60mg/dL%** **<40mg/dL%** **>300mg/dL%** **Efficient Insulin Use** **Basal insulin if inpatient hyperglycaemia%** **Nutritional Insulin if inpatient hyperglycaemia and oral intake%** **Adequate initial dose of nutritional insulin%** **Supplemental insulin alone %** **Insulin order change if 2 or more previous day's glucose out of range%** **HbA1c testing during hospitalization if not available within last 30 days%** **Length of stay (days)**	**Control** 71.3 158.3 3.5 0.3 14.8 63 22 20 58 26 48 5.7	**Intervention** 74.6 148.2 6.8 0.5 7.3 76 41 67 25 37 63 6.2	**Effect Size (Adjusted)** RR=1.36 AD=12.5 OR=1.85 OR=2.54 OR=0.38 **(Unadjusted)** OR=1.8 OR=2.4 OR=8 OR=0.2 OR=1.65 OR=1.8	**P Value** <0.05 <0.05 NS NS <0.05 NS NS <0.05 <0.05 NS <0.05 NS
Schnipper, 2009 [116]	USA	Before and after study	**The study intervention consisted of three components,** initiated in January 2006: **1.** Glycaemic management protocol **2**. Diabetes education **3**. **Order Set: an order set, built into the proprietary computer provider order entry (CPOE) system**	Before – 63 After- 106	Before-63.0 After-64.7	**Prior to Intervention:** 5 months **Post Intervention:** 5 months	**Glucose Control** **Mean % glucose readings 60-180mg/dL per patient** **Patient day weighted mean POC Blood Glucose (mg/dL)** **Percent patient days with any glucose** **<60mg/dL%** **<40mg/dL%** **Efficient Insulin Use** **Basal insulin if inpatient hyperglycaemia%** **Nutritional Insulin if inpatient hyperglycaemia and oral intake%** **Adequate initial dose of nutritional insulin%** **Supplemental insulin alone %** **Insulin order change if 2 or more previous day's glucose out of range%** **HbA1c testing during hospitalization if not available within last 30 days%** **Length of stay (Hours)**	**Before** 59.1 174.7 5.5 1 81 40 22 29 56 60 112.2	**After** 64.7 164.6 6.1 1.2 91 75 45 8 56 70 86	**Effect Size** **(Adjusted)** AD=9.7 AD=15.6 OR=1.1 OR=1.1 **(Unadjusted)** OR=2.2 OR=4.5 OR=2.9 OR=0.2 OR=1 OR=1.5 **(Adjusted)** RI=-25%	**P Value** <0.05 <0.05 NS NS NS <0.05 NS <0.05 NS NS <0.05

Study	County	Design	Intervention and Description	Number of Study Participants*	Mean Age (Yrs)	Duration of Study	Key Outcomes
Maynard, 2009 [126]	USA	Observational prospective study	**Interventions evaluated had three components:** **1. Structured Subcutaneous Insulin Order Set** (Introduced as paper based in Nov 2003 and then as **computer based from Jan 2004 to Sep 2004).** **2. Inpatient insulin management algorithm** **3. Background educational programme**	**Glucose Control Assessment** **Baseline(TP1)** – 2504 patients **After structured order set (TP2)** - 4515 patients **After structured order set plus protocol (TP3)–** 2295 patients **Effective Insulin use assessment –** 70 to 90 orders sampled each month Baseline – 477 & TP1 - 499 patients	**Baseline period (TP1)–** 56 **After Structured Order period (TP2)** – 56 **After structured order set and protocol period (TP3)–** 56	**Baseline period (TP1) –** Nov 2002 to Oct 2003 **After Structured Order period (TP2)** – Nov 2003 to Apr 2005 **After structured order set and protocol period (TP3)–** May 2005 to Dec 2005	**Glucose Control** **Patient day weighted mean (mg/dL)** TP1: 179; TP1: 170; TP2: 165; RR (TP3 Vs. TP1): NA; P Value: NR **% Uncontrolled patient days (Patient day mean> 180mg/dL)** TP1: 37.8; TP1: 33.9; TP2: 30.1; RR (TP3 Vs. TP1): 0.79; P Value: <0.005 **% Uncontrolled patient stay** TP1: 41.5; TP1: 37.6; TP2: 34.2; RR (TP3 Vs. TP1): 0.84; P Value: <0.005 **% Hypoglycaemic patient days (<60mg/dL)** TP1: 3.8; TP1: 2.9; TP2: 2.6; RR (TP3 Vs. TP1): 0.68; P Value: <0.05 **% Hypoglycaemic patient stay** TP1: 11.8; TP1: 9.7; TP2: 9.2; RR (TP3 Vs. TP1): 0.77; P Value: <0.05 **% Severe hypoglycaemic patient days (<40mg/dL)** TP1: 0.74; TP1: 0.52; TP2: 0.57; RR (TP3 Vs. TP1): 0.77; P Value: NS **%Severe hypoglycaemic patient stay** TP1: 2.9; TP1: 2.1; TP2: 2.4; RR (TP3 Vs. TP1): 0.82; P Value: NS **Efficient Insulin Use** **Sliding scale insulin %** TP1: 72; TP1: 26; TP2: NR; RR (TP3 Vs. TP1): ; P Value: <0.0001 **Length of stay (Days)** TP1: 4.6; TP1: 4.6; TP2: 4.8; RR (TP3 Vs. TP1): ; P Value: NS
Murphy, 2009 [125]	USA	Observational Retrospective study	**Multi-component interventions included:** **1.** Education regarding basal bolus concept and release of Non-ICU hyperglycaemia management protocol **2. Insulin order sets in electronic medical records** **3.** Guideline for inpatients on continuous tube feed	Analysis done on blood glucose values. Number of values ranged from 29 591(2003) to 48 965 (2007)	Not reported	Stepwise introduction of intervention component from 2004 to 2005. Data analysis period 2003-2007	**Glucose Control** **Median Glucose Level** – Before 159mg/dL (2003) to After 135mg/dL (2007) **Hyperglycaemia –** (% Patients with a measurement of >180mg/dL in a day) Before 66% After 53% **Hypoglycaemia** - (% Patients with a measurement of <60 mg/dL in a day) Before 6% After 6%
Achtmeyer, 2002 [119]	USA	Observational retrospective study	**Modification of CPOE** to prescribe insulin sliding scale according to best practice	Prescriptions of insulin: Pre-/ Post-intervention (n= 1007/n=398)	Not reported	34 weeks before (Dec 98 to Aug 99)and 16 weeks after (Aug to Nov 99)	Sliding scale insulin orders as a proportion of regular insulin prescription reduced from 97.1% to 63.8% (P<0.001). (Denominator are insulin prescriptions and do not include prescriptions for oral medications).
Connectivity technology based interventions (POC blood glucose values transferred to a central information system to analyse)							
Cook, 2009 [113]	USA	Descriptive observational study	**Connective software** to automatically transfer and analyse POC BG	12,559,305 POC-BG values from 1,010,705 patients	Not reported	1 year (Jan to Dec 2007)	Ability to describe glucose control for a given period: **1. Patient-day-weighted mean POC-BG** Non-ICU 166 mg/dL and ICU - 165 mg/dL **2.Hyperglycaemia -** Proportion of patient-days with a patient-day-weighted mean POC-BG >180 mg/dL - 31.3% in non-ICU and 26.3% in ICU. **3. Hypoglycaemia Proportion of patient days with a recorded BG** <70 mg/dL -3.5% of patient-days in the non-ICU and 10.1% of patient-days in the ICU setting. **4.Relationship between hospital patient-day-weighted mean POC-BG values and specific hospital characteristics:** ICU - Hospitals with <200 beds had significantly higher patient-day-weighted mean POC-BG levels than those with 200 to 299 beds (P < 0.05), 300 to 399 beds (P < 0.01), and 400 beds (P < 0.001). Rural hospitals - higher patient day- weighted mean POC-BG values compared to urban community and academic hospitals (both P < 0.001). Similar less pronounced differences in non-ICU.
Boaz, 2009 [114]	Israel	Observational retrospective	Program for the Treatment of the Hospitalised Patient having diabetes with the **Institutional Blood Glucose Monitoring System (IGMS)** as an integral component	5951 POC-BG values	Not reported	14 months (Aug 2007 to Oct 2008)	**1) Mean blood glucose** prior Vs after program: 206 vs. 186 mg/dl, (p < 0.0001). **2) Hyperglycaemic events** (> 300 mg/dl) prior Vs after program: 16.2% Vs 10.2% (p < 0.0001) **3) "In target"** values (between 80 and 200 mg/dl) prior Vs after program: 55.4% Vs 61.6% (p < 0.0001) **4) Hypoglycaemic events** (<60 mg/dl) prior Vs after program: 1.48 Vs. 1.4%. (p = 0.2).

Active case finding of in need patients using information systems							
Thompson, 2009 [120]	USA	Observational retrospective study	Multiple components implemented in stages over a period of 3 years. Multidisciplinary committee (Early 2003) established to develop glucose control program. The program consisted of 1) subcutaneous insulin order form (May 2004) 2) **Out of range glucose report derived electronically (Feb 2006),** and 3) Clinical Intervention team (Aug 2006)	18 088 Dysglycaemic patients	48.4 years for all four years	4 years (Jan 2003 to Dec 2006)	**Glucose Control** **1)** No significant decline in hyperglycaemia over 4 years **2)** % of hypoglycaemia increased from 2003 to 2004. From 2005 significant decline (P=0.003). 3**)** % dysglycaemic patients receiving basal insulin increased (≈ 10% to 27%) **Efficient Insulin Use** **4)**. % dysglycaemic patients receiving short acting insulin increased (≈ 35% to 52%). **5)** The ratio of short acting to basal insulin decreased from 3.36 (2003) to 1.97 (2006). **6)** Subset random analysis of 100 case notes - Reduction in sliding scale insulin from 16% to 4% and an increase in prandial correction dose from 8% to 32%. **7)** No significant change in length of stay
O'Neill, 2006 [118]	USA	observational descriptive study	Real time data displayed in a **Diabetic Dashboard**, which **alerts** the clinician to abnormal blood glucose values for hospitalised patients	Not reported	Not reported	11 months	Mean blood glucose level reduced from 171.6 to 158.2 mg/dl with fewer "diabetes related health complications"
Roman, 1995 [122]	USA	Observational retrospective study	Identification of patients <40 mg/dL or >450 mg/dL on two occasions or positive serum acetone >1+ **through laboratory information system** and reviewing documentation and management of these patients based on 4 continuous quality improvement indicators	**Eligible for:** **Quality Indicator 1 and 2** - (1989) -101 , (1990) -90 and (1991)- 135 patients **Quality Indicators 3 and 4 -** (1989) -52 , (1990)- 48 and (1991) -50 patients	Not reported	3 years	**Quality Indicator 1 - Documentation of Capillary Blood Glucose Monitoring** (1989) -83/101, (1990) 90/90 and (1991) 135/135 p<0.001. **Quality Indicator 2** - **Appropriate response to hypo and hyperglycemias** (1989) -94/101 , (1990) 78/90 and (1991) 132/135 p=0.1 **Quality Indicators 3 - Implementation and documentation of intravenous insulin infusions** (1989) -23/52 , (1990) 26/48 and (1991) 46/50 p<0.001 **Quality Indicators 4 - Appropriate use and management of intravenous insulin infusion** (1989) -42/52 , (1990) 42/48 and (1991) 46/50 p=0.1
Miscellaneous clinical decision support system initiatives							
Piwernetz, 1990 [121]	German y	Observational descriptive study	**Clinical information system** to store, retrieve and evaluate long term blood glucose monitoring data and to help identify type of patients with diabetes. Three components of the information systems: **DIALIN** - Data bank designed for the use in hospitals or out-patient clinics **CAMIT** - Diabetes management system for advanced evaluation of long-term blood glucose monitoring data. **DIACONS** - Expert system which determines diabetes type and adequate initial therapy	CAMIT - 10 type 1 patients with diabetes. Acceptability of computers in hospitals - 37 discharged patients with diabetes. DIACONS validity in identifying type of diabetes –83 patients with diabetes.	Not reported	NA	CAMIT - precision of data 96% tested with 10 type 1 patients with diabetes. Questionnaire on attitude towards information system for diabetes reported "positive attitude" Type of diabetes derived by DIACONS was 94% identical to that of the judgement of two experts.
Schulz, 1985[117]]	German y	Case series	Insulin dose adjustment program based on handheld computer	10 inpatients	Not reported	7 days	Mean blood glucose value dropped from 194 mg/dL to 136 mg/dL in 5 days among inpatients.

*individuals unless specified otherwise (example: prescriptions, blood glucose values)

BG –Blood glucose, POC BG – Point of care blood glucose, RR-Relative risk, AR – Absolute difference, OR – Odds ratio, RI – Relative increase, NR – No results available, NA – Not applicable, NS – Not significant

2.4 Discussion

There is consistent evidence that CDSS can improve glucose control in inpatients and reduce sliding scale insulin use and to a more limited extent promote basal-bolus insulin regimen. However the studies are sub-optimal in quality and often the intervention is part of a complex programme making it difficult to attribute the effect solely to the CDSS alone. Active case finding of patients with diabetes in need of specialist team review utilising information systems can be useful but there were no clear criteria or mechanisms on how this can be achieved.

The findings can be explained by exploring the mechanisms by which CDSS could lead to improved care for patients with diabetes (Figure 2.2). Reviews [85,89,128,129] have shown change in prescription behaviour and better compliance with guidelines where CPOE systems have been utilised. This should lead to efficient prescription of insulin and oral hypoglycaemic agents which in turn will result in avoidance of inappropriate sliding scale insulin and increased basal insulin regimen prescriptions. Reduction in adverse drug events have been shown to reduce with CDSS system used for prescription of other medications [83,87,130]. Considering insulin prescriptions are prone to error and often can lead to harm [36] an efficient CPOE will negate these adverse events.

Connectivity technology where POC BG results can be automatically integrated into the laboratory system will enable monitoring of hospital performance and thereby enhance actions to improve care. It will also allow for an online quality control program to validate the performance of POC BG meters [131]. Soon systems can also be instrumental in actively identifying patients that need to be managed by the multidisciplinary diabetes team. At present diabetes teams depend on inpatient

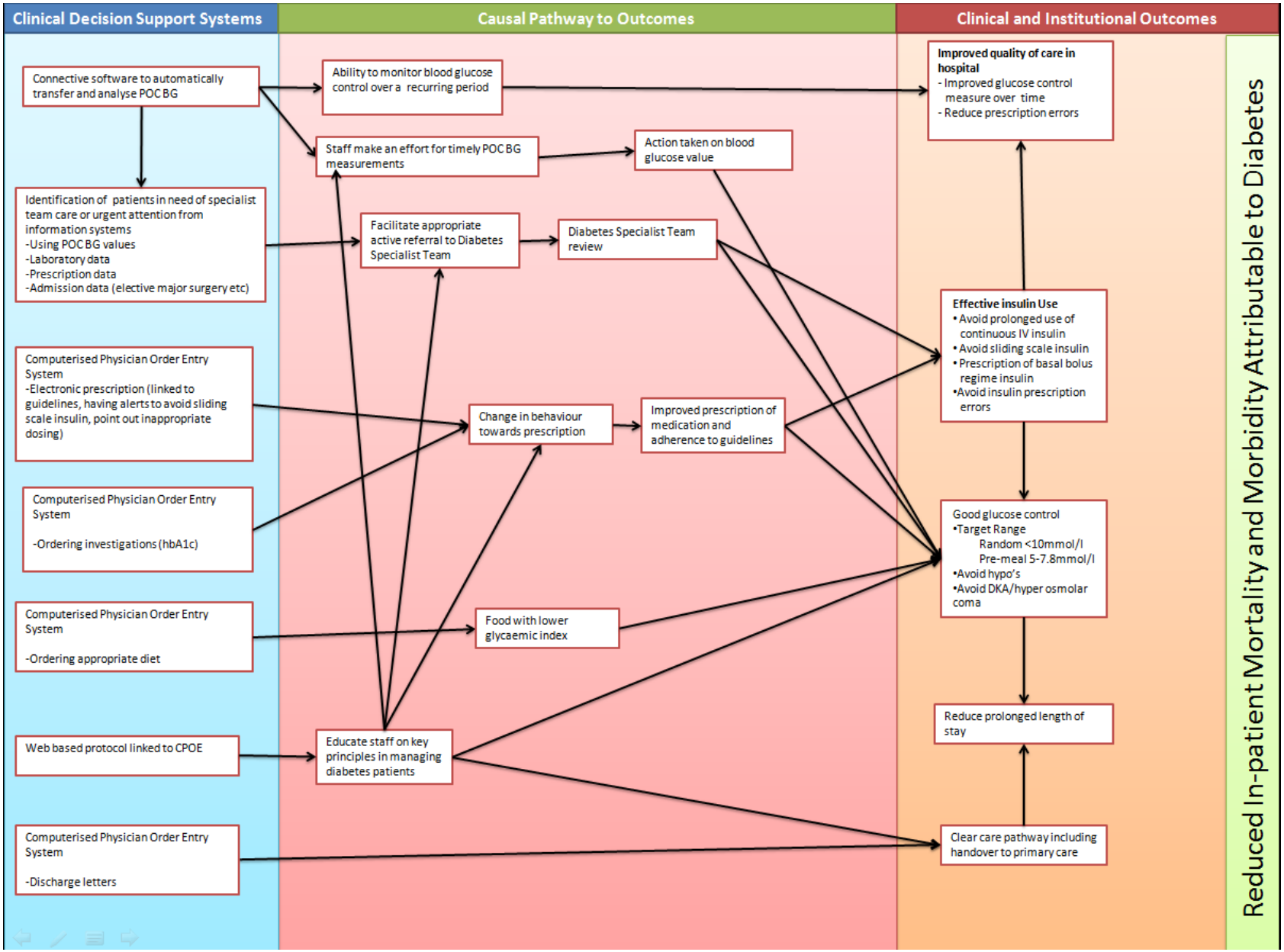
referral from other teams to intervene in patients needing their expertise. Information systems [118,120,122] and electronic referrals can be utilised to provide efficient referral to specialist teams. Previous studies have demonstrated better patient outcomes and reduced length of stay where, for example, diabetes specialist nurses have been utilised in the care of patients with diabetes [132,133].

On the other hand not all electronic alerts are adhered to [134] and provision of the CDSS does not guarantee staff engagement or uptake of the system [135]. Even more often social, organisational and contextual characteristics are overlooked when implementing such systems [136]. In designing CDSS it is important they are not only based on evidence but take consideration of these factors to increase health care provider's adoption and to reduce prescription errors.

The main strengths of this review are its clearly defined search strategy and its inclusive approach in the types of interventions studied. The search strategy had few limits, spanned across all languages and included a secondary search strategy to minimise the chance of missing a relevant study. However most of the studies were from USA with only a few from elsewhere. Considering many European countries have implemented CDSS as well it was surprising to note the lack of evaluation of these systems in diabetes care. Therefore the existence of publication bias cannot be ruled out. The studies often contained a before and after analysis without a concurrent control group. The interventions were often part of a complex strategy such that it was not possible to identify specifically the impact the CDSS has had on diabetes care. A previous review on the quality of studies reported in CPOE suggested time series analysis and regression-discontinuity analysis as alternative to randomised controlled trials where they are not pragmatic to conduct [110]. We were also not able to carry out a meta-analysis on the impact such system have on control

of blood sugar since the interventions were heterogeneous and the outcomes were reported in different metrics. The challenges we faced are similar to other reviews in CDSS [110,137]. Nevertheless the review identifies pragmatic approaches that can be incorporated into an efficient information system to maximise the care for hospitalised patients with diabetes.

Figure 2.2: Mechanism through which CDSS improve diabetic care in hospitals



2.5 Conclusions

In the UK, electronic health records and CDSS have been increasingly implemented in the last decade within hospital setting. The findings of the study should help diabetes care providers to decide on the elements that need to be incorporated into the CDSS. These include (1) implementing validated alerts and guidelines on prescriptions of antidiabetic medications especially insulin, (2) planning ahead to capture POC BG values into their information system to provide timely care and monitor hospital performance, and (3) identifying referral criteria that can be incorporated into the CPOE to target patients with diabetes in need of specialist team input. Guidance on safe insulin prescription and glucose parameters to include in the alerts for hypoglycaemia are available from the Joint British Diabetes Society guidelines [47,48]. Future studies evaluating CDSS should consider improving their methodology to study them within a complex programme in a controlled environment.

CHAPTER 3

Electronic prescription data can be useful in finding ‘lost’ discharge codes for diabetes

3 Electronic prescription data can be useful in finding ‘lost’ discharge codes for diabetes

3.1 Background

In the first chapter we noted hospital admissions of patients with diabetes have been increasing steeply in parallel with the increasing prevalence of known diabetes in the general population. Research has also highlighted the financial implication of diabetes related hospital admissions, currently estimated to be about 12% of total hospital expenditure [103,138]. An accurate assessment of inpatient prevalence of diabetes is critical for effective planning of hospital diabetes services. The National Diabetes Inpatient Audit (NaDIA) for 2010 and 2011 found that 15% of audited beds were occupied by people with diabetes [14,15] . However current systems for data capture do not provide this level of accuracy, and appear to under-estimate the actual prevalence of hospitalised patients with diabetes. Anwar et al [139] linked primary care data to hospital data in Scotland and Whitston et al [42] linked Hospital Episode Statistics (HES) to the National Diabetes Audit (NDA) data in England and they estimated that underreporting occurred in 41% and 33% respectively of admissions with a diabetes diagnosis.

As a result national bodies (in England) have asked for systems to be designed and implemented to improve diabetes-related discharge diagnostic coding [140]. Although the data linkage methodologies used in the analyses described above are useful for estimating diabetes underreporting, they are inadequate for real-time correction of missed diagnostic codes. I aimed to estimate the frequency of missed discharge diagnostic codes for diabetes using inpatient electronic prescription data and also to look at the feasibility of this approach in real-time correction. Based on

the correction I also aimed to estimate the impact it would have on diabetes related payments to the hospital Trust.

3.2 Methods

3.2.1 Population and health information systems

University Hospital Birmingham (UHB) is a large (approximately 1200 bed) teaching hospital based in the West Midlands, UK which delivers secondary care services to the adult population of South Birmingham. However given that it is a tertiary hospital, patients are admitted from across the West Midlands region and beyond. Furthermore UHB is the main hospital in UK that provides care for military personnel (Royal Centre for Defence Medicine). A separate hospital (Birmingham Women's Hospital) situated close to UHB provides women's health services and another hospital (Birmingham and Solihull Mental Health NHS Foundation Trust) provides mental health services. A children's hospital is situated a mile away and provides health care for children below the age of sixteen (Birmingham Children's Hospital). These are not part of the services provided by the UHB.

Inpatient admissions, aged 16 years old and older were identified using the Patient Administration Database (PAS) in the period 2007 to 2010 inclusive (4 years). The PAS database record information on age, gender, ethnicity, address (post code), admission, discharge and transfers, number of consultant episodes, inpatient death, type of admission, and discharge destination. Admission is defined as the time spent by an individual from recorded time of entry to recorded time of exit from the hospital, irrespective of the number of 'finished consultant episodes' the patient had during the entire stay. Elective and emergency care admissions were included; regular day attendees and day cases were excluded from the analysis.

The PAS database was linked using unique patient identifiers (hospital number) and admission date/ time to a locally-developed electronic prescription computer system (Prescribing, Information and Communication System or PICS) which records all inpatient prescriptions. It is a purpose-designed system which also records laboratory results and electronic observations and generates alerts to reduce prescription errors and notify abnormal blood results [141]. Considering most of the analyses carried out required information from the PICS database (for example prescriptions, electronic observations and blood results), only data that we were able to link has been used for analyses throughout this thesis.

3.2.2 Categorising diagnosis of diabetes

Initially an admission was defined as having diabetes mellitus if they had an International Classification of Diseases version 10 (ICD-10) diagnostic codes of E10-E14 or any of their sub classifications in the PAS database. I then interrogated the PICS audit database looking for admissions that were prescribed diabetes related medication. Medications included were from chapter 6.1 of British National Formulary [142] including all types of insulins, suphonylureas, biguanides and other anti-diabetic medications. Patients were categorised as having diabetes based on this prescription data if they were on any of the medications used for diabetes and did not meet the following exclusion criteria: 1) patients on metformin alone with a discharge diagnostic code for polycystic ovarian syndrome, or 2) patients who received short or rapid acting insulin only (unless clearly specified it was for DKA or Hyper-Osmolar hyperglycaemic Non-Ketotic coma (HONK)). The latter exclusion criterion was chosen on the basis that some patients have been noted to receive insulin infusions for optimal blood glucose control in acute illness (intensive care

units) despite recent contrary evidence of benefit [143-145] or may have received these treatments for correction of hyperkalaemia.

3.2.3 Comparison of admissions with diabetes who had and did not have a discharge diagnostic code for diabetes

I compared the demographic characteristics, admission type, use of insulin, co-morbidities (using the Charlson score[146]) and length of stay of patients who had discharge diagnostic code of diabetes and those who did not have but were identified through their prescribed medication. Demographic characteristics included were age, gender, ethnicity and deprivation quintile. Deprivation quintiles were defined using disaggregated income deprivation score rather than the entire Indices of Multiple Deprivation (IMD) score [147]. Income deprivation is often preferred in health care research considering the entirety of IMD includes health related domains, which can mask or exaggerate the effect size when studying health outcomes. Where analyses were limited to admissions with diabetes, as is the case in most parts of this thesis, I modified the Charlson co-morbidity score [146] to identify burden of co-morbidities other than diabetes by excluding the scores linked with diabetes [58]. Charlson co-morbidity score was categorised as those with a score of 0, 1 and 2 or more.

3.2.4 Cost of missed discharge diagnostic codes for diabetes

In order to assess the financial impact of potentially missed diabetes codes on the inpatient tariff, I added the diabetes code to the Healthcare Resource Group (HRG) for those admissions identified from prescription data alone. HRG codes group the different ICD-10 discharge diagnostic codes for each admission along with the operative procedure codes (known as OPCS codes) to derive a tariff code. For consistency for the four year period under study (2007 – 2010) I used the HRG v4

software to derive the tariff code. Whilst prescription data can sometimes inform the diagnostic coding (for example classifying patients on any oral anti-diabetic medications as having non insulin dependent diabetes mellitus (E11)), this is not true for all patients. Therefore I took a pragmatic approach and gave an ICD-10 diagnostic code of E10 (insulin dependent diabetes mellitus) if they were less than 40 years old and on Insulin and E11 (non insulin dependent diabetes mellitus) for all other admissions.

3.2.5 Statistical analysis

3.2.5.1 Descriptive analysis of all admissions

Initially a descriptive analysis was performed to identify any differences between the PAS data we were able to and not able to link with PICS. Continuous variables are described as means (standard deviation) if normally distributed and in medians (inter-quartile range) if skewed. Categorical variables are given as proportions.

3.2.5.2 Capture-recapture technique to estimate missed discharge codes for diabetes

Even by combining diagnostic codes and prescription data it is unlikely that all cases of diabetes will be captured in the linked dataset. The capture-recapture technique was therefore used to estimate the true frequency of missed diagnostic codes for diabetes [148,149]. This statistical technique was originally developed by ecologists to estimate animal populations. In an ecological setting the animal of interest are counted twice. In the first stage within a predefined area they are captured, counted then marked and released. In the second stage at a different time point in the same defined area they capture and count the total and within that they also make a note of the marked ones (subjects that were recaptured). Therefore there are three parameters: 1) captured only in the first phase (a); 2) only in the second phase (b);

3) in both phases (c). In a closed population if these two phases were to occur independent to each other then we could estimate the total (T) numbers by the following formula:

T = (a+c) * (b+c) / c

And the unknown (X) numbers by:

X= (a) * (b) / c

Since then the capture-recapture technique has been used extensively in epidemiological studies to determine incidence of disease (including diabetes) [150-154] and in evaluating the completeness of registers [155-158]. A key assumption is the independence and equal "catch-ability" of the two sources. However, in health care data there is often dependence and at times for specific reasons only one source may be able to identify the subject. For example patients with diabetes on diet control alone may not be identified by using prescribed medication lists. To overcome these limitations, dependence and unequal "catch-ability" between the two sources, I used Chao's formula [159,160]. This is given in the box below.

Box 3.1: Chao's formula

$X = f_1^2 / (2f_2)$

$N = N_{obs} + f_1^2/(2f_2)$

Where:

x = Estimate of Unknown

N = Estimate of total

N_{obs} = Number Observed

f_1 = Number of Subjects Captured once (a + b)

f_2 = Number of Subjects Captured twice (c)

The calculation of variance is by:

$$Var_N = \frac{1}{4}\frac{f_1^4}{f_2^3} + \frac{f_1^3}{f_2^2} + \frac{1}{2}\frac{f_1^2}{f_2} - \frac{1}{4}\frac{f_1^4}{(f_2^2 n)} - \frac{1}{2}\frac{f_1^4}{f_2(2f_2 n + f_1^2)}$$

I have reported the frequency of admissions with a missed diagnosis of diabetes as a percentage of admissions with diabetes estimated using the capture-recapture technique.

