Anaesthesia for emergency and elective hip surgery: improving patient outcomes.

Thesis by

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Word Count

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Author's Declaration

The work described in this thesis was carried out by me while I was employed as an StR on the West of Scotland School of Anaesthesia training scheme and latterly, as a Consultant Anaesthetist in Glasgow Royal Infirmary. This work was performed between May 2011 and January 2015.

The majority of patient recruitment was performed by me. The remainder of patient recruitment was performed by colleagues who are acknowledged in this thesis. Data collection and data analysis for the work on hip fracture outcomes and warfarin management in GRI was collected by Miss Katherine Cameron, a 3rd year medical student whom I supervised during an intercalated BSc degree. The concept for this work was my own. Ongoing data collection, analysis and quality improvement work were performed by myself.

The remainder of the work was carried out by myself. The writing of the thesis was entirely my own work.

The review of clinical guidelines for hip fracture was published in the journal *Anaesthesia*, 2013 and the protocol for the study; "Intrathecal opioid versus ultrasound guided fascia iliaca block for total hip arthroplasty – a randomised, controlled, double blind, non-inferiority study" was published in the journal *Trials* 2011.

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Abstract

This thesis is presented in two parts. The first is concerned with the management of patients undergoing repair of hip fracture while the second part describes a randomised controlled trial examining analgesic options after total hip replacement.

Musculoskeletal disease has the fourth greatest impact on the health of the world's population (when both death and disability are considered) and is the second most common cause of disability globally (1-3). Disability due to musculoskeletal disease has risen by 45% over the last 20 years compared to the 33% average increase seen across other disease groups. This is likely to increase unless action is taken to resolve some of the problems. This has been recognised by The European Parliament Leading Committee on the Horizon 2020 Programme (the European Union Research Framework Programme) resulting in the identification of rheumatic and musculoskeletal conditions as a priority for research over the next 7 years (4).

Glasgow Royal Infirmary is a tertiary referral centre for orthopaedic and trauma surgery undertaking a high volume of both elective and emergency procedures each year. I wished to investigate current standards of care relating to patients undergoing emergency surgery and to establish whether by benchmarking our practice against national data, we could identify areas for improvement. Hip fracture repair was chosen for analysis as it is a common, serious and costly condition that occurs in an increasingly elderly, frail and dependent patient population (5-7). Hip fracture is a worldwide concern and a significant public health challenge.

Important patient outcomes such as time to theatre, 30 day mortality and length of stay were analysed and compared against national audit data (8). These data compared favourably. Prior to commencing this work, staff members were asked to communicate any opportunities they saw for care to be improved. Certain sub-populations were identified by staff as meriting particular attention. These were patients admitted to ICU and patients taking warfarin. The sub-population of patients who were taking warfarin and required admission for

repair of hip fracture were particularly frail and resulted in a number of management challenges for staff. A quality improvement endeavour was employed in order to standardise management, reduce confusion, expedite time to theatre and ensure adequate thromboprophylaxis throughout the peri-operative period. This work resulted in the production of a protocol to guide management and is subject to ongoing review and audit.

The role of anaesthesia in the performance of elective total hip replacement surgery was also investigated. Total hip replacement is one of the most commonly performed surgical procedures in the United Kingdom, can result in improved quality of life, and is considered to be cost effective (9). In Glasgow Royal Infirmary, anaesthesia is most commonly performed using spinal anaesthetic with the addition of an opioid. Spinal opioids, whilst effective, are associated with side-effects of which the most serious is respiratory depression. Other adverse effects such as pruritus and nausea and vomiting may delay recovery and impact upon a patient's satisfaction with their experience. I carried out a randomised controlled, double blinded trial to assess whether a regional anaesthetic technique (ultrasound guided fascia iliaca block) could be used as an alternative to spinal morphine. This technique has not yet been assessed clinically in the published literature, though it has shown promise as being more reliable when compared to the landmark based technique (10). A non-inferiority design was employed in order to compare these two techniques. The primary outcome was 24 hour intravenous morphine consumption. After obtaining the necessary approvals from the West of Scotland Research and Ethics Committee and the West of Scotland Research and Development Department, recruitment was commenced in May 2011. Peer review was received from a journal of trial methodology and the protocol was published (11). Further peer review and funding was received from the European Society for Anaesthesia and Pain Therapy as well as a local peri-operative research fund.

This study shows that ultrasound guided fascia iliaca block is not non-inferior to spinal morphine, or in other words, that ultrasound guided fascia iliaca block is unacceptably worse than spinal morphine in the provision of analgesia after hip replacement. Adverse effects were not statistically significantly different between groups and reassuringly, there were no episodes of respiratory

depression or sedation in either group. This study has clear implications for practice and would suggest that spinal morphine remains an effective anaesthetic and analgesic agent in this patient group.

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Publications

- Kearns RJ, Moss L, Kinsella J. A review of clinical practice guidelines for proximal femoral fracture. *Anaesthesia* 2013; **68:** 159-66

- Kearns RJ, Macfarlane AJR, Anderson KJ, Kinsella J. Study Protocol: Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty – a randomised, blinded non-inferiority trial. *Trials* 2011; **12:** 51. http://dx.doi.org/10.1186/1745-6215-12-51

- Kearns RJ, Macfarlane A, Grant A, Puxty K, Harrison P, Shaw M, Kinsella J. Spinal opioid versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty: a randmoised, controlled, double blind, non-inferiority study, Submitted to *The Lancet* May 2015. Under revision.

Peer reviewed correspondence

- Kinsella J, Kearns R. Correspondence: Antibiotics for Community-Acquired Pneumonia in Adults. *N Engl J Med* 2015;**373:**683-686

Abstracts

Cameron K, Kearns RJ, Kinsella J. Hip fracture – comparing standards and investigating the role of critical care. *Anaesthesia* 2013; 68(10): 1090-3

Presentations

Presented at the Scottish Society of Anaesthetists Annual Conference, Crieff, May 2013.

- Cameron K, Kearns R, Kinsella J. Hip fracture – a comparison with national data.
- Cameron K, Kearns R, Kinsella J. The role of the ICU in hip fracture care.
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- Kearns RJ, Macfarlane A, Anderson K, Shaw M, Kinsella J. Ultrasound guided fascia iliaca block versus spinal morphine for analgesia after total hip arthroplasty. Choice and interpretation of statistical approach in a non-inferiority study.
- Kearns RJ, Macfarlane A, Grant A, Puxty K, Harrison P, Anderson K, Kinsella J. Analysis of the primary outcome for the study: Ultrasound guided fascia iliaca block versus spinal morphine for analgesia after total hip arthroplasty.
- Kearns RJ, Macfarlane A, Grant A, Puxty K, Harrison P, Anderson K, Kinsella J. Analysis of secondary outcomes for the study: Ultrasound guided fascia iliaca block versus spinal morphine for analgesia after total hip arthroplasty.
- Kearns RJ, Shaw M, Kinsella J. Linear regression modeling as a tool to predict 24 hour morphine consumption in atients undergoing total hip arthroplasty.

- Kearns RJ, Cameron K, Glennie S, Kinsella J. The introduction of a protocol to guide the management of patients on warfarin requiring repair of hip fracture.

Definitions / Abbreviations

AAGBI	Association of Anaesthetists of Great Britain and Ireland
ACC/AHA	The American College of Cardiology and American Heart Association
ACCP	American College of Chest Physicians
AIC	Akaike's Information Criterion
ASA	American Society of Anesthesiologists
AMT	Abbreviated Mental Test score
APTT	Activated Partial Thromboplastin Time
BCSH	British Committee for Safety in Haematology
BMI	Body Mass Index
BPT	Best Practice Tariff
CACI	Charlson Age Co-morbidity Index
CEA	Continuous epidural analgesia
CFNB	Continuous femoral nerve block
CI	Confidence Interval
CLPB	Continuous lumbar plexus block
COTE	Care of the Elderly
CT	Computed tomography

DALY	Disability-Adjusted Life Year
DBP	Diastolic Blood Pressure
DLA	Disability Living Allowance
DVT	Deep Venous Thrombosis
ED	Emergency Department
FFP	Fresh Frozen Plasma
FNB	Femoral nerve block
GA	General Anaesthesia
GP	General Practitioner
GRI	Glasgow Royal Infirmary
HALE	Healthy Life Expectancy
HipPeN	The Hip Fracture Peri-operative Network
Hz	Hertz
INR	International Normalised Ratio
LA	Local anaesthetic
LMWH	Low Molecular Weight Heparin
LPB	Lumbar plexus block
mA	milli ampere
mcg	micrograms

MHRA	Medicines and Healthcare products Regulatory Authority
NHFD	National Hip Fracture Database
NCEPOD	National Confidential Enquiry into Perioperative Outcome and Death
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNH	Number needed to harm
NHFS	The Nottingham Hip Fracture Score
OA	Osteoarthritis
OR	Odds ratio
PCA	Patient controlled analgesia
PCC	Prothrombin complex concentrates
PE	Pulmonary Embolism
PFF	Proximal femoral fracture
PNS	Peripheral nerve stimulator
POSSUM	The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
PT	Prothrombin Time
QALY	Quality Adjusted Life Years
QoL	Quality of Life

RA	Regional Anaesthesia
RCoA	Royal College of Anaesthetists
RCRI	Revised Cardiac Risk Index
RCT	Randomised controlled trial
RR	Relative Risk
RRR	Relative Risk Reduction
RhA	Rheumatoid Arthritis
SD	Standard Deviation
SHFA	The Scottish Hip Fracture Audit
SAB	Subarachnoid block
SIGN	Scottish Intercollegiate Guidelines Network
SBP	Systolic Blood Pressure
THA	Total Hip Arthroplasty
UFH	Unfractionated Heparin
UK	United Kingdom
US	United States of America
USG	Ultrasound guided
VQ	Ventilation-perfusion
VTE	Venous Thromboembolism

WHO	World Health Organisation
WMD	Weighted mean difference
YLL	Years of Life Lost
YLD	Years Lived with Disability

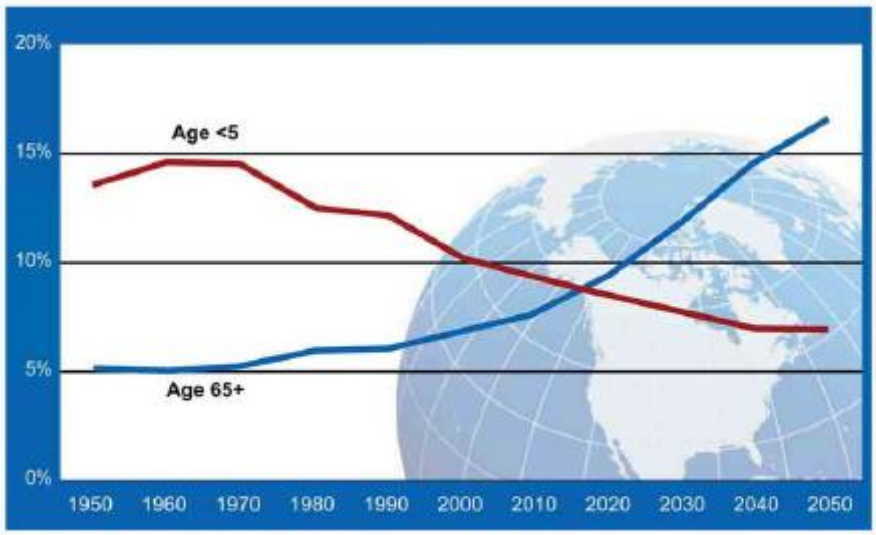
PART 1

Chapter 1

Introduction

1.1 The ageing population and societal expectations on health care delivery

It has long been established that the world's population is ageing. Average life-span continues to increase and there are now a greater number of older people living around the world than at any other time in history. In around 5 years time it is predicted that the worldwide over 65 population will out-number the under 5 age group for the first time (12). This is due to a combination of factors including reduced levels of fertility and increased longevity. Such population growth is expected to continue and even accelerate over the next few decades with the over 65 population predicted to increase from 524 million in 2010 to 1.5 billion by 2050. Indeed, the over 85 category is the fastest growing demographic with numbers projected to rise by 351% between 2010 and 2050 (12).



Source: United Nations. *World Population Prospects: The 2010 Revision.*
Available at: http://esa.un.org/unpd/wpp.

Figure 1.1-1 - Young children and older people as a percentage of the global population 1950 - 2050. Available at: http://esa.un.org/unpd/wpp (12).

In Scotland, a similar picture is seen. A report published by the Scottish Executive in 2007 summarises the demographic changes seen in the Scottish people over the past century and predicts what is likely to happen over the next 30 years (13). In 1900 the average Scottish life expectancy was 40 years, whilst in 2004 it was just over 74 years for males and 79 for females. By 2031, the number of people aged over 50 is projected to rise by 28% and the number aged

over 75 years by 75% (13). A further report issued by National Statistics for Scotland in 2010 further highlights the change in age distribution seen in the Scottish population over the last decade (2000 - 2010) (14). An increase is seen in each of the three oldest age groups (+14% in the 45-59 age group, +13% in the 60-75 and +14% in the >75 age group). A decrease of 7% is seen in the youngest age category of 0 - 15 years (14).

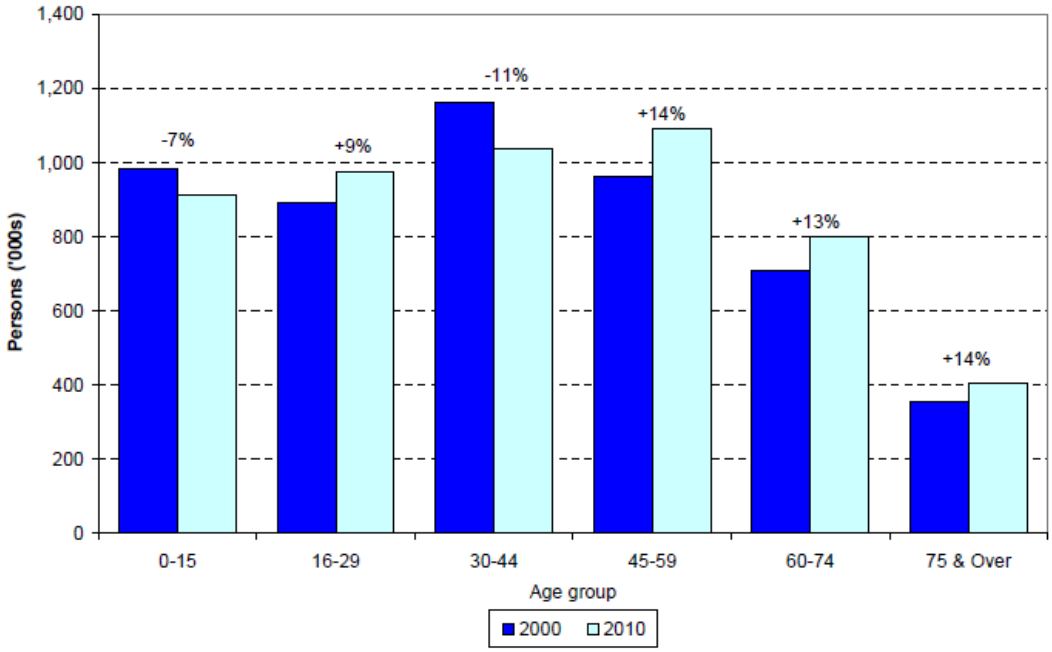


Figure 1.1-2 - The changing age structure of Scotland's population, 2000 - 2010.

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Whilst an increase in life-span is a welcome development, ageing does not occur without co-morbidity. Although improvements in hygiene and the effective treatment of communicable diseases (such as infection and parasites) has done much to reduce the death rates of the younger population, there has been an increase in the prevalence of non-communicable diseases such as heart disease, diabetes, cancer and arthritis. Older people are generally more likely to suffer from such chronic, often complex, conditions requiring long-term management with consequent increased per capita health expenditure. This population is also more likely to be admitted to hospital acutely as a result of such conditions as well as other afflictions of ageing such as falls and associated injury. The economic cost associated with chronic conditions is enormous. A World Health

Organisation (WHO) study estimated that the cost of managing just three chronic illnesses (heart disease, stroke and diabetes) in 23 low / middle income countries would amount to $84 billion over a 9 year period (12).

In the United Kingdom (UK), a report by the audit commission confirms that unscheduled hospital admissions are increasing year on year within the National Health Service (NHS) (16). According to a 2012 Royal College of Physicians report, 65% of all UK hospital admissions are accounted for by the over 65 demographic (17). Each acute admission is estimated to cost in the region of £470 (18). In Scotland, older people have a higher demand for surgical procedures. A Report by the Scottish Executive published in 2006 reported the rate of elective admissions in the over 65 years category to be 235 per thousand population compared with 90 per thousand population in the under 65 age group (19). Similarly for emergency cases, the annual number of admissions for patients aged 85 and over increased four-fold between 1981 to 1999 and has continued to increase since (19).

An increase in the older demographic decreases the proportion of people in the workplace as well as placing unprecedented demands upon healthcare, social care and social security resources. If such increasing demands are to be met, societal and economic adaptation must occur. The need to reconfigure healthcare systems to account for this changing demographic has been recognised for some time. In 2002, The Wanless Report suggested that the United Kingdom was falling behind other countries in terms of the quality of healthcare provided and needed to prepare for the demands of an ageing population within a sustainable, publicly funded service (20). These themes have continued in the initiatives of subsequent governments. Such concerns co-exist with the inexorable advance of medical technology and the increasing capability to treat previously untreatable conditions. Resources are therefore scarcer than ever and more information is required to determine which interventions, in which populations, exhibit the most value for money. The development of the economic downturn and world-wide recession serve to highlight that healthcare resources are limited and must be used in the most efficient way possible if benefits are to be maximised.

As well as the successful treatment of illness, it is vital that the disability associated with disease is reduced and that the number of people living out their older years with independence and acceptable quality of life is maximised. This is challenging in a number of ways. From a societal perspective, changes in lifestyle such as reduction in number of offspring, increased divorce levels, non-marriage, increase in the proportion of female offspring undertaking full-time employment, rise in emigration, and growing financial pressures, have a negative impact in the ability to provide traditional family-based care. This has implications for the state in terms of the provision of alternative forms of care. In contrast, as our average life expectancy increases, so might our ability to work to an older age. This is not reflected in the current retirement age which has remained relatively constant. While there are many misconceptions about ageing, it is recognised that the expertise, experience and skill-set exhibited by an older workforce has much to add to the workplace. Increasing activity into old age may also help to prevent cognitive decline (12). Old age must not be seen as a term interchangeable with ill health but should be seen as additional years with which to enjoy life and contribute to society (13). The ability to live out one's later years in a healthy fashion is something to which we can all aspire.

1.2 The global burden of disease

Disability is the common end point of a variety of chronic diseases and can greatly influence quality of life. In this last century, there has been a transition from disease-related mortality, to disease-related disability throughout remaining years of life. The ability to accurately and consistently describe the diseases and risk factors associated with disability is of great importance in the planning of healthcare, future research and allocation of resources. The WHO Global Burden of Disease group has performed the largest ever analysis of the health effects related to disease and injury on a worldwide scale over the past 20 years (1-3;21-24). This has resulted in a comprehensive estimate of mortality, morbidity and disability by age, sex, and region for a wide range of diseases.

The most recent report from this group is formatted as a collection of seven articles and was published in The Lancet in December 2012 (1-3;21-24). Each report focuses on a different aspect of the enormous volume and scope of data collected

In summary, the findings of this large volume of work with regard to musculoskeletal disease specifically are as follows: Musculoskeletal disease has the fourth greatest impact on the health of the world's population (when both death and disability are considered) and is the second most common cause of disability globally. Osteoarthritis is the fastest growing health condition as a result of the ageing population, obesity and falling levels of physical activity. Disability due to musculoskeletal disease has risen by 45% over the last 20 years compared to the 33% average increase seen across other disease groups. This is likely to increase unless action is taken to resolve some of the problems. This significant burden of disease has been recognised by The European Parliament Leading Committee on the Horizon 2020 Programme (the European Union Research Framework Programme). This programme, which determines European Union funding for research from 2014 to 2020, has identified rheumatic and musculoskeletal conditions as a priority for research over the next 7 years (4).

In the United Kingdom (UK), the extent of this problem was depicted in a prospective 2 year study performed by the Medical Research Council in 2006. This work aimed to determine the onset of disability (defined as requiring help from another person at least several times a week and by dependency in activities of daily living) in the over 65 demographic in five areas throughout England and Wales (25). Data on those who were eligible to receive a disability living allowance (DLA) served as a marker of those who were the most severely disabled. DLA was a benefit for people who had personal care needs, mobility needs or both before their 65th birthday. The most common condition resulting in people receiving DLA was 'arthritis', representing 18% of all recipients. This is equivalent to half a million people aged less than 65. A further 7% of people received DLA for muscle / bone / joint disease. This represents an expenditure of around £48 million each week for arthritis and muscle / bone / joint disease combined (25).

1.3 Femoral pathology in adults. Why is it associated with ageing?

Bone deteriorates in structure, composition and function with increasing age. The development of arthritis, osteoporosis and consequent fracture occurs as a result of such deterioration, accompanied by the “wear and tear” accumulated throughout life.

1.3.1 Osteoporosis

Osteoporosis is a disorder of the skeleton characterised by low bone mineral density and subsequent bone fragility. Bone is a hard material which is in a constant state of flux. Bone formation by osteoblasts is predominant in childhood and adolescence, while bone resorption performed by osteoclasts increases with age (26). Minerals essential to the formation of new bone include calcium and phosphate. Deficiencies in these minerals, due to inadequate diet or poor absorption, impair the formation of new bone and increase the risk of osteoporosis. Bone mineral content decreases by around 4% per decade in males after the age of 20, and by 15% per decade in females after menopause (26). Secondary causes of osteoporosis include; malignancy, pharmacological agents (such as steroids), endocrine disorders, malnutrition, immobility, bone marrow dysfunction, renal disease and disorders of the gastrointestinal or biliary tract (27). Work carried out by the WHO in 2004 estimated that the prevalence of osteoporosis among post-menopausal, white American women is 14% in those aged 50-59 years, 22% in the 60-69 years of age group, 39% in 70-79 year olds and 70% in those aged 80 years and older (28). In the UK, around 3 million people are thought to have osteoporosis (29).

Deterioration in bone architecture leads to increased bone fragility and susceptibility to fracture. It is estimated that the lifetime risk of fragility fracture related to osteoporosis is around 40% in women over 50 years of age (26). This is particularly common in the bones of the wrist, spine and hip. There were an estimated 1.7 million hip fractures worldwide in 1990 and this is estimated to rise to 6 million by 2050 (26). Surgical repair remains the most common management strategy for hip fracture with non-operative management usually reserved for those considered too frail for surgery. Osteoporotic

fractures are increasingly common with age, result in disability, present a significant burden to healthcare systems, and are a major public health challenge. The combined social and healthcare costs associated with the management of hip fracture in the UK alone is around £2.3 billion per year (29).

1.3.2 Degenerative hip disease and osteoarthritis

Degenerative hip disease occurs mostly as a result of osteoarthritis and rheumatoid arthritis. Other less common causes of degenerative hip disease include: Paget's disease, avascular necrosis of the femoral head, Perthe's disease, slipped upper femoral epiphysis and trauma. Pain resulting from degenerative hip disease frequently becomes severe and is difficult to control using standard analgesics. This can result in a loss of functional ability and hence independence.

Osteoarthrtitis (OA) is defined as joint pain associated with functional limitation and reduced quality of life (30). OA describes the degeneration of cartilage and bone within a joint with resultant tissue loss. At the same time, proliferation of bone in the form of osteophytes occurs. While this process aims to repair a joint after an insult, it may fail to achieve this and instead result in ongoing joint damage. This can culminate in pain and stiffness in a variety of joints most commonly knees, hips, hands and spine (31). OA may be considered Primary if occurring in the absence of anatomical, traumatic, metabolic, endocrine or neuropathic causes, or Secondary if such an abnormality is present (32). Factors associated with the development of OA include genetic factors, female sex, joint laxity, occupations involving heavy lifting, elite sports and obesity (32;33). OA is more common in Caucasians than in other ethnic groups such as Asians, Africans and Hispanics suggesting a significant genetic component (32).

OA is common and is the most prevalent cause of walking related disability amongst the older population in the US (33). According to data compiled by the US National Arthritis Data Work Group, OA affects 33.6% (12.4 million) of patients over the age of 65 (34). This equates to an estimated 26.9 million of all US adults in 2005, an increase from around 21 million in 1990 (34). OA of the hip occurs in 88 per 100,000 patient years and increases with age (35). In the UK, OA is thought to affect 8.5 million people (36).

Total Hip Arthroplasty (THA) is commonly performed in the treatment of pain and disability related to hip joint disease and is considered one of the most effective orthopaedic procedures in current practice. From data published in 2011 by the UK National Joint Registry, 93% of patients undergoing hip replacement surgery require to do so as a result of osteoarthritis (37).

1.4 The medical profession and the difficulties with this patient group.

The management and care of elderly patients presents a specific challenge to the medical team, including the anaesthetist (5). Age-related alterations in physiology, pharmacokinetics, pharmacodynamics, increased co-morbidity, polypharmacy, cognitive impairment and considerations relating to social circumstances result in the necessity for a careful and thoughtful management plan during any hospital admission. Elderly patients have reduced functional reserve when compared to younger patients (38). This can be thought of as a reduction in the gap between basal performance level (i.e. when the patient is at rest) and maximal performance level. The requirement for a surgical procedure, whether elective or emergent, represents a further significant insult from which even the fittest of elderly patients may struggle to compensate. Older patients also have an increased incidence of post-operative complications (39;40). Fluid shifts, hypoxia, infection, as well as transient peri-operative renal and cognitive impairment may all have more severe consequences in the elderly patient. This can result in a prolonged and more turbulent recovery period.

In a prospective cohort study of 594,911 American patients undergoing non-cardiac surgery over the period 1991 to 1999, 30 day all cause mortality was found to be significantly increased in the subset of patients aged over 80 years (8% versus 3%, $p<0.001$). 20% of patients over 80 years had at least one post-operative complication, and those who suffered such a complication had a higher 30-day mortality than those who did not (26% versus 4%, $P<.001$) (39). A more recent US study analysing prospectively collected peri-operative data for 7696 patients over the period 2002 to 2005, reported an overall 28% morbidity rate and 2.3% mortality rate. This was increased to 51% and 7% respectively when

the over 80 age group were analysed separately. Post-operative morbidity and mortality were noted to increase progressively with advancing age. Age was statistically significantly associated with morbidity (wound $p = 0.021$, renal $p = 0.001$, cardiovascular $p = 0.0004$, respiratory $p < 0.0001$) and mortality ($p = 0.001$) (40).

Careful, thoughtful pre-operative assessment and optimisation of elderly patients is paramount if adverse events are to be minimised. This is emphasised in a 2010 document by the National Confidential Enquiry into Peri-operative Outcome and Death (NCEPOD) examining peri-operative care in the elderly population within the UK (excluding Scotland) (41). This report aimed to;

> *"explore remediable factors in the processes of care of patients aged 80 or older"*

Investigators reviewed notes relating to all patients aged ≥ 80 years who died within 30 days of a surgical procedure. This was performed over a two month period in 2008. Surgeons, anaesthetists and organisations involved in the care of each patient were required to complete a questionnaire examining events relevant to the case. All documents pertaining to each of the 1120 identified cases were then anonymised and reviewed by external advisers. The majority of patients (83.4%) were admitted as an emergency and had an American Society of Anesthesiologists (ASA) score of 3 or more (84%) signifying severe systemic illness. The most common surgical procedure performed was repair of proximal femoral fracture (37.9% of cases). Of all patients with sufficient data for analysis (n=740), around 30% (220/740) died within the first three days of the procedure and 52% (385/740) died within one week of the operation. Of notable concern was that only 37.5% of patients (295/786) were considered to have received good care with 43.6% (343/786) assessed as having room for improvement in either clinical or organisational care. 6.4% (50/786) of patients were considered to have received care which was less than satisfactory (41).

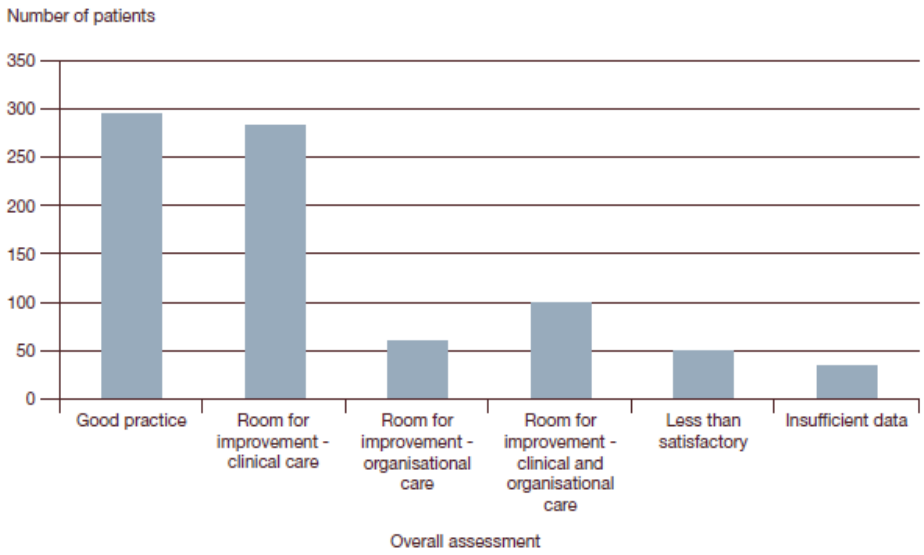

Figure 1.4-1 - Overall assessment of care, NCEPOD 2010(41).

Reproduced with permission from NCEPOD.

High quality care of elderly patients often involves complex decision making processes highlighting the importance of multi-professional input (41). The NCEPOD report makes a number of recommendations regarding appropriate care in this vulnerable patient group. These include: the involvement of a multi-disciplinary team, regular input from Care of the Elderly (COTE) physicians, recognition that co-morbidity, disability and general impression of frailty act as independent markers of risk in the elderly, avoidance of delays to theatre, appropriate assessment of nutritional status and cognitive impairment, avoidance of hypothermia, management of hypotension, adequate treatment of pain, increased use of level 2 and 3 beds post-operatively, appropriate use of peri-operative monitoring including cardiac output monitoring, and necessity for consultant involvement (41).

1.4.1 Frailty

The concept of frailty is interesting and variably defined with nutritional, functional and medical components. Frailty may be regarded as a state of reduced resistance to stressors (42). This results in general decline and is associated with a high level of vulnerability for adverse outcomes such as disability, dependency, falls, need for long-term care and death (43-45). There

is no “best” definition of frailty and several scales and scoring systems have been proposed. These are outlined in a 2008 review article examining the relationship between frailty and cardiovascular disease (44). Weight loss, self-reported exhaustion, weakness of grip, slow walking speed, physical inactivity, sensory loss, incontinence and depressive symptoms are included variably in such definitions (44). A 2004 consensus report from the Interventions on Frailty Working Group further refines the frailty phenotype as relating to a deterioration in: mobility, strength, balance, motor processing, cognition, nutrition, endurance and physical activity (46). These markers may be used alongside the “end of the bed” clinical assessment often used in clinical practice. The prevalence of frailty is therefore difficult to determine in view of the different definitions and variable populations studied. However, early recognition of frailty as a risk factor for poor peri-operative outcome can be helpful in planning optimal pre-, intra- and post-operative care (41). A multi-disciplinary approach involving surgeons, anaesthetists, COTE physicians, nurses, physiotherapists, dieticians, occupational therapists, pharmacists, speech therapists and social workers is desirable if optimal care and good outcomes are to be achieved (5).

1.4.2 Deprivation and “The Glasgow Effect”

At this juncture, it is interesting to consider why the health of Scotland and more specifically, the population of Glasgow is poorer than that of the rest of the UK. “The Glasgow Effect” is a term used to describe the phenomenon of poorer health and higher levels of mortality seen in Glasgow beyond that which might be expected due to poorer socio-economic circumstances (47). Whilst the link between deprivation and poorer health related outcomes is well established (48), it is now thought that this does not account for all of the differences seen in outcomes between populations in different cities. This concept was investigated by Walsh *et al* in 2010 (49). These investigators compared rates of “income deprivation” (a measure known to be very highly correlated with UK indices of multiple deprivation) for small areas (average population size 1600) in Glasgow, Liverpool and Manchester. Liverpool and Manchester were chosen as they are cities known to have high levels of poor health, deprivation and have the lowest life expectancy of all cities in England(50). Standardised mortality ratios were calculated for Glasgow and compared to those seen in Liverpool and

Manchester. Results were standardised for age, gender and income deprivation. Despite all cities having almost identical levels of deprivation, premature deaths in Glasgow were > 30% higher [SMR 131.4, 95% confidence interval (CI) 128.6–134.1] with deaths in all age groups around 14% higher (SMR 114.4, 95%CI 113.2–115.5) (49). Interestingly, childhood (0–15 years) mortality was significantly lower in Glasgow relative to Liverpool and Manchester (SMR 81.3, 95%CI 71.2–91.3). Therefore the biggest excess of deaths were seen in adults of working age (15-64 years). The additional mortality was seen in both male and females (although was more marked in males) and across the entire spectrum of affluence and deprivation. In deaths considered to be premature, alcohol and drugs were found to account for around 50%. When cause of death was considered, Glaswegians had significantly higher rates of lung cancer (27%), suicide (70%), alcohol related causes (2.3 times higher) and drug related causes (2.5 times higher). The authors calculated that there were more than 4500 excess deaths in Glasgow over a 4 year period when compared to Liverpool and Manchester despite all cities exhibiting almost identical levels of deprivation. These findings of poorer health and increased mortality in Scotland, even after correction for socio-economic status, have also been noted by other authors(49;51;52).

The reasons for these differences remain unclear. Walsh *et al* postulated that they may be due to undetected differences in deprivation not captured by the indices analysed (which rely on information about benefits claims as well as other databases). They also explore the possibility that the socio-economic status of Glasgow has changed in recent years with higher levels of deprivation in the past still yielding effects but not being detected on analysis of up to date data. However, their analysis of historical data makes this theory seem unlikely. Another theory centres on Glaswegians having more extreme “adverse health behaviours” (i.e. smoking, drinking to excess, drug abuse and poor eating habits) than English people of similar socio-economic groupings. However, the authors did not have sufficient data to make this conclusion and remarked that further analysis would be required to explore this further. Other postulated theories to explain the “Glasgow Effect”include: the breakdown of social and moral norms leading to increased instances of “self-destructive behaviours”, genetic factors, cultural differences, the effects of migration and the breakdown of the family

unit. Further investigation of these factors is ongoing but as yet, no clear explanation for this effect has been found (53-55).

1.5 Peri-operative risk stratification

Peri-operative morbidity is associated with prolonged hospital stay, poorer surgical outcome and reduced long-term survival. Systems to estimate peri-operative risk may be desirable in providing useful information to patients and families, obtaining informed consent from patients, planning interventions to minimise risk, utilising resources most effectively and allowing comparisons between units and countries. Various scoring systems have been developed to this end. An ideal risk prediction score is accurate, simple, reproducible, cheap, devoid of the need for expensive equipment and easily available.

Existing risk prediction scores include the American Society of Anesthesiologists' (ASA) Physical Status Score (56), the Revised Cardiac Risk Index (RCRI) (57), The Charlson Age Comorbidity Index (CACI) (58), The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) (59) and The Nottingham Hip Fracture Score (60).

The ASA score is a widely used scoring system consisting of six categories which is simple to perform, useful for predicting outcome in a population and valuable for audit and research purposes. Whilst the ASA classification has stood the test of time and remains widely used, it has a number of limitations and is not useful as a tool for predicting risk in individual patients. The RCRI is used for the estimation of peri-operative risk in patients undergoing non-cardiac surgery (61). It should be highlighted that the RCRI is designed for predicting adverse peri-operative cardiac events and is not a tool for predicting peri-operative morbidity and mortality from all causes. Cardiac events account for only a small proportion of post-operative complications thus limiting the role of the RCRI to a specific sub-set of patients. The Charlson Age Co-morbidity Index (CACI) is used to predict the 10 year mortality for a patient who may have a variety of co-morbidities. The CACI relies upon patient self-reporting of co-morbid conditions and does not incorporate surgical information, both of which can limit its effectiveness as a predictive tool. The Physiological and Operative Severity Score

for the enUmeration of Mortality and Morbidity (POSSUM) was developed by 1991 as a scoring system for surgical audit (59).

The POSSUM score has been evaluated in orthopaedic surgery using a modified equation to allow for orthopaedic operations (62). An analysis of 2236 elective and emergency patients over a 12 month period in a single centre was performed. The POSSUM logistic regression equations yielded an overall predicted mortality of 53 patients (versus 51 observed) and a predicted morbidity in 254 patients (versus 252 observed). Given the close correlation between predicted and observed events, the authors concluded that the POSSUM score was a useful audit tool with which to assess the quality of orthopaedic care (62).

Further to this work, the POSSUM score was evaluated in 1164 patients who had sustained a hip fracture over a 21 month period in a single centre (63). The POSSUM score was found to over-predict death overall with 181 predicted versus 119 observed. The area under the receiver operating curve was 0.62 indicating that the POSSUM score was a poorly predictive test in this patient group (63). To put this into context, the area under the receiver operating curve in the analysis of general orthopaedic patients was >0.85 (62). Possible reasons for this were felt most likely to relate to the physiological variables inputted (as the surgical data were fairly similar in patients undergoing this type of surgery). An argument was made that as the population sustaining fractured hips is generally very elderly, some of the physiological variables considered to put patients “at risk” using the scoring system, were more likely to be within a “normal range” for this particular population. Also, the way in which items were weighted was felt to be less appropriate for the elderly demographic, with other variable such as haemoglobin and albumin considered as being potentially useful as markers of risk (these are not included in the POSSUM scoring system). The authors concluded that the POSSUM score was not suitable for risk prediction or comparison of outcomes in patients undergoing surgery for proximal femoral fracture (63). Despite its limitations, the POSSUM score (and its variations) remain a useful tool for predicting individual patient risk in the peri-operative period.

1.5.1 The Nottingham Hip Fracture Score

The Nottingham Hip Fracture Score (NHFS) is a summative assessment tool designed specifically to predict post-operative mortality in patients undergoing surgical repair of hip fracture. This provides the anaesthetist with objective information which can be used in planning the most appropriate pre-, intra- and post-operative management, as well as to inform patients and relatives of potential outcomes in this particularly frail group.

The NHFS score was developed using a prospectively gathered dataset of 4967 patients undergoing repair of hip fracture in a single centre over a seven year period (1999 - 2006) (60). Univariate logistic regression analysis was performed on all potential variables (identified from published research as being potentially influential upon outcome) in order to select those which were predictors of mortality at 30 days. An automated, stepwise, forward multivariate, logistic regression analysis was then applied to each independent variable in a subset of patients (approximately half of the dataset) in order to create the score. After the score had been constructed, its validity was assessed against a further subset of patients (the other half of the dataset). The variables found to be independent predictors of 30 day mortality on multivariate logistic regression analysis were age (66–85 and ≥86), sex (male), number of co-morbidities (≥2), mini-mental test score (≤6 out of 10), admission haemoglobin concentration (≤10 g/dl), living in an institution and presence of malignant disease. Calculation of the Hosmer–Lemeshow goodness-of-fit statistic showed that there was good concordance between observed and predicted deaths at 30 days (Chi^2 test, P=0.79) (60).

The Hosmer-Lemeshow statistic divides cases into 10 groups according to increasing score values, and compares the predicted with the observed death rates. A lack of difference between predicted and the observed mortality indicates good concordance of the score (64). “Goodness-of-fit” tests are considered to have more relevance as an evaluation of scoring systems concerned with risk. This is because they assess how well the score predicts outcome for bands of risk. When a Receiver Operating Curve (ROC) was calculated, the area under the curve was 0.719. This makes the NHFS superior to the POSSUM score when applied to patients with hip fracture (63), though

inferior to the POSSUM score when applied to the general orthopaedic population (62).

Variable	Points
Age 66 – 85 years	3
Age ≥ 86	4
Male	1
Haemoglobin concentration ≤ 10g/dl on hospital admission	1
Abbreviated mental test score ≤ 6/10 on hospital admission	1
Living in an institution	1
More than one co-morbidity	1
Active malignancy within last 20 years	1

Figure 1.5-1 - Calculation of NHFS (60).

Further analysis of the NHFS was performed on data from 6202 patients over a ten year period (1999-2009) to evaluate its accuracy in predicting mortality at one year (65). The seven item score (maximum score 10) was calculated for each patient and patients subsequently divided into high risk (score > 4) or low risk (score ≤ 4) groups. Survival was significantly higher in the low risk compared with the high risk group at 30 days [96.5% compared with 86.3% (P<0.001)] and at 1 yr [84.1% compared with 54.5% (P<0.001)]. One year survival in patients who survived beyond 30 days was also greater in the low risk group compared with the high risk group [87.1% compared with 63.1% (P<0.001)]. In the analysis of the effects of delay to surgery, a delay of > 48 hours was associated with an increased mortality at 1 yr of 31% compared with 26% (P<0.001). As the mortality difference persisted even when those who died early were excluded, the authors concluded that pre-operative factors had an ongoing influence on mortality risk after hip fracture surgery. The NHFS is therefore an accurate predictive tool in assessing mortality risk at one year after hip fracture surgery (65).

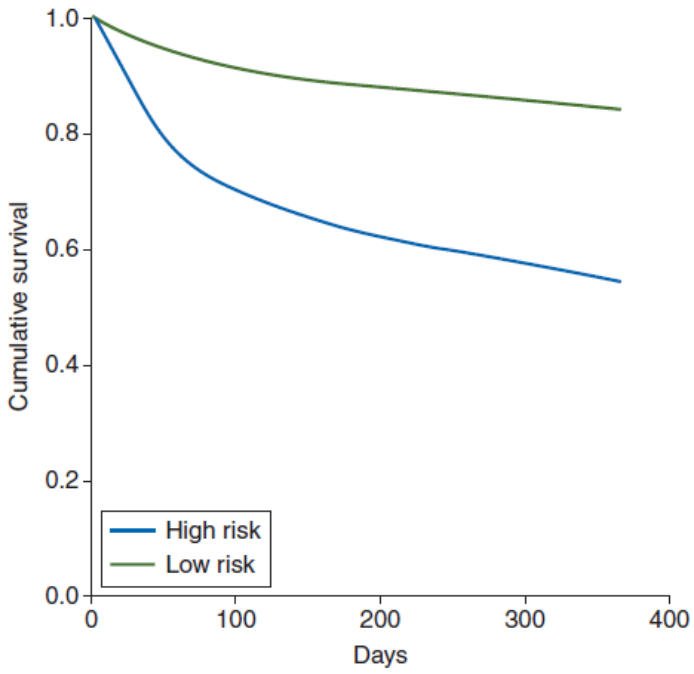

Figure 1.5-2 - Kaplan-Meier curve showing 1 year post-operative mortality after hip fracture surgery. Low- and high risk groups have an NHFS of ≤ 4 and > 4 respectively (65).