3.2.5.3 Analyses of admissions with diabetes with and without a discharge diagnostic code for diabetes

To investigate associations between admission characteristics and a missed discharge diagnostic code, a logistic regression model was fitted (outcome with that as missed diagnostic discharge codes), adjusting for admission characteristics. To account for multiple admissions of the same patient Generalised Estimated Equations (GEE) were used. The admission characteristics included in the model were age (years), gender, ethnicity, deprivation quintile (income deprivation score based on the patient's postcode), modified Charlson co-morbidity score, type of admission (emergency or elective), insulin use and length of stay (LOS). I checked linearity of effect for both age and LOS. The effect of age was found to be reasonably approximated by a linear relationship; whereas the effect of LOS was non-linear, but linear on the log scale. Therefore log LOS was included as a covariate (rather than LOS itself). Data were analyzed using Stata® 10 software, using the GEE class of models.

3.3 Results

There were 222,104 inpatient admissions recorded in the PAS database between 2007 and 2010 of which we were able to link 171,067 admissions with the PICS audit database (77% linkage). Admissions that were not linked in comparison to those that were linked were younger (mean age 52.4 vs. 55.8); had a lower frequency of diabetes diagnostic code (8.9 vs. 13.1%); less likely to have Charlson

co-morbidity score of 1 or more (41.7 vs. 50.8%); and had a shorter median length of stay (0.88 vs. 2.83 days) (Table 3.1).

Further description is limited to linked data. The majority (79.2%) of the admissions were from white ethnic background, with south Asians constituting 9% of the admissions. Most admissions came from the lowest two deprivation quintiles (60.7%); reflecting the higher deprivation levels in Birmingham. Two thirds of the overall admissions were emergency admissions. (Table 3.1)

Table 3.1: Characteristics of admissions identified in PAS database that were linked and not linked to PICS database

	Linked to PICS (N=171 067)	Not Linked to PICS (N=51 037)
Age in years Mean (SD)	55.8 (20.6)	52.4 (21.1)
Gender N (%)*		
Male	91 018 (53.2)	27 992 (54.8)
Female	80 038 (46.8)	23 045 (45.2)
Ethnicity %		
White	135 550 (79.2)	39 570 (77.5)
Asian	15 422 (9.0)	4 114 (8.1)
Black	5 817 (3.4)	1 702 (3.3)
Other	14 278 (8.3)	5 651 (11.1)
#Deprivation quintile %		
Most deprived 5	63 753 (38.6)	18 219 (38.2)
4	36 493 (22.1)	10 444 (21.9)
3	31 485 (19.0)	8 742 (18.3)
2	20 122 (12.2)	5 868 (12.3)
Least deprived 1	13 455 (8.1)	4 420 (9.3)
Diabetes code		
Yes	22 412 (13.1)	4 550 (8.9)
No	148 655 (86.9)	46 487 (91.1)
Charlson co-morbidity score		
0	84 074 (49.1)	29 752 (58.3)
1	36 480 (21.3)	7 324 (14.4)
2 or more	50 513 (29.5)	13 961 (27.4)
Type of Admission %		
Elective	56 601 (33.1)	16 458 (32.2)
Emergency	114 466 (66.9)	34 579 (67.8)
Length of stay Median (IQR) in days	2.83 (1.12 – 7.58)	0.88 (0.25 -3.08)

* Adds to 171 066 instead of 171 067 in the first column due to one missing value.

#Deprivation quintile is based on income deprivation score of the patient's post code. Adds to 165 308 instead of 171 067 and 47 693 instead of 51 037 respectively in the first and second column due to missing post code values.

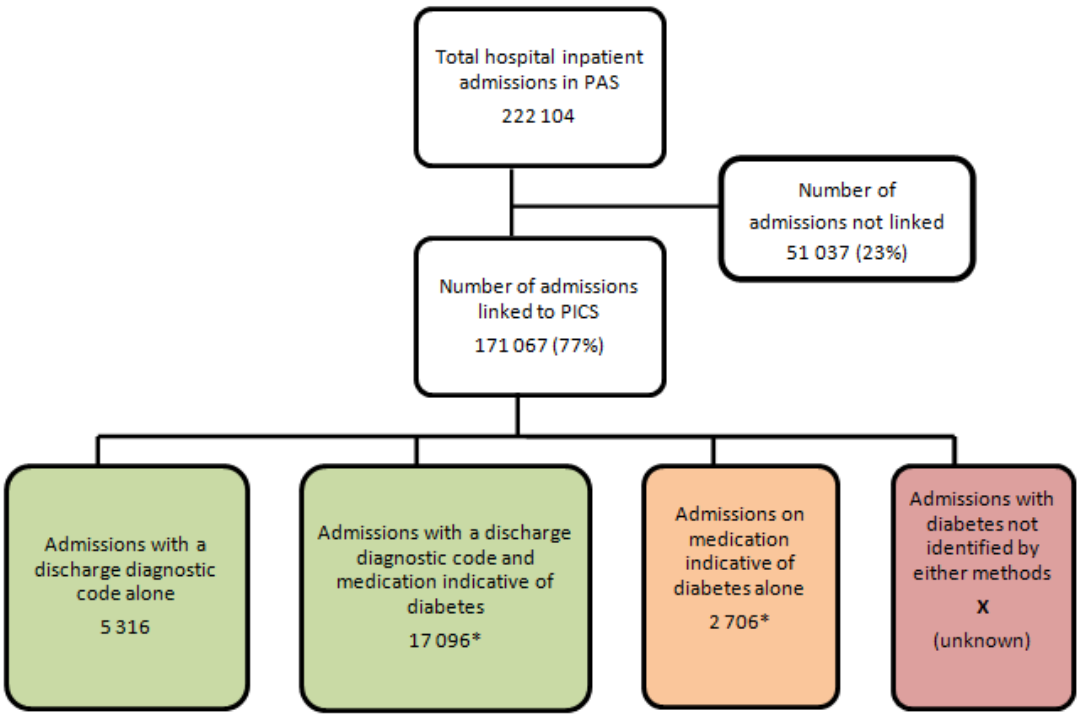
3.3.1 Determining the missing discharge diagnostic codes for diabetes using electronic prescription data

Among the 171,067 linked admissions, 22,412 (13.1%) were coded with diabetes at discharge (Table 3.2 and Figure 3.1). On the other hand in the prescription data there were 26,017 admissions that were on anti-diabetic medications, of which 19,802 met our inclusion criteria for a prescription defined diabetes admission (Figure 3.1 and 3.2). 17,096 admissions were common to both databases (Figure 3.1 and 3.2).

An additional 2,706 admissions could therefore be classified as having diabetes based on prescription data, which would increase in-patient cumulative incidence of diabetes from 13.1% to 14.7% over this period of 2007 to 2010. The total number of admissions with diabetes estimated by the capture-recapture technique suggests that the number of admissions with diabetes not captured by both lists is likely to be 1,882 (95%CI 1,765 – 1,999) which would further increase the estimated cumulative incidence to 15.8% (95% CI (15.7-15.9%) for the same period (Table 3.3).

Therefore on the basis of using capture recapture technique in the linked data I was able to estimate that the overall admissions with a discharge diagnostic code of diabetes should total 27,000 and of the 4,588 (17% of total estimated admissions with diabetes and 2.7% of all admissions) that are missed by current coding, 2,706 (60%) could be obtained from prescription data.

Figure 3.1: Patients admitted with diabetes identified through discharge diagnostic code and electronic prescription data for 2007-2010



*flow chart of the medication defined patient with diabetes are shown in figure 3.2

Figure 3.2: Flow chart for medication based diagnosis of diabetes

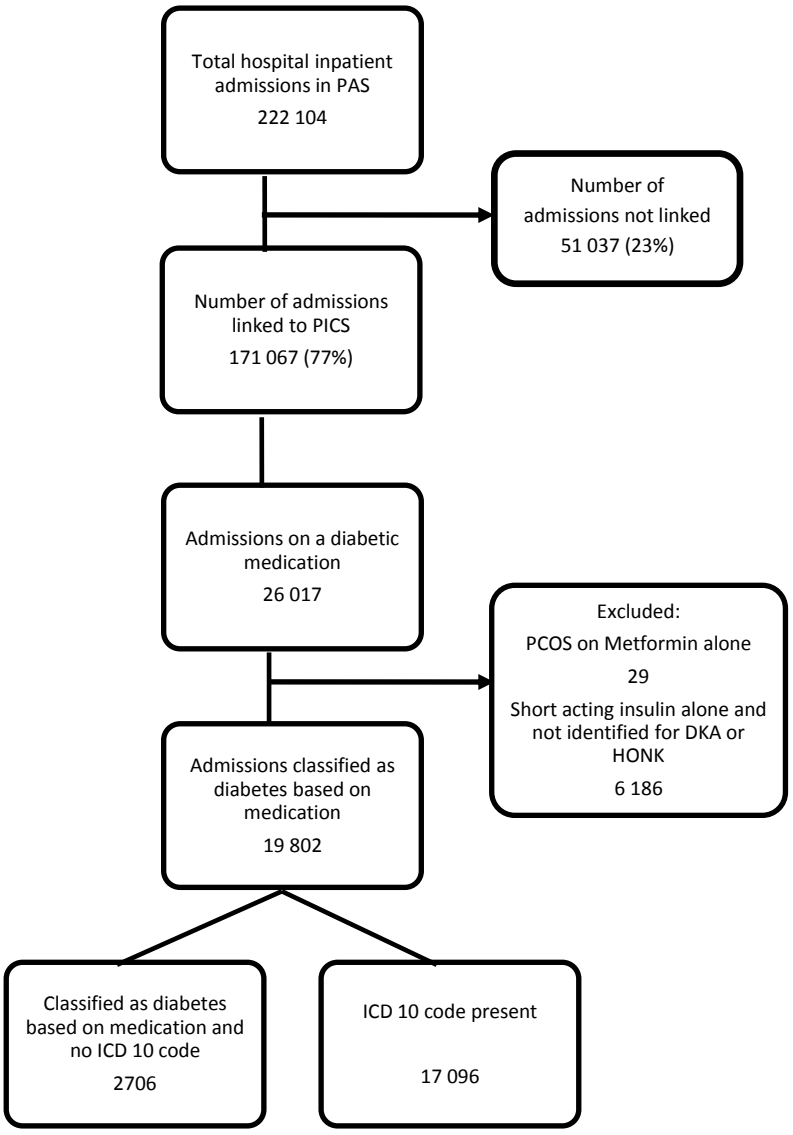


Table 3.2: Estimation of missed discharge diagnostic code and cumulative incidence using electronic prescription data

	Discharge diagnostic code present	Either discharge diagnostic code or electronic prescription present	Estimated number of admissions with diabetes and 95% CI*
Admissions with diabetes	22 412	25 118	27 000 (26 882 – 27 117)
Cumulative Incidence per 100 linked admissions$	13.1%	14.7%	15.8% (15.7% – 15.9%)

* Estimation based on two source capture recapture technique (see appendix 3)
$ Denominator 171,067 linked admissions

3.3.2 Characteristics associated with missing discharge diagnostic codes for diabetes

After adjusting for covariates missed discharge codes for diabetes that were identified only through electronic prescribing data had lower levels of co-morbidity score (Odds Ratio (OR) for score of 1 = 0.65; 95%CI 0.58-0.72 and for score of 2 or more = 0.70; 95%CI 0.63-0.77) and shorter length of stay (Median days 2.25 vs. 3.92 (P<0.001)). They were also more likely in females (OR 1.12; 95%CI 1.03-1.22) and less likely in black ethnic minority population (OR for black 0.77; 95%CI 0.62-0.96). No significant associations were found with age, deprivation quintiles, admission type and use of insulin (Table 3.3).

3.3.3 Cost implication of missing discharge codes for diabetes

Extrapolating these results we can calculate the financial impact of using prescription data to improve diagnostic coding of diabetes. By including missed diagnostic codes driven by the prescription data there would be a change to the HRG tariff code and payment in only 12.8% (347 out of 2,706) of admissions with a missing diabetes diagnostic code. If coded correctly, on average for each of these admissions, this change in tariff would have been associated with a financial gain of £550 (95%CI £500-600).

Table 3.3: Characteristics of admissions identified by a diagnostic code and those identified only through prescription data; adjusted odds ratios for missing diagnostic codes

	ICD 10 Diagnostic code present (N=22 412)	ICD 10 Diagnostic code absent (N=2 706)	Adjusted[$] Odds Ratio (OR) and 95% CI	P value
Age in years Mean (SD)	64.9 (15.1)	64.3 (15.0)	1.001 (0.998-1.003)	0.58
Gender N (%)*				
Male	12 991 (58.0)	1 507 (55.7)	1	
Female	9 420 (42.0)	1 199 (44.3)	1.12 (1.03-1.22)	**0.01**
Ethnicity %				
White	15 929 (71.1)	1889 (69.8)	1	
Asian	3 929 (17.5)	500 (18.5)	1.05 (0.93-1.18)	0.43
Black	1 223 (5.5)	108 (4.0)	0.77 (0.62-0.96)	**0.02**
Other	1 331 (5.9)	209 (7.7)	1.22 (1.04-1.43)	**0.02**
[#]Deprivation quintile %				
Most deprived 5	9 955 (45.5)	1 171 (44.7)	1	
4	4 905 (22.4)	549 (20.9)	0.97 (0.86-1.10)	0.52
3	3 741 (17.1)	481 (18.3)	1.10 (0..97-1.24)	0.09
2	2 093 (9.6)	263 (10.0)	1.08 (0.92-1.26)	0.26
Least deprived 1	1 199 (5.5)	158 (6.0)	1.11 (0.92-1.34)	0.21
Modified Charlson co-morbidity score[#]				
0	8 893 (39.7)	1 366 (50.5)	1	
1	4 904(21.9)	469 (17.3)	0.65 (0.58-0.72)	**<0.001**
2 or more	8 615 (38.4)	871 (32.2)	0.70 (0.63-0.77)	**<0.001**
Type of Admission %				
Elective	6 586 (29.4)	851 (31.4)	1	
Emergency	15 826 (70.6)	1 855 (68.6)	0.96 (0.88-1.05)	0.42
Use of Insulin %				
Yes	12 023 (53.6)	1 378 (49.1)	1	
No	10 389 (46.4)	1 328 (50.9)	1.04 (0.95-1.13)	0.39
Length of stay Median (IQR) in days[~]	3.92 (1.42–10.08)	2. 25 (1.00–7.96)	0.88 (0.85-0.91)[~]	**<0.001**

* Adds to 22 421 instead of 22 422 in the first column due to one missing value.

[#]Deprivation quintile is based on income deprivation score of the patient's post code. Adds to 21 893 instead of 22 422 and 2 622 instead of 2 706 respectively in the first and second column due to missing post code values.

[$] Adjustment made for all covariates displayed in this table and none independence between patients with multiple admissions using mixed effects logistic regression.

[~] Odds ratio is for log transformed data of the LOS. Log transformation was necessary to meet the assumption of linear association between the outcome and length of stay.

3.4 Discussion

The study suggests that in UHB, about 17% of admissions with a likely case of diabetes are missed in the PAS data. Electronic prescription data can be useful in correcting up to 60% of the missed codes at discharge. Patients with fewer co-morbidities and who had a shorter length of stay were more likely to have a missed code at discharge. However, adding a diabetes discharge code to the admissions with a missing code only made a difference to the tariff payment in 12.8% of these admissions.

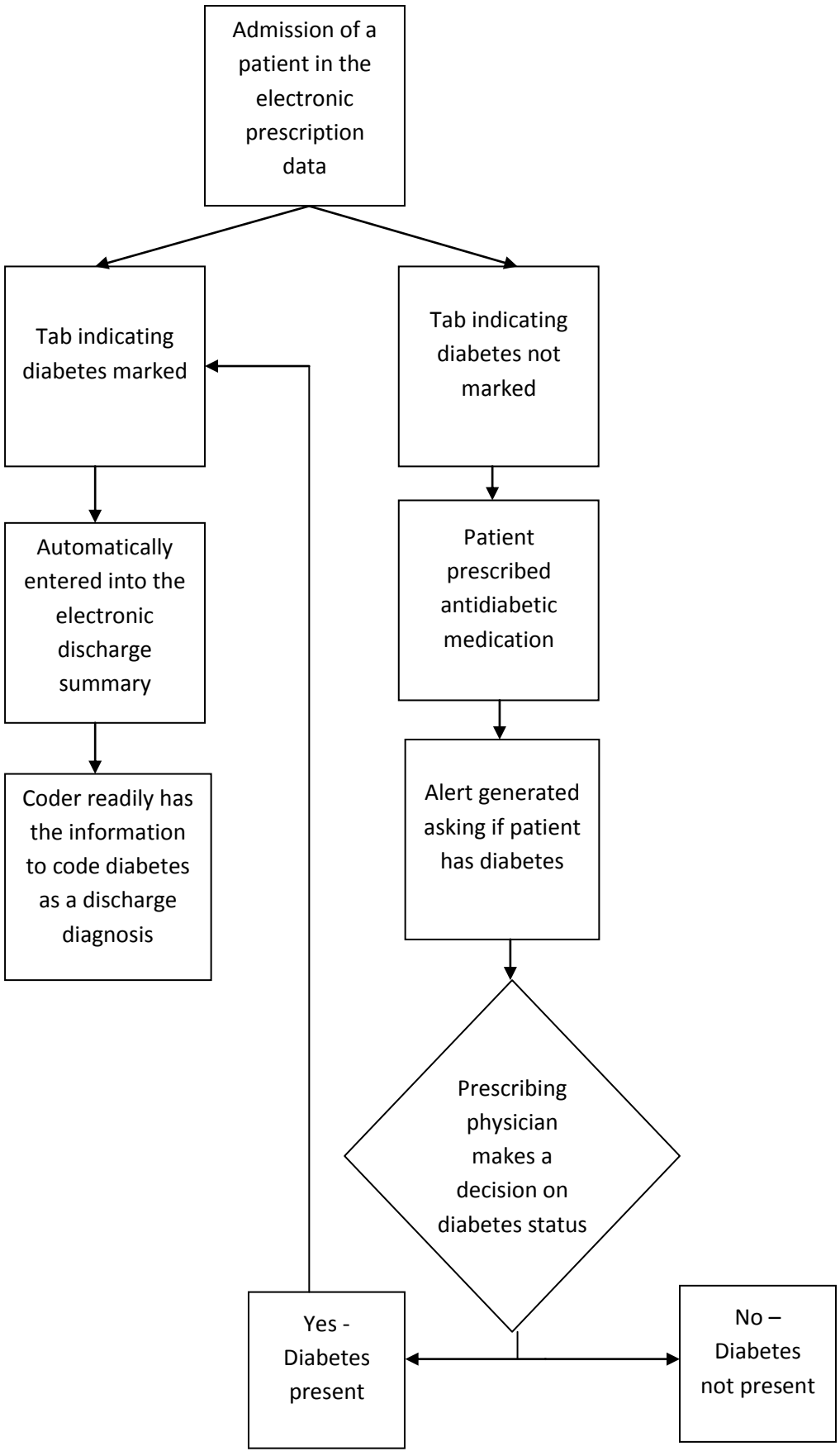
The estimate of missed discharge diagnostic code for diabetes (17%) using these novel techniques in one large hospital is lower than that of previous estimates in Scotland (41%) [139] and in England (33%) [42]. The differences could be due to a different time period, population characteristics or better coding practice by local clinical staff and coders. One advantage in UHB is the availability of electronic discharge summaries generated within the PICS system in addition to the traditionally available case notes and written discharge summaries (also known as Korner Medical Record or KMR) which may have impacted on better coding. Furthermore the England estimate also took patients who were admitted as day cases and regular day attendees, which I did not consider. The finding of the association between missed diagnosis and lower co-morbidity score and shorter length of stay is consistent with the Scottish study [139]. Adding the missed diagnostic code had only a minor impact on the tariff code (HRG) with only 1 in 8 corrected admissions resulting in any potential financial gain. This latter finding may indicate a weakness of the tariff system in costing for diabetes patients, and is supported by a recent paper where Simmons et al [161] showed that the actual cost of treating diabetes patients is far higher than the tariff that they are paid for. This

clearly indicates that any future review of tariff codes should take into consideration diabetes and similar co-morbidities with adverse hospital outcomes.

The method used to correct missed discharge diagnostic code can be undertaken in any hospital with electronic prescription data. However this will need data linkage with corrections taking place on a regular basis. Therefore I have proposed to incorporate an algorithm within the PICS system that can identify patients on a diabetic medication and clarify if these patients have diabetes or not to make a real-time impact. A flow chart of the algorithm is given in figure 3.3. This will automatically ensure that a diagnosis of diabetes is part of the discharge summary and thereby reduce the proportion of missed discharge diagnostic codes for diabetes.

This study has limitations and strengths. Not all of the inpatient admissions were linked, as many admissions with shorter periods of stay do not get entered into the electronic prescribing system. In addition the prescription source used to identify the missed discharge diagnostic codes itself may be incomplete. For example, there are difficulties in differentiating between the use of short acting insulin for diabetes and other clinical needs and in identifying patients with diabetes who are managed with diet control alone. The estimated correction of 60% may be lower if extrapolated to the whole inpatient admissions including those that were not linked. The strengths of this study include the use of capture-recapture methodology, rather than simply assuming both sources of data adequately capture all diabetes patients; obtaining estimates that tally with the prevalence noted in the national inpatient audit [14]. The cost estimates are crude and do not take into account of the admissions not identified by both sources or any complications associated with diabetes. However in my view findings of this study suggest HRG codes poorly estimate the cost incurred by patients with diabetes.

Figure 3.3: Proposed algorithm to incorporate into electronic prescription and health information system to reduce missed discharge diagnostic codes



3.5 Conclusions

Electronic prescribing systems may be a simple solution to correct missed discharge diagnostic codes and could make a difference in real-time if incorporated with decision support reminders. Further in-depth analysis of the validity of HRG codes in reflecting the cost of caring for diabetes patients needs to be undertaken to inform any future revision of HRG codes.

CHAPTER 4
Inpatient Hypoglycaemia and Glucose Metrics

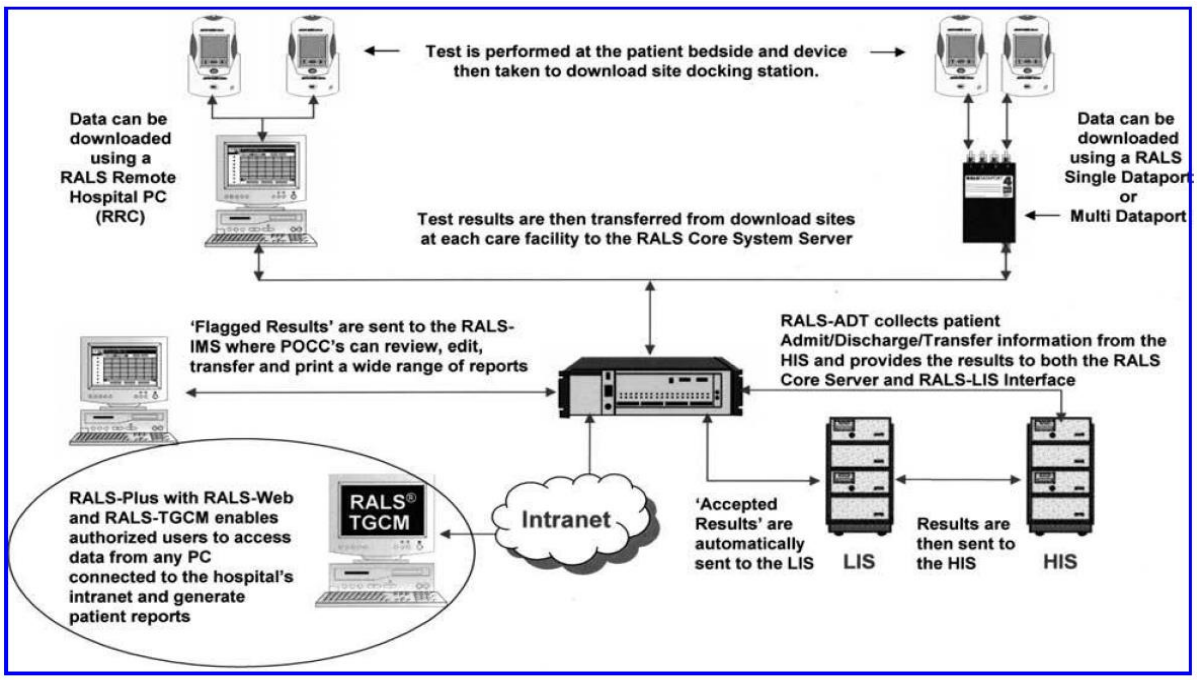
4 Inpatient Hypoglycaemia and Glucose Metrics

4.1 Overview

In chapter two I identified the usefulness of having an institutional blood glucose monitoring system [162]. Firstly this can enable a hospital to keep track of the number of admissions with 'poor glucose control' [113,114]. Secondly a centralised system with recording of point of care blood glucose (POC BG) can alert diabetes specialist teams to proactively identify and guide treatment of patients with severe or recurrent hypoglycaemia as well as patients with persistent hyperglycaemia [118,122]. An additional benefit is the ability to have an online quality control program to validate the performance of the glucose meters [131]. Furthermore it may be possible for diabetes specialist nurses to support wards with unexplained poor glucose control. This will lead to improvement of staff skills in managing patients with diabetes.

In UHB until early 2012 all POC BG values were encouraged to be entered into the PICS system. This meant POC BG values were available as electronic observation charts. However this was dependant on health care professionals entering values manually into the computers rather than using an automated system. Often there were missing blood glucose values during the period of the data I have analysed (2007-2010). At present some units have started replacing previous glucose meters with newer ones that can automatically feedback the values into the central server from a docking station (Figure 4.1).

Figure 4.1: Institutional blood glucose monitoring system



*RALS –Remote Automated Laboratory System; HIS - Health Information System; POCC – Point of Care Co-ordinator; TGCM – Tight Glycaemic Control Module; IMS – Information Management Station; LIS – Laboratory Information System; RRC – RALS Remote Connect

Source: Cook CB et al. Diabetes Technol.Ther. 2007; 9:493-500. [163] (reproduced with permission)

Before implementing strategies to incorporate an institution wide glucose monitoring system we need to answer the question: "how do we define good quality glucose control in a non critical care setting?" This question arises because, even though there is evidence that hyperglycaemia is associated with poor clinical outcomes as noted in the introduction (chapter 1), there is no clear evidence of the benefit of good glycaemic control and the best target range for patients with diabetes in non critical care setting. Further findings in critical care suggest tight glycaemic control (<6.1mmol/l) may be harmful to patients [144,164] contrary to previous belief. It is in this context that based on available evidence the American Diabetes Association (ADA) and UK guidelines recommended to keep the pre-meal glucose to below 7.8mmol/l and post-prandial glucose to less than 10mmol/l in non-critically ill patients

[47,104]. At the same time hypoglycaemia should be avoided as this could lead to poor clinical outcomes [58]. However data to support the latter among in-patients with diabetes in non critical care is lacking, especially here in UK. This is addressed in the first section below (4.2) where I look at the: “Association of hypoglycaemia with length of stay and inpatient mortality in hospitalised patients with diabetes”.

Recent events in Stepping Hill Hospital, where malicious use of insulin is suspected to have caused hypoglycaemia and death in elderly patients [165], has highlighted patient safety issues with insulin use. Unexplained hypoglycaemia in a non-diabetic patient or a cluster of hypoglycaemic incidents might be the only initial clue to such untoward incidents. One of the benefits of an institution wide glucose monitoring system is its ability to function as a surveillance tool in monitoring frequency of hypoglycaemia both in patients with and without diabetes. The system may have the potential to identify unexplained non diabetic hypoglycaemia provided: 1) they can be identified as non diabetic, which could be achieved by incorporating the algorithm in chapter 2; and 2) the number of occurrences of hypoglycaemia is within a manageable number to monitor in real-time and where necessary to review case notes. At present there are no precise estimates of the frequency of non diabetic hypoglycaemia in a non critical care setting. Furthermore as discussed earlier, in UHB the electronic observation charts of POC BG are not sufficiently complete to establish such a surveillance system. In the second section (4.3) of this chapter titled “Frequency of hypoglycaemia in non-diabetic hospitalised patients and the feasibility of setting up a surveillance system”, I have aimed to estimate the frequency of non diabetic hypoglycaemia in non critical care setting. At the same time I have looked at the feasibility of using available blood glucose values, prescription data of treatments given for hypoglycaemia and discharge diagnostic codes for hypoglycaemia as

databases that may assist in establishing a surveillance system to detect unexplained non diabetic hypoglycaemia.

Finally in the last section of this chapter (4.4) I examine the utility of the quality indicators that have been described in the literature to monitor inpatient glucose control.