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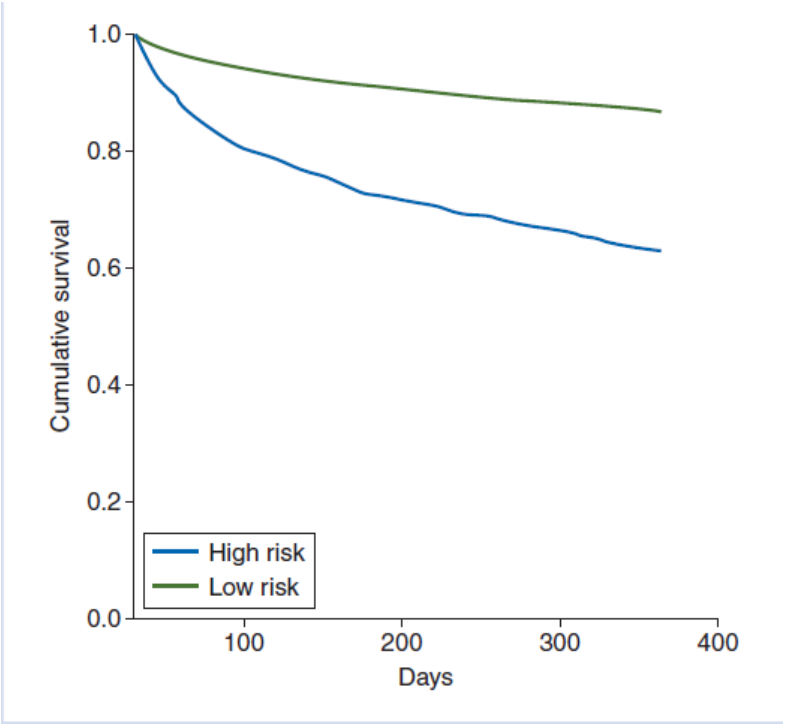

Figure 1.5-3 - Kaplan-Meier curve showing 1 year post-operative mortality in patients who survived 30 days after hip fracture surgery. Low- and high risk groups have an NHFS of ≤ 4 and > 4 respectively (65).

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Further work from this group applied the NHFS to three geographically distinct sites in order to assess its applicability outside of its parent hospital. Data from 7290 patients were analysed for the outcome of 30 day mortality (66). This was found to be 6.6% for the complete cohort though the NHFS was found to over-estimate mortality in the higher risk groups. Following a revision of the equation used to derive the score, the NHFS was found to calibrate well across data from all three sites confirming its status as a robust and useful tool for risk prediction (66).

Total NHFS	Predicted 30 day mortality (%)	
	Original NHFS	New NHFS
0	0.9	0.7
1	1.5	1.1
2	2.4	1.7
3	3.8	2.7
4	6.2	4.4
5	9.8	6.9
6	15	11
7	23	16
8	33	24
9	47	34
10	57	45

Table 1.5-1 - Calculated 30 day mortality using original and revised NHFS (66).

The Nottingham Hip Fracture Score therefore provides a disease specific scoring system which is validated in the frail population for which it is intended and can be used to predict 30 day mortaility, 1 year mortality and functional outcome.

Identification of high risk patients may allow for specific measures to be taken in terms of optimisation, use of invasive monitoring and cardiac output monitoring, involvement of senior personnel, expedition of surgery, information provision to relatives and use of critical care facilities as well as audit and quality improvement work.

1.6 Chapter 1 Summary

- The world's population is ageing.
- While mortality levels have fallen, levels of morbidity and associated disability are rising.
- Musculoskeletal disease has the fourth greatest impact on the health of the world's population and is the second most common cause of disability globally.
- This is associated with large costs in terms of health care and social support, and is an area of priority for the research community.
- The elderly population requires special consideration in the peri-operative period and presents a number of challenges to health care professionals.
- A number of scoring systems have been developed to help quantify peri-operative risk.
- The Nottingham Hip Fracture Score has been evaluated specifically in patients admitted with hip fracture and is useful in this patient group.

Chapter 2

Evidence to date – Emergency surgery for fractured femur

2.1 Burden to the NHS and expected projections

Hip fracture is a common, serious and costly condition that occurs in an increasingly elderly, frail and dependent patient population (5-7). This is a worldwide concern. There were an estimated 1.6 million cases of hip fracture worldwide in 1990 and this is projected to surpass 6 million by 2050 (5;67). According to the findings of a recent systematic review examining the worldwide distribution of hip fracture, incidence can vary 10 fold between countries. The United Kingdom was classified as a "high risk" country due to its high age-standardised annual risk of hip fracture (68).

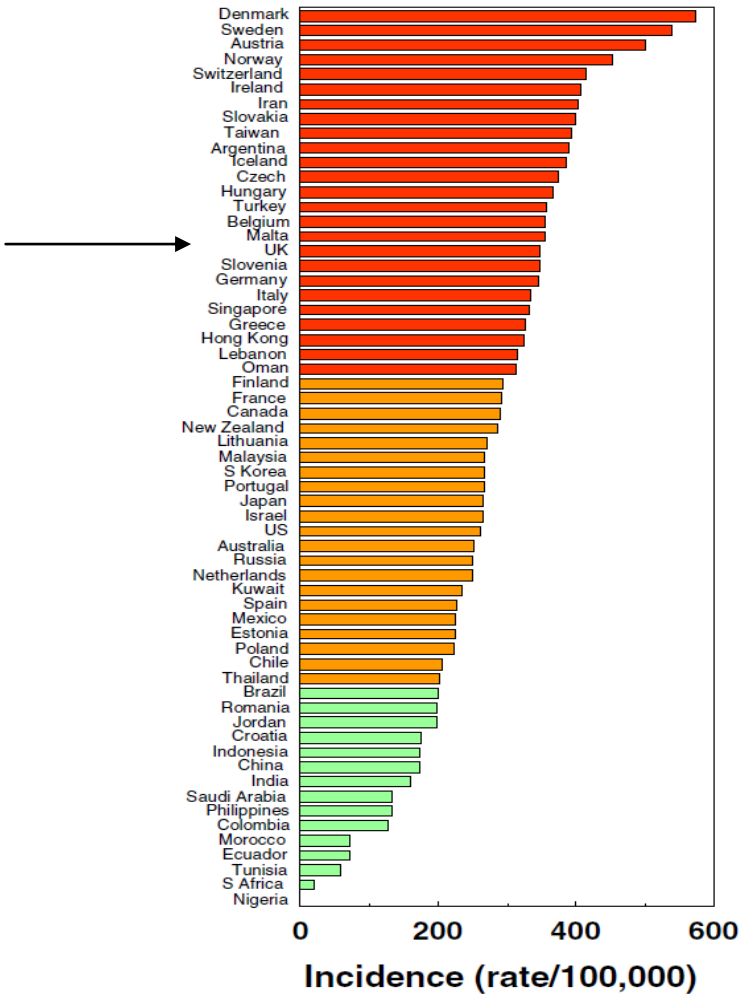


Figure 2.1-1 - Age-standardised annual risk of hip fractures in women (/100,000) according to country (68).

Data from the National Hospital Discharge Survey in the US estimates that hip fracture accounted for around 281,000 hospital admissions in adults over 65 years of age in 2007 (69). In the UK it is estimated that 70 000 – 80 000 cases of hip fracture occur annually, accounting for 1.5 million bed-days and resultant in-patient costs of £0.785 billion (70-72). This is projected to rise to around 100 000 cases in England alone by 2033 with an estimated associated cost of £3.6-5.6 billion (73). In Scotland, according to information from the Information Services Division, there were around 6266 cases of hip fracture in 2009 (74). This figure has remained relatively constant over the preceding decade despite an ageing population.

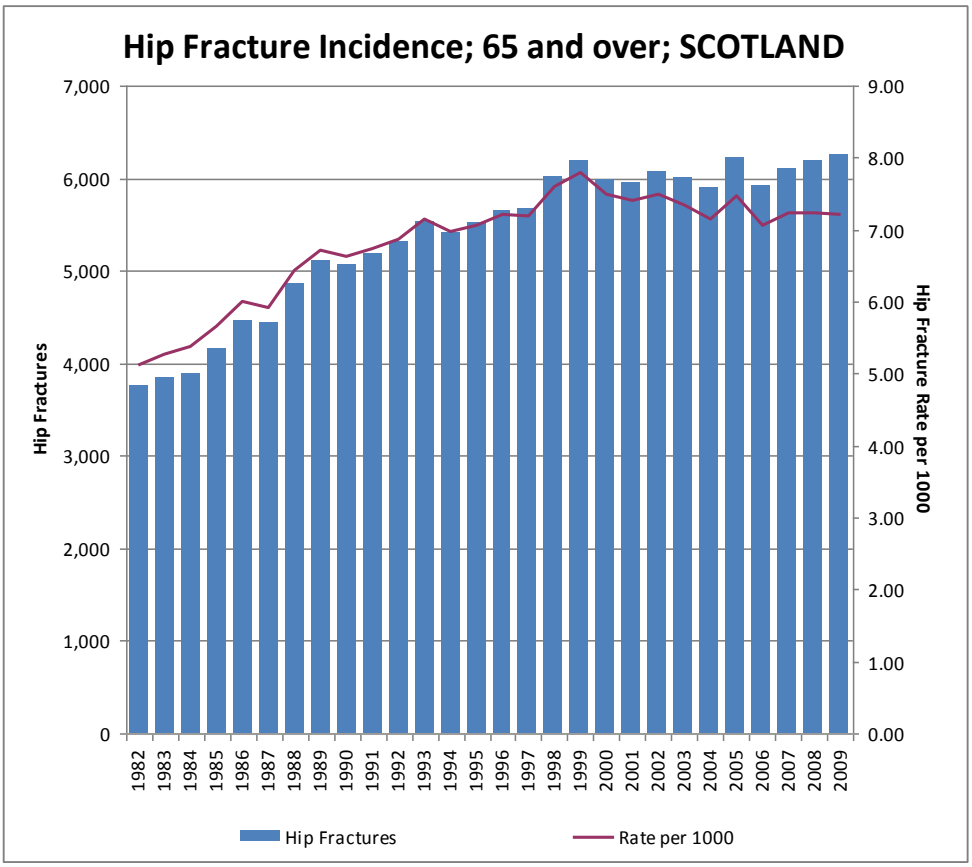


Figure 2.1-2 - Hip fracture incidence in patients ≥ 65 years in Scotland (74).

The vulnerability of this patient group is apparent in its associated prolonged length of hospital stay, complex care journey, ongoing care needs and high levels of morbidity and mortality (75). Data from national audit suggest a consistent and persistent mortality rate of around 7-10% at one month and 30% at one year (8;71;76). Hip fracture therefore results in significant levels of

financial and human expenditure and is a burgeoning public health challenge (73;77;78). Outcomes following hip fracture are used as a marker of the quality of healthcare across all the relevant disciplines. The peri-operative management of hip fracture is an important example of a challenging clinical area where evidence is lacking and practice varies (8).

2.2 Emergency surgery – proximal femoral fracture

Hip fracture is a serious injury which can result in severe pain and requires admission to hospital. The consequences of a fractured hip can be devastating resulting in disability, reduced mobility and subsequent loss of independence. Many people who suffer this injury are unable to continue living in their own home and have to be cared for in alternative accommodation once the acute hospital admission is over.

There is a time-pressure to operate on patients who have suffered a hip fracture. Surgery is the optimal analgesic for these patients and therefore early repair has merits on a humanitarian level alone. Surgery remains the mainstay of treatment. As it would be unethical to perform an RCT comparing expedited with delayed surgery in this vulnerable patient group, the majority of evidence is obtained from cohort studies and is of low quality. This is highlighted in the analysis of optimal time to theatre in the 2011 NICE guideline: Management of patients with hip fracture (79). In this analysis, 10 studies with a total of 193,793 participants were reviewed. Analyses for 24, 36 and 48 hour time periods revealed significant improvements in morbidity (e.g. pressure ulcers), increased return to independent living and some evidence for reduction in mortality for early surgery. It should be highlighted that the evidence was generally deemed to be of low or very low quality by the NICE assessors. Despite the low quality of evidence, there was no observable benefit from delaying surgery and no harm seen with its expedition. NICE concluded that surgery should be performed *"on the day of or day after admission"* (79). Surgical delay of greater than 48 hours after admission is associated with prolonged hospital stay, increased morbidity (e.g. pressure sores, thromboembolic complications, pneumonia) and increased mortality (if delay is prolonged) (80;81).

2.2.1 Anatomy of the hip joint

In order to understand the relevant surgical procedures, knowledge regarding the anatomy of the hip joint is required.

2.2.1.1 Bony structure

The hip joint is a ball-and-socket synovial joint in which the femoral head is the ball, and the acetabulum the socket. The adult hip bone is formed by the fusion of the ischium, the ilium and the pubis. The ischium forms the inferior aspect of the pelvis and the infero-posterior aspect of the acetabulum (82). The bilateral hip bones are united anteriorly by the pubic symphysis and along with the sacrum and the coccyx, form the bony pelvis. The hip joint connects the axial skeleton with the lower limb and is thus essential in the maintenance of posture and balance (82;83).

The proximal end of the femur comprises the femoral head, neck and greater and lesser trochanters. The femoral head is angled anteriorly, superiorly and medially at approximately 130 degrees to the femoral shaft and articulates with the acetabular component of the hip joint (see Figure 2.2-1). The greater trochanter lies on the antero-lateral surface of the femoral neck and is the insertion site for the gluteus medius and minimus muscles whereas the lesser trochanter lies medially and provides the insertion site for the iliopsoas muscle (82;83).

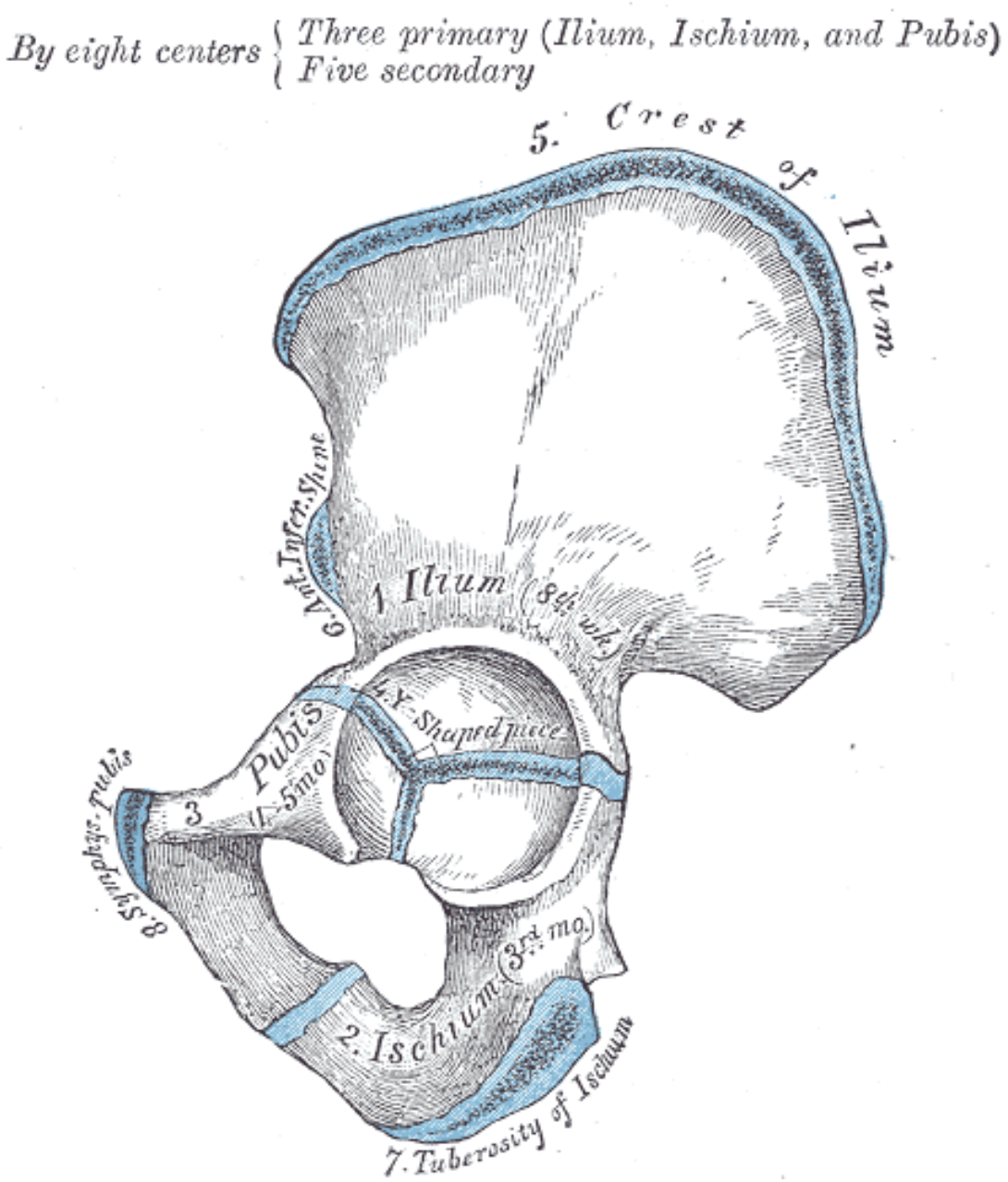


Figure 2.2-1 - Anatomy of the hip joint (84).

Reproduced from Gray's Anatomy, 20th edition.

2.2.1.2 Musculature of the hip

Movement at the hip joint occurs due to the actions of 4 different muscle groups: the gluteal, iliopsoas, adductor, and lateral rotator groups.

Gluteal group: These include gluteus maximus, medius, minimus and tensor fascia lata. Gluteus maximus originates from the sacrum and ilium and is the

main muscle of hip extension, while gluteus medius and minimus are involved in abduction and medial rotation.

Adductor group: Adductors brevis, longus, magnus, as well as gracilis and pectineus originate from the pubis bone and are the main adductors of the hip joint.

Lateral rotator group: Piriformis, gemelli, quadratis femoris and obturator muscles.

Iliopsoas group: This includes iliacus and psoas major which comprise the main hip flexors. Psoas major arises from the transverse processes of T1-5 and inserts upon the lesser trochanter (after merging with iliacus). Iliacus is a flat, triangular-shaped muscle which originates from the iliac bone, sacrum and iliolumbar ligaments. Iliacus covers the curved, inner surface of the iliac bone before merging with psoas major at the inguinal ligament. It is innervated by branches of the femoral nerve and direct branches of the lumbar plexus (82;83).

2.2.1.3 Innervation of the hip joint

Sensory innervation of the hip joint is complex and involves several afferent nerves. The anteromedial capsule is supplied by articular nerves from the obturator nerve with further anterior innervation arising from the femoral nerve. Articular branches of the sciatic nerve innervate the posterior compartment and articular branches of the nerves supplying quadratis femoris supply the posteriomedial component. Cadaveric studies have demonstrated that articular branches of the superior gluteal nerves have a role in the supply of the posterolateral component of the hip joint (85). Cutaneous innervation of the skin overlying the incision site on the lateral thigh is supplied by the lateral cutaneous nerve of thigh and by the lateral cutaneous branch of the subcostal nerve. The ilioinguinal and genitofemoral nerves also provide some sensory fibres to the upper aspect of the anterior portion of the thigh (86).

2.2.2 Types of femoral fracture

Hip fractures may be classified as intra-capsular or extra-capsular depending on the relationship between the fracture location and the insertion of the capsule of the hip joint.