4.2 Association of hypoglycaemia with length of stay and inpatient mortality in hospitalised patients with diabetes

4.2.1 Background

Hypoglycaemia is common in hospitalised patients with diabetes [58,144,164,166]. In critical care hypoglycaemia is associated with prolonged length of stay and mortality irrespective of the diabetes status [144,164]. Limited evidence exists on the effect of hypoglycaemia on length of stay and mortality in a non critical care setting. A study by Turchin et al [58] based on analysis of 4,368 admissions in one teaching hospital (Boston, USA), showed that among inpatients with diabetes an episode of hypoglycaemia (< 2.8mmol/l), in comparison to no hypoglycaemia, was associated with increased length of stay, an 85% increase in the odds of inpatient death and a 65% increase in the odds of death at 1 year. The study elicited the relationship by categorising the exposure (hypoglycaemia) based on lowest recorded blood glucose as those with and without a value less than or equal to <2.8mmol/l and comparing their outcome during inpatient stay (length of stay and mortality) and after discharge (1 year mortality). In addition to these findings he showed that there was an incremental higher risk of inpatient mortality and excess length of stay with an increase in the number of hypoglycaemic days they encountered during their hospital stay. Another recent study from New York, USA reporting on mortality in a mixed population of patients, with and without diabetes, suggested that hypoglycaemia is a marker of disease burden and the greater mortality observed can be explained by the association between the hypoglycaemia and co-morbidities [166].

UK data is sparse on the outcome of in-patients with diabetes who have had a hypoglycaemic episode. It is important we know these outcomes to monitor and improve care through implementation of interventions that will reduce hypoglycaemic

episodes and adverse outcomes associated with them. To address this I studied the difference in length of stay and inpatient mortality of patients with diabetes who had and did not have an episode of hypoglycaemia in a non critical care setting at University Hospital Birmingham (UHB). The hospital as described previously has a purpose-designed computer-based patient information system, the Patient Information and Communication System (PICS), which records laboratory results, electronic observations and medication orders, and a Patient Administration System (PAS) which records discharge diagnostic codes. Therefore I had the opportunity to analyse retrospective data available for the year 2007 to 2010 from blood glucose concentration measurements, both from the bedside (POC BG) and the laboratory results of patients identified as having diabetes based on discharge diagnostic codes and prescribed diabetic medication.

4.2.2 Methods

4.2.2.1 Data sources

Data sources have been described in detail in chapter 3. In summary I identified all patients 16 years old and above who were registered in the PAS as having been admitted to UHB during the period of 2007 to 2010 as either an elective or emergency inpatient admission. PAS data were linked to the PICS data and patients with a recorded diagnosis of diabetes in the PAS, or who did not have a diabetes diagnostic code but were identified in PICS as having received treatment with anti-diabetic medication, were classed as having diabetes if they did not meet the exclusion criteria. The exclusion criteria were 1) patients on Metformin but without a discharge diagnostic code of diabetes and with a discharge diagnostic code for polycystic ovarian syndrome 2) patients who received short or rapid acting insulin alone but without a discharge code of diabetes. The latter criteria was chosen to

avoid misclassifying patients as having diabetes when they might have received this treatment for hyperkalaemia or control of blood sugar in seriously ill patients with hyperglycaemia.

Only admissions with at least one recorded blood glucose concentration were included for the study. All admissions with a stay in intensive care unit (ICU) were excluded from the analysis. Any inconsistent records, where a discharge diagnostic code for hypoglycaemia was present but blood glucose values did not indicate hypoglycaemia, were also excluded from the analysis.

I identified episodes of hypoglycaemia at any point during the admission by interrogating blood glucose concentrations from the PICS database, recorded either from bedside (POC BG) or laboratory. I did not differentiate between laboratory blood glucose values and point-of-care blood glucose values, or consider the type of equipment used to measure glucose values.

4.2.2.2 Cut-off value for hypoglycaemia

I used the NHS Diabetes guideline treatment cut-off value (3.9mmol/l or less) to categorise hypoglycaemia [48]. Severe hypoglycaemia is best categorised by the need for third party assistance in treating the episode. Considering this information is not possible to obtain from the data, a cut-off value of 2.2mmol/l was used to describe severe hypoglycaemia [167]. Therefore blood glucose concentration of greater than 3.9 mmol/l were categorised as non hypoglycaemic; 2.3 to 3.9mmol/l as mild to moderate hypoglycaemia; and less than or equal to 2.2mmol/l as severe hypoglycaemia. Admissions were categorised based on the lowest value of blood glucose recorded during the spell.

I then compared the inpatient mortality and length of stay among these three groups to look for any association. Length of stay was calculated by deducting the admission time from the discharge time to the closest hour.

4.2.2.3 Statistical analysis

The demographic and morbidity characteristics of the patients with and without an episode of hypoglycaemia are summarised using means (standard deviation; SD) or medians (inter-quartile range; IQR) for continuous data and using proportions for categorical data. To allow for the clustering effect of some of the patients being admitted more than once Generalised Estimation Equations (GEE) were used. Logistic regression was used to study the inpatient mortality outcome; and linear regression model was used to study the effect on length of stay. Due to the skewed length of stay data, a log transformation was carried out to normalise the data before multivariate analysis. Covariates controlled for in the regression analyses were age (years), gender, ethnicity, deprivation quintiles (based on income deprivation score), admission type (emergency / elective), modified Charlson co-morbidity score, and use of insulin. Modified Charlson co-morbidity score is calculated by deducting the score given for diabetes [58]. Effect size from the multivariate analysis is reported as odds ratio for inpatient mortality and as relative ratio (exponential of the regression coefficient of the log transformed data) for the length of stay. Confidence interval is given at 95% and P-value of less than 0.05 was deemed significant. Data were analyzed using Stata® 12 software, using the GEE class of models.

4.2.3 Results

There were 25,118 admissions with diabetes between 2007 and 2010. Of these, 6,374 met the inclusion criteria (figure 4.1). There were 148 admissions (2.3%) with severe hypoglycaemia (≤2.2mmol/l), 500 admissions (7.8%) with mild to moderate

hypoglycaemia (2.2-3.9mmol/l) and 5,726 admissions with no hypoglycaemic episodes (>3.9mmol/l) (table 4.1).

Patients with increased severity of hypoglycaemia tended to have an older mean age and were more likely to be admitted as an emergency and be on insulin. Fewer of those who did not have a hypoglycaemia episode had a co-morbidity score of 1 or higher (64%) compared to 73% of those with mild to moderate and 74% of those with severe hypoglycaemia (table 4.1).

Median length of stay (days) in the >3.9mmol/l group was 5.9 (IQR 2.1-12.9), 11.0 (IQR 4.7-21.1) in the 2.3-3.9mmol/l and 17.0 (IQR 8.0-37.2) in the ≤2.2mmol/l group (table 4.1). The adjusted length of stay was increased by 1.51 (95%CI: 1.35-1.68) times in the 2.3-3.9mmol/l group and 2.33 (95%CI: 1.91-2.84) times in the ≤2.2mmol/l group when compared to those without a hypoglycaemic episode (>3.9mmol/l). The associations were highly significant (P<0.001) for both (table 4.2 & figure 4.3).

Inpatient mortality was 15% in the ≤2.2mmol/l group, 10% in the 2.3-3.9mmol/l group and 5% in the >3.9mmol/l group (table 4.1). The adjusted odds ratio was 1.62(95%CI: 1.16-2.27) in the 2.3-3.9mmol/l group and 2.05 (95%CI: 1.24-3.38) in the ≤2.2mmol/l group in comparison to the non hypoglycaemic group. Both again were highly significant (P≤0.005) (table 4.2 & figure 4.3).

Figure 4.2: Flow diagram of admissions included for analysis

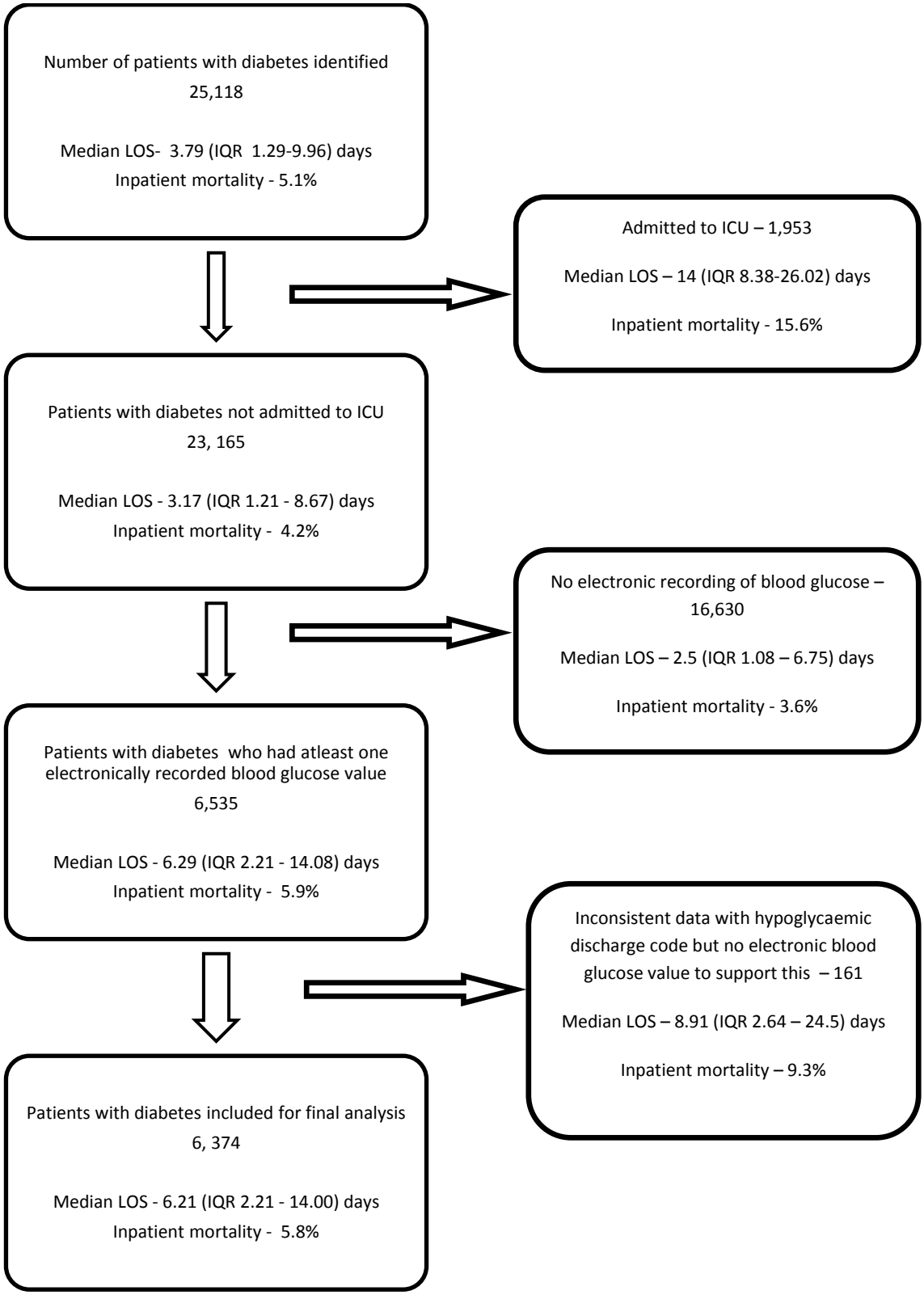
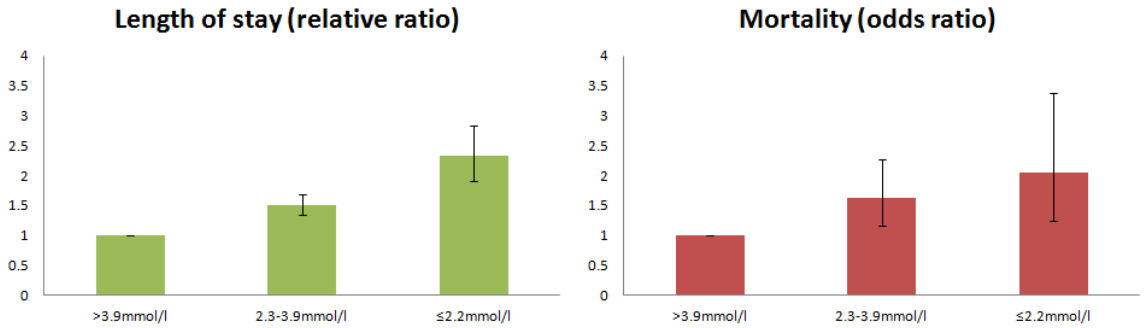


Table 4.1: Characteristics and outcome of the admissions based on presence and severity of hypoglycaemia

Patient Characteristics	No hypoglycaemia > 3.9 mmol/l (N=5,726)	Mild to moderate 2.3 – 3.9 mmol/l (N=500)	Severe hypoglycaemia <=2.2 mmol/l (N=148)
Age mean (SD) years	63.8 (15.9)	65.1 (15.3)	67.8 (15.4)
Gender N (%)			
Male	3,303 (57.7)	278 (55.6)	85 (57.4)
Female	2,423 (42.3)	222 (44.4)	63 (42.6)
Ethnicity N (%)			
White	3,904 (68.2)	338 (67.6)	108 (73.0)
Asian	1,099 (19.2)	99 (19.8)	26 (17.6)
Black	362 (6.3)	39 (7.8)	8 (5.4)
Other	361(6.3)	24 (4.8)	6 (4.1)
*Social class N (%)			
Least deprived 1	295 (5.3)	25 (5.1)	6(4.2)
2	484 (8.7)	45 (9.3)	13 (9.0)
3	936 (16.8)	86 (17.7)	31 (21.5)
4	1,201 (21.6)	95 (19.5)	36 (25.0)
Most deprived 5	2,647 (47.6)	235 (48.4)	58 (40.3)
Type of Admission N (%)			
Elective	934 (16.3)	56 (11.2)	7 (4.7)
Emergency	4,792 (83.7)	444 (88.8)	141(95.3)
Modified Charlson co-morbidity score N (%)			
0	2,045 (35.7)	133 (26.6)	39 (26.4)
1	1,188 (20.7)	86 (17.2)	29 (19.6)
2 or more	2,493 (43.5)	281 (56.2)	80 (54.1)
Insulin use N (%)			
Yes	3,442 (60.1)	357 (71.4)	119 (80.4)
No	2,284 (39.9)	143 (28.6)	29 (19.6)
Outcome			
In-patient death N (%)			
Yes	298 (5.2)	49 (9.8)	22 (14.9)
No	5,428 (94.8)	451 (90.2)	126 (85.1)
Length of stay median (IQR) days	5.9 (2.1,12.9)	11.0 (4.7,21.1)	17.0 (8.0,37.2)

*Social class based on income deprivation score. Adds up to 6,193 instead of 6, 374 due to missing post code values

Figure 4.3: Presence and severity of hypoglycaemia vs. inpatient mortality and length of stay*



* Adjusted odds ratio for mortality and adjusted relative ratio for length of stay. Relative ratio here is the exponential of regression coefficient obtained from the analysis of log transformed length of stay data. Covariates adjusted for are age, gender, ethnicity, social class, admission type, insulin use and modified Charlson co-morbidity score.

In multivariable (adjusted) analysis, increasing age, emergency admission, being on insulin and higher co-morbidity score were independently associated with both increasing length of stay and inpatient mortality (table 4.2).

In assessing the bias of the excluded sample, admissions without a recording of blood glucose had a lower length of stay (median 2.5; IQR 1.08-6.75 days) and inpatient mortality rate (3.6%) (Figure 4.1). Interestingly those with a discharge code of hypoglycaemia but without any evidence of hypoglycaemia in the electronic blood glucose recording had similar inpatient mortality (9.3%) to that of mild to moderate hypoglycaemia group (9.8%). Admissions that resulted in Intensive Care Unit (ICU) had a similar mortality rate (15.6%) to that of the severe hypoglycaemia group (14.9%) (Figure 4.1).

Table4.2: Adjusted* odds ratio for inpatient mortality and adjusted* relative ratio# for length of stay in patients with diabetes

Characteristics	Unadjusted odds ratio for inpatient mortality	Adjusted odds ratio For inpatient mortality	P value (adjusted analysis)	Unadjusted relative ratio# for length of stay	Adjusted relative ratio# for length of stay	P value (adjusted analysis)
Age	1.06 (1.06-1.08)	1.07 (1.05-1.08)	<0.001	1.018 (1.016-1.020)	1.015 (1.013-1.018)	<0.001
Gender						
Male	1	1		1	1	
Female	1.13 (0.91-1.39)	1.02 (0.82-1.28)	0.83	1.07 (0.99-1.15)	1.06 (0.99-1.13)	0.10
Admission type						
Elective	1	1		1	1	
Emergency	5.81 (3.26-10.35)	4.63 (2.57-8.35)	<0.001	1.24 (1.13-1.36)	1.29 (1.18-1.40)	<0.001
Ethnicity						
White	1	1		1	1	
Asian	0.70 (0.52-0.94)	0.75 (0.54-1.03)	0.07	0.86 (0.79-0.95)	0.89 (0.81-0.97)	0.01
Black	0.85 (0.54-1.33)	0.70 (0.44-1.12)	0.14	1.00 (0.86-1.15)	0.91 (0.79-1.05)	0.21
Other	0.80 (0.50-1.28)	0.94 (0.57-1.54)	0.79	0.58 (0.50-0.67)	0.68 (0.60-0.78)	<0.001
Social Class						
(Most Deprived) 5	1	1		1	1	
4	1.02 (0.78-1.34)	0.86 (0.65-1.15)	0.32	1.02 (0.93-1.12)	0.97 (0.89-1.06)	0.53
3	0.89 (0.66-1.22)	0.81 (0.58-1.12)	0.21	1.10 (1.00-1.22)	1.06 (0.97-1.17)	0.21
2	0.98 (0.66-1.44)	0.88 (0.58-1.33)	0.54	1.16 (1.02-1.32)	1.07 (0.95-1.21)	0.26
(Least Deprived) 1	1.02 (0.63-1.65)	1.08 (0.65-1.78)	0.77	1.09 (0.93-1.29)	1.06 (0.90-1.23)	0.52
Unavailable Post Code	0.09 (0.01-0.63)	0.11 (0.02-0.82)	0.03	1.23 (0.99-1.53)	1.30 (1.06-1.59)	0.01
Modified Charlson co-morbidity score						
0	1	1		1	1	
1	3.21 (2.15-4.80)	2.56 (1.70-3.85)	<0.001	1.64 (1.50-1.80)	1.49 (1.37-1.63)	<0.001
2	5.85 (4.14-8.26)	5.16 (3.63-7.34)	<0.001	2.46 (2.29-2.65)	2.14 (1.99-2.30)	<0.001
Insulin use						
No	1	1		1	1	
Yes	1.52 (1.21-1.91)	1.69 (1.32-2.16)	<0.001	1.60 (1.50-1.72)	1.57 (1.47-1.68)	<0.001
Hypoglycaemia						
None	1	1		1	1	
Hypo 2.3-3.9mmol/l	1.98 (1.44-2.72)	1.62 (1.16-2.27)	0.004	1.76 (1.57-1.99)	1.51 (1.35-1.68)	<0.001
Hypo <2.2mmol	3.18 (2.00-5.08)	2.05 (1.24-3.38)	0.005	2.97 (2.40-3.67)	2.33 (1.91-2.84)	<0.001

* Covariates included in the multivariate analysis were age, gender, ethnicity, social class, admission type, modified Charlson co-morbidity score, insulin use and hypoglycaemia category.

Relative ratio is the exponential of regression coefficient obtained from the analysis of log transformed length of stay data

4.2.4 Discussion

Hypoglycaemia in people with diabetes admitted to hospital associates with increased length of stay and inpatient mortality. Length of stay was 51% greater in those having mild to moderate hypoglycaemia and 133% greater in those having severe hypoglycaemia. The odds of inpatient mortality increased by 62% in those with mild to moderate hypoglycaemia and by 105% in those with severe hypoglycaemia.

My findings are consistent with that of Turchin et al who found an 85% increase in inpatient mortality with a hypoglycaemic episode [58]. This consistency persists despite the differing definitions of hypoglycaemia (2.8mmol/l) compared to my cut off value (3.9mmol/l). The findings indicate hypoglycaemia as either being a marker of poor prognosis or that the patients are being at risk of an adverse outcome as a consequence of hypoglycaemia. Increase in length of stay in patients with hypoglycaemia may result from the need to optimise glycaemic control prior to discharge, or may result from the increased chance of having and detecting an episode of hypoglycaemia with a longer inpatient stay.

The limitations of the study were the inconsistent availability of electronic blood glucose values for admissions with diabetes and the retrospective nature of the study. The definition of severe hypoglycaemia was based on a biochemical cut-off value (<2.2mmol/l) rather than the accepted categorisation based on the need for third party assistance. By using the Charlson co-morbidity index I have adjusted for key confounding illnesses such as liver disease, renal impairment and congestive heart failure but this does not encompass all possible confounders such as excessive alcohol intake and septicaemia. Inconsistent availability of blood glucose values might have led to the low (10.1%) number of hypoglycaemic admissions

noted in our analysis. The estimates reported in national audits using case note analysis are much higher (20-25%) [14, 15]. However the dataset is large with over 6,000 admissions and findings are consistent with previous studies that used similar approaches [58,166]. Furthermore looking at the excluded data without blood glucose recordings which have much shorter length of stay and inpatient mortality, perhaps the effect sizes for inpatient mortality and length of stay derived in this study if at all are likely to be underestimates.

4.2.5 Conclusions

Hypoglycaemia is associated with increased length of stay and inpatient mortality. Whilst causative evidence is lacking, the data is consistent with the need to try and avoid hypoglycaemia in our current and continued approach for optimal glycaemic control in people with diabetes admitted to hospital. A computerised glucose monitoring system may have an important role to play in the management and monitoring of inpatient hypoglycaemia in patients with diabetes.

4.3 Frequency of hypoglycaemia in non-diabetic hospitalised patients and the feasibility of setting up a surveillance system

4.3.1 Background

Hypoglycaemia in hospitalized patients with diabetes is common and can lead to seizures, coma, death and increased length of stay [48,58,168]. Hypoglycaemia in patients without diabetes is much rarer. There is a wide range of potential causes for non-diabetic hypoglycaemia which includes excess alcohol intake, septicaemia, liver disease, renal impairment, haemodialysis, heart failure, cancer, dementia, pneumonia, self-harm with hypoglycaemic agents and autoimmune mediated hypoglycaemic disorders [169-181]. It has sometimes been the result of the malicious administration of insulin [46,165,182].

Insulin related murder may be under-reported worldwide [46]. In reported cases, perpetrators are often carers or clinical staff, and victims their patients [46]. Prominent cases in the United Kingdom have involved multiple deaths of elderly hospital patients [183], and of children [184,185]. Similar cases have occurred in the United States [186-188] , at a Vienna medical centre [189] , and at old-age homes in Belgium and the Netherlands [46,186]. While confirmation of insulin poisoning requires serum insulin and C-peptide concentrations, the first suspicion may be raised by the occurrence of unexplained hypoglycaemia [165]. Better knowledge of the frequency of non diabetic hypoglycaemia in hospital patients is required to understand these complex forensic and clinical questions.

Hypoglycaemia is common in critical care settings [144,190], partly because of attempts to achieve tight blood glucose control, although this has now been shown to be harmful [144,164]. Few studies [169,172,179,191,192] have examined the incidence of non diabetic hypoglycaemia outside the critical care setting. Shilo et al [172] reported a frequency of 0.5% in elderly patients (>65 years) in a series of

nearly 12 000 admissions. Mannucci et al [179] described a remarkably high frequency of 8.6% in patients aged above 65 years but their relatively small study of 678 patients was undertaken in a single geriatric unit, defined hypoglycaemia as a blood glucose concentration of 3.3 mmol/l or less even if patients were asymptomatic and did not specify if any of the patients received intensive care unit support. Three other studies included both diabetic and non-diabetic patients but did not give the non-diabetic denominator population [169,179,191,192]. The differences between studies may result from differences in the population, the proportion of patients who have a blood glucose test performed, the cut-off value chosen to define hypoglycaemia, and the point in the course of their illness the test was done.

Colleagues and I wished to establish the frequency of observed hypoglycaemia in patients outside the intensive care unit in UHB, a large university hospital with approximately 1200 beds. As described previously the hospital has a purpose-designed computer-based patient information system, the Patient Information and Communication System (PICS), which records laboratory results, electronic observations and medication orders, and a Patient Administration System (PAS) which records discharge diagnostic codes. Therefore I had the opportunity to analyse retrospective data available for the year 2010 from three distinct sources: blood glucose concentration measurements, both from the bedside and the laboratory; medication records for treatments (glucose, glucagon) commonly given to reverse hypoglycaemia; and diagnostic codes for individual patients. Each data source identifies a different sample of all hypoglycaemic episodes, but no single data source can be regarded as definitive. However the extent to which different data sources identify the same hypoglycaemic episodes allows the use of capture-

recapture methods to establish the likely true rate of hypoglycaemia in non-diabetic in-patients outside intensive care units.

Colleagues and I also considered whether it might be feasible to set up a hospital surveillance system to detect any unexpected increase in the frequency of hypoglycaemia, as might occur with the malicious administration of insulin.

4.3.2 Methods

I identified all adult patients (≥16 years) who the Patient Administration System (PAS) identified as having been admitted to UHB during the calendar year 2010 and where the episode was noted as either an elective or non-elective (ie emergency) inpatient admission. PAS data were linked to the PICS data and patients with a recorded diagnosis of diabetes in the PAS or who were identified in PICS as having received treatment with anti-diabetic medication were excluded. This broad exclusion criterion was used because the main purpose was to determine the frequency of hypoglycaemia that could not be explained by the use of prescribed hypoglycaemic agents. The denominator also included patients admitted to the intensive care unit (ICU), as they invariably have a period of stay outside ICU (susceptible population). This identified a population of non-diabetic in-patients who could suffer a hypoglycaemic episode in a non-critical care setting.

I identified episodes of hypoglycaemia in three ways. Firstly episodes were directly identified from low concentrations of blood glucose from the PICS database, recorded either from bedside or laboratory blood glucose estimations; secondly episodes were indirectly identified from prescribed treatments for hypoglycaemia from the PICS database; and lastly diagnostic codes for hypoglycaemia were identified from the PAS database. If the trigger occurred during a period of time the patient spent in ICU these were excluded from the numerator.

4.3.2.1 Cut-off value for hypoglycaemia

Various blood glucose concentrations have been used to define hypoglycaemia in non-diabetic patients. Previous studies have used 2.7 [172,191], 3 [192] and 3.3 mmol/l [169,179]. Meanwhile 2.2 mmol/l is used to define severe hypoglycaemia in Whipple's triad [167] and 2.5 mmol/l has been used for forensic investigations [193]. Considering the uncertainty, I analysed the data at different values of blood glucose concentration, to establish the effect on perceived occurrence, and the optimum cut-off value for surveillance. I did not differentiate between laboratory blood glucose values and point-of-care blood glucose values or apply any correction factors. The point of care blood glucose system in place at UHB during the study period was the ACCU-CHEK inform system marketed by ROCHE.

4.3.2.2 Medication as an indirect trigger to indicate hypoglycaemia

Electronic prescription records for medication used to treat severe hypoglycaemia were examined, to establish whether these may serve as triggers in detecting hypoglycaemia in non-diabetic patients. The triggers extracted from PICS were intramuscular glucagon injection; intravenous glucose 10%, 20%, and 50% solutions; and oral glucose 40% gel. The case-notes of patients who received any of these but had neither a prescription for anti-diabetic medication in PICS nor a diagnostic code for diabetes in PAS were reviewed to establish whether they had in fact been hypoglycaemic. Reasons for false positives were documented.

4.3.2.3 Discharge diagnostic codes for hypoglycaemia as an indirect trigger

ICD10 discharge diagnostic codes for hypoglycaemia (E15, E16.0, E16.1, and E16.2) were identified from the PAS system for the year 2010. The case-notes of all patients who had neither a prescription for anti-diabetic medication in PICS nor a diagnostic code for diabetes in PAS were reviewed to determine the validity of the

triggers in identifying non-diabetic hypoglycaemia. Again reasons for false positives were recorded.

4.3.2.4 Electronic point-of-care and laboratory blood glucose concentrations as direct triggers

From available electronic observations derived from PICS, point-of-care or laboratory blood glucose values were used to identify patients who had been hypoglycaemic during their in-patient spell. I reviewed the case-notes of patients categorised as non-diabetic by the criteria described above.

4.3.2.5 Determining the causes of hypoglycaemia in non-diabetic patients

Information on diagnosis that was noted in the discharge diagnostic codes from PAS was first verified as an accurate description by case-note review. Any missed diagnostic codes were documented. A check list of potential causes derived from previous literature was used to identify possible reasons for the hypoglycaemia [169-181]. Considering the limitation of the ICD 10 codes in describing aetiology, for patients with a blood glucose value less than 2.7 mmol/l, based on the co-morbidity and patient condition, I made a judgement as to whether any of these patients may have had an unexplained hypoglycaemia. This was verified by a consultant diabetologist (PN).

4.3.2.6 Statistical analysis

4.3.2.6.1 Estimating the frequency of non-diabetic hypoglycaemia

Data were analyzed using Stata® 10 software. Cases identified by any of the three triggers were used to estimate the incidence of hypoglycaemia in non-diabetic patients. As none of the three data sources is complete the capture-recapture technique for three sources was used [149]. As discussed in chapter 3 capture-recapture methods have been used in health care to estimate population prevalence using multiple incomplete sources [194-199]. In summary, eight log-linear models,

each specifying different interactions between the three sources, are derived to estimate the size of the total population. The layout of the three-source models is given in the box below.

Box 4.1: Three source model layout for estimating the numbers of non diabetic hypoglycaemia

Three source model layout for estimating the numbers of non diabetic hypoglycaemia

		Source 1: Anti-hypo treatment			
		Yes		No	
		Source 2: Blood Glucose Values		Source 2: Blood Glucose Values	
		Yes	No	Yes	No
Source 3: Discharge Diagnostic code	Yes	a	b	e	f
	No	c	d	g	X

N_{obs} = a+b+c+d+e+f+g (total observed)

N_1=a+b+c+d (Source 1 total)

N_2=a+c+e+g (Source 2 total)

N_3=a+b+e+f (Source 3 total)

X= Unknown value

$N_{total}=N_{obs}$ + X

Model depicting different interaction between sources	DoF	Formula to estimate X
Independent	3	$X = N_{total} - N_{obs}$ Where N_{total} is the solution of: $(N_{total}-N_1)\ (N_{total}-N_2)\ (N_{total}-N_3) = N_{total}^2(N_{total} - N_{obs})$
1-2	2	X = (c + d + g)(f) / (a + b + e)
1-3	2	X = (b + d + f)(g) / (a + c + e)
2-3	2	X = (e + f + g)(d) / (a + b + c)
1-2, 1-3	1	X = gf / e
1-2, 2-3	1	X = df / b
1-3, 2-3	1	X = gd / c
1-2, 1-3, 2-3	0	X = (adfg) / (bce)

Applying correction to the model: For model stability 1 is added to cells b, c and e when performing the analysis

Adapted from: Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. [Review] [140 refs][Erratum appears in Am J Epidemiol 1998 Dec 15;148(12):1219]. *Epidemiologic Reviews* 1995; **17**: 243-264.

Calculations are based on the overlap between the three sources. The best estimate of the eight given is chosen using the Akaike Information Criteria (AIC) and the Bayesian Information Criteria (BIC). The 95% confidence intervals around the estimates were calculated using the goodness-of-fit based method [200]. An example of the working using the three source model is given in the box below [148].

Box 4.2: Example; three source model for estimating the numbers of non diabetic hypoglycaemia (<3.3mmol/l)

		Source 1: Anti-hypo treatment			
		Yes		No	
		Source 2: Blood Glucose Values		Source 2: Blood Glucose Values	
		Yes	No	Yes	No
Source 3: Discharge Diagnostic code	Yes	1	7	1	9
	No	5	19	29	X

Odel	DoF	G^2	P value	AIC	BIC	X	N	N (lower)	N (Upper)
Independent	3	7.42	0.06	1.42	1.58	67	**141**	106	209
1-2	2	5.72	0.06	1.72	1.83	44	**118**	89	187
1-3	2	0.77	0.68	-3.23	-3.12	115	**189**	124	352
2-3	2	5.06	0.08	1.06	1.17	50	**124**	95	185
1-2, 1-3	1	0.74	0.39	-1.26	-1.2	130	**204**	104	953
1-2, 2-3	1	0.42	0.52	-1.58	-1.53	21	**95**	79	138
1-3, 2-3	1	0.2	0.66	-1.8	-1.75	91	**165**	107	343
1-2, 1-3, 2-3	0	0	1	0	0	51	**125**	75	851

DoF- Degree of Freedom

AIC – Akaike Information Criterion

BIC – Bayesian Information Criterion

X – Missing or unknown numbers with blood glucose of <3.3mmo/l

N – Total numbers and estimate lower and upper values

The value in the highlighted line is the selected best estimate based on the AIC and BIC value

I estimated the frequency at different cut-off values: 3.3, 3.0, 2.7, 2.5 and 2.2 mmol/l. Frequency is reported as a count for the observed number of admissions of patients who did not have diabetes or receive diabetic medication in a non critical care setting for the year 2010. I repeated the same analysis stratifying the population by age into those 65 years and above and those who were less than 65 years old. This was done as previous researches have limited the estimations to elderly population; this is therefore useful to make valid comparison. Furthermore often malicious use of insulin has been reported in elderly population within health care setting, making it useful to have an estimate for this age group for future reference in forensic cases.

4.3.2.6.2 Estimating the validity of a surveillance system

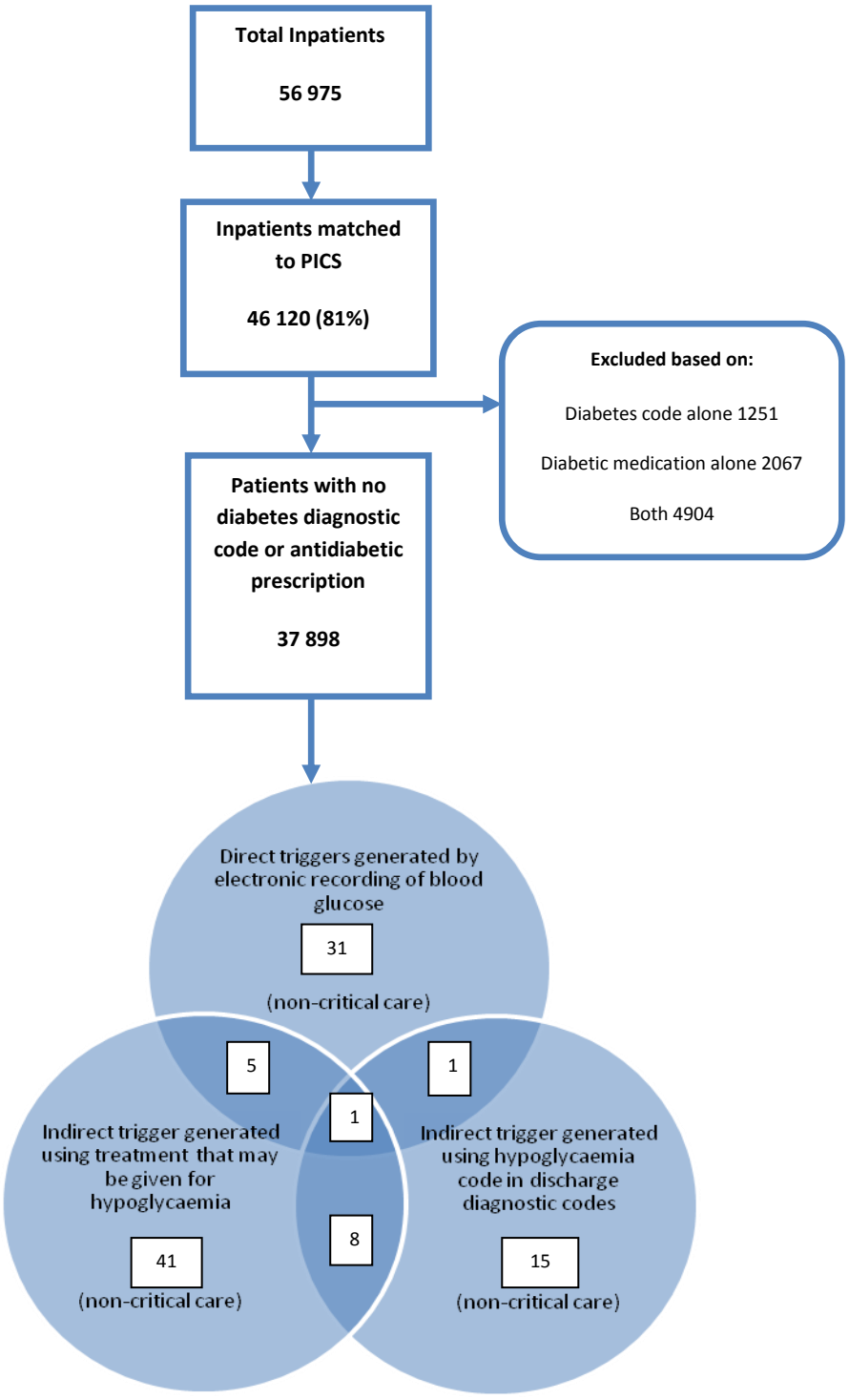
To look at the feasibility of monitoring the occurrence of non diabetic hypoglycaemia using the three sources I calculated the estimated sensitivities and positive predictive values if this was to be implemented as a surveillance tool. These are presented for each of the cut-off values. Positive predictive values for the indirect triggers and for the whole system were calculated and confidence intervals derived using exact binomial methods. Estimated sensitivities of the surveillance system proposed were derived by dividing the observed episodes by those of the estimated total. All confidence intervals are reported at 95%.

I did the same calculations to evaluate the impact of only using the two real time triggers as a live surveillance tool. The two live triggers are blood glucose observations and electronic prescriptions of anti hypoglycaemic agents.

4.3.3 Results

There were 56 975 inpatient admissions to the hospital in 2010. The information analyst was able to match 81% of the PAS data to the PICS system (46 210 admissions). Among them 37 898 were categorised as non-diabetic based on the absence of either discharge diagnostic code of diabetes or a record of the prescription of diabetic medication. There were 38 direct triggers from the blood glucose concentrations using 3.3 mmol/l as the cut-off value, 55 indirect triggers using treatment for hypoglycaemia and 25 indirect triggers using discharge diagnostic codes, yielding a total of 102 unique non-diabetic admissions with at least one episode of hypoglycaemia, excluding overlaps between the three sources (Figure 4.4). Case-notes were available for review for 95 (93%) admissions.

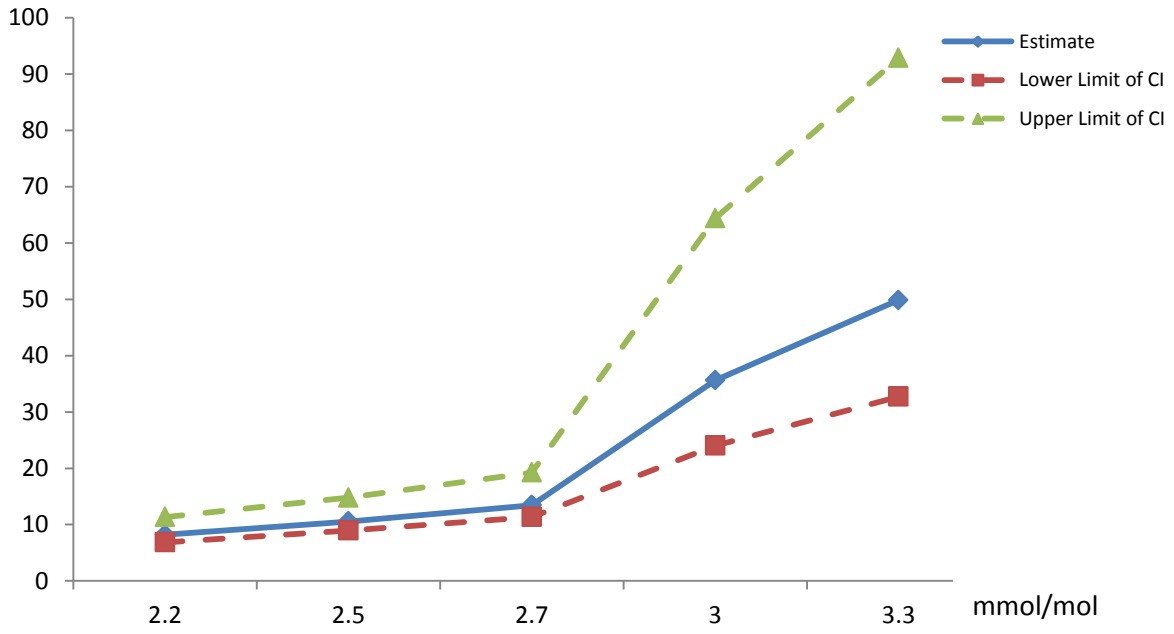
Figure 4.4: Flow diagram of the non diabetic hypoglycaemia triggers generated



4.3.3.1 The frequency of hypoglycaemia among non-diabetic patients in non critical care setting

In combination the triggers identified 71 hypoglycaemic episodes at a cut-off of 3.3 mmol/l, 59 at 3 mmol/l, 37 at 2.7 mmol/l, 30 at 2.5 mmol/l and 23 at 2.2 mmol/l (see appendix 4.2). Each of these admissions was of a unique patient. Using capture-recapture method at 3.3 mmol/l cut-off an estimate of 189 (95%CI 124 to 352) hypoglycaemic episodes is predicted in a non diabetic population of 37 898 giving a cumulative incidence of 50 per 10 000 admissions (95%CI 33 – 93). Estimated cumulative incidence at 3.0 mmol/l was 36 (95%CI 24 – 64), at 2.7 mmol/l, 13 (95%CI 11 -19), at 2.5 mmol/l, 11 (95%CI 9-15) and at 2.2 mmol/l, 8 (95%CI 7-11) per 10 000 admissions (Figure 4.5).

Figure 4.5: Number of hypoglycaemic episodes -v- threshold blood glucose concentration (mmol/l) and upper and lower 95% confidence bounds per 10 000 admissions



Analysis showed admissions of patients aged over 65 years were more (approximately 50% more) likely to have an episode of hypoglycaemia compared to the younger age group at all cut-off points. Estimated frequency above the age of 65 years at 3.3 mmol/l was 55 (95%CI 32 – 149), at 3.0 mmol/l, 39 (95%CI 24-158), at 2.7 mmol/l, 18 (95%CI 15 -27), at 2.5 mmol/l, 15 (95%CI 13-23) and at 2.2 mmol/l, 13 (95%CI 11-21) per 10 000 admissions (table 4.3).

Table 4.3: Estimated number of hypoglycaemic episodes for different cut off values per 10,000 elderly (≥65 years) and younger (<65years) admissions

Cut-off value (mmol/l)	2.2	2.5	2.7	3	3.3
Age > =65 years (per 13 494)	18	20	24	53	74
Lower 95% Confidence Interval Limit	15	18	20	32	43
Upper 95% Confidence Interval Limit	28	31	37	213	201
Frequency (per 10 000) with 95% CI	**13 (11-21)**	**15 (13-23)**	**18 (15-27)**	**39 (24-158)**	**55 (32-149)**
Age <65 years (per 24 404)	15	22	33	65	87
Lower 95% Confidence Interval Limit	14	18	25	45	59
Upper 95% Confidence Interval Limit	22	36	59	115	155
Frequency (per 10 000) with 95%CI	**6 (6-9)**	**9 (7-15)**	**14 (10-24)**	**27 (18-47)**	**36 (24-64)**

4.3.3.2 Possible surveillance system

Assuming the observed results were used in a surveillance system, a cut-off value of 2.7 mmol/l would have a sensitivity of 73% and a positive predictive value of 50% if all the datasets were used (table 4.4 and appendix 4.1 for detailed information).

Table 4.4: Best estimates for the number of admissions of 37 898 patients without diabetes in which one or more episodes of hypoglycaemia occurred

Cut of value	Observed episodes	Triggers generated	Best estimate for total episodes (95% CI)	*PPV% (95% CI)	#Estimated sensitivity% (95% CI)
2.2 mmol/l	23	65	31 (26-41)	35 (24-48)	74 (53-88)
2.5 mmol/l	30	68	40 (34-56)	44 (32-57)	75 (54-88)
2.7 mmol/l	**37**	70	**51 (43-73)**	**53 (41-65)**	**73 (51-86)**
3.0 mmol/l	59	82	135 (91-244)	72 (61-81)	44 (24-65)
3.3 mmol/l	71	91	189 (124-352)	78 (68-86)	38 (20-57)

*PPV = Observed episodes / Triggers generated by proposed surveillance system

#Estimated sensitivity = Observed episodes / best estimate for total episodes

If only the two 'real time' data sources, namely blood glucose trigger and the treatment trigger were used the sensitivity and positive predictive value would be 63% and 49% respectively at a cut off value of 2.7mmol/l (table 4.5).

Table 4.5: Analysis for live triggers using blood glucose values and treatment triggers alone

Cut of value	Observed episodes	Triggers generated	Best estimate for total episodes (95% CI)	PPV% (95% CI)	Estimated sensitivity% (95% CI)
2.2mmol/l	21	60	31 (26-41)	35 (23-48)	68 (49-81)
2.5mmol/l	27	63	40 (34-56)	43 (30-56)	68 (48-79)
2.7mmol/l	**32**	65	**51 (43-73)**	**49 (37-62)**	**63 (44-74)**
3.0mmol/l	51	78	135 (91-244)	65 (54-76)	38 (21-56)
3.3mmol/l	62	87	189 (124-352)	71 (61-80)	33 (18-50)

4.3.3.3 Causes of non-diabetic hypoglycaemia

Characteristics of the non-diabetic patients who had hypoglycaemia at a cut-off point of 3.3 and 2.7 mmol/l are given in Table 4.6. Most patients (>90%) were admitted as an emergency. The commonest co-morbidities linked to hypoglycaemia were sepsis, renal disease and alcohol dependence. Others included pneumonia, liver disease, cancer and self-harm with hypoglycaemic agents. Most patients had multiple possible reasons for their hypoglycaemia.

Detailed case-note review of those with blood glucose concentrations less than 2.7 mmol/l revealed seven patients who did not have a plausible reason to explain the occurrence of hypoglycaemia. However all seven were either admitted for investigation of hypoglycaemia that occurred elsewhere or had an episode that was noted on admission; there was no unexplained hypoglycaemia that occurred after admission during inpatient stay (figure 4.6). A matrix showing the co-morbidities of these patients is shown in table 4.7. Over a third of patients whose blood glucose concentration was lower than the cut-off point of 3.3 mmol/l, and nearly 40% below 2.7 mmol/l, died.

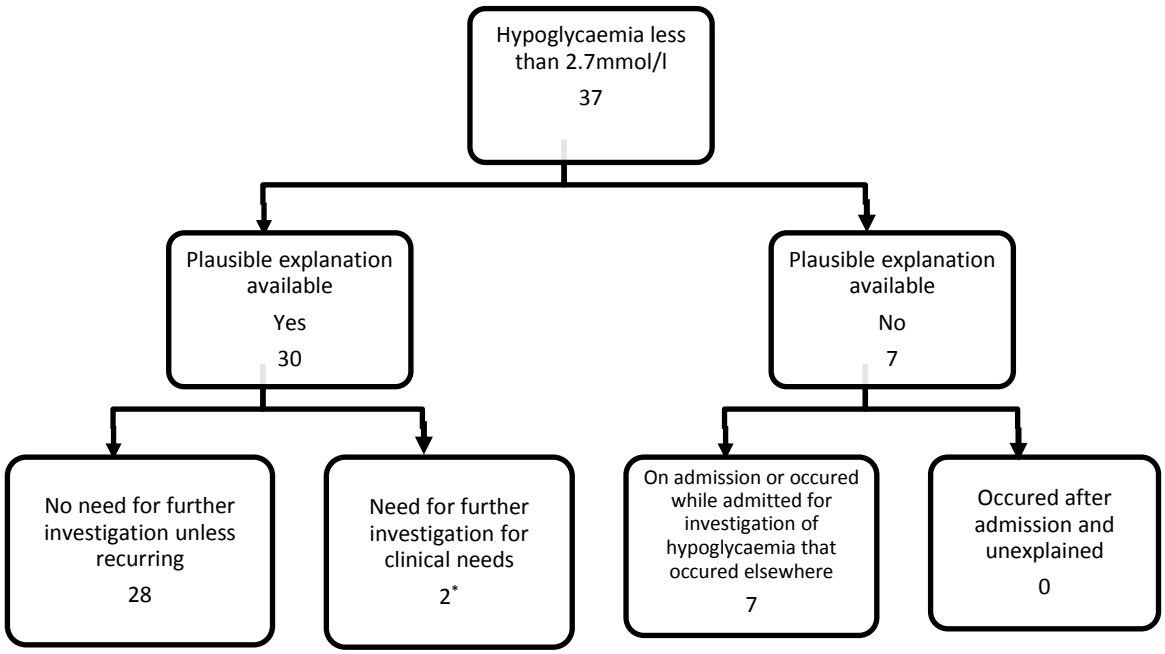
Table 4.6: Characteristics of the patients identified as non diabetic hypoglycaemic patients

Patient Characteristics	Glucose <3.3 mmol/l (N=71)	Glucose <2.7 mmol/l (N=37)
Age mean (SD) years	59.2 (22.5)	60.2 (23.6)
Age Group		
<65 years	41 (57.7)	20 (54.1)
>65 years	30 (42.3)	17 (45.9)
Gender N (%)		
Male	37 (52.1)	20 (54.1)
Female	34 (47.9)	17 (45.9)
Ethnicity N (%)		
White	50 (70.4)	26 (70.3)
Asian	8 (11.3)	4 (10.8)
Black	5 (7.0)	3 (8.1)
Other	8 (11.3)	4 (10.8)
*Social class N (%)		
Least deprived 1	4 (5.6)	0 (0.0)
2	7 (9.9)	3 (8.1)
3	17 (23.9)	10 (27.0)
4	11 (15.5)	5 (13.5)
Most deprived 5	31 (43.7)	18 (48.6)
Type of Admission N (%)		
Elective	7 (9.9)	2 (5.4)
Emergency	64 (90.1)	35 (94.6)
In-patient death N (%)		
Yes	24 (33.8)	14 (37.8)
No	47 (66.2)	23 (62.2)
Length of stay median (IQR) days	6.92 (11.54)	7.42 (13.88)
On admission %	22 (31.0)	17 (45.9)
#Aetiology for hypoglycaemia		
Sepsis	20 (28.2)	11 (29.7)
Renal Disease	20 (28.2)	12 (32.4)
Alcohol	15 (21.1)	11 (29.7)
Pneumonia	17 (23.9)	6 (16.2)
Liver disease	9 (12.7)	6 (16.2)
Congestive Heart Failure	9 (12.7)	6 (16.2)
Cancer	10 (14.1)	2 (5.4)
Self harm	4 (5.6)	4 (10.8)
Under investigation for hypo occurring elsewhere	5 (7.0)	3 (8.1)

*Social class based on deprivation index score. Adds up to 70 & 36 instead of 71 & 37 respectively at 3.3 and 2.7mmol/l due to one missing post code

Will add up to more than 100% due to multiple co-morbidities in patients. All co-morbidities are based on ICD 10 code (verified by case-note review). Where ICD 10 code was not available a documentation of the diagnosis in case-note was accepted.

Figure 4.6: Plausible explanation for hypoglycaemia



*****One patient had leiomyosarcoma and hypoglycaemia. The association between these have been reported in association with insulin-like growth factor 1, which was not determined in this patient.

One patient had SLE and admitted with sepsis but was very young (23 years) and had a blood glucose concentration less than 1.5 mmol/l. While hypoglycaemia may have been linked to sepsis, other clinical explanations were not excluded.

Table 4.7: Matrix showing co-morbidity linked to hypoglycaemia in patients with glucose <2.7mmol/l

	Renal disease	Sepsis	Alcohol	Cancer	Liver disease	Pneumonia	Congestive heart failure	Dementia	Self harm	Dialysis	Occurred on Admission	Admitted to investigate hypo
1	1	0	1	0	1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	1	0	1	0
3	0	0	0	0	0	0	0	0	0	0	0	1
4	0	0	0	1	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	1	1
6	1	1	0	0	0	1	0	0	0	0	1	0
7	0	0	1	0	1	1	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	1	1
9	0	0	0	0	0	0	0	0	1	0	1	0
10	0	0	0	0	0	0	0	0	0	0	1	0
11	1	1	0	0	0	0	1	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	1	1
13	0	1	0	0	0	0	0	0	0	0	1	0
14	1	1	0	0	0	0	0	0	0	1	0	0
15	0	0	1	0	0	0	0	0	0	0	1	0
16	0	0	0	0	0	0	0	1	0	0	0	0
17	0	1	0	0	0	1	0	0	0	0	0	0
18	1	0	0	0	0	0	1	0	0	0	1	0
19	1	0	0	0	1	0	0	0	0	1	0	0
20	1	1	0	0	0	1	1	0	0	0	0	0
21	0	0	1	0	0	0	0	0	0	0	1	0

	Renal disease	Sepsis	Alcohol	Cancer	Liver disease	Pneumonia	Congestive heart failure	Dementia	Self harm	Dialysis	Occurred on Admission	Admitted to investigate hypo
22	0	1	0	0	0	1	0	0	0	0	0	0
23*	0	0	1	0	1	0	0	0	0	0	0	0
24	0	0	1	0	0	0	0	0	0	0	1	0
25	0	1	0	0	0	1	1	0	0	0	0	0
26	0	1	0	0	0	0	0	0	0	0	0	0
27	1	0	0	0	0	0	1	0	0	0	1	0
28	0	0	1	0	1	0	0	0	0	0	1	0
29	1	1	0	0	0	0	0	0	0	0	0	0
30	0	0	1	0	0	0	0	0	1	0	1	0
31	0	0	0	0	0	0	0	0	1	0	1	0
32	1	0	1	0	0	0	0	0	0	1	0	0
33	0	0	0	0	0	0	0	0	0	0	1	0
34	1	0	0	0	0	0	0	0	0	1	0	0
35	0	1	1	0	1	0	1	0	0	0	0	0
36	1	0	1	0	0	0	0	0	0	1	0	0
37	0	0	0	1	0	0	0	0	0	0	0	0
	12	**11**	**11**	**2**	**6**	**6**	**6**	**1**	**4**	**5**	**17**	**4**

All diagnoses are based on the ICD 10 coding and mostly reflect the codes used in Charlson co-morbidity (Except self harm, dialysis, sepsis and pneumonia)

4.3.4 Discussion

4.3.4.1 Summary of findings

Non-diabetic hypoglycaemia is rare in hospital in-patients. Estimates show that at a cut-off value of 2.7 mmol/l, 13 (95% CI 11–19) episodes per 10 000 admissions occurred in one year; and with a cut-off value of 3.3 mmol/l 50 (95% CI 33–93) episodes per 10 000 admissions per year. Estimates are slightly higher in patients above the age of 65 years (39 and 55 per 10 000 admission respectively at cut-off values of 2.7 and 3.3 mmol/l). All the cases of hypoglycaemia that occurred after admission could be explained by co-morbid conditions, principally alcohol dependence, renal failure, and sepsis.

4.3.4.2 Comparison with other studies

The estimates are similar to previous studies [172,191,192] except that of Mannucci et al [179] who reported an incidence of 8.6% in an elderly population from a single medical unit. However the study was often based on routine blood glucose concentrations measured in fasting state, at a cut-off point of 3.3 mmol/l, in patients with a high mean age (81 years) and admitted with co-morbidities commonly associated with hypoglycaemia. The study supports the previous observations that non-diabetic patients who develop hypoglycaemia are more likely to die than those who do not [169,179,191]. Similarly, hypoglycaemia in my study was often associated with renal disease, sepsis or pneumonia, and alcohol dependence, and other co-morbid diseases, in accord with previously suggested associations [176,179,181,191].

4.3.4.3 Future surveillance

Based on my analysis, a surveillance system could be established to detect an unexpected increase in the incidence of hypoglycaemia in non-diabetic patients. The optimal cut-off value of blood glucose concentration using the three sources was 2.7

mmol/l, which gave an estimated sensitivity of 73% and a positive predictive value of 53% in the training set. The value of 2.7mmol/l has also been used by others to define and establish the causes of hypoglycaemia in non-diabetic hospital patients [172,191]. The surveillance system would allow non-diabetic hypoglycaemia to be monitored, but for it to become routine, it would be necessary to integrate real-time blood glucose concentration estimates and the treatment trigger with the discharge data from the hypoglycaemic code trigger.

There were false positives in the proposed surveillance system, for the treatment trigger this was often a higher blood glucose value than 3.3mmol/l being treated or rare metabolic diseases that needed carbohydrate replacement. Reasons identified for the false positives are summarised in the box below.

Box 4.3: False Positives

Hypoglycaemia in discharge diagnostic code but no blood glucose value below 3.3 mmol/l:

1) Known to have hypoglycaemia intermittently linked to endocrinopathy following non Hodgkin's lymphoma but no episode while in hospital

2) Lowest blood sugar value in hospital was 3.4 mmol/l even though had a much lower value before admission

3) Likely coding error where hypoglycaemia was coded instead of hypokalaemia.

Hypo treatment given but no blood glucose value less than 3.3mmol/ l:

1) Treatment that was given for a higher blood glucose value than that of the cut-off stated (3.3mmol/l) – 5 admissions
2) Treatment given for a rare metabolic conditions to increase carbohydrate levels as an alternative energy source(Glutaryl Coenzyme A Dehydrogenase deficiency and Citrullinaemia) – 5 admissions (One patient admitted 4 times)
3) Possibly to prevent hypoglycaemia in a liver disease patient and one during surgery – 2 admissions
4) Possibly for a malnourished patient as a nutritional source – 1 admission
5) For collapse thinking it was due to hypoglycaemia but was not – 1 admission
6) Unable to determine or prescribed and not given – 3 admissions

4.3.4.4 Limitations

The study was retrospective and therefore has many limitations. All three sources of information were incomplete. I was able to overcome this by using capture-recapture technique and provide estimates of the true rates with relatively narrow confidence intervals. The estimates are derived using both, point of care blood glucose concentrations (capillary blood glucose) and laboratory blood glucose concentrations without applying any corrections. Therefore the estimates for each cut-off value could vary when comparing with estimates that are derived from either source alone. This may also alter the validity indicators (sensitivity and positive predictive values) of the proposed surveillance tool. However I would expect them to be within the confidence intervals calculated in my analysis. While I believe that PICS and the discharge diagnostic codes can be used together for surveillance of the incidence of non-diabetic hypoglycaemia, I have not formally tested this in a prospective data set. My study involves only one large hospital in UK but the reported frequency is unlikely to be an underestimate given the hospital has specialist renal and liver units where the incidence is likely to be higher.