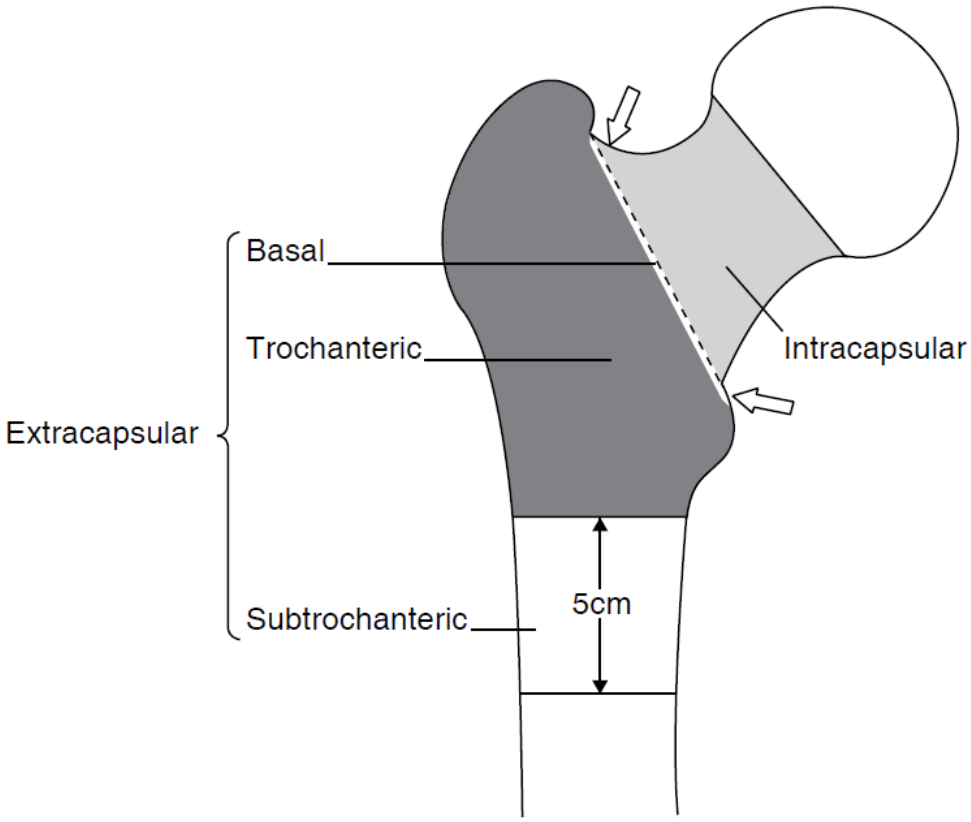


Figure 2.2-2 - Classification of fractures of the proximal femur (hip fractures).

(87) This figure is reproduced from SIGN 111 (Management of hip fracture in older people) by kind permission of the Scottish Intercollegiate Guidelines Network.

Intra-capsular fractures occur proximal to the attachment of the hip joint capsule to the femur and tend to result in minimal blood loss due to the poor vascular supply at the fracture site and tamponade by the capsule. Intra-capsular fractures can be further divided into displaced or non-displaced categories and are generally treated surgically using either implants or femoral prostheses. Undisplaced intra-capsular fractures are usually managed with surgical fixation in order to reduce the risk of dislocation at a later stage, while displaced fractures require fracture reduction with consequent fixation in order to maintain stability and prevent damage to the blood supply of the femoral

head. Surgery for undisplaced fractures generally involves the insertion of screws or pins across the fracture site under x-ray guidance. A 2011 Cochrane review of 30 studies involving 6334 patients aimed to determine which of the available fixation devices was superior for intra-capsular hip fracture (88). The review concluded that the quality of the evidence was generally poor with only one study describing allocation concealment and that there was inconsistent reporting of outcomes between studies. Sliding hip screws were found to result in a reduced incidence of avascular necrosis when compared with cancellous bone screws. However, sliding hip screws were associated with longer insertion time and higher blood loss. The review concluded that there was no clear benefit of one technique over another (88).

In the case of displaced intra-capsular fractures, internal fixation, hemi-arthroplasty and total hip replacement can be considered. Arthroplasty (either partial or total) is recommended in guidelines produced by the National Institute for Clinical Excellence (NICE) due to the lower re-operation rates, improved pain control, and superior functional and quality of life scores seen with these techniques (79). In guidance produced by the Scottish Intercollegiate Guideline Network (SIGN), a more conservative approach is suggested for younger, fitter patients who are recommended to receive internal fixation whilst older, frailer patients should undergo either a hemi-arthroplasty or total hip replacement. The reason for this is a concern that the more invasive arthroplasty techniques produce better short term outcomes but have a higher incidence of longer term problems such as dislocation. Where either hemi-arthroplasty or total hip replacement are being considered, patients with pre-existing joint disease, medium / high activity levels and a reasonable life expectancy, are recommended to receive total hip replacement rather than hemi-arthroplasty as the primary treatment (87).

Extra-capsular fractures can be per-, inter-, or sub-trochanteric and are usually described by their degree of comminution. Fractures which occur at the base of the femoral neck are often around the level of the joint capsule and behave as extra-capsular fractures. Extra-capsular fractures occur in cancellous bone and therefore have the potential to generate greater blood loss. As these fractures are outwith the joint capsule, they are unlikely to damage the blood supply to the femoral head and are usually repaired using internal fixation techniques such

as sliding hip screws or intra-medullary nails (79;87). Conservative management with traction and bed-rest is rarely practiced in this country due to an increased rate of morbidity, prolonged hospital stay and increased costs (79;87).

2.3 National Audits of proximal femoral fracture

2.3.1 The National Hip Fracture Database

The National Hip Fracture Database (NHFD) is a web-based audit of all patients admitted with a hip fracture in England, Wales, Northern Ireland and the Channel Islands (76). This audit has collected data for over 200,000 patients from 188 hospitals since its inception in 2007, making it the largest audit of hip fractures in the world. The aim of the audit is to allow hospitals to bench-mark their service against national data, highlight areas for improvement and optimise patient care (76). As a result of the data generated from this audit, hip fracture has become a "Best Practice Tariff" (BPT) initiative for the National Health Service (NHS) in England prompting extra payments for trusts meeting all of the defined standards for best care.

The NHFD examines care against six standards set by the British Orthopaedic Association / British Society of Geriatricians' (BOA/BSG) "Blue Book". These are prompt admission to orthopaedic care, surgery within 48 hours and within normal working hours, nursing care aimed at minimising pressure ulcer incidence, routine access to ortho-geriatric medical care, assessment and appropriate treatment to promote bone health and falls assessment (89). The audit produced initial improvements in all of these standards, although some of these have now reached a plateau with some having worsened slightly since the audit's launch. Ongoing improvements in ortho-geriatric input, bone protection medication prescription and falls assessment provide ongoing evidence of the audit's success (76).

Standard	2009	2010	2011	2012
1. Admission to orthopaedic ward within 4 hours	N/A	55%	56%	52%
2. Surgery within 48 hours and during working hours	75%	80%	87%	83%
3. Patients developing pressure ulcers	N/A	6%	3.7%	3.7%
4. Pre-operative assessment by an orthogeriatrician	24%	31%	37%	43%
5. Discharged on bone protection medication	N/A	57%	66%	69%
6. Received a falls assessment prior to discharge	44%	63%	81%	92%

Table 2.3-1 - Compliance with BOA/BSG Blue Book standards (76).

The NHFD reports on a number of additional outcomes examining all aspects of the patient journey during admission with hip fracture. These include: age, gender, housing status on admission, ASA grade, walking ability, fracture type, Abbreviated Mental Test (AMT) score, admission to orthopaedic ward from emergency department (ED) in 4 hours, type of anaesthesia, surgery performed within 36 hours, surgery performed within 48 hours and during normal working hours, reason for delay > 36 hours, presence of pressure ulcers, pre-operative medical assessment, bone protection medication, falls assessment, length of acute and post-acute stay, discharge destination, re-operation within 30 days, return to home at 30 days, 30 day mortality and proportion of patients treated conservatively. As with any major exercise in data collection, the NHFD suffers from certain limitations, namely incomplete case ascertainment by hospitals and denominator problems due to uncertainty regarding whether all cases are being reported.

The NHFD was not initially designed to examine outcomes relating to anaesthesia specifically but does contain an analysis of anaesthetic technique. In the 2012 report, 52.7% of patients received a general anaesthetic with 42.4% receiving spinal anaesthesia and 29.4% given a supplementary nerve block (76). This has since been revised with inclusion of more anaesthetic related data fields (see section 2.3.3)

2.3.2 Scottish Hip Fracture Audit

The Scottish Hip Fracture Audit (SHFA) was a national audit performed in Scottish hospitals during the period 1993 to 2008. While initially a small project

incorporating only four hospitals, the latter two years of the audit (2007 and 2008) included all 21 mainland Scottish hospitals and was funded by the Scottish Government. Data collection ceased in 2008 when funding was transferred to the Musculoskeletal Access Group (MSk). Data collection in the last two years of this audit was performed by dedicated data collectors with telephone interviews used to collect data at later time points. Data relating to 6369 patients from Jan 1st 2007 to 31st December 2007 are reported in the 2008 SHFA report. Patients under 50 years of age are excluded (71).

Similar to the NHFD, the SHFA reports on outcomes relating to the processes of care in patients sustaining hip fracture and does not specifically examine anaesthetic care. The outcomes reported by SHFD are as follows: percentage of patients transferred through the Emergency Department in 2 and 4 hours, percentage of patients going to theatre within 24 safe operating hours, discharge destination, length of stay, place of residence at 30 and 120 days post admission, survival to 30 and 120 days post-admission, return to home at 120 days for patients admitted from own home, 120 day mobility levels, patients living independently at 120 days, pain levels at 120 days and further falls after discharge. A separate report explores in detail the reasons for delay to theatre (90).

It is apparent that there are some significant differences in the standards assessed between NHFD and SHFA. For example, the SHFA audits the standard:

> *"98% of medically fit patients who have sustained a hip fracture should be operated on within 24 hours of 'safe operating time' (i.e. between 8 am and 8 pm, seven days a week)".*

In contrast, the NHFD audits compliance with;

> *"surgery on the day of, or the day after admission".*

The reason for this variation relates to the different guidelines used to inform audit standards. The NHFD bases its standards mainly upon those set in NICE guidelines(79) and the BOA/BSG Blue book (89). The SHFA bases its analysis upon The Scottish Government Health Delivery Directorate's "Time to Theatre" targets (91).

From 2009, data on hip fracture care has been collected under the Scottish MSk Audit. Part of this is a MSk and Orthopaedic Quality Drive of which hip fracture care is one of four priority work strands. Data on hip fracture care are collected in a one week sample during a rolling 4-week audit pattern. Outcomes were last reported from 2012-2013 (92). This report showed that survival and other outcomes remained broadly similar to outcomes from the previous Scottish Hip Fracture Audit in 2007 and 2008. Although sample sizes in the current audit were small, there was a trend towards hip fracture patients in 2012-13 being less likely to be in hospital at 120 days than those in 2007-08. They were also less likely to have returned home (but were more likely to be independent at home), and were less likely to be fully mobile. A longer-term analysis of data revealed no difference in overall 30 and 120 day mortality rates between 2008 and 2013. The report recommended that all hip fracture patients should follow the "Scottish Standard of Care for Hip Fractures", an evidence based summary of best practice recommendations to support early recovery and return to independent living (93). This was published in 2015, after the performance of the audit detailed in this thesis.

2.3.3 The Hip Fracture Peri-operative Network

The Hip Fracture Peri-operative Network (HipPeN) is an initiative aimed at linking anaesthetists with an interest in the management of proximal femoral fractures in hospital trusts throughout England and Wales for the dissemination of evidence-based, best practice and the performance of collaborative nationwide audit. This concept was first outlined at the Age Anaesthesia Association meeting held in 2007 and published its first report in 2010 (8).

The first report from HipPeN provides an introductory study of current national management of proximal femoral fractures and examines patient demographics, delays in admission to operation, grade of surgical and anaesthetic personnel, 30-day mortality and method of anaesthesia. Data for all patients undergoing hemi-arthroplasty, dynamic hip screw, total hip replacement or proximal femoral fracture operations were accrued manually using specially designed data-capture sheets over a two month period. Twenty two hospitals provided

data for 1195 patients over the 59 days study period. Unfortunately, this represented only 13% of the 168 eligible acute hospitals within the NHS in England and Wales (8).

While demographic data were found to be similar to other large scale audits (71;76), other variations in practice were seen. Forty two percent of operations were performed after the standard 48 hour post-admission period. In addition, there was a five-fold variation between hospitals in the delay between admission and operation, a 12-fold variation in 30-day postoperative mortality and considerable variations in the seniority of attending surgeons and anaesthetists present during surgery (8).

The report highlights the lack of research in this patient group and discusses the considerable challenges inherent in performing randomised controlled studies. For example, in order to compare general versus regional anaesthesia in terms of 1 year mortality, around 9000 patients would be required in each group. As many clinical outcomes are dependent on multiple factors (e.g. physiotherapy availability, nursing presence etc.), problems concerning which outcomes to report are rife in this population. In addition, the high incidence of cognitive impairment has significant implications for the ethical recruitment of patients.

The second report focuses on the epidemiology of hip fracture, the resources required to manage it and its financial implications (73). Data from a 10 year period were used to calculate the incidence, bed usage and costs associated with hip fracture and projections made regarding the implications for future resource management. Despite noting a decline in the prevalence of hip fracture among the ageing population (2.98% since 2002), it was estimated that around 100,000 patients annually will require surgery for hip fracture by 2033 in England, with a 30 day mortality of 8.9–9.3% resulting in costs of £3.6–5.6 billion (when adjusted for inflation) in total care.

The third report from HipPeN was an electronic survey of blood transfusion practices in patients with hip fracture in the UK and was published as an abstract in the journal *Anaesthesia* (94). Only 8% of respondents checked a haemoglobin level immediately post-operatively in this patient group. The

authors concluded that there was a high level of variability in practice which is reflective of the controversies in the evidence in this area.

A fourth report resulted from a survey of UK anaesthetists' practice in relation to the management of hypotension during repair of hip fracture and was published as an abstract in the journal Anaesthesia (95). This survey which targeted anaesthetists who regularly anaesthetised for trauma patients and had a high response rate again showed significant variation in practice with regard to the diagnosis and management of hypotension.

The Anaesthesia Sprint Audit of Practice (ASAP) was a large scale project conducted jointly by HipPeN in conjunction with the Association of Anaesthetists of Great Britain and Ireland (AAGBI), The National institute of Academic Anaesthesia (NIAA) and the National Hip Fracture Database (NHFD) (96). This large audit carried out over a 3 month period aimed to establish compliance with the AAGBI guideline: *The management of proximal femoral fracture* in hospitals throughout England, Wales and Northern Ireland (72). Anaesthesia related information was incorporated into the NHFD dataset in order to allow large scale data collection. Data from 11130 patients and 182 hospitals were analysed resulting in a comprehensive set of data regarding management and outcomes (see Section 4.5.1). The data from this audit were not available at the time of performing the audit detailed in the forthcoming chapters of the thesis.

Furthermore, an analysis of outcome by type of anaesthesia was performed using data collected as part of the NHFD (97). By incorporating anaesthesia-related outcomes into this large scale and established system of data collection, data for around 5000 cases per month was able to be collected. Data for 65 535 patients over a 1 year period were analysed, with 90% of these having data relating to anaesthesia. The authors found no difference in 5 day or 30 day mortality in patients receiving general compared with regional anaesthesia, even when adjusted for age and ASA. 24 hour mortality was found to be higher in cemented when compared with uncemented hemiarthroplasty. The authors concluded that mortality may not be the optimal endpoint with which to assess anaesthetic influence on outcome and that further research should focus on the optimal performance of general and regional techniques as well as other outcomes such

as pain, post-operative confusion, respiratory infection, hypotension and mobilisation.

The Hip Fracture Peri-operative Network is an important agency which continues to explore the advantages of large-scale data collection and audit as a means of determining current practice and establishing how variations in practice impact upon outcome.

2.4 Chapter 2 Summary

- Hip fracture is a common and serious condition with high levels of associated morbidity and mortality.

- Hip fracture is associated with the utilisation of significant health care resources and cost.

- Expedited surgery is beneficial.

- A number of national audits have been performed to inform practice and identify areas for improvement.

Chapter 3

Anticoagulation in the peri-operative period.

3.1 Thromboprophylaxis

The term venous thromboembolism (VTE) incorporates deep venous thrombosis (DVT) as well as pulmonary embolism (PE). Thrombus formation is favoured by changes in Virchow's Triad: blood stasis, increased coagulability of blood and damage to the vessel wall. The risk of thromboembolic disease is elevated in the peri-operative period and in several medical conditions such as malignancy, thrombophilia and nephrotic syndrome.

According to a classification of risk published by the American College of Chest Physicians (ACCP), patients admitted with PFF are considered as being in the highest risk group for the development of VTE (98). The rate of VTE detected in patients with PFF depends somewhat upon which definition is used. The rate of asymptomatic VTE is significantly higher than that of symptomatic VTE. If venography or ventilation-perfusion (VQ) scanning is performed in all patients with a hip fracture, 36% will have a DVT and 6% a PE (72;99;100). If symptomatic DVT is considered, its incidence is thought to lie somewhere between 1% and 3% of patients, while the risk of PE is thought to lie between 0.5% and 3% (72;100;101). While thromboprophylaxis has the benefit of reducing the potential for VTE, this must be balanced against an increased risk of bleeding. This is of particular concern in patients undergoing surgical procedures. Options for thromboprophylaxis include mechanical methods (e.g. TED stockings and intermittent compression devices) and pharmacological methods such as heparin.

3.1.1 Mechanical compression devices

A 2008 Cochrane Review identified 5 studies (487 patients) examining mechanical compression devices compared with control with regard to DVT in patients admitted with hip fracture (102). The authors concluded that there was a likely benefit of mechanical compression devices in preventing DVT after hip fracture and that this intervention was not associated with an increased risk of bleeding or blood transfusion. The American Association of Chest Physicians specifies that only intermittent pneumatic compression devices which can record and report proper time-wear data should be used and that patients should wear these devices for 18 hours per day (103). Unfortunately, but perhaps

unsurprisingly, the use of these devices was found to be limited by poor compliance due to blisters / foot sores etc. Such side-effects are likely to limit the effective use of these devices in everyday practice.

While graduated compression stockings have been found to reduce the incidence of DVT in many other surgical settings, they do not appear to be effective in patients with hip fracture (102).

3.1.2 Heparin

Heparin (in both unfractionated and low molecular weight forms) is licensed for VTE prophylaxis in the UK (104). When used for VTE prophylaxis, heparin is most commonly given subcutaneously and in a reduced dose to that used in the treatment of thromboembolism. Low molecular weight heparin (LMWH) is frequently used in the peri-operative setting as it can be given once daily and does not result in a prolonged anti-coagulant effect. It is recommended that LMWH is commenced at least 12 hours prior to the planned operation in order to allow adequate time for the anti-coagulant effects to reduce to a level safe for neuraxial blockade and surgery. In patients undergoing surgery for PFF, guidelines from the American College of Chest Physicians recommend the use of LMWH in preference to other agents, ideally in combination with a mechanical compression device (which should be worn for 18 hours per day). They also state that this should be continued for 35 days post-operatively where possible (103).

A Cochrane Review of 15 studies (1199 patients) analysing thromboprophylaxis in patients with hip fracture found that both LMWH and unfractionated heparin (UFH) reduced the risk of DVT by 41% and 36% compared with placebo (102). However, there was no difference in the incidence of VTE when low molecular LMWH and UFH were compared (102). As LMWH has a favourable side-effect profile, it is generally considered the preferred agent. When heparin was compared to mechanical compression devices, no difference was seen in terms of DVT, PE or mortality. This may have been due to a lack of studies making this comparison. While the use of mechanical compression devices is appealing, there are significant limitations in terms of poor compliance and the development of skin sores / blister etc. No difference was detected in VTE or

bleeding complications when two different LMWHs were compared (Enoxaparin versus Dalteparin) (102).

3.1.3 Aspirin

The use of aspirin as a thromboprophylactic agent was the subject of one of the largest trials to date in this area. The Pulmonary Embolism Prevention (PEP) study (2000) was a multi-national, multi-centre study incorporating over 13,000 patients undergoing surgery for hip fracture and was published in the Lancet (105). Patients received either 160mg of aspirin daily or placebo. However, patients could also receive other forms of thromboprophylaxis such as heparin if deemed necessary. This study resulted in a positive outcome for the aspirin intervention. PE or DVT was confirmed in 105 (1.6%) of 6679 patients assigned aspirin, compared with 165 (2.5%) of 6677 assigned placebo. This represented an absolute reduction of 9 per 1000 and a proportional reduction of 36% (19-50; p=0.0003). Despite these positive findings, this study has been criticised for the large numbers of patients receiving other concurrent forms of thromboprophylaxis such as mechanical compression devices and heparin. The implication that only those at lowest risk would have received aspirin alone may be a source of significant bias. Sub-group data also showed that concomitant use of aspirin and LMWH did not produce any additional reduction in the risk of DVT (event rate 1·4% for aspirin + LMWH versus 1·8% for LMWH alone, p=0·37). The thrombosis risk for aspirin alone was 1·7%, 1.6% for unfractionated heparin plus aspirin, and 1.8% for LMWH alone. Aspirin was also associated with an increase in bleeding events (excess of 6 bleeds per 1000 patients treated).

3.1.4 Fondaparinux

Fondaparinux is a synthetic pentasaccharide anticoagulant which inhibits factor Xa and affects the coagulation cascade in a similar manner to heparin. Patients taking Fondaparinux do not require to be monitored with laboratory tests (in contrast to patients taking vitamin K antagonists such as warfarin). There is no antidote to the actions of Fondaparinux. The Pentasaccharide in Hip-Fracture Surgery study (PENTHIFRA) compared fondaparinux with enoxaparin in patients with PFF (106). This 99 centre, multi-national, randomised, double-blind trial included 1,711 patients admitted with PFF (of which 1250 were included in the

final analysis). Patients were excluded if an epidural catheter was planned for more than 6 hours postoperatively, if the patient had surgery more than 48 hours from the time of admission, or if the serum creatinine level was greater than 2 mg/dL. Fondaparinux 2.5 mg daily subcutaneously was commenced 6 to 8 hours after surgery and the second dose was given at least 12 hours after the first. The group receiving enoxaparin were given a dose of 40 mg subcutaneously at approximately 12 hours before surgery and at 12 to 24 hours after surgery. Treatment continued for 5 to 9 days. The use of mechanical compression devices, anti-platelet and other anticoagulant drugs was not permitted. The primary outcome was VTE (defined as deep-vein thrombosis, pulmonary embolism, or both) up to day 11. Secondary outcomes were total, proximal, or distal DVT or symptomatic VTE up to day 11 and symptomatic VTE up to day 49. Venography was performed to identify DVT and PE was confirmed by either ventilation perfusion scan, pulmonary angiography, helical computed tomography CT) scan or autopsy.

The incidence of VTE was significantly lower in the Fondaparinux group (8.3% vs 19.1%, P <.001). However, the risk of symptomatic DVT and fatal and non-fatal PE was the same in both groups. By day 49, the incidence of symptomatic VTE was similar in both groups (2.0% in fondaparinux and 1.5% in enoxaparin). No differences in clinically relevant bleeding rates were observed.

The PENTHIFRA Study had some notable limitations. Firstly, only one dose of study drug was required for the patient to be included in the efficacy analysis. Secondly, only a minority of patients received the pre-operative dose of heparin. In addition, a significant number of the members of the steering committee were from the pharmaceutical company and statistical analysis was also performed by the sponsor (this was fully acknowledged in the paper) (106).

Twenty two of the 30 symptomatic VTE events and 11 of the 15 fatal PEs in the PENTAHIFRA study occurred in days 11 to 49 prompting the authors to question whether Fondaparinux should be continued for longer than one week post-operatively (106).

A further study was performed in 2003 in order to investigate the effects of prolonging the course of Fondaparinux. The PENTAHIFRA-plus study enrolled 656

participants from 57 centres in 16 countries and randomised them to receive either Fondaparinux 2.5mg or placebo for a further 19-21 days after the original week of thromboprophylactic treatment (Fondaparinux) (100). The authors found that prolonged thromboprophylaxis with Fondaparinux reduced the incidence of VTE from 35.0% to 1.4% resulting in a Relative Risk reduction (RRR) of 95.9% (95% CI, 87.2%-99.7%; P<0.001) when compared to placebo. The incidence of symptomatic VTE was also reduced from 2.7% to 0.3% (RRR 88.8%, 95% CI 67.7-100%). There were 3 fatal PEs in the placebo group and none in the Fondaparinux group. The Fondaparinux group had a higher bleeding rate than the placebo group but there were no differences between the 2 groups in clinically relevant bleeding episodes (100).

Fondaparinux and heparin are both recommended as potential thromboprophylactic agents in SIGN guidelines for patients with hip fracture (87). As Fondaparinux has a longer half life (18 hours) than LMWH, administration pre-operatively may preclude the use of neuraxial anaesthetic techniques for over 24 hours and as such, SIGN recommend Fondaparinux as being used in the post-operative period only (87). Fondaparinux is the preferred agent post-operatively and it is recommended that this be continued for 28 days post-operatively. Fondaparinux may also be considered as an alternative agent in patients in whom heparin is contraindicated (e.g. patients with heparin induced thrombocytopaenia). The higher cost of Fondaparinux may limit its clinical use.

3.1.5 Dabigatran

This drug works via the direct inhibition of thrombin and as with Fondaparinux, does not require laboratory monitoring. It has a peak time to anticoagulant activity of 2 – 3 hours and an elimination half life of 12 – 14 hours in patients with normal renal function. There is no antidote to Dabigatran. It has recently been approved by NICE as being suitable for use as a thromboprophylactic agent in patients undergoing total hip or knee replacement (107).

3.1.6 Rivaroxaban

This drug is a direct inhibitor of factor Xa and inhibits both the extrinsic and intrinsic components of the coagulation cascade. As with Dabigatran, Rivaroxaban has a rapid onset of action and similar elimination half life. Rivaroxaban has been approved by NICE as suitable for thromboprophylaxis after total hip and knee replacement operations (108).

3.2 Warfarin in the peri-operative period

Warfarin is a synthetic coumarin derivative that exerts its action by inhibiting the synthesis of vitamin K dependent clotting factors (II, VII, IX and X) in the liver. The formation of clotting factors is dependent upon the carboxylation of their precursor proteins. During this carboxylation reaction, vitamin K is oxidised to form vitamin K 2,3-epoxide. Warfarin prevents the reduction of vitamin K 2,3-epoxide back to its original state resulting in reduced levels of vitamin K and subsequent reduced levels of clotting factors (109). Warfarin has an oral bioavailability of 100%, is predominantly protein bound (99% to albumin) and is metabolised in the liver. Its metabolites are excreted in the urine and faeces with an elimination half life of 35 to 45 hours. This is prolonged in the elderly and in patients with renal impairment (109). Warfarin is commonly used as an anticoagulant drug for patients with conditions such as; atrial fibrillation, thromboembolic disease, prosthetic valves and cerebrovascular disease. The average daily dose of warfarin required to achieve therapeutic anticoagulation is around 5mg, though there is large inter-individual variation (1 – 15mg). This is due to genetic variability in drug metabolism. Intra-individual variability in response may also occur as a result of dietary content of vitamin K and drugs causing interactions with warfarin.

3.2.1 Monitoring of warfarin therapy

The response to warfarin treatment is monitored using a laboratory test known as the Prothrombin Time (PT). This is the time take for the blood to clot after the addition of tissue factor and measures the activity of the extrinsic and common pathways within the clotting cascade. The normal range for this measurement is 10-14 seconds. This measurement is standardised in each

individual laboratory to an International Normalised Ratio (INR). The normal range for INR is 0.8 - 1.2 for a patient on no anticoagulant. Each patient is assigned a target INR range. This can range from 2 to 4 depending on the indication for warfarin therapy.

3.2.2 Management strategies for warfarin in the peri-operative period

Anti-coagulated patients present a challenge to the peri-operative team. While the patient is fully anti-coagulated, they should be at lower risk of thromboembolic phenomena. However, they are at higher risk of bleeding during surgery. The impact of this will depend on the indication for anti-coagulation and the type of surgery being performed. Options for the management of warfarin in patients undergoing invasive procedures include: withholding warfarin and waiting for INR to self-correct, or the administration of pharmacologic compounds such as vitamin K, fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC).

3.2.2.1 Cessation of warfarin alone

When warfarin is withheld in a patient with an INR of 2–3, it will take around 4 – 5 days for the INR to drop below 1.5 (110). However, there is inter-individual variation in the time taken for the effects of warfarin to be reversed. In patients in whom warfarin is withheld, an initial increase in INR may occur due to the stress response and prolonged periods of fasting. This makes cessation of warfarin alone an impractical option for reversal in patients who are actively bleeding or who require to undergo time-dependent surgery (such as repair of hip fracture).

3.2.2.2 Vitamin K

Vitamin K is a fat soluble vitamin essential for the formation of clotting factors and which is depleted by the actions of warfarin. The administration of vitamin K therefore reverses the effects of warfarin. The onset of vitamin K is at least 4 – 6 hours after intravenous administration and 24 hours for oral administration (111;112). It is thought that excessive doses of vitamin K may result in a state of warfarin resistance which can persist for up to one week. This has resulted in a

call for lower doses (1 – 2.5mg to be given) in cases where immediate reversal is unnecessary. Doses of 1mg vitamin K have been reported to result in reversal of warfarin within 24 – 27 hours with the avoidance of a prolonged time to return to therapeutic INR (110;113). Vitamin K can be associated with anaphylactic reactions when given intravenously and should be given as a slow infusion. Oral vitamin K, while slower in onset, is well absorbed from the gastrointestinal tract and does not cause the same adverse effects as the intravenous preparation (110).

3.2.2.3 Fresh Frozen Plasma

Fresh Frozen Plasma (FFP) will reverse the effects of warfarin rapidly and without causing later resistance to warfarin. Its effects dissipate within 8 – 12 hours of administration and it should be administered within 4 hours of the procedure to obtain optimal effect. FFP has to be thawed prior to its use and this can result in delays of around 45 minutes. Risks of FFP administration include: anaphylactoid reactions, alloimmunisation, transfusion related lung injury, fluid overload and transmission of infection.

3.2.2.4 Prothrombin Complex Concentrates

PCC contain high concentrations of clotting factors II, VII, IX and X and can be used to rapidly reverse the effects of warfarin. PCC is more rapid and effective at reducing INR than FFP (114) and smaller volumes of concentrate are effective thus reducing the risk of fluid overload (115). Risks of PCC are those of immediate allergic reactions, heparin-induced thrombocytopenia for the preparations containing heparin) and thromboembolic complications. The primary safety concern with PCC has been their association with thrombotic events such as stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation (111). Transfusion related lung injury has not been reported.

3.3 Guidelines for the management of warfarin in the peri-operative period

Guidelines differ in their approach to this issue. For example, a recent SIGN guideline (SIGN 129: Antithrombotics; indications and management, 2012)

examined the use of warfarin in the peri-operative period (116). In low risk procedures such as dental extractions, no change in warfarin therapy is recommended. However, in patients undergoing more invasive procedures, warfarin reversal is usually required.

In procedures where the risk of bleeding is considered significant, SIGN 129 makes the following recommendation:

> *"Decisions regarding interruption of warfarin therapy for other surgical and invasive procedures, and whether bridging therapy is advisable, should be made on an individual basis dependent upon the perceived risks of bleeding and thrombosis associated with continuation of anticoagulation and discontinuation of anticoagulation, respectively, and the nature of the proposed procedure (116)."*

Recommendations from other relevant guidelines are as follows: A guideline by the British Committee for Safety in Haematology (BCSH) in 2011 recommends:

> *"For surgery that requires reversal of warfarin and that can be delayed for 6-12 h, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin and which cannot be delayed for vitamin K to have time to take effect the INR can be corrected by giving Prothrombin Complex Concentrate (PCC) and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (117)."*

The 2005 AAGBI guideline; Blood transfusion and the anaesthetist: blood component therapy recommends the following approach:

> *"Vitamin K +/- prothrombin complex concentrate (PCC) is recommended to reverse warfarin. Fresh Frozen Plasma (FFP) is indicated when there is severe bleeding or when PCC is unavailable (118)."*

SIGN guideline 111; the management of hip fracture in older people states:

> *"Withholding warfarin combined with administration of oral or intravenous vitamin K (1 – 2.5mg) is recommended if reversal of the*

anticoagulant effects of warfarin to permit earlier surgery is deemed appropriate (87).”

The 2011 AAGBI guideline; management of hip fracture states;

“Hospital guidelines concerning the peri-operative management of patients taking warfarin should be followed; in general, the International Normalised Ratio (INR) should be < 2 for surgery and < 1.5 for neuraxial anaesthesia. Small amounts of vitamin K may be used to ‘reverse’ the effects of warfarin; supplemental peri-operative anticoagulation with heparins is usually indicated. Prothrombin complex concentrates rapidly reverse the effects of warfarin but are expensive and rarely indicated. Warfarin should be recommenced 24 h after surgery, although some departments recommence it later on the day of surgery.

The advice of haematologists should be sought if in doubt about the peri-operative management of patients on chronic anticoagulant therapy. Regular anticoagulant medication requires that the anaesthetist balance the attendant risks of neuraxial and lumbosacral plexus blockade (i.e. haemorrhage and neuropraxia) against the benefits of these procedures for the elderly (72).”

The NICE guideline; the management of hip fracture in adults, 2011 states (79):

“INR should be corrected promptly to avoid undue delay to theatre”

The differences seen between guidelines reflect the lack of high quality evidence in this area.

3.4 Management of warfarin in patients undergoing repair of proximal femoral fracture

Warfarin is currently the most commonly prescribed anticoagulant drug in the UK (119). It is estimated that around 1 - 1.5% of the UK population are treated with warfarin (119). This figure rises with age and around 5% of people admitted with hip fracture are thought to be taking the drug (72).

In a retrospective audit of 57 patients in a single centre undergoing repair of hip fracture, patients receiving either cessation of warfarin or pharmacologic

management were compared. The authors found that the delay to theatre was 4.4 days in the group receiving cessation of warfarin, and 2.4 days in the group receiving pharmacologic therapy ($p<0.01$) (120). In a prospective audit of 90 patients admitted with hip fracture in two hospitals, the authors compared their standard management of warfarin cessation in the first 45 patients, with the subsequent 45 patients treated with 1mg Vitamin K intravenously. In patients receiving standard treatment, the mean time to achieve INR < 1.5 was 158 hours compared with 63 hours in the patients receiving vitamin K. This translated into an improvement in mean time to theatre from 91 hours to 38 hours. These results were statistically significant (121).

3.4.1 The role of bridging therapy

A further important consideration is the risk of thromboembolism while warfarin is being withheld. A risk assessment may be performed in order to stratify patients into high or low risk categories. In those considered to be at high risk of thromboembolism, bridging therapy with an alternative anticoagulant is usually considered necessary. Heparin is mainly used in this situation. Heparin may be administered as either unfractionated heparin (UFH) or as low molecular weight heparin (LMWH).

LOW RISK

- AF with normal heart valves and no previous embolism or stroke.
- Single episode of venous thromboembolism > 3 months ago.
- Sinus rhythm, with tissue or modern (post 1990) metal aortic valve inserted > 2 months previously.

HIGH RISK

- AF with previous stroke, embolism, valve disease or any type of valve replacement.
- Metal mitral valve, any 'ball and cage' valve, or pre-1990 metal aortic valve.
- Artificial valve plus previous embolism.
- Any valve replaced within previous 2 months.
- Arterial embolism or venous thrombosis within previous 3 months.
- Prior recurrent venous thrombosis.
- Prior venous thrombosis and known high risk thrombophilia.
- Patient with target INR of 3-4.

Table 3.4-1 - Thomboembolic risk stratification for patients taking warfarin (122).

3.4.1.1 Unfractionated Heparin

Unfractionated heparin (UFH) is a naturally-occurring glycosaminoglycan with a molecular weight range of 5,000-35,000 Daltons. UFH potentiates the effect anti-thrombin and inhibits the coagulation cascade at several points. It prolongs the laboratory measurement of the intrinsic coagulation pathway, the activated partial thromboplastin time (APTT), when given in therapeutic doses. UFH is administered either by intravenous (IV) injection or by subcutaneous injection. Intravenous administration has an immediate effect and short plasma half-life (30 minutes to two hours) while subcutaneous injection has a delayed onset (two hours) but more prolonged effect (around 10 hours). There is wide variability among patients in response to a given dose of heparin. The anticoagulant effect (APTT ratio) of unfractionated heparin therapy must therefore be monitored at least daily and the dose adjusted to achieve the target therapeutic range. This should in turn minimise the risks of bleeding and thrombosis. UFH has a short half-life after intravenous administration (30 - 120 minutes), and cessation of therapy results in reversal over a few hours. Protamine sulphate can be given if immediate reversal is required. The advantages of UFH relate to its relatively rapid onset and offset times and its reversibility. Disadvantages include its inter-individual variability and the practicalities of frequent blood monitoring with possibility of over or under-shooting target APTT (109).

3.4.1.2 Low Molecular Weight Heparins

Low molecular weight heparins (LMWH) are manufactured from UFH and consist of short chains of polysaccharide with an average molecular weight of <8,000 Daltons. LMWH have better availability than UFH when administered by the subcutaneous route. They have an onset time of round 1 hour with peak anticoagulant activity at 5 hours and a half life of 3 – 5 hours. In contrast to UFH the anti-Xa effect predominates over the anti-thrombin effect. The APTT is therefore not used to monitor the effects of LMWH. The anti-Xa level can be used to monitor LMWH but its predictive value in terms of efficacy against thrombosis and bleeding risk is sub-optimal. As LMWH is excreted by the kidney, the dose should be reduced in patients with renal failure (109).

In a meta-analysis of 12 studies involving 4971 patients, LMWH was associated with a statistically significant increase in the risk of major bleeding in patients with a creatinine clearance of 30 mL/min or less compared with those with a creatinine clearance of greater than 30 mL/min (5.0% vs 2.4%; odds ratio, 2.25 [95% CI, 1.19 to 4.27]; p = 0.013) (123). Reduced doses of LMWH or the use of UFH may therefore be more prudent in patients with a creatinine clearance of <25ml/min.

In general, decisions regarding bridging therapy warrant an individualised consideration of risks and benefits taking into account the perceived risk of thrombosis and the likelihood and consequences of surgical bleeding. For example, the consequences of bleeding after neurosurgery could be catastrophic making this one of the higher risk surgeries from a bleeding perspective. On the other hand, a patient undergoing a procedure with a relatively low risk of bleeding may be at greater risk from harm by thrombosis and thus merit bridging therapy.

In a non-randomised cohort study of 1024 patients (mainly with AF), warfarin was withheld on 1293 occasions to allow various procedures to be performed. Bridging therapy was instituted in only 8.3% of cases. Six patients (0.6%, 95% CI 0.2-1.3) had a “major” bleeding episode, while 17 patients (1.7%, 95% CI 1-2.6) had a “non-major” bleeding episode. Four of the 6 patients with major bleeding and 10 of the 17 with non-major bleeding had received bridging therapy. This resulted in an overall bleeding rate of 13% in bridged patients. Thromboembolism occurred in 7 patients in the first 30 days post-operatively (0.7%, 95% CI 0.3-1.4). None of these patients had received bridging therapy, and two of the seven would have been considered at high risk for thrombosis (124).

In a second cohort of 345 patients with AF undergoing invasive procedures, warfarin was withheld and bridging therapy (UFH or LMWH) given to those considered at high risk of thromboembolism. The incidence of thromboembolism was 1.1% in the first 3 months post-operatively and did not differ significantly between those who had received bridging therapy and those who had not. The three month post-operative incidence of major bleeding was 2.7% and was not different between groups. The authors concluded that the 3-

month cumulative incidence of thromboembolism and bleeding among patients with AF in whom anticoagulation was temporarily interrupted for an invasive procedure was low and was not significantly influenced by bridging therapy (125).

A meta-analysis of 34 studies (only one of which was a randomised controlled trial) over the period 2001 – 2010, examined the use of heparin bridging therapy in elective surgery. Thromboembolic events occurred in 73 of 7118 bridged patients and 32 of 5160 non-bridged patients (pooled incidence 0.9% versus 0.6%, odds ratio 0.8; 95% CI 0.42-1.54) in the eight studies comparing these two groups. The authors concluded that there was no significant difference between groups for the occurrence of thromboembolism. The risk of bleeding was increased in the group receiving bridging anticoagulation (odds ratio 5.4, 95% CI 3-9.74) while the risk of major bleeding was also increased with an odds ratio of 3.4 (95% CI 1.52-8.5). When full therapeutic doses of bridging heparin were compared with prophylactic doses, there was no increase in thromboembolic events (odds ratio 0.3, 95% CI 1.27-4.08). However, there was an increase in bleeding episodes (odds ratio 2.28, 95% CI 1.27-4.08) (126). The studies analysed in this meta-analysis were not of high quality and included only one RCT. This could have resulted in the introduction of bias as patients at higher risk of thromboembolism would have preferentially received bridging therapy. Caution should therefore be exercised in the interpretation of these data (126).

A further study of 328 patients examined the use of sub-therapeutic doses of LMWH (e.g. 40mg enoxaparin or 3800IU Naroparin) once daily in patients considered to be at low risk for VTE and given twice daily in those considered to be high risk. The overall incidence of VTE was 1.8% and this was not significantly different between those in the low (0.54%) and high risk groups (3.4%). The overall risk of bleeding was 2.1% and was not significantly different between low and high risk groups (127).

This approach may be considered a reasonable compromise between the risks of bleeding and VTE in surgical patients.

3.5 Chapter Summary

- Patients suffering hip fracture are at high risk of developing venous thromboembolism and should be prescribed thromboprophylaxis both pre- and post-operatively.

- Both low molecular weight heparins and Fondaparinux are recommended for this purpose by SIGN. Mechanical compression devices may also be used but are limited by adverse effects such as skin trauma. Graduated compression stockings are not recommended.

- Patients taking warfarin present a particular challenge in the peri-operative period, and the risks of thrombosis while warfarin is stopped must be weighed up against the risks of bleeding.

- The use of small doses of vitamin K is recommended to expedite reversal of warfarin and allow early surgery in patients with hip fracture.

- Evidence regarding the use of bridging therapy is lacking and there is considerable variation in practice in this area.

- A reasonable compromise could be to use sub-therapeutic dose enoxaparin in those deemed low risk for VTE with higher dose enoxaparin reserved for use in patients at high risk for VTE.

Chapter 4

Clinical Practice Guidelines and their role in the management of hip fracture

4.1 Clinical Practice Guidelines

Guidelines are designed to assist clinical decision making by summarising evidence and forming recommendations. Health care professionals working in all disciplines are expected to practice according to current policies and guidelines from a variety of sources. Robust, evidence-based guidelines should lead to the most effective therapy, result in improved outcomes and reduce unnecessary variations in practice.

4.1.1 Problems with guidelines – volume of information

Evidence-based medicine should manifest as the integration of best research evidence with clinical expertise and patient values (128). However, the quality of published evidence is variable and is being produced at such a rate that remaining "up to date" is nigh on impossible. Pubmed has reached the 20 million citation mark (129) and one new citation is added to Medline each minute of every day (130). It is therefore not feasible to expect a practicing clinician to attain and maintain an in depth knowledge of anything other than a small fraction of the available medical literature. The volume of literature (which is of variable quality) needs to be summarised so that where evidence of superiority of a particular approach exists, clinicians can be advised of that benefit. This leads many of us to rely on others to read, evaluate and summarise on our behalf.