4.3.5 Conclusions

Significant non-diabetic hypoglycaemia in hospital in–patients (at or below 2.7mmol/l) outside critical care is rare. It is sufficiently rare for occurrences to merit case-note review and diagnostic blood tests, unless an obvious explanation is found.

4.4 Glucose Metrics

4.4.1 Background

In primary care and outpatient clinics, glycaemic control of patients with diabetes is assessed using HbA1c; however HbA1c may have limited prognostic value in acute admissions [201,202] and in assessing glycaemic control for the inpatient stay. Therefore during inpatient admission blood glucose values are the only parameter available to assess patients' glucose control for the given period of stay. Even though evidence is lacking on what would constitute high quality targets for glucose control in non-critical care settings, there is consensus that both hyperglycaemia (>10mmol/l) and hypoglycaemia (<3.9mmol/l) should be avoided [47,104].

There are many indicators proposed in the literature to assess glucose control. Most have been reported relating to patients treated in intensive care units. They include mean morning glucose, maximum glucose, mean blood glucose, time averaged glucose and hyperglycaemic index. Mean morning glucose is the arithmetic mean of all blood glucose values collected in the morning, often defined as between 6.00 and 8.00AM [16,203]. Maximum glucose refers to just one glucose value, the highest observed during the inpatient stay [204]. However the mean morning glucose fails to take into account day time glucose and the maximum glucose indicator fails to give a comprehensive picture of all glucose values especially those indicating hypoglycaemia which have been shown to be harmful [58,59,144,164]. Mean blood glucose reflects the average of all blood glucose concentrations taken during a spell [205]. Time averaged glucose is described as the area under the curve after plotting all the blood glucose concentrations (y axis) in a specific time period and dividing it by the length of the observation period [203,206] . Hyperglycaemic index is again plotted in the same way but only the area above a predetermined cut off point (for

example above 7mmol/l) is taken into account and divided by the observation period [203,206]. The mean blood glucose and time averaged glucose don't give a clear picture of high and low values, both of which are just as important in clinical practice as the average glucose. The hyperglycaemic index reflects only hyperglycaemia. Both the time averaged glucose and hyperglycaemic index are also complex to calculate in routine practice and therefore are difficult to translate into practice in non critical care settings.

It is in this context that Goldberg et al [127] and colleagues proposed "Glucometrics", a composite of indicators, as a measure of quality glucose control in critical and non critical care settings. The aim of this section is to use a sample of POC BG data from UHB to describe the indicators proposed by Goldberg et al in a non critical care setting [127] .

4.4.2 Methods

In this section (4.4) instead of using the blood glucose values that are in the database for the period of 2007-2010, we extracted POC BG value for September 2012 to illustrate the different properties of Glucometrics and to look at the merits of using the different specified measures. This was done as current recordings of blood glucose values are much more complete than to previous years and will be pragmatically easier to demonstrate the indicators. September was chosen because it was the most recent month at the time of data extraction (October 2012). As the exercise is only to illustrate the value of indicators based on recorded POC BG values in measuring quality of blood glucose control in an institution, the data (POC BG values) derived from PICS were not linked to the PAS database or prescription data in PICS, therefore there is no differentiation between diabetes and non diabetic admissions. Blood glucose values are from non critical care setting.

Definitions of the indicators are derived from the publication by Goldberg [127] and the website [207] they have created to perform the Glucometric analysis for any institution. They describe three properties using three possible units (patient sample, patient day and patient stay). The first property, reflects the glucose exposure (mean glucose value); the second, reflects the efficacy of the glucose control (proportion within good control); and the third, a measure of adverse events (proportion with hypoglycaemia or hyperglycaemia).

Calculations were done using the web tool maintained by Yale Centre for Medical Informatics & Yale School of Medicine [207]. The tool excludes patients with only one recording of blood glucose for a given spell. This is done as an admission with one glucose value cannot reflect the institutional performance [207]. Considering the data extraction was to reflect the blood glucose values available in September, admissions that started before September and continuing into the month of September and likewise admissions starting in September and continuing into the next few months have been trimmed to the days they contributed in September alone.

Definitions of each indicator under the three properties are given below.

Glycaemic exposure

- Sample mean - This is calculated as the mean of all blood glucose values for the given period irrespective of whom and which date it originates from.
- Patient stay mean - Each patient's blood glucose throughout the stay is averaged and the mean of all average patient stays is calculated.
- Patient day weighted mean - Here each day of every patient's stay forms the unit of analysis. Therefore for a given patient on a given day the average of blood

glucose values are calculated. Thereafter the mean of all patient day averages is calculated.

Efficacy

- Samples within target range - The proportion of all available blood glucose concentrations that were within 4 – 10mmol/l (target range).
- Patient stays within target range - The proportion of all patient stays that had all their blood glucose concentrations between 4 -10mmol/l.
- Patient days within target range - Proportion of patient days that had all blood glucose concentrations within 4-10mmol/l (target range).

Adverse events

Hypoglycaemia

- Proportion of blood samples with a blood glucose concentration ≤ 3.9mmol/l (mild to moderate hypoglycaemia) and ≤2.2mmol/l (severe hypoglycaemia).
- Proportion of patient stays observed with a blood glucose concentration ≤3.9mmol/l and ≤2.2mmol/l.
- Proportion of patient days with a recorded blood glucose concentration ≤3.9mmol/l and ≤2.2mmol/l.

Hyperglycaemia

The definition used in the tool was blood glucose concentration ≥16.7mmol/l (300mg/dl).

- Proportion of blood samples with a blood glucose concentration ≥ 16.7mmol/l.
- Proportion of patient stays observed with at least one blood glucose concentration ≥16.7mmol/l.
- Proportion of patient days with at least one recorded blood glucose concentration ≥16.7mmol/l.

4.4.3 Results

There were 2,181 spells with POC BG values during the month of September 2012. Just over 50% (1,111 spells out of 2,181 total spells) had more than one POC BG. The 1,111 spells (patient stays) included in the analysis contributed to 18,531 samples and 6,231 patient days. Summary of the results are given in table 4.8 and described below.

Table 4.8: Glucose control indicators in UHB for the month of September 2012

	Patient-samples		Patient-stays		Patient-days	
Numbers contributing to analysis	18503		1111		6230	
Median (mmol/l)	8.0		7.8		7.9	
Mean (mmol/l)	9.3		8.6		8.8	
Adverse events	**N**	**%**	**N**	**%**	**N**	**%**
At least one glucose ≤ 2.2mmol/l	76	0.4	36	3.2	52	0.8
At least one glucose ≤ 3.9mmol/l	721	3.9	207	18.6	450	7.2
At least one glucose ≥ 16.7mmol/l	1553	8.4	256	23.0	790	12.7
Target range						
3.9 mmol/l < glucose < 10 mmol/l	11,592	62.7	832	74.9	4,461	71.6
Other ranges						
3.9mmol/l ≤ glucose < 6.1mmol/l	3,830	20.7	201	18.1	1,249	20.1
6.1 mmol/l ≤ glucose < 7.8mmol/l	4,069	22.0	347	31.2	1,679	27.0
7.8 mmol/l ≤ glucose < 10mmol/l	3,693	20.0	284	25.6	1,533	24.6
10 mmol/l ≤ glucose < 13.3mmol/l	3,117	16.9	200	18.0	1,085	17.4
13.3mmol/l ≤ glucose < 16.7mmol/l	1520	8.2	57	5.1	386	6.2

4.4.3.1 Glycaemic exposure in University Hospital Birmingham (September 2012)

The sample mean was 9.3mmol/l (median 8mmol/l) for the month of September in 2012. Using the same data calculated patient stay mean was 8.6mmol/l (median 7.8mmol/l) and patient day weighted mean was 8.8mmol/l (median 7.9mmol/l).

4.4.3.2 Efficacy in University Hospital Birmingham (September 2012)

The proportion of samples within target range (4 – 10mmol/l) was 62.7%. With patient stay as the unit of analysis proportion of patient stays within target range was 74.9%. A similar proportion (71.6%) was within target range when the unit of analysis was patient day.

4.4.3.3 "Adverse events" in University Hospital Birmingham (September 2012)

Hypoglycaemia

A blood glucose value ≤3.9mmol/l was found in 3.9% of blood samples, 18.7% of patient stays and 7.2% of patient days. A blood glucose value ≤2.2mmol/l was found in 0.4% of blood samples, 3.2% of patient stays and 0.8% of patient days.

Hyperglycaemia

A blood glucose value ≥ 16.7mmol/l was found in 8.5% of blood samples, 23.4% of patient stays and 12.8% of patient days.

4.4.4 Discussion

Among the three units used to assess glucose control in an institution, samples derived from all patients as a unit have limited value. They reflect blood glucose control for a short period of time and are dependent on the number of samples taken and can exaggerate adverse events where multiple samples are taken in quick succession after a hypoglycaemic or hyperglycaemic event. Patient stay as a unit helps to identify a subset of population prone to adverse events. However the number of days a patient stays considerably varies resulting in inconsistent assessment of glucose control across different patients and therefore in or between institutions and hospital wards. In contrast the patient day unit has a fixed time

period (24 hours) and is not dependent on varying length of stay between patients and is therefore often recommended as the preferred unit [207,208].

Glycaemic exposure with patient day as a unit can help hospitals to look at seasonal fluctuation in glycaemic control and determine improved control over time.

Describing the glucose control in a hospital based on all three properties has many advantages. As pointed out in the beginning of this chapter these metrics can act as a quality indicator for the care received by patients with diabetes. In particular monitoring of adverse blood glucose levels can instigate institution based initiatives that could help reduce these outcomes. Subset analysis of wards can identify educational needs of underperforming wards to improve their glucose control. Further any clustering of adverse outcomes such as severe hypoglycaemia in non diabetic patients may trigger the need to investigate for any unusual causes, such as malicious administration of insulin.

These metrics as quality indicators are only valuable if the population it refers to can be identified as diabetic or not. The algorithm I have proposed in chapter 3 or an alternative one is a necessity to ensure identification of patients who are diabetic or not. In addition to this there will be wards that may have an atypical population such as the liver unit, where avoiding hypoglycaemia is one of the mainstays of treatment, which might result in blood glucose values often reaching the hyperglycaemic threshold. Similarly certain specialities may have high co-morbidities, such as the geriatric units, leading to higher fluctuation in blood glucose in the patients in these units. Therefore a league table of “good control” wards and “poor control” wards should not be displayed but the information used after careful assessment of the

circumstances to provide support to improve competencies of staff in any poorly performing units.

4.4.5 Conclusions

Electronic recording of point of care blood glucose can assist in assessment of the quality of blood glucose control in an institution. Glucose meters with an automated system that are due to be implemented in UHB should reduce the workload for nursing staff and capture most of the point of care blood glucose values. Glucometrics, a composite of indicators, can be a useful tool to measure quality of institutional blood glucose control. Identification of diabetes status is important to meaningfully interpret the results.

CHAPTER 5

Identifying predictors and building a model to predict patients with diabetes who may have an adverse clinical outcome

5 Identifying predictors and building a model to predict patients with diabetes who may have an adverse clinical outcome

5.1 Overview

We noted in the introduction that people with diabetes are twice as likely to be admitted to hospital, have longer lengths of stay, higher frequency of complications and higher mortality rates compared to non-diabetics [14,20,23,28-30,33]. The Institute for Innovation and Improvement in UK (2008) has suggested that models of care based on specialist diabetes teams providing enhanced care, dietetic and foot care services for high risk inpatients, staff education and better care pathways can reduce these poor outcomes, a notion supported by clinical guidelines and other research findings [47,49,104,132,133]. However, as 15-20% of hospital beds are occupied by patients with diabetes, it has become increasingly difficult to identify which of these patients most need specialist team or nurse input. Recent national audits have shown that only a third of those in need of specialist input actually receive it [14,15] . I therefore hypothesized that an active case finding approach using clinical information systems to detect patients most in need of specialist input, without relying on referrals, may assist diabetes specialist teams to focus on the patients with the greatest need.

Criteria need to be defined to identify patients most in need of specialist input. To be of practical use, these criteria preferably should be available on hospital information systems. The “Think Glucose” campaign in England identified criteria (table 5.1) for specialist input, some of which can be incorporated as part of an active case finding approach using clinical information systems with clinical decision support [209]. These criteria include patients on insulin infusions (including those admitted with diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome) who can be

identified through electronic prescriptions; and patients having severe or recurrent hypoglycaemia or persistent hyperglycaemia who can be identified through electronic observations. But these criteria may still only identify a small proportion of patients in need of specialist input. Meanwhile several patient characteristics, biochemical and haematological profiles and co-morbidities have been identified as useful markers of prognosis in secondary care for both patients with and without diabetes [146,210-215]. These could be useful to identify patients for specialist input. These markers are described in the methods of section 5.3.2. In this chapter:

1) I will first examine one such prognostic marker, presence of foot disease, to determine if it is associated with increased length of stay and in-hospital mortality. I chose to look at this for the following reasons; a) to determine if these patients with foot disease have poor clinical outcome in University Hospital Birmingham; b) to advocate the documentation of presence of foot disease in the PICS information system on admission to automatically alert these patients to the foot care team; c) to add to the evidence base on excess mortality linked with diabetic foot disease, as there is sparse evidence on in-hospital mortality as an outcome; and d) if found to have a link, to use this as part of the model (section 5.3) I will be building to identify patients with diabetes whom may have an adverse outcome during their inpatient stay.
2) I aim to develop a prediction model that will help identify patients with diabetes who are most likely to have an adverse event during their stay. Adverse events are defined as either “excessive” length of stay or inpatient mortality. I chose to do this as there is no formal prognostic model that is available to identify, at or around the time of admission, patients with diabetes who may end up with poor clinical outcomes. I am particularly interested in

variables available at or around the time of admission, as a model built on this basis will be useful for anticipatory care (active case finding). If a useful model could be built then it could be incorporated into the PICS system and used to alert the diabetes specialist team just after admission or within the first few days of admission. This may have a positive impact on the patient related clinical outcomes and hospital related costs.

Table 5.1: "Think Glucose" campaign referral criteria for specialist team input

Referral Criteria	Can it be identified by PICS
Admission for urgent or major elective surgical procedure	Possible if wards are specified, such as orthopaedic wards, and if identifiable codes are present stating if they are major surgical procedure
Acute coronary syndrome	Possible if either documented as reason for admission in PICS or using ward as an indicator (example: Coronary Care Unit)
DKA/HONK	Identifiable using prescribed insulin regime
Hyperglycaemic state	Possible as discussed in chapter 4
Severe hypoglycaemia	Possible as discussed in chapter 4
Newly diagnosed type 1 diabetes	Not identifiable. Reliant on referral
Newly diagnosed type 2 diabetes	Not identifiable. Reliant on referral
IV Insulin infusion with glucose outside limits	Possible using electronic prescription data and electronic observation together
Previous problems with diabetes as inpatient	Not identifiable
IV insulin infusion for over 48 hours	Possible using electronic prescription data
Impaired consciousness	Possible only in wards where Glasgow Coma Scale (GCS) is recorded as part of electronic observation chart
Unable to self-manage	Not possible. Reliant on referral
Parenteral or enteral nutrition	Possible using electronic prescription data
Foot ulceration	Only possible if foot examination is documented in PICS on admission
Sepsis	Not possible directly but blood results such as high CRP, Neutrophil count in combination with request for blood culture may give indications
Vomiting	Not identifiable. Reliant on referral
Patient request	Not identifiable. Reliant on referral

5.2 Inpatient outcomes in patients with foot disease who have diabetes

5.2.1 Background

In the introduction we noted national audits in the UK and USA suggest that 15-20% of hospitalised patients have a diagnosis of diabetes mellitus [15,103]. Around 10% of patients admitted with diabetes have active diabetic foot disease during their hospital stay [15]. Recent national reports have highlighted the economic cost of this problem [66] , the lack of a multidisciplinary team approach to foot care in hospitals [15] and the need for setting up such care to prevent adverse outcomes as per National Institute for health and Clinical Excellence (NICE) guidelines [216].

Diabetic foot disease is often the precursor to severe sequelae such as amputation. Long term follow up studies have demonstrated poor quality of life and increased long term mortality among these patients [61,63-65,217,218]. Although evidence exists that diabetic foot disease is associated with increased length of stay during hospital admission [66], there is limited evidence on its association with inpatient mortality. Studies that investigated inpatient mortality included small cohorts of patients and had no control groups [219-221], or focused only on outcomes of those who had amputation [222]. Inpatient mortality and length of stay in patients with foot disease who do not undergo amputation are equally important to: 1) understand excess mortality observed in patients with diabetes in hospital settings; and 2) emphasise the need to establish multidisciplinary foot care teams providing the best quality of care.

Therefore here I have aimed to determine whether in-patient mortality and length of stay in patients with diabetes is greater in those with foot disease than those without foot disease at University Hospital Birmingham (UHB).

5.2.2 Methods

As previously described the setting is UHB and patients with diabetes were identified as having diabetes based on the diagnostic code for diabetes in PAS and based on prescribed diabetic medication in PICS [92].

Definition of foot disease

Foot disease was defined based on NICE guideline definition by using ICD 10 codes and Office of Population, Censuses and Surveys Classification of surgical operations and procedures version 4 (OPCS 4) codes. NICE described foot disease as feet affected by neuropathy, peripheral arterial disease, foot deformity, infections, ulcers and gangrene [216]. I identified a list of codes (ICD 10 and OPCS 4) that may indicate foot disease. Then two colleagues, a consultant diabetologist with a special interest in foot disease (MS) and a clinical specialist podiatrist (IW), and myself, categorised them as either 'highly' or 'less' indicative of foot disease. I predefined that those in the highly indicative category would be used as our case definition of foot disease in patients with diabetes. The final set of codes that were in the 'highly' indicative category were mostly similar to the ones used in the national report [223] produced by Diabetes Health Intelligence. There were two exceptions. One was the code for decubitus ulcer, which was used in the national economic study but we considered as less indicative. The common site for decubitus ulcer is the sacrum region, buttocks and the heel region [224,225]. However, due to these multiple common sites the predictive value of the code for foot disease is likely to be low. Further those with decubitus ulcers are known to have poor clinical outcomes [226] and therefore will bias any results obtained. We therefore categorised them as less likely to be indicative of foot disease. The other exception was we accepted the ICD 10 codes for atherosclerosis of arteries in extremities (I702), neuropathic arthropathy

(M146) and peripheral neuropathy (G632) as codes that independently describe foot disease. These codes indicate foot problem in diabetes patients and are in line with the NICE guideline definition [216], whereas these were not part of the Diabetes Health Intelligence definition [223]. Diabetes Health Intelligence primarily focussed on amputation and foot ulcers and therefore did not include these codes. Our approach meant we could also perform sensitivity analyses using; 1) only the highly specific category as predefined; and 2) the same codes as in the national report. Details of the codes included in each category are given in appendix 5.1.

Outcomes

I compared the inpatient mortality and length of stay recorded in PAS among patients with diabetes 1) who had amputation, 2) had foot disease but did not have an amputation, and 3) those without foot disease. I didn't differentiate between major or minor amputation as the numbers in the amputation category was small. Length of stay was calculated by deducting the admission time from the discharge time to the closest hour.

In the three groups I also looked at the available blood results taken in the first 48 hours of admission that may indicate an underlying presence of inflammation (C-Reactive Protein/CRP, platelet), infection (neutrophil, CRP), or tendency to develop foot disease (underlying poor nutritional status indicated by albumin and poor renal function indicated by creatinine & estimated Glomerular Filtration Rate (eGFR)).

Statistical analysis

The demographic characteristics, blood results and morbidity characteristics of the patients with and without foot disease are summarised using means (standard deviation; SD) or medians (inter-quartile range; IQR) for continuous data and using

proportions for categorical data. To allow for the clustering effect of patients being admitted more than once Generalised Estimated Equations (GEE) were used. A linear regression model was used to study the length of stay; and a logistic regression model was used to study the effect on inpatient mortality outcome. Due to the skewed length of stay data, a log transformation was carried out to normalise the data before multivariate analysis. Covariates controlled in the regression analyses were age (years), gender, ethnicity, deprivation quintile (based on income deprivation), admission types (emergency or elective), modified Charlson co-morbidity score, admission to Intensive Care Unit (ICU) and use of insulin. The modified Charlson co-morbidity score was calculated by deducting the score given for diabetes [58]. The effect sizes from the multivariate analyses are reported as relative ratios (exponential of the regression coefficient of the log transformed data) for the length of stay and as odds ratios for inpatient mortality. Confidence intervals are given at 95% (95%CI) and P-values less than 0.05 were deemed significant. Data were analyzed using STATA® 12 software, using the GEE class of models. The analyses was repeated (sensitivity analysis) using the combination of diagnostic codes used by Diabetes Health Intelligence as described earlier, to determine if this had any effect on the estimates obtained using highly indicative codes alone.

5.2.3 Results

As described in previous chapters 25,118 admissions with diabetes consisting of 12,817 patients in the period of 2007 to 2010 were identified. In this period 1,149 admissions (4.6%) had highly indicative codes for foot disease and another 195 admissions (0.8%) had an amputation involving their lower limb carried out (table

5.2). In all three groups median ages were similar (varying between 66 to 68 years). Compared to those without foot disease, admissions with foot disease had a similar gender ratio (approximately 58% males) but in the amputation category three quarters (75%) were males. There was an incremental increase in the use of insulin observed from those without foot disease (52%), to those with foot disease (67%) and to those with amputation (91%). Similarly increasing co-morbidity burden was noted in these three categories (modified Charlson co-morbidity score of 1 or more 59% in no foot disease; 63% in foot disease; and 77% in amputation related admissions) (table 5.2).

Table 5.2: Characteristics and outcome of the admissions based on presence of foot disease

Patient Characteristics	No Foot Disease (N=23,774)	Foot Disease excluding amputations (N=1,149)	Amputations (N = 195)
Age median (IQR) years	67 (55,76)	68 (56,77)	66 (56,74)
*Gender N (%)			
Male	13,675 (57.5)	676 (58.8)	147 (75.4)
Female	10,098 (42.5)	473 (41.2)	48 (24.6)
Ethnicity N (%)			
White	16,690 (70.2)	963 (83.8)	165(84.6)
Asian	4,310 (18.1)	103 (9.0)	16 (8.2)
Black	1,268 (5.3)	49 (4.3)	14 (7.2)
Other	1,506 (6.3)	34 (3.0)	0 (0.0)
*Social class N (%)			
Least deprived 1	1,302 (5.6)	50 (4.4)	5 (2.6)
2	2,219 (9.6)	110 (9.8)	27 (14.1)
3	3,999 (17.2)	195 (17.3)	28 (14.6)
4	5,098 (22.0)	310 (27.5)	46 (24.0)
Most deprived 5	10,579 (45.6)	461 (40.9)	86 (44.8)
Type of admission N (%)			
Elective	7,271 (30.6)	120 (10.4)	46 (23.6)
Emergency	16,503 (69.4)	1,029 (89.6)	149 (76.4)
ICU Use			
No	21,897 (92.1)	1,092 (95.0)	176 (90.3)
Yes	1,877 (7.9)	57 (5.0)	19 (9.7)
Modified Charlson co-morbidity score N (%)			
0	9,793 (41.2)	421 (36.6)	45 (23.1)
1	5,055 (21.3)	253 (22.0)	65 (33.3)
≥2	8,926 (37.5)	475 (41.3)	85 (43.6)
Insulin use N (%)			
Yes	12,452 (52.4)	772 (67.2)	177 (90.8)
No	11,322 (47.6)	377 (32.8)	18 (9.2)
Outcome			
In-patient death N (%)			
Yes	1,175 (4.9)	97 (8.4)	14 (7.2)
No	22,599 (95.1)	1,052 (91.6)	181 (92.8)
Length of stay in median (IQR) days	3.4 (1.2,9.2)	9.7 (3.97,20.9)	17.5 (9.0,31.6)

*Deprivation quintile based on income deprivation score. Adds up to 24,515 instead of 25,118 due to missing post code values. Gender adds up to 25,117 instead of 25,118 due to one missing value.

In-hospital mortality was 4.9% in the no foot disease group, 8.4% in the foot disease group and 7.2% in the amputation group. In comparison to those without foot disease the adjusted odds ratio was 1.31 (95%CI 1.04-1.65 P=0.02) in the foot disease group, and 1.02 (95%CI 0.56-1.85 P=0.95) in the amputation group (Table 5.3). Association between in-hospital mortality and foot disease persisted when using the codes suggested by Diabetes Health Intelligence Unit but the odds ratio was much larger (1.87 vs. 1.31- Table 5.4). Other variables with key significant associations with in-hospital mortality noted were increasing age, emergency admission, ICU care, increasing modified Charlson co-morbidity score and use of insulin (Table 5.3).

Median length of stay was 3.4 (IQR 1.2-9.2) days in the no foot disease group, 9.7 (IQR 4.0-20.9) days in the foot disease group and 17.5 (IQR 9.0-31.6) days in the amputation group. Compared to those without foot disease the adjusted relative ratio was 2.01 (95%CI 1.86 – 2.16 P<0.001) in the foot disease group and 3.08 (95%CI 2.60-3.65 P<0.001) in the amputation group (Table 5.3). In the sensitivity analysis this association persisted when the Diabetes Health Intelligence Unit codes (including decubitus ulcer) were used, although relative ratio was slightly larger (2.34 vs. 2.01 and 3.16 vs. 3.08 respectively for foot disease and amputation-Table 5.4). Other highly significant (P<0.001) predictors noted were increasing age, female gender, emergency admission, ICU care, increased modified Charlson co-morbidity score and use of insulin (Table 5.3). Asian ethnicity interestingly was associated with shorter length of stay (OR 0.89, 95%CI 0.85-0.94, P<0.001).

On admission, based on available blood results, there were gradient increases noted in markers of inflammation (CRP, platelet) and infection (neutrophil) when comparing no foot disease group, foot disease group and amputation group (Table 5.5). Median

CRP was 23mg/dL (IQR 8, 75 mg/dL) in the no foot disease group; 60mg/dL (IQR 22, 135 mg/dL) for those with foot disease not resulting in amputation; and 84 mg/dL (IQR 40, 180 mg/dL) for those with amputation. Estimated GFR was lower in the foot disease and amputation groups (approximate median eGFR 50 ml/min/1.73m^2) than the no foot disease group (median 60 ml/min/1.73m^2). Lower levels of albumin were present on admission in the foot disease group (mean 36.0g/L) and amputation group (mean 34.2g/L) in comparison to the no foot disease group (mean 38.6g/L).

Table 5.3: Adjusted* Odds Ratio for inpatient mortality and adjusted* relative ratio# for length of stay in patients with diabetes

Characteristics	Unadjusted odds ratio for inpatient mortality	Adjusted odds ratio For inpatient mortality	P value (adjusted analysis)	Unadjusted relative ratio# for length of stay	Adjusted relative ratio# for length of stay	P value (adjusted analysis)
Age	1.06 (1.05-1.06)	1.06 (1.05-1.07)	<0.001	1.016 (1.015-1.018)	1.015 (1.014-1.016)	<0.001
Gender						
Male	1	1		1	1	
Female	1.11(1.00-1.25)	1.06(0.94-1.20)	0.32	1.05(1.01-1.09)	1.09 (1.05-1.13)	<0.001
Admission type						
Elective	1	1		1	1	
Emergency	5.44 (4.42-6.69)	6.83 (5.48-8.50)	<0.001	1.35 (1.30-1.40)	1.44 (1.39-1.49)	<0.001
Ethnicity						
White	1	1		1	1	
Asian	0.76 (0.65-0.90)	0.87 (0.73-1.04)	0.13	0.81 (0.77-0.85)	0.89 (0.85-0.94)	<0.001
Black	0.83 (0.64-1.08)	0.74 (0.56-0.99)	0.04	0.98 (0.89-1.07)	0.95 (0.87-1.03)	0.21
Other	0.72 (0.55-0.93)	1.03 (0.78-1.37)	0.84	0.60 (0.55-0.65)	0.79 (0.73-0.84)	<0.001
Social Class						
(Most Deprived) 5	1	1		1	1	
4	1.21 (1.05-1.39)	1.03 (0.88-1.20)	0.75	1.08 (1.02-1.14)	0.99 (0.95-1.04)	0.75
3	1.03 (0.87-1.21)	0.92 (0.77-1.09)	0.33	1.08 (1.02-1.14)	1.02 (0.97-1.08)	0.39
2	0.96 (0.78-1.18)	0.83 (0.66-1.04)	0.11	1.17 (1.09-1.26)	1.05 (0.98-1.11)	0.16
(Least Deprived) 1	0.87 (0.67-1.15)	0.84 (0.63-1.13)	0.26	1.20 (1.10-1.30)	1.13 (1.04-1.22)	0.002
Unavailable Post Code	0.41 (0.24-0.73)	0.40 (0.23-0.72)	0.002	1.35 (1.19-1.53)	1.23 (1.10-1.38)	<0.001
ICU care received						
No	1	1		1	1	
Yes	4.18 (3.64-4.80)	6.87 (5.80-8.13)	<0.001	4.33 (4.07-4.59)	3.41 (3.22-3.62)	<0.001
Modified Charlson co-morbidity score						
0	1	1		1	1	
1	3.22 (2.65-3.92)	2.47 (2.02-3.03)	<0.001	1.59 (1.52-1.67)	1.40 (1.34-1.45)	<0.001
2	6.10 (5.15-7.22)	5.46 (4.59-6.50)	<0.001	2.21 (2.12-2.30)	1.85 (1.78-1.92)	<0.001
Insulin use						
No	1	1		1	1	
Yes	1.67 (1.49-1.88)	1.34 (1.18-1.53)	<0.001	2.22 (2.14-2.30)	1.78 (1.72-1.85)	<0.001
Foot Disease						
No	1	1		1	1	
Yes	1.77 (1.43-2.20)	1.31 (1.04-1.65)	0.02	2.37 (2.18-2.57)	2.01 (1.86-2.16)	<0.001
Yes with amputation	1.49 (0.86-2.57)	1.02 (0.56-1.85)	0.95	4.17 (3.44-5.04)	3.08 (2.60-3.65)	<0.001

* Covariates included in the multivariate analysis were age, gender, ethnicity, social class, admission type, modified Charlson co-morbidity score, ICU care, insulin use and foot disease category.