The number of guidelines being produced is equally vast with local health boards, learned societies, governing bodies and government agencies within local, national and international spheres all contributing to the plethora of information. This has the potential to create duplication and the risk of contradictory or conflicting advice (131-133). In performing a review of guidelines relating to all stages of the management of a patient with proximal femoral fracture, Carthey and colleagues identified 75 relevant guidelines and trust-wide policies (134). Carthey *et al* go on to highlight the 80 plus guidelines produced by the Royal College of Anaesthetists (RCoA) and Association of Anaesthetists of Great Britain and Ireland (AAGBI) alone. This is in addition to the further 15 bodies also identified as producing guidelines relating to anaesthesia, and the 1000 plus guidelines produced by NICE (each of which may

be several hundred pages long). Indeed, even identifying all relevant recommendations from the vast number of available sources is intensely time consuming. When one considers the actual dissemination and realisation of these guidelines, it becomes clear that this is in reality profoundly difficult.

4.1.2 Problems with guidelines - methodology

While there is compelling evidence that guideline implementation has in some cases resulted in improved outcome (135;136), the issue of quality control has been brought into question (135;137). In a review of 279 guidelines published over a 12 year period, only 43% were found to adhere to set methodological standards (135;138) and in a 2009 evaluation of all guidelines produced by the American College of Cardiologists, a majority of recommendations were found to be based on expert opinion or consensus with only 11% of recommendations fitting into the Class A category (recommendation based on evidence from multiple randomised trials or meta-analyses) (135;139). This, in such a high profile field of medicine, is perhaps surprising.

Concerns regarding variability in guideline methodology and integrity have resulted in the formation of tools designed to further assess quality and applicability. The Appraisal of Guidelines Research & Evaluation (AGREE) Instrument seeks to provide a framework for assessing the quality of guidelines to ensure that recommendations are both internally and externally valid and feasible for practice. Refinement in the form of the AGREE II instrument has provided a validated and internationally agreed tool to assess methodological rigour and transparency of published guidelines. In essence, AGREE II aims to provide the busy clinician with a degree of reassurance that a guideline can be trusted (140). A recent appraisal of peri-operative guidelines using the AGREE assessment found that guidelines issued by government funded organisations were of the highest quality (141). This evaluation tool has been adopted by organisations throughout the world.

The way in which recommendations are graded is also a source of some concern. Traditionally, recommendations were graded in relation to the strength of the supporting evidence, using study design as the dominating criterion for quality without relating this to clinical relevance or importance. This is considered by

many to be impractical and a serious limitation of guidelines. Clinical groups, including the Scottish Intercollegiate Guideline Network (SIGN), have adopted the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to evaluate evidence (142). The GRADE system is designed to separate the quality of evidence (very low, low, moderate, or high quality) from the level of recommendations (strong or weak). Achieving such clarity mandates a thorough evaluation of methodology, synthesis of a comprehensive evidence base and interpretation of relevance and applicability to the target population. An assessment of risks and benefits, as well as the likely clinical impact of the intervention is also made.

Do it	A judgement that most well-informed people would make.
Don't do it	A judgement that most well-informed people would make.
Probably do it	A judgement that requires full and careful consideration of patients' values and preferences when offering an intervention.
Probably don't do it	A judgement that the majority of well-informed people would make but a substantial minority would not.

Table 4.1-1- Summary of GRADE recommendations (142).

In the GRADE system, a recommendation with a high quality evidence base, such as a well performed randomised controlled trial, may be downgraded to a lower level of recommendation if the treatment effect is thought likely to be small or if the evidence is thought not to be applicable to the target population. The strength of recommendation made reflects the likelihood of a new study coming to a different conclusion. Therefore, a study with a lower score would both lead to a weaker level of recommendation as well as identifying areas for further research. It should be noted that although GRADE has the potential to increase consistency between guidelines, it is also subject to operator subjectivity and is not without potential error.

The NHS Evidence accreditation scheme provides a further useful quality assurance process (143). Only guidelines with this seal of approval are used in

the development of NICE guidelines. Although such quality assurance processes are welcome, there are many highly useful and widely adopted guidelines which may not have been produced using such stringent conditions. For example, publications such as the AAGBI Safety Guidelines provide succinct, practical advice relating to anaesthetic emergencies such as local anaesthetic toxicity and malignant hyperpyrexia and have proven invaluable to anaesthetists at all stages in their careers (144;145).

In order to improve consistency, the policy of leading journals is to ask that guidelines are introduced in an agreed and unified way describing: The clinical problem to be addressed, the mechanism by which the statement was generated, a review of the evidence for the statement (if available) and a statement on practice itself.

Where more than one group or society has issued statements on the same topic, it is recommended that the following questions are answered in order to minimise confusion and improve transparency:

> *'What other guideline statements are available on this topic?*
>
> *Why was this guideline developed?*
>
> *How does this statement differ from existing guidelines?*
>
> *Why does this statement differ from existing guidelines?'*

4.1.3 Problems with guidelines – conflict

Even when strictly defined methodological processes are followed, guideline producers may come to surprisingly different conclusions. An interesting example may be found in the use of thromboprophylaxis in the intensive care unit.

SIGN guideline 122: Prevention and Management of Venous Thromboembolism, published in 2010, states the following in relation to intensive care patients;

> *"There are insufficient data to support the recommendation of routine use of heparin thromboprophylaxis in such patients"*

> *and*
> *"Other forms of thromboprophylaxis, including mechanical measures, have not been adequately studied in the ICU setting (104)."*

This is contradictory to the NICE guideline; venous thromboembolism- reducing the risk, also published in 2010 which recommends that clinicians;

> *"offer VTE prophylaxis to patients admitted to the critical care unit according to the reason for admission taking into account: any planned interventions and the use of other therapies that may increase the risk of complications (99)."*

In making these recommendations, SIGN and NICE appraise different publications. SIGN review two systematic reviews (incorporating nine randomised controlled trials [RCTs] and 11 cohort studies) (146;147), an RCT in patients within in a neurosurgical ICU (148), and an RCT in trauma patients (149). NICE's recommendation is derived primarily from one large RCT in medical ICU patients (150), and supported by a further RCT in septic patients (151). As illustrated in this example, the interpretation of evidence even when performed by eminent organisations may culminate in very different conclusions. This is particularly prevalent in areas in which there is a dearth of literature and the studied populations are heterogeneous. Conflict therefore often arises because the original research was not sufficiently robust to allow definitive guidance to be produced. Such conflict within guidelines has the disadvantage that it leads to confusion and may result in a degree of clinician dissatisfaction and disillusionment.

4.1.4 Problems with guidelines - applicability

Guidelines are generally focused on single conditions and can perform poorly when applied to more complex cases (152). The very presence of guidelines relating to coexisting medical conditions has been demonstrated to reduce clinician adherence to guidance for the underlying condition (153). Elderly patients, who often have several co-morbidities and in whom complex decisions must be made, are frequently under-represented in guidelines (154;155). The perceived lack of ability of guidelines to provide patient centred recommendations (which is arguably most apparent in the cohort of patients in whom guidance is most needed) remains a source of criticism.

4.1.5 Problems with guidelines - adherence

Despite efforts to improve the quality and reliability of guidelines, it is known that rates of clinician adherence to CPG vary between 20 - 100% (153). Adherence may be influenced by a number of factors including peer opinion and beliefs regarding consequences of non-compliance (156;157). A meta-analysis of existing literature on clinical adherence suggests six categories to describe why clinicians deviate from a published guideline (158). These categories have subsequently been verified in other clinical settings (159;160). A more detailed analysis of why clinicians deviate from guidelines has recently been published (134).

Lack of awareness	Inability to remain up to date with all published literature
Lack of familiarity	Inability to recall specific information from a guideline despite being aware of its existence
Lack of agreement	Clinician disagreement with a specific guideline or guidelines in general
Lack of outcome expectancy	Disbelief that following a guideline will lead to improved outcome
Lack of self-efficacy	Lack of confidence in ability to perform a behaviour resulting in failure to adhere to a recommended practice
Inertia of previous practice	Lack of motivation to change
External barriers	Guideline deemed to be difficult to follow, conflicting guidelines. Patient preferences in conflict with recommendations. Financial and resource related constraints

Table 4.1-2 - Barriers to clinician adherence to guidelines adapted from Cabana et al (158).

4.1.6 Problems with guidelines – accessibility and reliability

Policies and guidelines are often stored on the hospital intranet. Having such documents available in an online format allows them to be accessed more conveniently than if they were in a library and should also allow for more reliable mechanisms for updating documents. However, the amount of information on such servers can be vast and the identification of the necessary piece of information can be difficult. Equally, while having electronically modifiable information should allow for updates where relevant, it can also allow the presence of multiple different versions of the same guideline (and permit out of date versions to continue in circulation.

4.2 A comparison of clinical practice guidelines for proximal femoral fracture

The following section provided the basis for an article published in the journal Anaesthesia, February 2013:68;159-166. The article was written by me with contributions from my co-authors Dr Laura Moss (clinical physicist and honorary lecturer, University of Glasgow), and Professor John Kinsella (Professor of Anaesthesia, University of Glasgow).

4.2.1 Background

In 1990, the Institute of Medicine proposed that clinical guidelines be developed in order to bridge the gap between evidence and practice, reduce variations in healthcare, assist clinical decision-making, improve patient care and decrease costs (161). While opinion and consensus amongst practitioners with years of clinical wisdom undoubtedly is of huge value in providing guidance to those with less experience, the paradigm shift of recent years has led away from eminence and towards evidence as the basis for best practice. Increasingly, guidelines may be referred to as examples of customary or best practice (162). In common with all healthcare professionals, anaesthetists are faced with complex patients in whom several clinical guidelines may apply. This creates a number of challenges in an increasingly time and resource-pressured environment. The peri-operative management of patients admitted with hip fracture is an important example of a challenging clinical area where evidence is lacking and practice varies (8).

Hip fracture is a common, serious and costly condition that occurs in an elderly, frail and dependent patient population (6;7). It is estimated that 70,000 – 80,000 cases of hip fracture occur each year in the UK (70;71). This is projected to rise to around 100,000 cases in England alone by 2033, with an estimated associated cost of £3.6 – 5.6 billion (73). The vulnerability of this patient group is illustrated by the associated prolonged length of hospital stay, complex care journey, ongoing care needs and high levels of morbidity and mortality (75). Data from national audits suggest a consistent and persistent mortality rate of around 7–10% at one month and 30% at one year (8;71;76). Hip fracture therefore results in significant levels of financial and human expenditure, accounts for the useage of a huge amount of health resource and is a burgeoning public health challenge (73;77;78).

Several guidelines designed to standardise and improve care for patients with hip fracture group have been created over the last five years (72;79;87;89;163). A review of guidelines relating to the management of hip fracture exploring the similarities, differences and conflicts encountered was performed.

4.2.2 Methods

The PubMed, Medline, Embase and Cochrane databases were searched for papers in the English language published from 1996 to September 2012 using the search terms ‘clinical practice guidelines’, ‘practice policies’, ‘protocols’ and ‘consensus statements’, and combining these with ‘femoral fracture’ and ‘hip fracture’. Current local and national (UK) guidelines relating to the peri-operative management of hip fracture were accessed via the former NHS National Library of Guidelines (164) and NHS Evidence websites (165). The websites of relevant government organisations, professional societies, and guideline publishers were reviewed for publications of interest and reference lists examined.

4.2.3 Results

Five clinical guidelines issued over a five-year period in the UK were identified. These were: the British Orthopaedic Association/British Society of Geriatricians (BOA/BSG2007) (89), the Scottish Intercollegiate Guideline Network (SIGN 2009)

(87), the National Institute for Health and Clinical Excellence (NICE 2011) (79), the Association of Anaesthetists of Great Britain and Ireland (AAGBI 2011) (72), and the British Orthopaedic Association (Standards for Trauma; BOAST 2012) (163). Guidelines ranged in length from one to 664 pages.

4.2.4 General recommendations and timeline

All guidelines highlighted the high levels of comorbidity and frailty apparent within this patient group, advising a thorough assessment of any factors that may have caused the fall as well as level of physical and cognitive function. Recommendations relating to general aspects of management such as delivery of adequate patient information, multidisciplinary management, the benefits of orthogeriatric input, a dedicated trauma team and theatre list and consultant-delivered care were common to all guidelines. General care issues including pressure area protection, nutritional assessment and supplementation, adequate hydration, and coordinated rehabilitation with supported discharge were also consistently acknowledged. Recommendations regarding timing of surgery were addressed in all guidelines. A four-hour time period from hospital to orthopaedic ward admission was specified in BOA/BSG 2007, NICE 2011 and AAGBI 2011 publications. This was reduced to two hours in SIGN 2009, and was not specified in the updated BOAST 2012 guideline. All guidelines emphasised the advantages of expedited surgery with all but SIGN 2009 setting a standard of surgical repair on the day of or day after surgery and within daylight hours. This was reduced to 24 hours in the SIGN 2009 guideline.

4.2.5 Analgesia

Both SIGN 2009 and AAGBI 2011 advise early analgesia in the pre-hospital setting while the remaining guidelines focus on management in the emergency department. Guidelines generally recommend the use of regular oral paracetamol, the avoidance of non-steroidal anti-inflammatory drugs and regular assessment of pain at rest and movement taking into account the potential for the decreased capacity to express pain in the elderly population. The BOA/BSG 2007 guideline specified that oral or intramuscular opioids should be used in preference to the intravenous route, with codeine and tramadol also considered as useful agents. This is in contrast to the SIGN 2009 and AAGBI 2011 guidelines

which advise the careful titration of intravenous morphine and the avoidance of oral opioids and codeine due to adverse effects such as constipation peri-operative cognitive dysfunction and delirium. There was a lack of cited evidence in this area.

The use of peri-operative peripheral nerve blockade was discussed in SIGN 2009, NICE 2011 and AAGBI 2011. All three guidelines, after considering the same 2002 Cochrane review (166), concluded that peripheral nerve blockade should be considered as an adjunct for both pre- and postoperative analgesia. The NICE 2011 guideline specified further that peripheral nerve blockade should only be added if analgesia was inadequate after the administration of paracetamol and titration of systemic opioid analgesia.

4.2.6 Anaesthesia

The conduct of anaesthesia was discussed in all guidelines with the exception of BOAST 2012. Conclusions from both SIGN 2009 and NICE 2011 were based on the results of a 2004 Cochrane meta-analysis of 22 studies (167), with an additional paper on cost-effectiveness included by NICE (168). Whilst SIGN 2009 made a consensus recommendation that regional anaesthesia should be considered for all patients unless contraindicated, NICE 2011 considered that patients should be offered a choice between regional and general anaesthesia after a patient-centred consideration of the risks and benefits. The AAGBI 2011 publication included another more recent meta-analysis that included 18,715 patients from 34 randomised controlled trials, 14 observational studies and eight reviews (169). The recommendation of this guideline was that regional anaesthesia be the preferred technique. The importance of patient-centred, multidisciplinary decision-making and considerate anaesthesia (regardless of technique) was highlighted. Other recommendations by AAGBI 2011 included: consideration of peripheral nerve blockade in all cases, low doses of local anaesthetic and use of the lateral position to reduce haemodynamic compromise with neuraxial block, the use of fentanyl in preference to morphine or diamorphine for spinal anaesthesia and avoiding the combination of general and spinal anaesthesia. Pragmatic guidance relating to the administration of general anaesthesia was also given.

4.2.7 Anticoagulation and antiplatelet therapy

Guidelines differed in their approaches to this issue. Recommendations are summarised in Table 4.2-1. It should be noted that guidelines on the peri-operative management of anticoagulation not specific to patients undergoing proximal femoral fracture repair are also available.

Source	Acceptable INR for surgery	Acceptable INR for neuraxial block	Vitamin K for reversal of warfarin	Fresh frozen plasma for reversal of warfarin	Plasma thromboplastin component for reversal of warfarin	Antiplatelet drugs
BOA/BSG 2007(89)	< 1.5	Not mentioned	Absence of relevant research	Absence of relevant research	Not mentioned	Clopidogrel: multidisciplinary discussion required
SIGN 2009(87)	Not mentioned	Not mentioned	Oral or intravenous (1.0-2.5 mg suggested)	Should be used in accordance with BCSH guidelines	Not mentioned	Surgery should not be delayed. General anaesthesia recommended in patients taking dual antiplatelet therapy. Transfuse platelets only in the event of excessive surgical bleeding.
NICE 2011(79)	Not mentioned	Not mentioned	INR should be corrected promptly to avoid undue delay	Not mentioned	Not mentioned	Not mentioned
AAGBI 2011(72)	<2 (follow hospital guidelines)	<1.5 (follow hospital guidelines)	Small amounts may be given (with supplemental heparin)	Not mentioned	Expensive and rarely indicated	Aspirin may be withheld during inpatient stay, unless indicated for unstable angina or recent / frequent transient ischaemic attacks. Clopidogrel generally not stopped on admission. Surgery should not be delayed. Platelets should not be administered prophylactically. Higher than normal surgical blood loss should be expected
BOAST 2012(163)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Table 4.2-1 - Summary of guidance for the management of anticoagulant / anti-platelet drugs in patients undergoing repair of proximal femoral fracture.

4.2.8 Cardiac murmur and anaemia

The presence of an undiagnosed systolic murmur is a common dilemma in this patient group. This is highlighted in the 2001 NCEPOD report (170), and this document is therefore included in the analysis. Guidance is summarised in Table 4.2-2.

Guidance related to anaemia is summarised in Table 4.2-3.

Source	Indications for pre-operative echocardiography
BOA / BSG 2007 (89)	If an echocardiogram can be obtained without causing delay, the information may be useful. The absence of echocardiography should not lead to delays in fixing the fracture.
SIGN 2009 (87)	Echocardiography should be performed if aortic stenosis is suspected, to allow confirmation of diagnosis, risk stratification and any future cardiac management. The need for echocardiography, based on clinical history, physical examination and ECG findings should not delay surgery unduly Rapid access to an echocardiography service is recommended for appropriate patients to avoid unnecessary delay to surgery Older people with hip fracture do not require routine additional cardiac investigation such as echocardiography before surgery.
NICE 2011 (79)	Not addressed.
AAGBI 2011 (72)	Echocardiography may be indicated: (i) to establish left ventricular function if the patient is breathless at rest or on low-level exertion (ii) to investigate the severity of an ejection systolic murmur heard in the aortic area, particularly if significant aortic stenosis is suggested by two or more of: - a history of angina on exertion - unexplained syncope or near syncope - a slow rising pulse - an absent second heart sound - left ventricular hypertrophy on the ECG without hypertension (although clinical signs of aortic stenosis can be difficult to elicit). “Awaiting echocardiography” is an unacceptable reason to delay surgery. A majority of clinicians favour proceeding to surgery with modification of their technique towards general anaesthesia and invasive blood pressure monitoring, with the proviso that patients should undergo echocardiography in the early postoperative period.
BOAST 2012 (163)	Not addressed.
NCEPOD 2001 (170)	An asymptomatic cardiac murmur may indicate significant cardiac disease and should be investigated with pre-operative echocardiography.

Table 4.2-2 - Summary of guidance for the management of cardiac murmurs in patients undergoing repair of proximal femoral fracture

Source	Perioperative management of anaemia
BOA / BSG 2007 (89)	Transfusion may be required as a drop in haemoglobin concentration of 2-3 $g.dl^{-1}$ over the peri-operative period can be anticipated in most patients In the absence of reliable evidence to guide the use of blood transfusion after hip fracture surgery, practice varies considerably. Local protocols are variably in use. Further research is required
SIGN 2009 (87)	Comments on paucity of evidence in this area Suggests referral to SIGN guideline on peri-operative blood transfusion
NICE 2011 (79)	Anaemia should be identified and corrected to avoid unnecessary delay to surgery
AAGBI 2011 (72)	Pre-operative transfusion should be considered for a haemoglobin concentration <9 $g.dl^{-1}$, or <10 $g.dl^{-1}$ with a history of ischaemic heart disease If haemoglobin concentration is 10–12 $g.dl^{-1}$, two units of blood should be crossmatched If haemoglobin concentration is within normal limits, a grouped sample is sufficient Consider cell salvage for peri-prosthetic fractures or revision surgery
BOAST 2012 (163)	Identify and treat correctable co-morbidities immediately so that surgery is not delayed

Table 4.2-3 - Summary of guidance for the management of anaemia in patients undergoing repair of proximal femoral fracture.

4.2.9 Discussion

Consider the care of an elderly patient arriving in hospital at 11:00am, who spent three hours in the emergency department, received oral opioids, was found to have an asymptomatic murmur and was investigated with an echocardiogram before being operated on the following afternoon. The management of this patient would be compatible with the BOA/BSG 2007, NICE 2011 and BOAST 2012 guidelines, whilst various aspects of the same patient's management would be contrary to AAGBI 2011 (in at least two aspects) and SIGN 2009 (in at least three aspects). It is also relatively easy to select other examples that are completely compatible with the SIGN 2009 and AAGBI 2011 guidelines but are contrary to the other guidelines.