Relative ratio is the exponential of regression coefficient obtained from the analysis of log transformed length of stay data

Table 5.4: Sensitivity analysis using different set of codes to define foot disease

Different set of ICD10 Codes	Adjusted* odds ratio for inpatient mortality	P value	Adjusted* relative ratio# for length of stay	P value
Foot disease based on highly indicative ICD10 codes				
No	1		1	
Yes	1.31 (1.04-1.65)	0.02	2.01 (1.86-2.16)	<0.001
Yes with amputation	1.02 (0.56-1.85)	0.95	3.08 (2.60-3.65)	<0.001
Foot disease based on ICD10 codes used by Diabetes Health Intelligence				
No	1		1	
Yes	1.87 (1.52-2.29)	<0.001	2.34 (2.17-2.51)	<0.001
Yes with amputation	1.06 (0.58-1.92)	0.85	3.16 (2.67-3.75)	<0.001

* Covariates included in the multivariate analysis were age, gender, ethnicity, social class, admission type, modified Charlson co-morbidity score, ITU care, insulin use and foot disease category.

Relative ratio is the exponential of regression coefficient obtained from the analysis of log transformed length of stay data

Table 5.5: Difference in available admission blood results between the three foot disease categories

Blood results (Based on available results in the first 48 hours)	No foot disease (N = 23,774)	Foot disease excluding amputation (n=1,149)	Amputation (N =195)
Albumin (g/L)			
N (%)	16,344 (69)	863 (75)	156 (80)
Mean (SD)	**38.6 (6.2)**	**36.0 (5.8)**	**34.2 (6.4)**
Creatinine (µmol/L)			
N (%)	17,984 (76)	934 (81)	170 (87)
Median (IQR)	**106 (80,173)**	**118 (89,190)**	**122 (90,191)**
eGFR (ml/min/1.73m^2)			
N (%)	17,984 (76)	934 (81)	170 (87)
Median (IQR)	**60 (38,81)**	**51 (31,73)**	**49 (33,73)**
CRP (mg/L)			
N (%)	10,344 (44)	746 (65)	148 (76)
Median (IQR)	**23 (8,75)**	**60 (22,135)**	**84 (40, 180)**
Neutrophil ($10^{9/}$L)			
N (%)	17,335 (73)	923 (80)	169 (87)
Median (IQR)	**6.4 (4.4, 9.4)**	**7.6 (5.3,10.8)**	**9.0 (6.5,12.1)**
Platelet ($10^{9/}$L)			
N (%)	17,194 (72)	919 (80)	168 (86)
Mean (SD)	**246.0 (104.5)**	**278.4 (112.9)**	**327.5 (121.9)**

N (%) indicate the number and the percentage of the total admissions contributing to the blood results

5.2.4 Discussion

5.2.4.1 Summary of findings

Foot disease in people with diabetes admitted to hospital is associated with higher inpatient mortality and increased length of stay. The odds of inpatient mortality and length of stay were respectively 31% and 101% greater in those with foot disease compared to those without foot disease. As expected, the length of stay for those with amputation was 3 times higher, although there was no difference in the odds ratio noted for inpatient mortality. The latter finding is likely due to the smaller numbers (N=195) in the amputation group and the fewer outcomes (14 deaths) noted during the period of study. In addition to these findings, admissions with foot disease (both with and without amputation) have higher CRP, neutrophil and platelet count. They also were found to have relatively poor renal function and nutritional status.

5.2.4.2 Potential explanations and implications of findings

Increased risk of inpatient mortality may be associated with complications arising from foot ulcers such as sepsis. Patients with foot ulcers identified early during their admission with raised markers of inflammation and infection such as CRP and neutrophils need to be managed aggressively to avoid such complications. The presence of foot disease may also be an indication of poor peripheral circulation; which has been shown to be associated with cardiovascular events and death [227,228]. Furthermore it may also be a marker of disease burden such as an indication of co-existing cardiovascular autonomic neuropathy, which is also associated with increased mortality [229]. The findings on length of stay is consistent with that of Kerr [66] who reported that people with diabetic foot ulcers even if admitted for reasons other than non ulcer related health conditions end up with

excess length of stay. Asian ethnicity interestingly was associated with reduced length of stay. One previous analysis in the same hospital over a much longer period of time (2000-2007) did observe this association [230]. As the association is limited to length of stay it may have been due to factors that were not accounted for in the analysis such as social circumstances and discharge care pathways. For example they may have extended family support that could facilitate early hospital discharge or they may have had premature discharge due to poor understanding of their care needs. In addition to these findings I found that renal function was worse in those with diabetic foot disease and in those who underwent amputation. Chronic renal disease and being on dialysis have been shown to be predictors of long term mortality in diabetes patients with foot ulcers [218]. Such patients with diabetic foot ulcers who have renal impairment and /or poor nutritional status may need additional care and support during their inpatient stay.

Altogether the findings highlight the presence of foot disease as an indicator for urgent action and the need for all hospital trusts to adhere to current NICE guidelines to assess the feet of patients with diabetes in the first 24 hours of admission and for each hospital to have a designated specialist foot care team. This on its own still could be inadequate without other interventions as only a third of clinically indicated patients are referred to these teams [15]. One option being discussed at UHB is to implement a proactive approach to use clinical decision support systems to make foot assessment mandatory and an automated alert of patients with foot problems to the multidisciplinary foot care team.

5.2.4.3 Limitations

The main limitation of the study is the likely bias created by the definition of foot disease using routinely available data. In particular peripheral vascular disease and

peripheral neuropathy are poorly documented; in fact foot examinations are rarely actively carried out during hospital stays [15]. However, I hoped to minimise this bias by using pre-specified criteria for defining diabetic foot disease codes and by conducting sensitivity analysis using a different definition. It was reassuring to note the criteria were similar to that used in the national report [223]. Other limitations include, the retrospective nature of the study; not controlling for factors such as smoking, diabetes duration and glycaemic control; and only patients admitted to one hospital being included in the analysis. These limitations do not allow direct inference of causality or generalisability to other settings.

5.2.5 Conclusions

Foot disease in hospitalised patients with diabetes is associated with increased length of stay and inpatient mortality. Even though causative evidence is lacking, the data supports the current national priority to set up specialist inpatient diabetes foot care teams with the hope that it will reduce adverse outcomes and improve quality of care for patients with diabetes admitted to hospitals. Future studies should evaluate the impact of implementing the recommendations of NICE guidelines and possibly study the impact of a decision support to automatically refer patients with foot disease to foot care teams.

5.3 A prediction model to identify hospitalised patients with diabetes who may have an adverse outcome

5.3.1 Background

Prediction models are widely used in primary care for clinical decision making, such as the cardiovascular risk scores [71,77] to determine the requirement for lipid lowering treatment. There are prediction models in a hospital setting as well, for example the Rockall score [231] to aid the management of upper gastrointestinal bleeding. As justified in the overview of this chapter there is no formal prediction model to identify patients with diabetes whom might have an adverse outcome during their hospital stay. Therefore in this section the aim is to develop one such prediction model that will help the diabetes specialist team to identify hospitalised patients with diabetes whom potentially may have an adverse event.

5.3.2 Methods

5.3.2.1 Setting and databases

The setting, University Hospital Birmingham (UHB), and the databases (PICS and PAS) have been previously described. Patients were identified as having diabetes using both discharge diagnostic codes and prescription data as explained in chapter 3.

5.3.2.2 Outcome of interest

The adverse outcome is a composite outcome and is defined as either “excessive” length of stay or death.

5.3.2.2.1 Calculating “excessive” length of stay

Initially all admissions (both with and without diabetes) were categorised into 260 groups of clinical conditions based on the primary diagnosis in the discharge diagnostic code. The 260 groups are defined as per the clinical classification system (CCS) produced by the Agency for Health Care Research and Quality (AHRQ) and

recently adopted by the NHS information centre [232] (appendix 5.2). The median length of stay was derived for each clinical condition for non-diabetic patients. The excess length of stay for each admission with diabetes was defined as the difference between the actual length of stay and the median length of stay for non-diabetic patients with the same group of clinical conditions. An “excessive” length of stay is defined as an excess length of stay greater than 75th centile of all diabetic admissions. This cutoff was selected because 25% of admissions with diabetes accounted for 85% of excess length of stay in patients with diabetes. The cutoff point also corresponds to 6 days more than what would be expected for any given group of clinical conditions in a non-diabetic patient.

The methodology avoids the need to know the condition with which the patient is admitted, this is important because the diagnosis (and hence group of clinical conditions) may not be clear at the time of admission.

5.3.2.3 Prognostic models

Three models are presented: a pragmatic model, a test model and an ideal model. The pragmatic model is intended to be used to predict adverse outcomes early in admission. It uses clinical pathological test results instead of a measure of co-morbidity because diagnoses may not be available at or around the time of admission. The test model replaces the clinical pathological test results from the pragmatic model with a measure of co-morbidity (modified Charlson co-morbidity score); to determine whether these clinical pathological test results are a good alternative for measuring case-mix. The ideal model includes all variables available at discharge and so includes clinical pathological test results, modified Charlson co-morbidity score and a measure of deprivation.

5.3.2.3.1 Prognostic factors included and not included in the pragmatic model

As the purpose of the pragmatic model is to identify patients whom may benefit from being seen by specialist team, variables included should reflect those that are usually available within first 24-72 hours of admission. Variables such as age, gender, ethnicity and admission type (emergency or elective) are readily available. Deprivation levels (based on income deprivation level of the post code of a patient) are difficult to compute and are pragmatically not obtainable during the initial period of admission. Furthermore they do not seem to impact on the outcome of interest based on my previous work on foot disease. Considering that the presence of foot disease may be recorded in the future as part of PICS at UHB or any other electronic health record in other hospitals, in the first 24-48 hours as per NICE guidelines [49], this variable will be included in the model. Foot diseases were defined based on ICD-10 codes as described in the previous section. Here one of the assumptions is that foot disease was present at the time of admission and has not developed during the hospital stay. Similarly I have assumed patients who were prescribed insulin during their stay were initiated on the medication within 72 hours of admission. If the patient is in Intensive Care Unit (ICU) setting or not will also be included considering most are admitted to ICU within the first 24-72 hours (75% at 72 hours; 68% at 48 hours; and 52% at 24 hours in our database). Information on co-morbidities may not be available to extract from hospital information system at time of admission and therefore a score such as modified Charlson co-morbidity score for patients with diabetes [58] may not be appropriate.

In view of the non availability of co-morbidities, additional predictors that are available on admission, which can sufficiently replace modified Charlson co-morbidity score, are needed. Albumin levels can reflect nutritional status or chronic

liver disease and similarly estimated Glomerular Filtration Rate (eGFR) can reflect renal disease: both liver and renal diseases are part of Charlson co-morbidity score. Low albumin levels and reduced eGFR have been cited in previous literature to be associated with poor clinical outcomes (mortality and increased length of stay) during hospital stay [233-235]. Low serum sodium levels have been also associated with increased length of stay and inpatient mortality [211,212,236]. In the same way high and low potassium levels have been cited as showing an association with inpatient mortality in acute myocardial infarction patients probably by precipitating arrhythmias [237]. Likewise inflammatory status, as indicated by C-reactive protein was found to be associated with higher length of stay, inpatient mortality, and subsequent 1-year hospital bed day occupancy [213]. Other clinical pathological results that have been reported to be associated with both the outcome include low haemoglobin [214], high white cell count [238] and high and low admission blood glucose concentrations [19,58,59,174,215]. I was not able to include admission glucose levels as they were sparsely available in the database (74% missing value for any glucose measurements). Instead of white cell count I have opted for neutrophil counts as markers derived from them have better predictability in terms of sepsis [239].

The first value of the clinical pathology tests for each admission was included in the analysis. Most were available (94%) within the first 72 hours of admission.Cut off points to categorise the clinical pathological results were based on; 1) normal ranges; 2) definitions of severity for a given marker (example GFR reflecting stages of renal disease as per guidelines [240]); 3) adequate number of groups to illustrate any dose response relationship; and 4) sufficient numbers in each group to observe any meaningful results.

5.3.2.4 Dealing with missing biochemical values

Missing values were mostly around 20% for most variables except for CRP where 44% of the admissions had a missing value. Multiple imputations (creating additional 10 datasets) were carried out using the Multiple Imputations by Chained Equations (MICE) with Predicted Mean Matching (PMM). Stata 12 supports these imputation methods allowing imputing different type of variables (categorical as well as continuous) at the same time using the CHAINED command. PMM command helps to restrict the range (by matching the predicted value to the closest value in the dataset) from which an imputed value could be picked for each variable and at the same has the property to be used with the CHAINED command. More details are available in appendix 5.3

5.3.2.5 Variable selection and model building

Considering the outcome was binary (adverse event or not) a logistic regression model was constructed. All variables were selected based on their clinical significance as identified from the literature. Therefore they were preserved in the model irrespective of their statistical significance [241,242]. This meant I did not carry out any stepwise procedure in selecting the variables to be included. Neither did I use any interaction terms as these will often add complexity and are difficult to use in clinical practice.

To account for the clustering effect created by the same patient being admitted more than once, Generalized Estimating Equations (GEE) were used [243,244].

5.3.2.6 Internal validation

This was carried out using bootstrapping techniques. For each of these 10 imputed datasets, I applied a bootstrap procedure (2000 re-samples) to obtain 10 sets of

shrunken regression coefficients and c-statistics which were then combined using Rubin's rule [245].

5.3.2.7 Assessment of model performance

I have assessed the model performance by its ability to discriminate those with and without the outcome of interest (discrimination) and by looking at the agreement between the observed and predicted outcome (calibration). In addition the sensitivity, specificity, positive predictive values, negative predictive values and likelihood ratios were determined. To assess discrimination, a Receiver Operating Characteristic (ROC) curve was constructed and area under the curve (Harrell's C-statistics) was calculated. C statistics were compared between the three models using non parametric tests. Calibration was assessed by plotting predicted probabilities of outcome, by decile groups, against observed probabilities of outcome (in same decile group) and by overlaying a smoothed calibration curves (using lowess algorithm) to judge against a linear line [241].

5.3.2.8 Presentation of findings and models

The demographic characteristics, blood results and morbidity characteristics of the patients with and without the adverse outcome are summarised using means (standard deviation; SD) or medians (inter-quartile range; IQR) for continuous data and using proportions for categorical data. Odds ratios are presented from multivariate analysis with 95% confidence intervals. P values less than 0.05 were deemed significant. Data analyses were carried out using Stata 12 software [246]. Coefficients, model performance and sensitivity analysis are reported for the pragmatic model only. For the other two models (test model and ideal model) only the area under the curve are reported.

5.3.3 Results

Out of the total 171,067 admissions to University Hospital Birmingham, during the period of 2007-2010, 25,118 (14.7%) had diabetes. Out of the 25,118 admissions 6,281 (25%) were categorised as having an “excessive” length of stay and 1286 (5.1%) died. Excluding overlaps this meant 6,928 (28%) had an adverse outcome. Among these 25,118 admissions, 10,596 (42%) admissions had an expected length of stay less than or equal to the median length of stay of the same presenting clinical condition of non diabetic patients. The remaining patients (N=14,522; 58%) contributed to 146,680 excess days with a median of 4.7 days and a mean of 10.1 days. The 6,281 admissions identified as contributing markedly to excess length of stay accounted for 85% (124,803 days) of the excess days.

Admission characteristics and clinical pathology tests of those with and without adverse events are given in table 5.6 and 5.7. Unadjusted and adjusted odds ratios of the predictors used in the final model are given in table 5.8. In the adjusted model with an increasing age group there was an incremental rise in the odds of adverse outcome. The oldest age group (≥85 years) had an OR of 5.64 (95%CI: 4.66-6.81) in comparison to the youngest (16-44 year). Females had a slightly higher odds of having an adverse event (OR=1.08, 95%CI: 1.00-1.16), while those of Asian ethnic minority had a significantly lower chance of having an adverse event (OR=0.86, 95%CI: 0.78-0.94). Those admitted as an emergency (OR=2.94, 95%CI: 2.69-3.21), or on Insulin (OR=1.89, 95%CI: 1.76-2.03), or with foot disease (OR=2.46, 95%CI: 2.16-2.80) were at high odds of having an adverse event. As expected being in an ICU setting had the highest odds ratio (OR=10.79, 95%CI: 9.52-12.22).

Severe (<125 mmol/l) hyponatraemia had higher odds (OR=1.71, 95%CI: 1.26-2.32) of having an adverse outcome than mild to moderate (125-134 mmol/l)

hyponatraemia (OR=1.17, 95%CI: 1.06-1.28). Similarly the greater the severity of hypernatraemia the larger the effect size was (145-154 mmol/l OR=1.31, 95%CI: 1.12-1.54 and >155 mmol/l OR=4.05, 95%CI: 1.84-8.91). Such a dose response relationship favouring an adverse outcome was also noted with; lowering haemoglobin level (anaemia) and hypoalbuminaemia; and rising CRP levels and neutrophil count. Hypokalaemia (OR=1.79, 95%CI: 1.34-2.39) but not hyperkalaemia (OR=1.00, 95%CI: 0.80-1.26) was associated with either having increased length of stay or death. An estimated GFR less than 30 ml/min/1.73m^2 had an odds ratio of 1.31 (95%CI: 1.15-1.48) in comparison to normal GFR (≥90 ml/min/1.73m^2).

Table 5.6: Baseline characteristics of admissions with and without the adverse outcome

Patient Characteristics	No adverse outcome (N=18,190)	Adverse outcome present (N= 6,928)
Age category N (%)		
16-44	2,051 (11.3)	373 (5.4)
45-54	2,698 (14.8)	686 (9.9)
55-64	4,039 (22.2)	1,245 (18.0)
65-74	4,789 (26.3)	1,867 (27.0)
75-84	3,755 (20.6)	2,031 (29.3)
≥85	858 (4.7)	726 (10.5)
***Gender N (%)**		
Male	10,632 (58.5)	3,866 (55.8)
Female	7,558 (41.5)	3,061 (44.2)
Ethnicity N (%)		
White	12,668 (69.6)	5,150 (74.3)
Asian	3,332 (18.3)	1,097 (15.8)
Black	939 (5.2)	392 (5.7)
Other	1,251 (6.9)	289 (4.2)
Deprivation Quintile N (%)		
Least deprived 1	8,169 (44.9)	2,956 (42.7)
2	3,875 (21.3)	1,579 (22.8)
3	3,055 (16.8)	1,167 (16.8)
4	1,673 (9.2)	683 (9.9)
Most deprived 5	990 (5.4)	367 (5.3)
Unknown	428 (2.4)	176 (2.5)
Type of Admission N (%)		
Elective	6,240 (34.3)	1,197 (17.3)
Emergency	11,950 (65.7)	5,731 (82.7)
Modified Charlson co-morbidity score N (%)		
0	8,360 (46.0)	1,899 (27.4)
1	3,844 (21.1)	1,529 (22.1)
2 or more	5,986 (32.9)	3,500 (50.5)
Insulin use N (%)		
Yes	8,700 (47.8)	4,701 (67.9)
No	9,490 (55.2)	2,227 (32.1)
ICU Care N (%)		
Yes	524 (2.9)	1,429 (20.6)
No	17,666 (97.1)	5,499 (79.4)
Foot Disease N (%)		
Yes	604 (3.3)	740 (10.7)
No	17,586 (96.7)	6,188 (89.3)

* Adds up to 25,117 instead of 25,118 due to one missing value

Table 5.7: Biochemical and haematological markers chosen for the model

Variable*	No adverse event – N (%)	Adverse event – N (%)
Albumin (g/L) T=19,220		
≤24	170 (1.3)	388 (5.8)
25-34	1,996 (15.9)	2,183 (32.7)
≥35	10,387 (82.8)	4,096 (61.4)
Haemoglobin (g/dL) T=20,035		
≤7.9	427 (3.2)	431 (6.5)
8-9.9	1,769 (13.2)	1,435 (21.6)
10-11.9	4,126 (30.9)	2,158 (32.4)
≥12	7,054 (52.7)	2,635 (39.6)
Neutrophil (10^9/L) T=20,221		
<8	10,259 (76.0)	4,178 (62.1)
8-15.9	2,888 (21.4)	2,149 (31.9)
≥16	345 (2.56)	402 (6.0)
CRP (mg/L) T=13,963		
0-9	2,670 (32.9)	1,039 (17.8)
10-49	3,037 (37.4)	1,946 (33.3)
50-99	1,127 (13.9)	1,121 (19.2)
≥100	1,278 (15.8)	1,745 (29.8)
Sodium (mEq/L) T=19,333		
≤124	105 (0.8)	122 (2.0)
125-134	1,953 (14.9)	1,323 (21.1)
135-144	10,506 (80.4)	4,418 (70.5)
145-154	496 (3.8)	352 (5.6)
≥155	8 (0.1)	50 (0.8)
Potassium (mEq/L) T=19.282		
≤2.9	88 (0.7)	118 (1.9)
3-5.9	12,660 (97.3)	5,932 (94.7)
≥6	268 (2.1)	216 (3.5)
eGFR (ml/min/1.73m^2) T=20,699		
≤30	2,286 (16.4)	1,497 (22.2)
30-59	4,295 (30.8)	2,381 (35.3)
60-89	4,615 (33.1)	1,851 (27.4)
≥90	2,756 (19.8)	1,018 (15.1)

*T- total number of blood results

Table 5.8: Regression co-efficients and odds ratios from the pragmatic and internally validated model

	Pragmatic Model			Validation Model (using bootstrap method)		
Characteristics	**Regression coefficients**	**Odds ratio**	**P value**	**Regression coefficients**	**Odds ratio**	**P value**
Age (years)						
<45	0	1		0	1	
45-54	0.431	1.54 (1.29-1.84)	<0.001	0.431	1.54 (1.31-1.81)	<0.001
55-64	0.606	1.83 (1.55-2.16)	<0.001	0.606	1.83 (1.58-2.13)	<0.001
65-74	0.894	2.45 (2.09-2.87)	<0.001	0.894	2.45 (2.12-2.83)	<0.001
75-84	1.249	3.49 (2.97-4.09)	<0.001	1.249	3.49 (3.01-4.03)	<0.001
>85	1.729	5.64 (4.66-6.81)	<0.001	1.729	5.64 (4.76-6.68)	<0.001
Gender						
Male	0	1		0	1	
Female	0.073	1.08(1.00-1.16)	0.050	0.073	1.08(1.01-1.14)	0.019
Admission type						
Elective	0	1		0	1	
Emergency	1.080	2.95 (2.69-3.22)	<0.001	1.080	2.95 (2.70-3.21)	<0.001
Ethnicity						
White	0	1		0	1	
Asian	-0.155	0.86 (0.78-0.94)	0.002	-0.155	0.86 (0.79-0.93)	<0.001
Black	0.052	1.05 (0.90-1.23)	0.510	0.053	1.05 (0.93-1.20)	0.428
Other	-0.350	0.70 (0.60-0.83)	<0.001	-0.351	0.70 (0.62-0.81)	<0.001
ICU care received						
No	0	1		0	1	
Yes	2.378	10.79 (9.52-12.22)	<0.001	2.378	10.79 (9.57-12.16)	<0.001
Insulin use						
No	0	1		0	1	
Yes	0.636	1.89 (1.76-2.03)	<0.001	0.636	1.89 (1.77-2.02)	<0.001
Foot Disease						
No	0	1		0	1	
Yes	0.898	2.46 (2.16-2.80)	<0.001	0.898	2.46 (2.17-2.78)	<0.001

Table 5.8: continued….

	Pragmatic Model			Validation Model (using bootstrap method)		
Characteristics	**Regression coefficients**	**Odds ratio**	**P value**	**Regression coefficients**	**Odds ratio**	**P value**
Albumin (g/L)						
≥35	0	1		0	1	
25-34	0.552	1.74 (1.59-1.90)	<0.001	0.553	1.74 (1.60-1.88)	<0.001
<25	0.970	2.64 (2.15-3.23)	<0.001	0.970	2.64 (2.16-3.22)	<0.001
GFR (ml/min/1.73m^2)						
≥90	0	1		0	1	
60-89	-0.037	0.96 (0.86-1.07)	0.477	-0.037	0.95 (0.87-1.05)	0.444
30-59	0.068	1.07 (0.96-1.19)	0.212	0.068	1.06 (0.97-1.17)	0.173
<30	0.267	1.31 (1.15-1.48)	<0.001	0.267	1.32 (1.18-1.48)	<0.001
HB (g/dl)						
≥12	0	1		0	1	
10-11.9	0.117	1.12(1.04-1.22)	0.004	0.117	1.12(1.04-1.21)	0.002
8-9.9	0.287	1.33(1.20-1.48)	<0.001	0.287	1.33(1.21-1.46)	<0.001
<8	0.492	1.64(1.38-1.94)	<0.001	0.492	1.62(1.38-1.91)	<0.001
Neutrophil count (10^9/L)						
0-7.9	0	1		0	1	
8-15.9	0.180	1.19(1.10-1.29)	<0.001	0.180	1.20(1.11-1.29)	<0.001
≥16	0.310	1.38(1.17-1.64)	<0.001	0.310	1.36(1.16-1.60)	<0.001
Sodium (mmol/l)						
<125	0.537	1.71 (1.26-2.32)	<0.001	0.537	1.71 (1.30-2.25)	<0.001
125-134	0.154	1.17 (1.06-1.28)	<0.001	0.154	1.17 (1.08-1.26)	<0.001
135-144	0	1		0	1	
145-154	0.272	1.31 (1.12-1.54)	<0.001	0.272	1.31 (1.13-1.52)	<0.001
≥155	1.400	4.05 (1.84-8.91)	<0.001	1.400	4.06 (2.28-7.21)	<0.001
Potassium (mmol/l)						
0-2.9	0.581	1.79(1.34-2.39)	<0.001	0.581	1.79 (1.37-2.34)	<0.001
3-5.9	0	1		0	1	
≥6	0.005	1.00 (0.80-1.26)	0.996	0.005	0.98 (0.82-1.23)	0.963
CRP (mg/L)						
0-9	0	1		0	1	
10-49	0.320	1.38 (1.25-1.51)	<0.001	0.320	1.38 (1.27-1.49)	<0.001
50-99	0.535	1.71 (1.49-1.96)	<0.001	0.535	1.71 (1.54-1.89)	<0.001
≥100	0.690	1.99 (1.77-2.25)	<0.001	0.690	1.99 (1.81-2.20)	<0.001

The pragmatic model had an area under the curve (AUC) of 0.802 (95%CI: 0.795-0.808), performing significantly (P<0.001) better than the test model (AUC 0.784; 95%CI: 0.777-0.790); suggesting that the clinical pathology results replaced co-morbidities as a measure of case-mix well. The ideal model performed better than the pragmatic model (AUC 0.810: 95%CI; 0.804-0.816, P<0.001) but the difference between the pragmatic model and ideal model was minimal (AUC 0.802 vs. 0.810) (Figure 5.1).

At a cut off of >25% predicted chance of having an adverse event, the sensitivity and specificity total was maximum. At this point the sensitivity was 76%, specificity was 70% and the positive predictive value was 49% (Table 5.9). However in reality, patients in ICU will not be part of the active case finding approach, and if one were to see only those in the non critical care setting, the approach will have a sensitivity of 69%; specificity of 72%; and a positive predictive value of 43%. On the other hand the so called “false positive” patients in non critical care whom will be seen in an active case finding approach have characteristics such as high co-morbidity index (41% had modified Charlson co-morbidity score of 2 or more), insulin use (66%), foot disease (10%) and age above 75 years (51%). Therefore false positives are not necessarily admissions that will not benefit from a specialist team review.

The lowess calibration plot was in close proximity to a line drawn at 45^0 suggesting the calibration of the model was good, that is the predicted probabilities were similar to that of the observed probabilities (Figure 5.2).

The internal validation on the bootstrapped sample had an AUC of 0.798 (95%CI: 0.792-0.805), only a marginal difference to that observed in the pragmatic model (AUC 0.802; 95%CI 0.795-0.808). The coefficients mostly varied only at third

decimal point and the odds ratios varied mostly at second decimal point (table 5.8). Therefore I did not make any adjustments to the coefficients obtained from the pragmatic model.

Figure 5.1: ROC curves for model comparison and assessment of discrimination

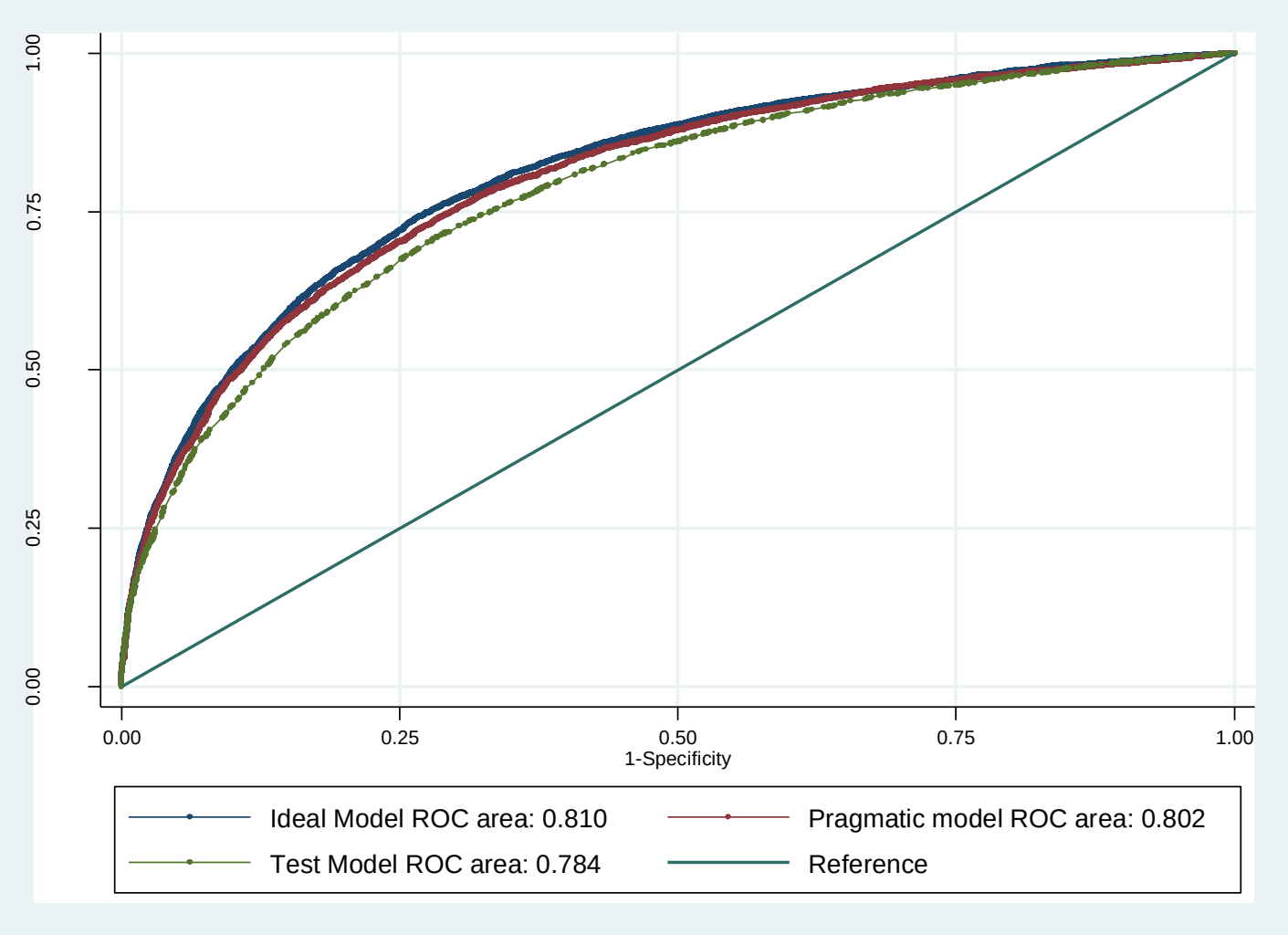


Table 5.9: Discriminating ability of the pragmatic model

Cut off point for the probability of having an adverse outcome	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Correct
0.05	0.99	0.09	0.29	0.95	1.08	0.15	0.33
0.1	0.95	0.29	0.34	0.94	1.34	0.18	0.47
0.15	0.89	0.47	0.39	0.92	1.69	0.22	0.59
0.2	0.83	0.60	0.44	0.90	2.06	0.29	0.66
0.25	0.76	0.70	0.49	0.88	2.50	0.35	0.71
0.3	0.68	0.77	0.53	0.86	2.98	0.42	0.75
0.35	0.60	0.83	0.58	0.85	3.60	0.48	0.77
0.4	0.54	0.88	0.62	0.83	4.34	0.53	0.78
0.45	0.47	0.91	0.66	0.82	5.19	0.58	0.79
0.5	0.40	0.93	0.69	0.80	5.98	0.64	0.79
0.55	0.35	0.95	0.73	0.79	7.11	0.69	0.78
0.6	0.30	0.96	0.76	0.78	8.45	0.73	0.78
0.65	0.25	0.97	0.79	0.77	9.99	0.77	0.78
0.7	0.21	0.98	0.81	0.76	11.35	0.81	0.77
0.75	0.17	0.99	0.84	0.76	13.79	0.84	0.76
0.8	0.13	0.99	0.87	0.75	17.34	0.88	0.75
0.85	0.08	1.00	0.88	0.74	19.38	0.92	0.74
0.9	0.04	1.00	0.90	0.73	24.02	0.96	0.74
0.95	0.01	1.00	0.97	0.73	87.53	0.99	0.73
1	0.00	1.00	-	0.72	-	1.00	0.72

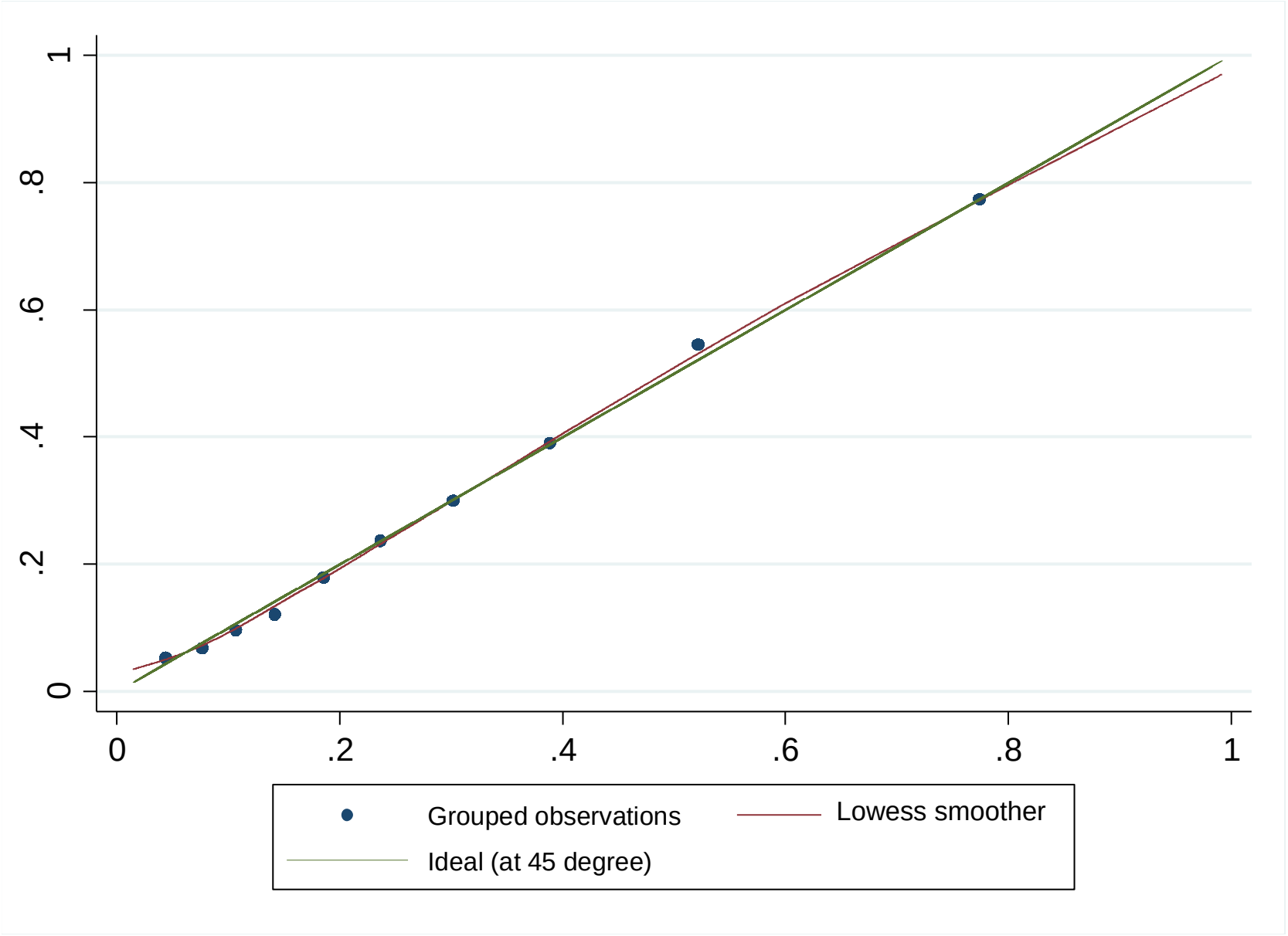
PPV – Positive predictive value

NPV – Negative predictive value

LR+ Positive likelihood ratio

LR- Negative likelihood ratio

Figure 5.2: Calibration plot to assess the pragmatic model performance



5.3.4 Discussion

The study shows that if key predictor variables are available at the time or in the first 72 hours of admission then it is possible to actively identify patients with diabetes likely to suffer either excessive length of stay (6 days or more for a given clinical presentation) or death. At a cut off of 25% probability of having an adverse outcome two thirds (sensitivity; 69%) of the admissions with adverse outcomes could potentially be identified in a non critical care setting. For every ten patients seen at this cut off point four will have an adverse outcome (PPV; 43%). The model performed well with an area under the curve of 0.802 with only a mild reduction being noted in the internal validation (AUC: 0.798; 95% CI 0.792-0,805).

The association of the biochemical and haematological predictors with excess length of stay and death noted in my analysis corresponds with previous studies we identified in the literature but were often based on any type of patients; both with and without diabetes. These include hyponatraemia [211,212], anaemia [214], hypokalaemia [237] and raised CRP levels [213]. The data in the study validates these findings in people admitted to hospital with diabetes. Furthermore, some of these criteria may be more relevant in the context of diabetes; sodium and potassium imbalance can challenge the management of diabetic ketosis, anaemia and reduced renal function may indicate advanced diabetic nephropathy, and an elevated CRP and neutrophilia may indicate compromised sepsis/wound healing in diabetes.

I believe the model will have important clinical utility. Timely identification of high-risk patients provides the opportunity for early intervention and improvement in clinical outcome. In UHB, we plan to incorporate the model as part of decision support within

the electronic medical records. On identification of high risk patients, an automated consultation request would be generated to the ‘Inpatient diabetes team’. They can then be reviewed early in their admission. I believe this will be beneficial as there is clear and prior evidence that specialist nurse review can reduce length of stay [132,133]. Other potential uses include redesigning care models and pathways for patients with diabetes admitted to hospital.

There are limitations to this approach. First it is assumed admissions with diabetes can be identified through information systems which may not be possible in all hospitals with electronic health information systems. However I have previously shown this is possible using either mandatory entry of the diabetes status on admission or in a compromised way using electronic prescription data alone [92]. Secondly I have assumed insulin treatment and ICU admissions took place early for all admissions even though this is not true for some patients. Thirdly many blood results may not be available and therefore these will be categorised as normal values when using the prediction model. Although this may compromise the validity of the model, my sensitivity analysis by replacing the missing categories with normal categories, and applying the coefficients obtained from the multiple imputation model to the dataset, suggested better performance than what I have shown (AUC: 0.816; sensitivity 73%; Specificity 75%; and positive predictive value 53%) (appendix 5.4). Other limitations include the inability to differentiate between type 1 diabetes and type 2 diabetes and not accounting for the admissions that were excluded due to non availability of information in PICs as discussed in chapter 3. Even though I have suggested a cut off value of 25% for the probability of having an adverse event, depending on hospital capacity this can be

varied to achieve better efficiency in terms of cost and staff time. The model might have performed better with additional important markers of poor outcome (especially mortality) such as smoking, duration of diabetes and glycaemic control. These variables were not available in the secondary care dataset and future studies should aim to improve on the model using linked primary and secondary care datasets. The strength of the study is that the model is developed in a hospital with a diverse population, from a large dataset with effect sizes that had narrow confidence intervals and rigorous methodological quality. Furthermore the definition of excessive length of stay is novel and mitigates the need to know the presenting condition. Similarly the model doesn't rely on knowing the co-morbidities, replacing this instead with routinely performed blood tests.

5.3.5 Conclusions

An active case finding model can be a future tool to identify patients with diabetes whom may be at risk of poor outcomes such as increased length of stay and death. Further studies should aim to; 1) externally validate the model; 2) assess the practicality of using the model; and 3) demonstrate if the active case finding model either on its own or in combination with additional clinical indicators of poor outcomes (such as hypoglycaemia, hyperglycaemia and insulin infusions identified through electronic records), followed by a review by the specialist diabetes team, will positively impact on reducing adverse outcomes for patients with diabetes.

CHAPTER 6

General discussion

6 General discussion

6.1 Findings in context of overall management strategy for hospitalised patients with diabetes

The key components in successfully managing hospitalised patients with diabetes are delineated by the guidelines produced here in UK [47-51] and in USA [104]. Important components identified include: 1) obtaining the institutional support for the initiative to improve care for diabetes inpatients; 2) establishing a multidisciplinary diabetes team and steering committee; 3) educating health care providers on the management of diabetic inpatients; and 4) providing adequate information and support to diabetes inpatients.

In a resource limited health care economy, institutions will naturally prefer to support initiatives that have a high impact on efficiency (value for money) and quality of care. The work on electronic prescription data in identifying missed discharge diagnostic codes for diabetes fulfils both the criteria where financial savings can be made and at the same time improved recording of patient information can be achieved. The studies establishing the association of hypoglycaemia and foot disease with in-hospital mortality and increased length of stay in diabetes inpatients have contributed to our understanding of poor inpatient outcomes for diabetes patients and can be valuable in persuading hospital managers to adapt national recommendations and guidelines in caring for in-patients with diabetes. In addition findings from the systematic review emphasises the need for implementation of CPOE system with CDSS functions to reduce prescription errors and promote appropriate insulin regimen.

A multidisciplinary diabetes team have a dual function: 1) to optimise individual patient care; 2) strategic role to drive policies behind good practice, to establish institution goals on management of glucose control and to develop or implement local and national guidelines. Depending on the size and capacity of the institution the second role could be fulfilled by the same individuals in a multidisciplinary team or by establishing a separate steering committee. The team should drive the agenda on setting up guideline based CPOE as identified in the systematic review; ideally persuade hospitals to accommodate institution wide glucose monitoring system as identified in the systematic review and discussed in chapter 4; and set out appropriate institutional glucose control goals as discussed in chapter 4. They should explore mechanisms to safeguard patients from insulin prescription errors including possible surveillance systems such as discussed for non diabetic patients in chapter 4. Wherever electronic health records exist, as proposed in chapter 3, identification of every possible diabetes patients in real time should be encouraged. This in turn will help with proactive identification of diabetes patients whom are in need of specialist diabetes team input. Tools to identify high risk patients such as using the model developed in chapter 5 or electronic observations with decision support functions which can alert patients that could benefit from specialist diabetes team review, for example those with severe or recurrent hypoglycaemia as discussed in chapter 4, should be incorporated into electronic health records.

The team also has a role in educating the wider health care providers in all wards and outpatient settings. Though not part of this thesis, computer and web based modules to train doctors and nurses on inpatient management of diabetes are being increasingly used [247-249]. These can have potential benefits that need to be further studied. This

is important as current evidence suggests there is clinical inertia in antidiabetic medication prescription (not intensifying treatment when there is persistent hyperglycaemia) and use of improper prescription such as sliding scale insulin where it is inappropriate [250,251] . Similarly innovative ways to educate patients are needed to achieve better patient satisfaction and empower them to self manage their illness during their inpatient stay.

6.2 Implementing the findings of this thesis and evaluation framework

In the introduction I briefly discussed planning and development of CDSS. Once the framework and health informatics tools have been developed or identified, as was the case in this thesis for diabetes inpatients, it is important to have partnership working between clinicians, IT professionals and if available clinical informaticians. A clinical informatician is a professional with clinical background whom use their knowledge on patient care with their understanding of informatics concepts to transform health care [252] . They achieve this by establishing the clinical need for a health informatics solution and contributing to the improvement in patient care and population health through analysing, designing, implementing and evaluating health information systems with decision support [252] . Partnership working will ensure the right specification for a tool is provided to the IT professionals whom in turn will develop the programme and validate its functions, i.e. clarify the programme is working according to specifications.

The next steps will involve evaluating the impact on users of the tool, patients and the institution. Evaluation can be quantitative, qualitative or both. In the example of reducing missed discharge diagnostic codes by implementing the algorithm specified in chapter 3 into health information system, impact assessment will focus mainly on the user and the

institution. If the algorithm were to interrupt the workflow of the user or add to the increasing number of alerts generated to them for action (alert fatigue) then they may not comply with the tool to reduce missed discharge diagnosis of diabetes. Often questionnaire surveys to junior doctors to study their understanding (qualitative) and potential usage (quantitative) of the tool and / or focus groups (qualitative) to identify any barriers for potential poor usage can be valuable to improve the programme specification to increase utilisation of the tool. Once implemented, usage by the junior doctors in the field setting can be further assessed by analysing routinely available secondary data. The impact to the institution, with reduction in missed discharge diagnostic code for diabetes as an outcome, can be studied by a before and after interventional study. A diagrammatic representation of how the evaluation framework can be applied for studying the implementation of active case finding approach for diabetes patients having hypoglycaemic episode and in need of specialist input is given in figure 6.1. A similar approach can be taken for implementing and evaluating the case finding model developed in chapter 5.

6.3 Evidence based health informatics

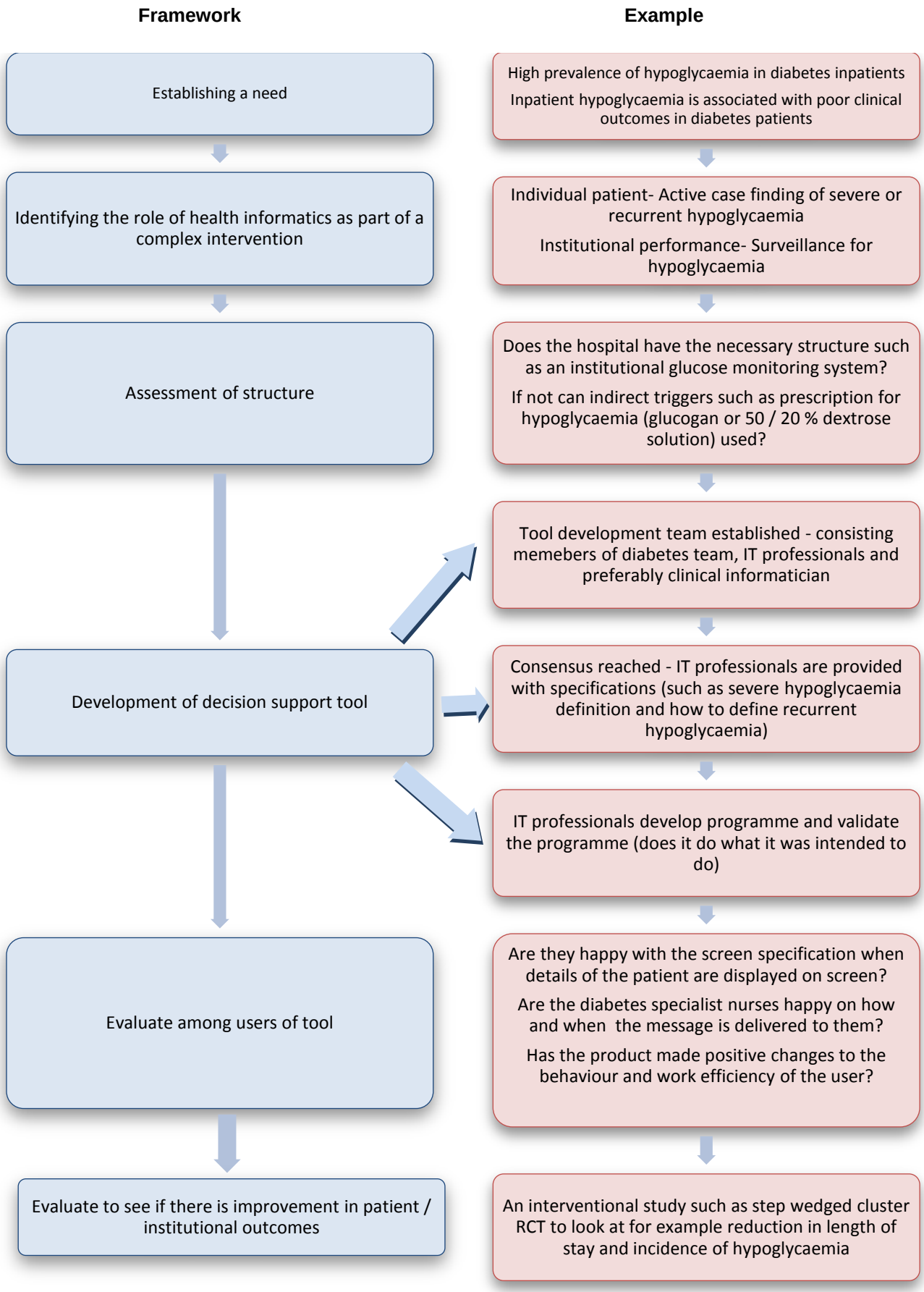
The evidence based medicine movement became prominent in the 1990s when for the first time it was defined by Sackett et al [253]. He articulated it as *"the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [253]* . It is an expression clarified further as giving recognition to not only the evidence but to that of the experience acquired by the clinician over the years and to that of patient held values. Following this evidence based health care was defined based on the available evidence, population health needs and available

resources [254] . In the field of health informatics, tools were introduced with limited evaluation therefore lacking adequate evidence on effectiveness and efficiency leading to many failures [255,256].

This has lead to the emergence of similar principles to that of evidence based medicine in health informatics termed Evidence Based Health Informatics (EBHI). Ammenwerth et al adapting from Sackett et al's definition defined EBHI as *"the conscientious, explicit and judicious use of current best evidence in making decisions about the introduction and operation of IT in a given health care setting" [110]*. However practicing EBHI is challenging due to the scarcity of studies examining implementation of health information systems and CDSS [257]. Further quality of studies tend to be poor and rarely randomised controlled trials (RCT) that are considered to be of gold standard in EBM is performed [110,257,258].

To maximise the impact of the research findings in this thesis it is essential when implementing the recommendations in each chapter they are evaluated to improve their performance and at the same time to maximise the chance of the findings to be considered as generalisable. Recently guidelines have been published on good evaluation practice and on structured reporting of evaluation studies in health informatics [259,260].

Figure 6.1: Evaluation framework to study the impact of clinical decision support tools



6.4 Future directions for research and action

This collection of work has addressed some gaps in the role of health informatics in hospitalised patients with diabetes. There are implications for practice and future research. Firstly tools used elsewhere that were identified through the systematic review such as the CPOE to reduce prescription errors and improve glycaemic control in diabetes patients need to be adapted locally and implemented. Tools that have been proposed after establishing need such as the algorithm to reduce missed discharge diagnostic codes and model to identify diabetes patients with poor clinical outcomes need to be implemented and evaluated as discussed in the evaluation framework. In addition the model needs to be externally validated. The key feature of the thesis is the process of establishing where health informatics can make a difference for a focussed group of patients (hospitalised diabetes patients) which may be transferable to other groups of hospitalised patients.

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8 Appendices

Appendix 2.1: Search Strategy

MEDLINE

	Searches	Results
1	exp diabetes mellitus/ or exp diabetes mellitus, experimental/ or exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/ or exp diabetes, gestational/ or exp diabetic ketoacidosis/ or exp prediabetic state/ or exp glycosuria/ or exp hyperglycemia/ or exp hypoglycemia/ or exp metabolic syndrome x/	286990
2	diabet$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	348048
3	exp Blood Glucose/ or exp Glucose Intolerance/ or glucose.mp. or exp Glucose/ or exp Blood Glucose Self-Monitoring/ or exp Glucose Tolerance Test/	343453
4	1 or 2 or 3	612045
5	exp informatics/ or exp dental informatics/ or exp medical informatics/ or exp nursing informatics/ or exp public health informatics/	240114
6	clinical informatics.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	98
7	exp medical informatics/ or exp medical informatics applications/ or exp decision making, computer-assisted/ or exp decision support techniques/ or exp "information storage and retrieval"/ or exp information systems/ or exp clinical laboratory information systems/ or exp databases as topic/ or exp decision support systems, clinical/ or exp geographic information systems/ or exp hospital information systems/ or exp integrated advanced information management systems/ or exp knowledge bases/ or exp management information systems/ or exp medical records systems, computerized/ or exp medlars/ or exp online systems/ or exp radiology information systems/ or exp reminder systems/ or exp medical informatics computing/ or exp pattern recognition, automated/	259147
8	clinical decision support$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	870
9	exp Computers/ or exp Clinical Pharmacy Information Systems/ or exp Medical Order Entry Systems/ or physician order entry system.mp. or exp Medication Errors/ or exp Medication Systems, Hospital/	76245

10	(physician order entry system$ or computerized physician order entry system$ or computerised physician order entry system$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	131
11	5 or 6 or 7 or 8 or 9 or 10	321329
12	exp hospitals/ or exp hospitals, community/ or exp hospitals, general/ or exp hospitals, group practice/ or exp hospitals, packaged/ or exp hospitals, private/ or exp hospitals, public/ or exp hospitals, rural/ or exp hospitals, satellite/ or exp hospitals, special/ or exp hospitals, teaching/ or exp hospitals, urban/	171739
13	hospital$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	866237
14	inpatient$.mp. or Inpatients/	50961
15	secondary care.mp.	2148
16	13 or 14 or 15	886663
17	4 and 11	6211
18	16 and 17	903

EMBASE

	Searches	Results
20	exp non insulin dependent diabetes mellitus/ or exp diabetes mellitus/ or diabet$.mp.	349026
21	exp GLUCOSE TOLERANCE/ or exp GLUCOSE/ or glucose.mp. or BLOOD GLUCOSE MONITORING/ or exp ORAL GLUCOSE TOLERANCE TEST/ or exp GLUCOSE INTOLERANCE/ or exp GLUCOSE TOLERANCE TEST/ or exp INTRAVENOUS GLUCOSE TOLERANCE TEST/ or exp IMPAIRED GLUCOSE TOLERANCE/	343453
22	20 or 21	598319
23	exp information system/ or exp clinical data repository/ or exp computerized provider order entry/ or exp decision support system/ or exp electronic bulletin board/ or exp electronic medical record/ or exp expert system/ or exp hospital information system/ or exp medical information system/ or exp nursing information system/ or exp online system/ or exp performance measurement system/ or exp reminder system/	131501
24	exp decision support system/ or exp medical informatics/ or exp computer program/ or clinical informatics.mp.	288397
25	exp medication error/ or physician order entry system.mp. or exp hospital information system/	28952
26	computerized physician order entry system.mp. or exp computerized provider order entry/	59
27	23 or 24 or 25 or 26	300107
28	exp UNIVERSITY HOSPITAL/ or exp HOSPITAL ADMISSION/ or exp DAY HOSPITAL/ or exp PEDIATRIC HOSPITAL/ or exp COMMUNITY HOSPITAL/ or exp MENTAL HOSPITAL/ or exp PUBLIC HOSPITAL/ or exp HOSPITAL READMISSION/ or exp GENERAL HOSPITAL/ or exp NON PROFIT HOSPITAL/ or exp TEACHING HOSPITAL/ or exp GERIATRIC HOSPITAL/ or exp PRIVATE HOSPITAL/ or exp HOSPITAL PATIENT/ or exp HOSPITAL/ or hospital$.mp.	873081
29	inpatient$.mp. or exp hospital patient/	50961
30	secondary care.mp.	2148
31	28 or 29 or 30	893320
32	22 and 27 and 31	880