So why do guidelines differ? Timing undoubtedly plays a major role. It is clearly impossible that a guideline published five years ago could appraise the same literature as one published several years later. Conversely, the authors of a new guideline might find that there is no recent evidence to review and be forced to analyse studies that are out of date and are not representative of current practice. Whilst this situation might seem surprising in view of the continuing increase in volume of medical literature (130), it is not infrequently encountered (as illustrated in the review of anaesthetic technique for proximal femoral fracture repair). Furthermore, guidelines can vary in the literature reviewed, even when they are published around the same time. This may relate to different search strategies and criteria, or could reflect differing perspectives, objectives and intended readership.

For example, although the AAGBI 2011 and NICE 2011 hip fracture guidelines were published in the same year, they differ in the literature reviewed on anaesthetic technique. While both guidelines include the 2004 Cochrane review by Parker and colleagues (167), the AAGBI document also considers a larger more recent meta-analysis by Luger et al (169). The reasons for this are not clear though may reflect the differing timescales in which guidelines are created, as well as the slightly later publication date of the AAGBI guideline. The AAGBI guideline is clinician driven and patient-centred, placing a greater emphasis on

the practical issues surrounding the patient journey, whilst NICE must balance an over-arching responsibility for the fair and optimal use of resources with that of current best practice and clinical will and is accountable to Government. This may at times create an interesting counterpoise. Differences in guidelines may result in fundamental differences in practice and are an important phenomenon.

Barriers to compliance with guidelines are well documented in a recent article by Carthey and colleagues (134). The exponential increase in the number of published guidelines brings with it a notable variability in guideline quality, an issue actively addressed by the AGREE (Appraisal of Guidelines for Research and Evaluation) collaboration (140;171). The AGREE II tool is designed to "assess the quality of practice guidelines across the spectrum of health, provide direction on guideline development, and guide what specific information ought to be reported in guidelines" (140). Despite laudable intentions, such tools are not infallible and have limitations. The AGREE II instrument is one of the most well-validated tools for guideline methodological assessment and incorporates 23 items within six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence (140). Within this process, methodological processes are systematically assessed. However, the quality of the literature assessed and the appropriateness of the conclusions reached are not independently evaluated. This is a potential weakness and leaves open the possibility for unanswered questions on a guideline's clinical validity. Equally, while allowing for a degree of comparison to be made between different guidelines on a topic, there is no watershed mark by which a guideline on a particular topic can universally be considered acceptable or clinically apt. Although AGREE II is undoubtedly a welcome addition to guideline development processes, it may not yet be adequate to fully determine the utility of an individual clinical guideline. Thus, even guidelines produced by organisations granted the AGREE seal of approval are not immune to criticism (172;173).

This raises further questions regarding the medicolegal implications of guidelines. In correspondence following a much debated editorial on NICE guidance of CardioQ^{TM} monitoring (174), Ghosh and colleagues suggested that clinicians might fear claims of negligence if they did not follow guidance produced by high-profile organisations such as NICE. They also considered that

the incorporation of guidelines into the Commission for Quality and Innovation (CQUIN) framework is likely to result in additional financially motivated pressures to comply (173;175). In reply to recent similar criticisms (176), NICE responded by clearly stating that guidelines are *"not in any way mandatory"* and are designed to help *"healthcare professionals and patients make informed choices"* (177). Despite these reassurances, the quasi-legal status of guidelines is a matter of understandable anxiety and uncertainty amongst practicing health care professionals. In a case of medical litigation, the main question that must be answered is whether or not a doctor has provided a standard of 'reasonable care' as required by law. This is judged by taking into account the circumstances surrounding a particular situation and balancing the differences inherent in medical practice against the interests of the patient. Traditionally, the standard of care in law has been determined according to the Bolam test (178). This is based upon the principle that a doctor does not breach the legal standard of care and thus is not negligent if their practice is upheld by a responsible body of professionals with expertise within the same clinical field. However, this principle has been criticised as relying unduly upon medical testimony with insufficient attention to the interests of the patient. More recently, there has been a move towards the requirement for an explanation of the logic underlying the standard of care deemed acceptable by the 'body of medical opinion'. This is known as the Bolitho test. As a result, the Courts enquire in increasing detail about the analysis of events, supporting evidence base and risk analysis of potential other courses of action (179). Although accepted practice will be established in the Court by the invitation of expert testimony, guidelines may be increasingly referred to by expert witnesses, as well as the judge, as evidence of customary and accepted best practice.

On a superficial level, it might seem reasonable to suggest that a competent clinician should follow all of the recommendations in an evidence-based guideline, all of the time. This assumes that the guideline is completely up to date, uses only completely robust evidence and is entirely applicable to the patient in question. Unfortunately, or perhaps fortunately, the medical literature is expanding rapidly at a rate far exceeding that possible for guideline production. The process by which guidelines are formed is hugely resource and labour intensive and cannot at present be repeated for every new piece of

evidence that is produced in a clinical field. Even once a guideline is accepted as being fit for purpose, its timely implementation in the clinical setting can create significant challenges in terms of resources, cost, staff training and ultimately acceptance and reliable implementation by the clinical team.

The presence of conflicting, out-of-date or methodologically flawed guidelines could have far-reaching and serious consequences though are hard to avoid in reality. Equally, the presence of guidelines containing polarised advice could highlight that the area under investigation is one in which there is clinical uncertainty (and likely low levels of clinical evidence) and thus aid both defendant and claimant on the same issue. Until these issues are resolved, if they ever are, guidelines should serve as a source of reference regarding best practice and not be legally binding. Despite this, it is certainly plausible that high-quality, peer-reviewed guidelines produced by a professional group (such as the AAGBI) may be seen as consistent with the tenets of both Bolam and Bolitho, and thus realise a greater importance as a source of reference during court proceedings. As discussed recently, it would seem reasonable that clinicians should be prepared to justify their reasoning when making any major deviations from relevant guidelines (180).

Advances in technology have the potential to provide solutions to some of the issues described above. The SIGN guidelines are now being published in electronic rather than paper-based formats to allow them to be read on mobile devices (181) and NICE has also taken measures to improve user-friendliness by creating ‘pathways’ mapping all sources of guidance on a particular topic and by enhancing its website (182). It is hoped that these measures will help to increase awareness, accessibility and utility of guidelines providing useful information where needed at a clinical interaction. Similarly, the Artificial Intelligence in Medicine research field recognises the inherent challenges (and potential advantages) of managing multiple, complex clinical guidelines and is currently active in the development of methodologies and systems to aid in this task (183;184). Although many advances have been made in the technology supporting the computerisation of guidelines, further investigation into which populations to target, the optimal types of system to use and most importantly effects on patient outcomes and overall cost-effectiveness are needed. The recognition that poorly programmed systems may result in harm due to poor

training, human error or improper use of software is also important and highlights the need for caution when such technologies are introduced into practice (183). Development and validation of the necessary technology represents only one of the barriers to its successful integration into the clinical environment. If the promise of its considerable potential is ever to be realised, advances must be made not only within the technical domain, but in the social, educational and cultural change that must accompany it.

4.2.10 Competing interests

JK is Chairman of SIGN. No external funding or other competing interests declared.

4.3 Chapter 4 Summary

- The use of clinical guidelines has a number of advantages but is also associated with significant limitations.

- Processes for formulating guidelines must be robust and open to evaluation by external parties.

- Making guidelines up to date and user-friendly is essential if they are to continue playing a meaningful role in clinical care

- Guidelines for the anaesthetic management of hip fractures vary.

- Reasons for this include: the date of guideline creation, nature of organisation creating the guideline and methodology used to create the guideline.

- Guidelines are useful aids with which to inform practice and clinicians should be prepared to justify any major deviations from relevant guidelines.

- Guidelines are not currently legally binding though they may be used to guide opinion in court.

Chapter 5

A one year retrospective audit of the management of patients with hip fracture in Glasgow Royal Infirmary

A significant proportion of the following chapter was performed as part of an intercalated BSc degree project for which I was principle supervisor. The concept for the audit and quality improvement intervention was mine. Under my direction and close supervision, Miss Katherine Cameron (KC, 3rd year medical student) performed the data collection and analysis informing this work. Ongoing data collection, analysis and quality improvement work are being performed by myself.

5.1 Rationale

As the SHFA had ceased reporting 4 years ago, prior to the commencememt of this work (71), and in keeping with recommendations for large scale data collection by HipPeN (8), we wished to study the management of patients admitted with proximal femoral fracture (PFF) in Glasgow Royal Infirmary over a one year period. We aimed to establish current practice, allow comparison against national data and identify possible areas for improvement.

The analysis performed was based mainly on the outcomes reported by HipPeN as these related more specifically to anaesthesia and peri-operative care (8). This was felt to be most relevant to our clinical practice and potential area of influence. Other outcomes of interest were compared against those reported in NHFD and SHFA where possible (71;185).

5.2 Methods

Ethical approval was sought from the West of Scotland Research Ethics Group and was deemed unnecessary as the intervention was considered to be one of service development.

Data for patients admitted between 1st August 2011 and 31st July 2012 were obtained by RK from the Bluespier Database (an orthopaedic theatre management system). Data for each patient (Table 5.2-1[a]) were collected by KC using Clinical Portal, North Glasgow laboratories' database, case notes and hospital admission records. The database was cross-checked for accuracy by a

second investigator (RK). All data were stored using an encrypted storage device. Data for comparison were extracted directly from the first report from the NHS Hip Fracture Per-operative Network (HipPeN) (8).

After consultation with clinical staff from a number of disciplines, patients admitted to ICU and patients taking warfarin were felt to be sub-groups meriting a more detailed analysis. Patients admitted to the Intensive Care Unit (ICU) were identified using the WardWatcher database. Patients on warfarin were identified using Clinical Portal, laboratory results and clinic letters (Data fields collected as outlined in Table 5.2-1[b & c]). Case notes of patients taking warfarin were subject to further analysis resulting in the production of individual management timelines. Results for patients taking warfarin are discussed in detail in Chapter 6.

(a)	Standard data (all hip patients with hip fracture)
	Age
	Sex
	ASA
	Postcode
	Date of surgery
	Delay to theatre
	Death at 30 days
	Length of stay
	Type of anaesthetic
	Grade of surgeon
	Grade of anaesthetist
(b)	Specific data for patients admitted to ICU
	Reason for admission
	Length of stay
	Co-morbidities
	Organ support
	APACHE score
	Predicted hospital mortality score
(c)	Specific data for patients taking warfarin
	INR on admission
	Time to reduce INR to < 1.5
	Time to theatre
	Method of warfarin reversal
	INR on day of surgery
	Prophylactic bridging therapy
	Time to restart warfarin post-operatively
	Time to achieve therapeutic INR

Table 5.2-1 - Data fields

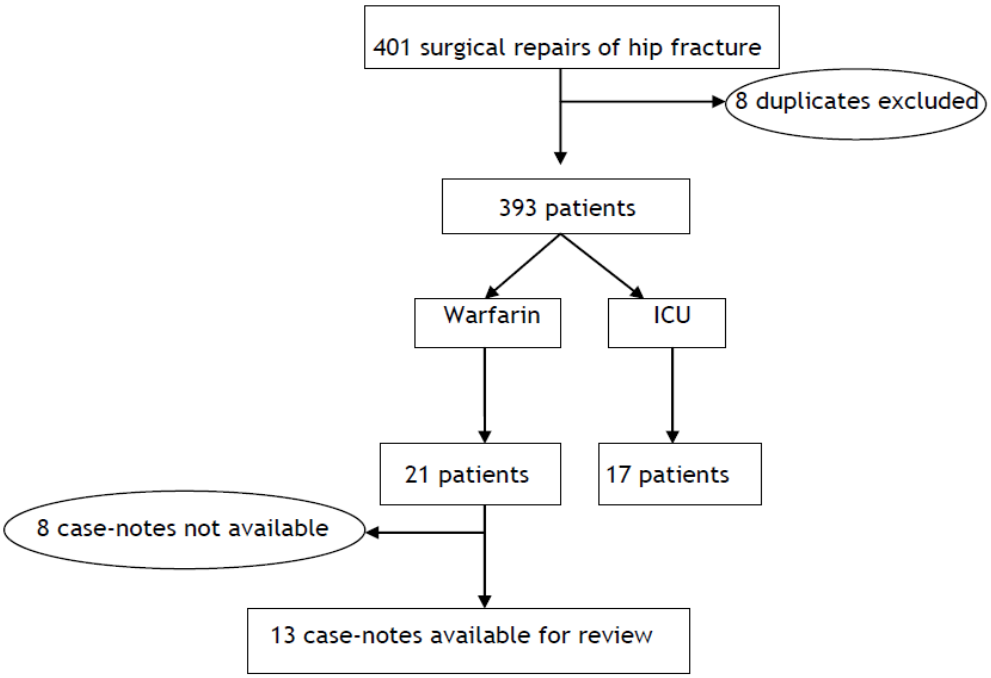


Figure 5.2-1 – CONSORT diagram of patient identification

Data were recorded and analysed using Microsoft Excel. Statistical analysis was performed using Minitab v15. Data were reported as Mean (SD) or Median (IQR) where appropriate. Tests of two proportions, Chi-square and Fishers exact tests were utilised dependant on the distribution of the data and statistical significance was assumed at the level of $p < 0.05$. For some outcomes, the national audits being used for comparison did not mention assessment of normality. In the case of our data being non-normally distributed, no statistical comparison could be made as we did not have access to the raw data from national audits.

5.3 Results

5.3.1 Benchmarking data from GRI against national data

Three hundred and ninety three surgical repairs of PFF were performed at GRI between August 2011 and July 2012. A comparison of data from GRI and HipPeN (2010) is shown in Table 5.3-1.

Variables	GRI	HipPeN	p value
Patients (n)	393	1195	
Male	120 (30%)	319 (27%)	0.140*
Female	273 (70%)	876 (73%)	
Age / years. Median (IQR) for GRI data. Mean (SD) for HipPeN	79 (76-86)	81 (11)	†
Male	72 (61-83)	78 (13)	†
Female	80 (73-87)	83 (10)	†
ASA Grade			
I	16 (4%)	30 (3%)	
II	107 (26%)	351 (29%)	0.146*
III	235 (60%)	619 (52%)	
IV	35 (10%)	119 (10%)	
Method of Anaesthesia			
General Anaesthetic (GA)	216 (55%)	596 (51%)	0.063*
Regional Anaesthetic (RA)	177 (45%)	579 (46%)	
Grade of Surgeon			
Consultant	158 (41%)	416 (38%)	
Registrar	93 (25%)	252 (23%) °	<0.001*
ST 3-7	82 (21%)	406 (37%) °	
ST 1-2	34 (9%)	22 (2%)	
SHO	15 (4%) §	0 §	§
Grade of Anaesthetist			
Consultant	368 (94%)	683 (58%)	
Registrar	20 (5%)	260 (32%) °	<0.001¶
Trainee Grades	5 (1%)	235 (20%) °	

Table 5.3-1 - Comparison of data between GRI and HipPeN

Values are n (%) unless stated otherwise

*Denotes chi-square analysis. † Denotes GRI data not normally distributed and therefore not suitable for comparison with HipPeN data. § Denotes data incompatible for statistical comparison removed from analysis due to values of 0. ¶ Denotes Fishers exact test (used due to small sample size). ° Denotes HipPeN data estimated from graphs

Ninety three patients (24%) underwent surgery on the same day as their hospital admission, with 190 (48%) being operated on within one calendar day, 64 (16%) within two calendar days and the remaining 46 (12%) thereafter (Range 0-22 days). The median length of stay was 15 days (IQR 8 - 30 days, Range 1 - 207 days).

Thirty day mortality was 6.1% (22/393). Results for thirty day mortality from national audits are listed for comparison: NHFD (8.1%), SHFA (9%) and HipPeN (9%). This did not reach statistical significance (p = 0.179). Mortality and length of stay data were compared with results relating to patients in GRI from the SHFA in 2008 and are tabulated (Table 5.3-2).

Variables	GRI (2008)	GRI (2011/12)	p value
30-day mortality	26 (7.3%)	22 (6.1%)	0.339‡
120-day mortality	55 (15.9%)	50 (13%)	0.226‡
Length of stay (median (IQR))	19 (10-45)	15 (18-30)	§

Table 5.3-2 - Comparison of data: SHFA 2008 versus GRI 2011-12

Values are n (%) unless stated otherwise. ‡denotes test of two proportions. § denotes data not suitable for comparison as not normally distributed and no access to raw data.

The Scottish Index of Multiple Deprivation (SIMD) 2012 was used to stratify patients for levels of deprivation (186). Two hundred and fifty one (64%) patients admitted for hip fracture repair were living in the 25% most deprived areas of Scotland.

5.3.2 Patients admitted to Intensive Care Unit

Demographic data for patients admitted to ICU / HDU are shown in Table 5.3-3. During the period 1st August 2011 and 31st July 2012, seventeen patients (4.3%) were admitted to the GRI ICU / HDU following surgery for hip fracture. Eleven patients had been admitted to ICU in the 4 year period 2007-2011 (2007 was the

time point at which WardWatcher began and hence the period from which reliable data could be obtained).

The mean length of stay in the ICU was seven days (SD = 11), median APACHE score was 19 (IQR 15-23), and median predicted hospital mortality was 15.9% (IQR 9.6-29.2). Actual hospital mortality was 29% (5 patients). “Surgery plus co-morbidity” (41%) was the most common reason for admission to ICU with cardiovascular disease constituting the majority of co-morbid conditions (13, 76%). Four patients required organ support (24%), three required ventilation and three underwent invasive cardiovascular monitoring. Renal replacement therapy was not required in any patient.

Variables		All GRI	ICU
Patients (n)		393	17
Sex			
	Males	120 (30%)	9 (53%)
	Female	273 (70%)	8 (47%)
Age (SD)		76 (14)	76 (9)
	Males	70 (16)	74 (9)
	Female	78 (12)	83 (6)
ASA			
	1	16 (4%)	0
	2	107 (26%)	1 (6%)
	3	235 (60%)	13 (76%)
	4	35 (10%)	3 (18%)
Length of stay median (IQR)		15 (8-30)	29.5 (22.5-42.5)
30 day mortality (n, %)		22 (6.1%)	3 (17.6%)

Table 5.3-3 - Demographic data for all patients compared with the sub-group of interest (patients admitted to ICU)

5.4 Discussion

5.4.1 Glasgow Royal Infirmary versus National Data

In this comparison of data obtained from patients in a single Scottish hospital (GRI) with data reported by the HipPeN group (English and Welsh hospitals), gender split was not significantly different with females accounting for around 70% of all operations (p=0.140). Although age distribution was not suitable for statistical comparison, the mean age for patients in GRI was 76 years, lower than that reported by HipPeN (81 years). Overall, ASA score distribution was not significantly different (p = 0.146). However, when higher ASA grades were analysed separately, a greater proportion of GRI patients had ASA III and IV status (70% in contrast to 62% in HipPeN).

The performance of high quality RCTs for hip fracture surgery is associated with significant challenges, including issues with eligibility criteria and informed consent. This has resulted in a lack of high quality evidence from randomised controlled trials (RCTs) (80). One proposed solution is the collection of large amounts of high quality data via large collaborative audits. Such audits aim to collect data on outcomes of interest as well as relevant information on potential sources of bias and confounding factors (such as co-morbidity data) and adjust appropriately (8). National databases such as HIPPeN, SHFA and NHFD have done much to advance our knowledge regarding the management of these patients.

In GRI, 72% of patients received surgery on the day of, or day after admission. Unfortunately, for logistical reasons, data could not be collected on number of hours to theatre, and this is a major limitation of this audit. HipPeN reported a median time to theatre of 47h, with 11 of the 22 included hospitals reporting a mean time >48 hours (8). Several meta-analyses have concluded that unnecessary delay is more likely to increase morbidity (80;81;187-189). Most guidelines therefore recommend expedited surgery (72;79;87;89;163). Timing of surgery is discussed further in Chapter 7.

The median length of stay within the study period in GRI was 15 days. This represents a 4 day reduction when compared to the data reported for GRI by the SHFA in 2008. Length of stay was not reported by HipPeN. Reducing the length

of hospital stay is considered to be one of the most important areas for improvement both in terms of patient outcomes and reducing costs. The NHFD estimate that each additional day in hospital results in an increased spend of £248 (76). It should be noted that length of stay is a relatively crude marker of care which can be affected by a number of wide-ranging factors outwith the realm of medical fitness for discharge.

Morbidity and mortality after hip fracture is high and 30-day mortality persists at around 7-10%. Thirty day mortality is the most frequently studied and reported measure of hip fracture outcome (75). Large studies employing multiple logistic regression methods have resulted in the acceptance that male sex, advanced age, an ASA grade of III or IV, and multiple co-morbidities are associated with higher mortality rates (60;65;66;190). The thirty day mortality rate in GRI was 6.1%, lower than that reported by HipPeN, NHFD and SHFA, though this was not statistically significant ($p = 0.179$). Comparison with data collected for GRI by the SHFA in 2008 also showed a reduction in both 30 and 90 day mortality, though, this did not achieve statistical significance ($p = 0339$ and $p=0.226$ respectively). Whilst these reductions are not statistically significant, any potential reduction in patient mortality may be considered beneficial.