CINAHL

	Query	Results
S18	S5 and S12 and S17	156
S17	S13 or S14 or S15 or S16	378272
S16	TX secondary care*	1328
S15	TX inpatient* or SU inpatient	53881
S14	TX hospital*	350164
S13	SU hospitals or hospitals, community or hospitals general or hospitals, group practice or hospitals, packaged or hospitals, private or hospitals, public or hospitals, rural or hospitals, satellite or hospitals, special or hospitals, teaching or hospitals, urban	42339
S12	S6 or S7 or S8 or S9 or S10 or S11	34709
S11	TX physician order entry system* or computerised physician order entry system*	113
S10	SU computers or clinical pharmacy information systems or medical order entry systems or medication errors or medication systems, hospital	14948
S9	TX clinical decision support*	400
S8	SU medical informatics or medical informatics applications or decision making, computer-assisted or decision support techniques or information storage and retrieval or information systems or clinical laboratory information systems or databases as topic or decision support systems, clinical or geographic information systems or hospital information systems or integrated advanced information management systems or knowledge bases or management information systems or medical records systems, computerized or medlars or online systems or radiology information systems or reminder systems or medical informatics computing or pattern recognition, automated	18630
S7	TX clinical informatics	234
S6	SU informatics or dental informatics or medical informatics or nursing informatics or public health informatics	4569
S5	(S1 or S2 or S3 or S4)	74130
S4	TX glucose*	19887
S3	SU blood glucose or glucose intolerance or glucose or blood glucose self monitoring or glucose tolerance test	19317
S2	TX DIABET*	66238
S1	SU diabetes or diabetes mellitus or diabetes mellitus, experimental or diabetes, mellitus, type 1 or diabetes mellitus, type 2 or exp diabetes, gestational or diabetic ketoacidosis or prediabetic state or glycosuria or hyperglycemia or hypoglycemia or metalbolic syndrome x	48849

COCHRANE

ID	Search	Hits
#1	MeSH descriptor **Diabetes Mellitus** explode all trees	12389
#2	(diabet*):ti,ab,kw	21675
#3	MeSH descriptor **Glucose** explode all trees	10442
#4	(glucose*):ti,ab,kw	18367
#5	(#1 OR #2 OR #3 OR #4)	32401
#6	MeSH descriptor **Informatics** explode all trees	52
#7	(informatics):ti,ab,kw	166
#8	MeSH descriptor **Decision Support Systems, Clinical** explode all trees	195
#9	(clinical decision support*):ti,ab,kw	649
#10	MeSH descriptor **Medical Order Entry Systems** explode all trees	31
#11	(physician order entry system* or computerised physician order entry system* or computer* or information system* or medical records system* or reminder system* or medical informatics computing):ti,ab,kw	16925
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	17389
#13	MeSH descriptor **Hospitals** explode all trees	3148
#14	(hospital*):ti,ab,kw	48251
#15	MeSH descriptor **Inpatients** explode all trees	570
#16	(inpatient*):ti,ab,kw	5388
#17	(secondary care):ti,ab,kw	3128
#18	(#13 OR #14 OR #15 OR #16 OR #17)	53183
#19	(#5 AND #12 AND #18)	118

Appendix 2.2: Inclusion Checklist

	Question	Yes	No
Q1	**Population** Did the study include in-patients with diabetes/hyperglycaemia or inpatients whom were screened for diabetes?	Go to Q2	Excluded based on population
Q2	**Interventions** Did the interventions include one of the following terms or equivalent: ○ Clinical decision support system (information systems designed to assist and improve clinical decision making) ○ Computerised physician order entry system with CDSS component **Comparator** Usual practice or no clinical decision support system where controls used	Go to Q3	Excluded based on intervention
Q3	**Outcomes** Did the study report any clinical outcomes (reduced acute diabetes related complication during inpatient stay (hypo's), better blood glucose control, fewer patients on insulin sliding scales etc), service related outcomes (reduced length of stay, readmission rates etc), patient satisfaction or improved efficiency of care provider (less time consuming for doctors, nurses etc)	Go to Q4	Excluded based on outcome
Q4	**Study design** Include study design other than case reports and case series with less than 5 patients	Meets inclusion criteria to obtain full manuscripts	Excluded based on study design

Appendix 2.3: Data Extraction Form

General information	**Study Reference Number**	
	Researcher performing data extraction	
	Date of data extraction	
	Included	
	Citation	
	Type of publication	
Study characteristics	**Aims/Objectives/hypothesis of the study**	
	Setting	
	Study design	
	Study inclusion and exclusion criteria	
	Recruitment procedures used (e.g. details of randomisation, blinding)	
	Unit of allocation (e.g. participant, GP practice, etc.)	
Participant characteristics	**Age**	
	Gender	
	Ethnicity Socio-economic status	

- **Characteristics of participants at the beginning of the study e.g. Age Gender**	**Disease characteristics**	
	Co-morbidities	
	Number of participants	
Measurements of Interventions and Outcomes	**Intervention**	
	Description of the intervention(s) and control(s)	
	Description of co-interventions	
	Outcome	
	Description of outcome	
	Length of follow-up, number and/or times of follow-up measurements	
Analysis Methods and Statistics	**Statistical techniques used**	
	For all intervention group(s) and control group(s): Number of participants and Summary outcome data	

	Type of analysis used in study (e.g. intention to treat, per protocol)	
Results	**Results of study analysis**	
	Outcome 2	
	Outcome 3	
	Outcome 4	
	Outcome 5	
Other Key Details	**Costs**	
	Resource use	
	Adverse events	
Notes	**Notes**	
Quality	**Possible Bias**	
	Confounders	
	Evidence Rating	
	Actions to take	

Appendix 4.1: Validity of triggers in detecting hypoglycaemia

Positive predictive values for each individual indirect trigger and for the system as a whole are shown below. At a cut-off value of 3.3mmol/l, 18 out of the 21 discharge diagnostic code triggers for hypoglycaemia were positive, giving a positive predictive value of 86%; and for the indirect trigger of hypoglycaemic treatment, the positive predictive value was 65% (32/49). Overall positive predictive value at 3.3mmol/l was 78%, at 3.0mmol/l, 72% at 2.7mmol/l, 50%, at 2.5mmol/l, 44%, and at 2.2mmol/l, 35%.

Predictive value of the triggers for non diabetic hypoglycaemia

	Electronic blood glucose values (Direct Trigger)	Electronic triggers by anti-hypo treatment (Indirect Trigger)	Discharge diagnostic codes for hypoglycaemia (Indirect Trigger)	Total triggers generated (taking into account of overlaps)
Case-notes needed reviewing to confirm hypoglycaemia for indirect triggers and confirm accuracy of diagnostic codes	38	55	25	102
Case-notes available for review	36 (95%)	51 (93%)	23 (92%)	95 (93%)
After exclusion of triggers that were found to be diabetic from case-notes	36	49	21	91
Positive triggers indicating hypoglycaemia at 3.3 mmol/l	36 PPV= NA	32 PPV = 65%	18 PPV=86%	71 OPPV=78%
Positive triggers indicating hypoglycaemia at 3.0 mmol/l	27 PPV= NA	30 PPV= 61%	17 PPV=81%	59 OPPV=72%
Positive triggers indicating hypoglycaemia at 2.7 mmol/l	14 PPV= NA	24 PPV= 49%	12 PPV=57%	37 OPPV=53%
Positive triggers indicating hypoglycaemia at 2.5 mmol/l	12 PPV= NA	21 PPV= 43%	9 PPV=43%	30 OPPV=44%
Positive triggers indicating hypoglycaemia at 2.2 mmol/l	9 PPV= NA	18 PPV=37%	7 PPV=33%	23 OPPV=35%

PPV = Positive predictive value
OPPV = Overall positive predictive value of the surveillance system (calculation of this is explained below)

Overall PPV for cut-off value 2.7mmol/l = 59/70(total triggers (91) – Direct triggers that were between 2.7 and 3.3mmol/l (36-14=22) + but add any that overlap with the other 2 triggers (1))

Appendix 5.1: ICD-10 codes and OPCS4 codes used to identify foot disease in patients with diabetes

We have defined diabetic foot disease based on the general description given by NICE guideline for inpatient management of diabetic foot disease. It describes it as feet affected by neuropathy, peripheral arterial disease, foot deformity, infections, ulcers and gangrene. Any difference between the codes we used and that of diabetes health intelligence unit is highlighted.

ICD10 Codes	DESCRIPTION	Highly indicative codes for foot disease	Codes used by Diabetes Health Intelligence	Explanation for difference
I702	Atherosclerosis of arteries of extremities	**x**		This will indicate peripheral circulation being compromised
L030	Cellulitis of finger and toe	X	X	
L031	Cellulitis of other parts of limb	X	X	
L89X	Decubitus ulcer and pressure area		**X**	As described earlier these can occur in many other areas (sacrum, buttock) other than the heel. They are likely to bias results.
L97	Ulcer of lower limb, not elsewhere classified	X	X	
R02	Gangrene, not elsewhere classified	X	X	
E105	Insulin-dependent diabetes mellitus with peripheral circulatory complications	X	X	
E115	Non-insulin-dependent diabetes mellitus with peripheral circulatory complications	X	X	
E125	Malnutrition-related diabetes mellitus with peripheral circulatory complications	X	X	
E135	Other specified diabetes mellitus with peripheral circulatory complications	X	X	
E145	Unspecified diabetes mellitus with peripheral circulatory complications	X	X	
M146	Neuropathic arthropathy	**X**		Commonly present in feet
G632	Diabetic polyneuropathy	**X**		Mostly this reflects peripheral neuropathy as per the ICD 10 definition

OPCS codes used were similar to both categories

These were: 1) Wound debridement (S571) of a foot/leg (Z504, Z505, Z506) 2) Amputations - X091, X092, X093, X094, X095, X098, X099, X101, X102, X103, X104, X108, X109, X111, X112, X118, X119, X121, X122, X123, X124, X125, X128, X129

Appendix 5.2: Clinical Classification System (CCS)

Category	label	category	Label
1	Tuberculosis	51	Other endocrine disorders
2	Septicaemia (except in labour)	52	Nutritional deficiencies
3	Bacterial infection; unspecified site	53	Disorders of lipid metabolism
4	Mycoses	54	Gout and other crystal arthropathies
5	HIV infection	55	Fluid and electrolyte disorders
6	Hepatitis	56	Cystic fibrosis
7	Viral infection	57	Immunity disorders
8	Other infections; including parasitic	58	Other nutritional; endocrine; and metabolic disorder
9	Sexually transmitted infections (not HIV or hepatitis)	59	Deficiency and other anaemia
10	Immunizations and screening for infectious disease	60	Acute post hemorrhagic anaemia
11	Cancer of head and neck	61	Sickle cell anaemia
12	Cancer of oesophagus	62	Coagulation and hemorrhagic disorders
13	Cancer of stomach	63	Diseases of white blood cells
14	Cancer of colon	64	Other hematologic conditions
15	Cancer of rectum and anus	65	Mental retardation
16	Cancer of liver and intra-hepatic bile duct	66	Alcohol-related mental disorders
17	Cancer of pancreas	67	Substance-related mental disorders
18	Cancer of other GI organs; peritoneum	68	Senility and organic mental disorders
19	Cancer of bronchus; lung	69	Affective disorders
20	Cancer; other respiratory and intra-thoracic	70	Schizophrenia and related disorders
21	Cancer of bone and connective tissue	71	Other psychoses
22	Melanomas of skin	72	Anxiety; somatoform; dissociative; and personality
23	Other non-epithelial cancer of skin	73	Pre-adult disorders
24	Cancer of breast	74	Other mental conditions
25	Cancer of uterus	75	Personal history of mental disorder; mental and be
26	Cancer of cervix	76	Meningitis (except that caused by tuberculosis or
27	Cancer of ovary	77	Encephalitis (except that caused by tuberculosis o
28	Cancer of other female genital organs	78	Other CNS infection and poliomyelitis
29	Cancer of prostate	79	Parkinson`s disease
30	Cancer of testis	80	Multiple sclerosis
31	Cancer of other male genital organs	81	Other hereditary and degenerative nervous system c
32	Cancer of bladder	82	Paralysis
33	Cancer of kidney and renal pelvis	83	Epilepsy; convulsions
34	Cancer of other urinary organs	84	Headache; including migraine
35	Cancer of brain and nervous system	85	Coma; stupor; and brain damage
36	Cancer of thyroid	86	Cataract
37	Hodgkin`s disease	87	Retinal detachments; defects; vascular occlusion;
38	Non-Hodgkin`s lymphoma	88	Glaucoma
39	Leukaemia	89	Blindness and vision defects
40	Multiple myeloma	90	Inflammation; infection of eye (except that caused
41	Cancer; other and unspecified primary	91	Other eye disorders
42	Secondary malignancies	92	Otitis media and related conditions
43	Malignant neoplasm without specification of site	93	Conditions associated with dizziness or vertigo
44	Neoplasms of unspecified nature or uncertain behaviour	94	Other ear and sense organ disorders
45	Maintenance chemotherapy; radiotherapy	95	Other nervous system disorders
46	Benign neoplasm of uterus	96	Heart valve disorders
47	Other and unspecified benign neoplasm	97	Peri-; endo-; and myocarditis; cardiomyopathy
48	Thyroid disorders	98	Essential hypertension
49	Diabetes mellitus without complication	99	Hypertension with complications and secondary hype
50	Diabetes mellitus with complications	100	Acute myocardial infarction

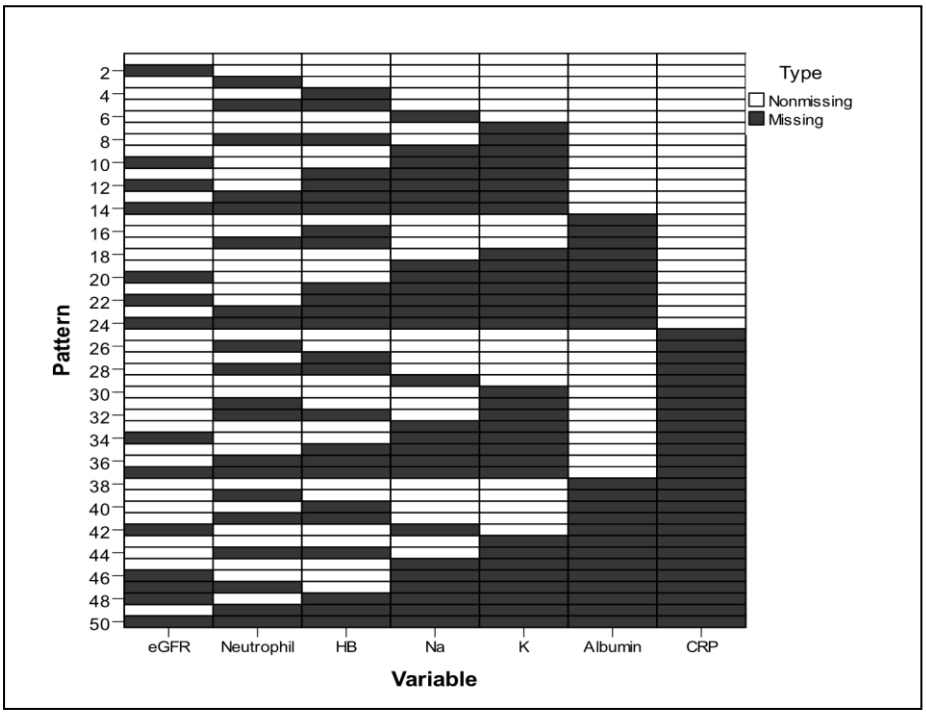
Category	label	category	Label
101	Coronary atherosclerosis and other heart disease	151	Other liver diseases
102	Nonspecific chest pain	152	Pancreatic disorders (not diabetes)
103	Pulmonary heart disease	153	Gastrointestinal haemorrhage
104	Other and ill-defined heart disease	154	Non-infectious gastroenteritis
105	Conduction disorders	155	Other gastrointestinal disorders
106	Cardiac dysrhythmias	156	Nephritis; nephrosis; renal sclerosis
107	Cardiac arrest and ventricular fibrillation	157	Acute and unspecified renal failure
108	Congestive heart failure; nonhypertensive	158	Chronic renal failure
109	Acute cerebrovascular disease	159	Urinary tract infections
110	Occlusion or stenosis of precerebral arteries	160	Calculus of urinary tract
111	Other and ill-defined cerebrovascular disease	161	Other diseases of kidney and ureters
112	Transient cerebral ischemia	162	Other diseases of bladder and urethra
113	Late effects of cerebrovascular disease	163	Genitourinary symptoms and ill-defined conditions
114	Peripheral and visceral atherosclerosis	164	Hyperplasia of prostate
115	Aortic; peripheral; and visceral artery aneurysms	165	Inflammatory conditions of male genital organs
116	Aortic and peripheral arterial embolism or thrombosis	166	Other male genital disorders
117	Other circulatory disease	167	Non-malignant breast conditions
118	Phlebitis; thrombophlebitis and thromboembolism	168	Inflammatory diseases of female pelvic organs
119	Varicose veins of lower extremity	169	Endometriosis
120	Haemorrhoids	170	Prolapse of female genital organs
121	the diseases of veins and lymphatics	171	Menstrual disorders
122	Pneumonia (except that caused by tuberculosis or s	172	Ovarian cyst
123	Influenza	173	Menopausal disorders
124	Acute and chronic tonsillitis	174	Female infertility
125	Acute bronchitis	175	Other female genital disorders
126	Other upper respiratory infections	176	Contraceptive and procreative management
127	Chronic obstructive pulmonary disease and bronchiectasis	177	Spontaneous abortion
128	Asthma	178	Induced abortion
129	Aspiration pneumonitis; food/vomitus	179	Post-abortion complications
130	Pleurisy; pneumothorax; pulmonary collapse	180	Ectopic pregnancy
131	Respiratory failure; insufficiency; arrest (adult)	181	Other complications of pregnancy
132	Lung disease due to external agents	182	Haemorrhage during pregnancy; abruptio placenta; pl
133	Other lower respiratory disease	183	Hypertension complicating pregnancy; childbirth an
134	Other upper respiratory disease	184	Early or threatened labour
135	Intestinal infection	185	Prolonged pregnancy
136	Disorders of teeth and jaw	186	Diabetes or abnormal glucose tolerance complication
137	Diseases of mouth; excluding dental	187	Malposition; malpresentation
138	Oesophageal disorders	188	Feto-pelvic disproportion; obstruction
139	Gastro duodenal ulcer (except haemorrhage)	189	Previous C-section
140	Gastritis and duodenitis	190	Fetal distress and abnormal forces of labour
141	Other disorders of stomach and duodenum	191	Polyhydramnios and other problems of amniotic cavity
142	Appendicitis and other appendiceal conditions	192	Umbilical cord complication
143	Abdominal hernia	193	OB-related trauma to perineum and vulva
144	Regional enteritis and ulcerative colitis	194	Forceps delivery
145	Intestinal obstruction without hernia	195	Other complications of birth; puerperium affecting
146	Diverticulosis and diverticulitis	196	Normal pregnancy and/or delivery
147	Anal and rectal conditions	197	Skin and subcutaneous tissue infections
148	Peritonitis and intestinal abscess	198	Other inflammatory condition of skin
149	Biliary tract disease	199	Chronic ulcer of skin
150	Liver disease; alcohol-related	200	Other skin disorders

Category	label	category	Label
201	Infective arthritis and osteomyelitis (except that	231	Other fractures
202	Rheumatoid arthritis and related disease	232	Sprains and strains
203	Osteoarthritis	233	Intracranial injury
204	Other non-traumatic joint disorders	234	Crushing injury or internal injury
205	Spondylosis; inter-vertebral disc disorders; other	235	Open wounds of head; neck; and trunk
206	Osteoporosis	236	Open wounds of extremities
207	Pathological fracture	237	Complication of device; implant or graft
208	Acquired foot deformities	238	Complications of surgical procedures or medical ca
209	Other acquired deformities	239	Superficial injury; contusion
210	Systemic lupus erythematosus and connective tissue	240	Burns
211	Other connective tissue disease	241	Poisoning by psychotropic agents
212	Other bone disease and musculoskeletal deformities	242	Poisoning by other medications and drugs
213	Cardiac and circulatory congenital anomalies	243	Poisoning by non-medicinal substances
214	Digestive congenital anomalies	244	Other injuries and conditions due to external cause
215	Genitourinary congenital anomalies	245	Syncope
216	Nervous system congenital anomalies	246	Fever of unknown origin
217	Other congenital anomalies	247	Lymphadenitis
218	Live born	248	Gangrene
219	Short gestation; low birth weight; and fetal growth	249	Shock
220	Intrauterine hypoxia and birth asphyxia	250	Nausea and vomiting
221	Respiratory distress syndrome	251	Abdominal pain
222	Haemolytic jaundice and perinatal jaundice	252	Malaise and fatigue
223	Birth trauma	253	Allergic reactions
224	Other perinatal conditions	254	Rehabilitation care; fitting of prostheses; and ad
225	Joint disorders and dislocations; trauma-related	255	Administrative/social admission
226	Fracture of neck of femur (hip)	256	Medical examination/evaluation
227	Spinal cord injury	257	Other aftercare
228	Skull and face fractures	258	Other screening for suspected conditions
229	Fracture of upper limb	259	Residual codes; unclassified
230	Fracture of lower limb	260	E Codes: All (external causes of injury and poison

Appendix 5.3: Dealing with missing values (table showing missing percentages and figure with pattern of missing)

Variable	Complete	Incomplete	Percent missing
Albumin	19220	5898	23%
CRP	13963	11155	44%
Sodium (Na)	19333	5785	23%
Neutrophil	20221	4897	19%
Potassium (K)	19282	5836	23%
Haemoglobin	20035	5083	20%
eGFR	20699	4419	18%

Three options were available to deal with the missing values; 1) complete case analysis; 2) single imputation method; 3) multiple imputation method. Complete case analysis is only possible if the variables are Missing Completely At Random (MCAR). MCAR assumes the data are missing independent of any other variables (both observed and unobserved), which if often not true for health care data. I have assumed the missing pattern is missing at random (MAR) where the missing values are dependent on other observed variables. Simple single imputation (allocating to the group with normal range) assumes if a blood test was not done or the result was not available they will be in the normal range category. The last option is to use multiple imputation techniques. I selected the latter considering the single imputation method will likely result in severe bias and overestimation of the effect size.

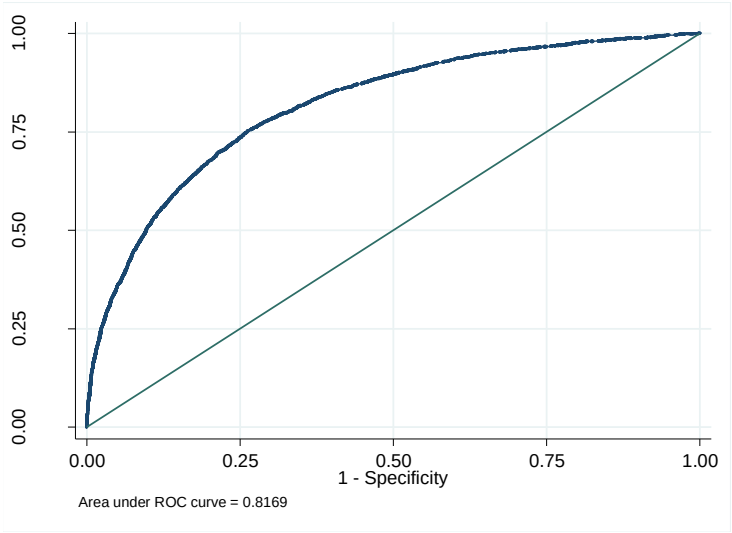


Multiple imputations were carried out using the Multiple Imputations by Chained Equations (MICE) with Predicted Mean Matching (PMM). Stata 12 supports these imputation methods allowing to impute different type of variables (categorical as well as continuous) at the same time using the CHAINED command. Predicted mean matching (PMM) command helps to restrict the range (by matching the predicted value to the closest value in the dataset) from which an imputed value could be picked for each variable and at the same has the property to be used with the CHAINED command.

Appendix 5.4: Performance on assuming missing values are in normal categories

Performance assessed by:

1) In the original dataset replace missing values with normal values
2) Apply the co-efficients obtained in the multiple imputation model to the dataset to predict the probability of having an event
3) Look at the performance using the ROC curve and by calculating the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios



	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Correct
0.05	0.99	0.13	0.30	0.96	1.14	0.10	0.37
0.1	0.94	0.37	0.36	0.94	1.50	0.16	0.53
0.15	0.88	0.54	0.42	0.92	1.91	0.22	0.63
0.2	0.80	0.67	0.48	0.90	2.40	0.29	0.70
0.25	0.73	0.75	0.53	0.88	2.95	0.35	0.75
0.3	0.65	0.82	0.57	0.86	3.55	0.42	0.77
0.35	0.59	0.86	0.62	0.85	4.20	0.48	0.78
0.4	0.52	0.90	0.65	0.83	4.96	0.54	0.79
0.45	0.46	0.92	0.68	0.82	5.65	0.59	0.79
0.5	0.39	0.94	0.71	0.80	6.38	0.65	0.79
0.55	0.34	0.96	0.74	0.79	7.56	0.69	0.79
0.6	0.29	0.97	0.77	0.78	8.97	0.73	0.78
0.65	0.25	0.98	0.80	0.77	10.67	0.77	0.78
0.7	0.20	0.98	0.82	0.76	12.18	0.81	0.77
0.75	0.16	0.99	0.85	0.76	14.91	0.84	0.76
0.8	0.12	0.99	0.87	0.75	18.06	0.88	0.75
0.85	0.08	1.00	0.88	0.74	20.03	0.92	0.74
0.9	0.04	1.00	0.91	0.73	25.19	0.96	0.74
0.95	0.01	1.00	0.96	0.73	64.99	0.99	0.73
1	0.00	1.00		0.72		1.00	0.72

Appendix on Outputs

The work around this thesis has yielded five papers that have been published in peer reviewed journals. Four of them have directly contributed to this thesis (identified as 1-4 of the articles listed below). Another two contributing to the thesis are currently under peer review (6 & 7).

Presentations were also made in regional, national and international conferences and meetings. These are also listed below.

Peer reviewed articles published

1. Nirantharakumar K, Chen YF, Marshall T, Webber J, Coleman JJ. Clinical decision support systems in the care of inpatients with diabetes in non-critical care setting: systematic review. Diabet Med 2012; 29(6): 698-708.

2. Nirantharakumar K, Marshall T, Hemming K, Narendran P, Coleman JJ. Inpatient electronic prescribing data can be used to identify 'lost' discharge codes for diabetes. Diabet Med 2012; 29(12): e430-e435.

3. Nirantharakumar K, Marshall T, Kennedy A, Narendran P, Hemming K, Coleman JJ. Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. Diabet Med 2012; Dec; 29(12):e445-8.

4. Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, Coleman JJ Ferner RE. Hypoglycaemia in non-diabetic in-patients: clinical or criminal? PLoS One 2012; 7(7): e40384.

5. Nirantharakumar K, Toulis KA, Wijesinghe H, Mastan MS, Srikantharajah M, Bhatta S, Marshall T, Coleman JJ. Impact of diabetes on inpatient mortality and length of stay for elderly patients presenting with fracture of the proximal femur. J Diabetes Complications. J Diabetes Complications. 2013 Jan 8. doi:pii: S1056-8727(12)00337-6. 10.1016/j.jdiacomp.2012.11.010. [Epub ahead of print]

6. Nirantharakumar K, Marshall T, Saeed M, Wilson I, Coleman JJ. In-hospital mortality and length of stay in patients with diabetes having foot disease. J Diabetes Complications. *2013. (In press).*

7. Nirantharakumar K, Hemming K, Narendran P, Marshall T, Coleman JJ. A prediction model to identify hospitalised patients with diabetes who may have an adverse outcome. *Diabetes Care 2013.(In press).*

Presentations in:

International Conferences

1. Nirantharakumar K, Wijesinghe H, Mastan MS, Srikantharajah M, Bhatta S, Marshall T, Coleman JJ. Impact of diabetes on inpatient mortality and length of stay for elderly patients presenting with fracture of the proximal femur. International /European Conference in Endocrinology. May 2012. *(Poster)*

2. Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, Coleman JJ, Ferner RE. Frequency of hypoglycaemia in non-diabetic in-patients: retrospective analysis. International / European conference in Endocrinology. May 2012. *(Poster)*

National Conferences

3. Nirantharakumar K, Marshall T, Hemming K, Narendran P, Coleman J.J**.** High impact admissions with diabetes contributing to excess length of stay and referral to diabetes specialist team in a large tertiary hospital: retrospective data analysis for the year 2010. Diabetes UK conference. March 2013. *(Poster)*

4. Nirantharakumar K, Marshall T, Hemming K, Narendran P, Coleman J.J. Electronic prescription data in validating discharge diagnostic codes for patients with diabetes. Diabetes UK conference. March 2012. *(Poster)*

5. Nirantharakumar K, Marshall T, Kennedy A, Narendran P, Coleman J.J. The value of electronic recording of point of care blood glucose in the surveillance of in-patient hypoglycaemia. Diabetes UK conference. March 2012. *(Poster)*

Regional Meetings

6. Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, Coleman JJ, Ferner RE. Surveillance for non diabetic hypoglycaemia. West Midlands Physicians Meeting. Nov 2012. *(Poster)*

7. Nirantharakumar K. Clinical Decision Support Systems in the Care of Patients with Diabetes. Birmingham and Black Country Diabetes meeting. July 2012. *(Oral)*