Our data showed that over half of patients undergoing hip fracture repair received a general anaesthetic. There was no statistically significant difference in the method of anaesthesia used in GRI compared with that HipPeN ($p = 0.063$). This was unexpected as regional anaesthesia is recommended by SIGN guidelines, commonly referenced in our institution. While there is some evidence that regional anaesthetic techniques may reduce post-operative confusion, respiratory complications and financial cost (72;87;187), there is a counter-argument that general anaesthesia may confer greater haemodynamic stability. A 2004 Cochrane review concluded that there was insufficient high quality evidence to rule out clinically important differences between the two methods (167). Type of anaesthesia remains an area of clinical variability and uncertainty. Both SIGN and AAGBI recommend that regional anaesthesia should be performed in preference to general anaesthesia where possible (72;87), whereas NICE adopt a more conservative approach in advocating a decision after full discussion with the patient (79).

GRI and HipPeN data differed significantly in the grade of both surgeon and anaesthetist (p = <0.001). A higher percentage of consultant surgeons operated in GRI than was seen in data from HipPeN, though the difference was small (3%). At GRI, 94% of anaesthetics were performed by consultant anaesthetists, compared to an average of 58% in data reported by HipPeN. This represents the most significant difference in our findings (p<0.001). This is likely to be due to a new departmental policy, where consultant anaesthetists provide resident anaesthetic cover for weekend trauma lists. This commenced in March 2011, just before the study period. Published literature relating to the professional grade of both surgeon and anaesthetist is sparse and any available is of "low quality", as reported by NICE (79). Guidelines generally recommend involvement of senior staff due to the high risk nature of this patient population.

Using SIMD 2012 data (186), 64% of our patients were found to be living in the 25% most deprived areas of Scotland. Comparable socio-economic data was not reported by HipPeN. Scotland has been reported to have poorer public health and higher general mortality than the rest of the UK (191). It is possible that the Glasgow Effect may offer some explanation as to why our patients showed a trend towards being younger and less fit than was reported nationally. Whilst level of deprivation was not discussed in the HipPeN data, it is interesting to consider as a confounding factor which may affect patient outcomes. We speculate that GRI patients, whilst chronologically younger than the demographic reported in HipPeN data, may be "physiologically" older. This could potentially explain some of the differences observed in both age and ASA score.

5.4.2 Subgroups of interest - Intensive Care Unit:

Patients admitted with hip fracture are already a high risk group. We wished to examine subgroups of patients admitted with hip fracture who were felt to be at the higher end of the spectrum of risk. It was considered that such an analysis may identify areas where care might be improved and / or resources targeted. Groups identified as meriting more detailed analysis were; (i) patients admitted to ICU and (ii) patients who were taking warfarin. The cohort of patients admitted to ICU was of interest in order to identify the frequency of admission,

the level of care required, their length of stay in critical care facilities, and the potential impact on future resources. During the audit period, our ICU changed from being a 10 bed unit ICU to a 20 bed combined ICU and HDU. We were interested to see whether this increase in bed availability had affected the number of patients admitted following hip fracture and whether this demand was likely to increase. As this is a frail patient group, it could be argued that critical care facilities are under-utilised and that patients may benefit from an area where enhanced post-operative care tailored to this patient group could be offered.

GRI patients undergoing hip fracture repair and admitted to ICU post-operatively, had higher ASA grades and an increased length of stay when compared with the main cohort. Thirty-day mortality was also higher (Table 3.4-3). Of the 17 GRI patients, most required only basic levels of ICU care such as post-operative monitoring due to concerns regarding co-morbidities. These patients did not require organ support and were discharged within a short time-frame. These data also showed that the use of ICU has increased substantially in recent years, which we speculate may be explained by the recent expansion of ICU to include high-dependency beds. It could certainly be argued that the majority of patients undergoing hip fracture repair could benefit from enhanced levels of care post-operatively. We predict that the demand for critical care beds will rise. Further work is required to evaluate whether a designated orthopaedic higher dependency area would be both beneficial and cost effective.

5.5 Limitations

Data published by HipPeN and used for comparison in this analysis was obtained from a published paper with no access to raw data. This meant that some values were incompatible for statistical analysis and formal comparison. Data reported by HipPeN were collected over a 2 month winter period, whereas data from GRI were collected over a full year. Data concerning time to surgery could not be collected in hours, as this was not reported in the available data and case-note analysis was not practical. Obtaining case-notes was a major barrier in the performance of this work due to secretarial shortages resulting in long delays and difficulties in obtaining notes. The lack of precise data regarding time to

theatre meant that this was incompatible for comparison with times reported in the relevant literature. These factors may impact on the credibility of our results.

5.5.1 Anaesthesia Sprint Audit of Practice

Since the performance of this analysis, a further publication from the HipPeN collaborators in conjunction with the Association of Anaesthetists of Great Britain and Ireland (AAGBI), National institute for Academic Anaesthesia (NIAA) and National Hip Fracture Database (NHFD) has been published. This Anaesthesia Sprint Audit of Practice (ASAP)(96) was performed following the publication of the AAGBI guidelines on the peri-operative management of patients with hip fracture and analysed care against the standards set in this document(72). Data were obtained for 11,130 patients (67.5% of all hip fracture operations in England and Wales) over a 2 month study period. The main findings from this report are discussed. The grade of most senior anaesthetist and surgeon was found to be a consultant or specialist in over 90% of cases denoting a significant improvement from the initial HipPeN report. Only 44% of patients received spinal anaesthesia with inter-hospital variability noted to be high ranging from <10% to >80%. The doses of bupivacaine used were greater than the recommended <10mg level in 79.5% of cases and only 22% of patients received spinal fentanyl in keeping with recommendations. Nerve blocks were performed in 56% of cases indicating that this technique is increasing in popularity though again this varied significantly between hospitals (range 8%-92%). The incidence of intra-operative hypotension was high with 90% of patients experiencing a blood pressure reduction of >20% from pre-operative values and 77% suffering a systolic BP of < 100mmHg. Hypotension was less prevalent in patients receiving a spinal and has been identified as an area requiring further research. The incidence of Possible Bone Cement Implantation Syndrome was reported as 19% though severe reactions involving hypoxia / hypotension (2.7%) or cardiovascular collapse (0.5%) were less common (96).

The results of this large scale audit have helped to define current practice and increase the evidence behind creating a consensus as to what defines best practice. This work has identified areas where practice is variable and where more research and large scale data collection may be required. The impact of

the institution of these standards upon patient outcomes has yet to be defined and this is the focus of ongoing work from ASAP and NHFD.

5.6 Conclusions

Outcomes for patients undergoing repair of hip fracture in GRI were satisfactory when compared with those reported by HipPeN in 2010. Areas of statistically significant differences include demographics (with GRI patients appearing younger yet with a higher level of comorbidity) and professional grade of anaesthetist and surgeon, which is representative of the importance placed on the peri-operative care of these patients in GRI. Although not statistically significant, mortality in GRI was lower than reported in national data and was shown to have decreased since 2008. The use of the intensive care unit for patients with hip fracture is increasing and this represents an area where further work is required. The collection of accurate data is challenging without a dedicated data collection system as utilised by the NHFD. Whilst the MSk group continue to collect data in Scotland, this is not a continuous process and cannot provide the level of data currently collated by the NHFD in England, Wales and Northern Ireland.

5.7 Chapter 5 Summary

- Current practice in Glasgow Royal Infirmary was analysed by comparing relevant outcomes to those reported in national data.

- Patients in Glasgow Royal Infirmary exhibited a trend towards being younger and having higher number of co-morbidities than was reported in national data.

- Data were found to be in keeping with standards reported in national data and data previously reported for GRI via the Scottish Hip Fracture Audit.

- A significantly higher proportion of care is delivered by consultants at Glasgow Royal Infirmary than is reported in national data.

- Ongoing collection of quality data on a national basis is important if continuedimprovement in care is to be achieved.

- Patients admitted to intensive care, and patients taking warfarin were analysed separately after being identified as sub-groups of particular interest by members of the multi-disciplinary team.

- The use of the intensive care unit is increasing. This may be due to an expansion in high dependency level beds. Patients admitted to the intensive care unit did not require high levels of organ support.

Chapter 6

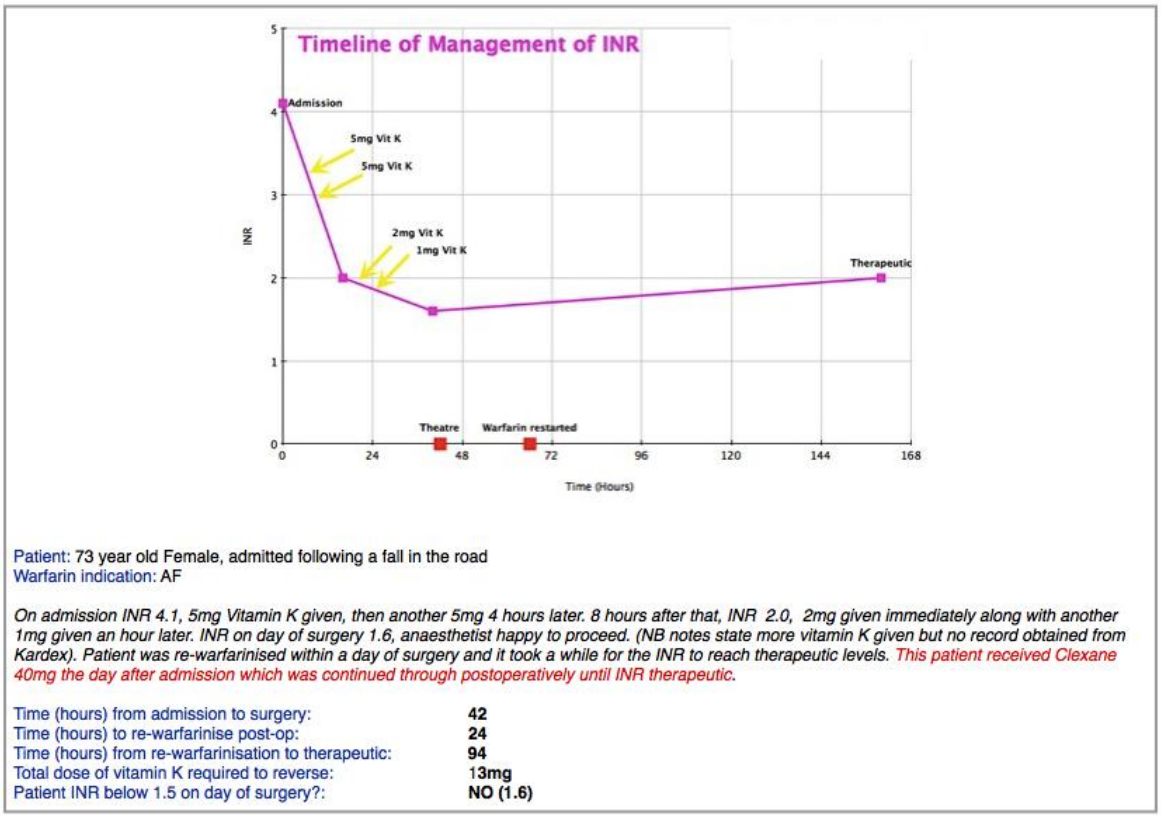
An audit of the management of patients taking warfarin and admitted with hip fracture in Glasgow Royal Infirmary

6.1 Rationale and methods

Using the database of 393 patients undergoing hip fracture repair within a one year period in Glasgow Royal Infirmary (Chapter 5), the management of patients taking warfarin was further examined. This sub-group of patients had been identified as being particularly challenging to manage by both medical and nursing staff working in this area. Management strategies were found to be variable and unpredictable constituting a significant clinical problem. While local guidelines are available to guide the reversal of warfarin in surgical patients, strategies are focused upon the immediate reversal of warfarin (i.e. in patients with ongoing haemorrhage) and in the management of patients undergoing elective surgery. As patients undergoing hip fracture repair require expedited surgery, they lie somewhere in between these two scenarios and therefore are not specifically catered for in these guidelines.

Patients taking warfarin were identified by undertaking a review of Clinical Portal and the North Glasgow Laboratories database. Data collected were: INR results, mention of warfarin in admission or discharge documentation, mention of warfarin in GP referral letter or mention of a diagnosis consistent with the use of warfarin (e.g. atrial fibrillation). This initial review was performed by a medical student (KC) and yielded 47 patients. A further review using Clinical Portal was performed by an anaesthetic consultant (RK). Of the initial 47 patients, 19 were taking warfarin at the time of admission and were therefore suitable for analysis. Case notes were requested for these 19 patients and were successfully retrieved for 13 patients. The other 6 sets of notes were unavailable despite frequent requests

Time-lines were created for each patient in order to describe each patient's journey through the peri-operative period in a graphical form. Clinical interventions (e.g. administration of agent to reverse warfarin, date of surgery and time for INR to become therapeutic post-operatively) were plotted against the patient's INR level in order to give a detailed depiction of the sequence of events. A written account of particular issues in each case accompanied the time-line to provide further relevant information.



Patient: 73 year old Female, admitted following a fall in the road
Warfarin indication: AF

On admission INR 4.1, 5mg Vitamin K given, then another 5mg 4 hours later. 8 hours after that, INR 2.0, 2mg given immediately along with another 1mg given an hour later. INR on day of surgery 1.6, anaesthetist happy to proceed. (NB notes state more vitamin K given but no record obtained from Kardex). Patient was re-warfarinised within a day of surgery and it took a while for the INR to reach therapeutic levels. This patient received Clexane 40mg the day after admission which was continued through postoperatively until INR therapeutic.

Time (hours) from admission to surgery:	**42**
Time (hours) to re-warfarinise post-op:	**24**
Time (hours) from re-warfarinisation to therapeutic:	**94**
Total dose of vitamin K required to reverse:	**13mg**
Patient INR below 1.5 on day of surgery?:	**NO (1.6)**

Figure 6.1-1 - Example of patient timeline

6.2 Analysis of results

Nineteen patients were on warfarin (4.8%). However, only 13 sets of patient notes could be located for review despite multiple attempts.

Demographic data are shown in Table 6.2-1. Indications for warfarin therapy were atrial fibrillation (10, 77%), mechanical heart valve (1, 8%), pulmonary embolism (1, 8%) and superior vena cava occlusion (1, 8%). Two patients (15%) were operated on within 24 hours, three (23%) within 36 and seven (54%) within 48 hours. Care was discussed with the on-call haematologist in two cases (in the patient with SVCO and the patient who received FFP).

Variables		All GRI	Warfarin
Patients (n)		393	13
Sex			
	Males	120 (30%)	5 (38%)
	Female	273 (70%)	8 (62%)
Age (SD)		76 (14)	74 (11)
	Males	70 (16)	70 (7)
	Female	78 (12)	77 (12)
ASA			
	1	16 (4%)	0
	2	107 (26%)	1 (8%)
	3	235 (60%)	12 (92%)
	4	35 (10%)	0
Length of stay median (IQR)		15 (8-30)	19 (13.5-23)
30 day mortality (n, %)		22 (6.1%)	0

Table 6.2-1 - Demographic data for GRI all patients versus warfarin sub-group

Table 6.2-2 provides a summary of warfarin management. The most common intervention for reversing warfarin was intravenous Vitamin K, administered to 10 (77%) of patients in a cumulative dose ranging from 0.5–13mg. Two patients were managed by withholding warfarin (15%), and one patient received fresh frozen plasma (FFP) (8%). No INR results were available on the day of surgery in 5 cases (38%).

Variables	
Admission INR(median, IQR)	2.2(1.74-2.78)
Time to reduce INR to <1.6/h (median, SD)	31.3 (17.7)
Total dose of Vitamin K / mg (median, range)	2 (0.5-13)
INR on day of surgery (median, IQR)	1.55 (1.17-1.6)
Time from admission to theatre / h (median, IQR)	45 (34-68.6)
Time to re-start warfarin postoperatively / h (median, IQR)	66.5 (24-149.5)
Time from warfarin re-start to therapeutic INR / h (median, IQR)	80 (42.4-109.2)

Table 6.2-2 - Results for patients on warfarin

Twelve sets of notes were available for review of thromboprophylaxis. Two patients received no thromboprophylaxis. Of the remaining ten patients, three (27%) received unfractionated intravenous heparin infusion, and seven (63%) received enoxaparin (six 40mg, and one 20mg). Post-operatively, five patients (45%) received 40mg of enoxaparin until therapeutic INR was reached, and one patient received 130mg of enoxaparin daily for 8 days in combination with warfarin therapy. No INR checks were made on this patient until day 8. One patient was given Fondaparinux (2.5mg) for 3 days followed by enoxaparin 40mg thereafter. All three patients given unfractionated intravenous heparin had significant problems with bleeding requiring blood transfusions. Notes and prescription charts were either incomplete or missing in 72% of cases.

None of the patients taking warfarin were dead at 30 days. One patient died at 38 days post surgery. The remainder were still alive at the time of data collection. (November 2012).

6.3 Discussion

The quality of evidence for the peri-operative management of warfarin is poor and consequently, guideline recommendations are often vague and conflicting. The lack of concrete guidance has been discussed since 2005 (120;121;192), with recent reviews reiterating and defining the discrepancies (132). Although certain authors have made suggestions for new local policies based on audit findings, these have omitted guidance on thromboprophylaxis and restarting warfarin (121;192).

In GRI, 4.8% of patients admitted with hip fracture were on warfarin, similar to figures reported elsewhere. Data collection for patients admitted with hip fracture was incomplete in that only 13 of 19 sets of case notes were available for review. This is unacceptable if accurate data are to be collected and quality is to be assured. It is likely that the availability of notes was affected by the transition between a paper-based and electronic patient record which occurred around the same time. This means that any conclusions based on these data should be treated with caution. However, we believe there are some issues which merit review.

Both quantitative and qualitative (through timeline) analysis revealed inconsistencies in patient management. Six patients (46%) were delayed to theatre beyond 48 hours, though inadequate reversal of anticoagulation was only responsible for this in two cases. The majority of patients (77%) underwent warfarin reversal with Vitamin K, though the dose range was wide (0.5 - 13mg) with many patients requiring repeated doses. Four patients did not have an INR check on the day of surgery which is a potential safety issue. Re-commencing warfarin therapy was sub-optimal with only 4 patients (30%) re-established within 24 hours of surgery. The prescription of thromboprophylaxis was variable. It should be noted that the finding of 19 patients on warfarin was a small number (though in keeping with what would be expected over a one year period) and the availability of only 13/19 sets of notes limited the value of the study.

Since this study, better electronic records have been introduced which have improved data availability and will increase the reliability of any findings.

Several common themes permeated the management of this patient group: confusion regarding best-practice management, lack of clear protocols, sub-optimal communication between members of the healthcare team and variability in care.

While these data have clear limitations in terms of the small number of cases, the retrospective nature of the data collection and missing data, they are consistent with the clinical concern that this is an area in which practice varies and where management could be improved. In particular, strategies for the reversal of warfarin and the time taken to reintroduce warfarin are variable and remain a source of confusion for staff. The development of an evidence based protocol to standardise management was felt to be of benefit in an attempt to expedite time to theatre and prevent prolonged periods without anticoagulation in the post-operative period.

6.4 Design of a protocol to direct management in patients on warfarin undergoing surgical repair of hip fracture

The initial audit identified clear areas for improvement in the sub-group of patients taking warfarin and admitted for surgical repair of hip fracture. These included standardising the process of warfarin reversal, reducing time from admission to theatre, standardising the process for the re-introduction of warfarin, reducing the time to achieve therapeutic INR post-operatively and improving compliance with thromboprophylaxis. These findings supported the initial concerns expressed by clinical staff. After liaising with relevant staff, it was concluded that it would be beneficial to design a protocol specific to the needs of this complex and vulnerable patient group to guide staff in their management. Staff were enthused that their concerns had been listened to and that an intervention to improve care and aid in the management of a challenging clinical area was being planned. They were reassured that they would be consulted during the process and that their feedback would influence the production of the final protocol.

It was proposed that the most suitable intervention to aid improvement in all of these areas would take the form of a structured protocol. The protocol was intended to standardise practice, reduce confusion and empower staff to manage these complex patients in a safe and timely manner. A multi-disciplinary focus group was assembled with representation from anaesthesia, haematology, orthopaedics, intensive care medicine, cardiology, stroke medicine, care of the elderly and orthopaedic nursing. The protocol was discussed and refined within this group before being shown to ward staff for further feedback. The protocol was produced in a flowchart style using a colour coding scheme in order to ensure that it was clear and easy to follow. It was reviewed by all disciplines prior to its implementation in order to ensure that it was unambiguous and would be practical to implement. All feedback was considered and changes made accordingly. The protocol was approved for clinical use by the Glasgow Royal Infirmary Thrombosis Committee and was displayed in the clinical areas used by ward staff so that it was easy to access at the point of care. This protocol was endorsed by the NHS Greater Glasgow and Clyde Thrombosis Committee. The protocol is displayed in Figure 6.4-1. Following endorsement by the Thrombosis Committee, education in protocol implementation was delivered to both anaesthetic and orthopaedic department personnel. Haematology staff were also made aware of the protocol. Nurse practitioners working on the relevant wards were recruited to be “local champions” and continue educating other staff about the use of the protocol. These champions were encouraged to liaise with the protocol authors to highlight any problems or areas where they felt change may be merited.

As the use of the protocol was anticipated to be relatively rare (around 20 cases per year from audit data), it was considered optimal to evaluate the impact of the protocol after a period of six months.

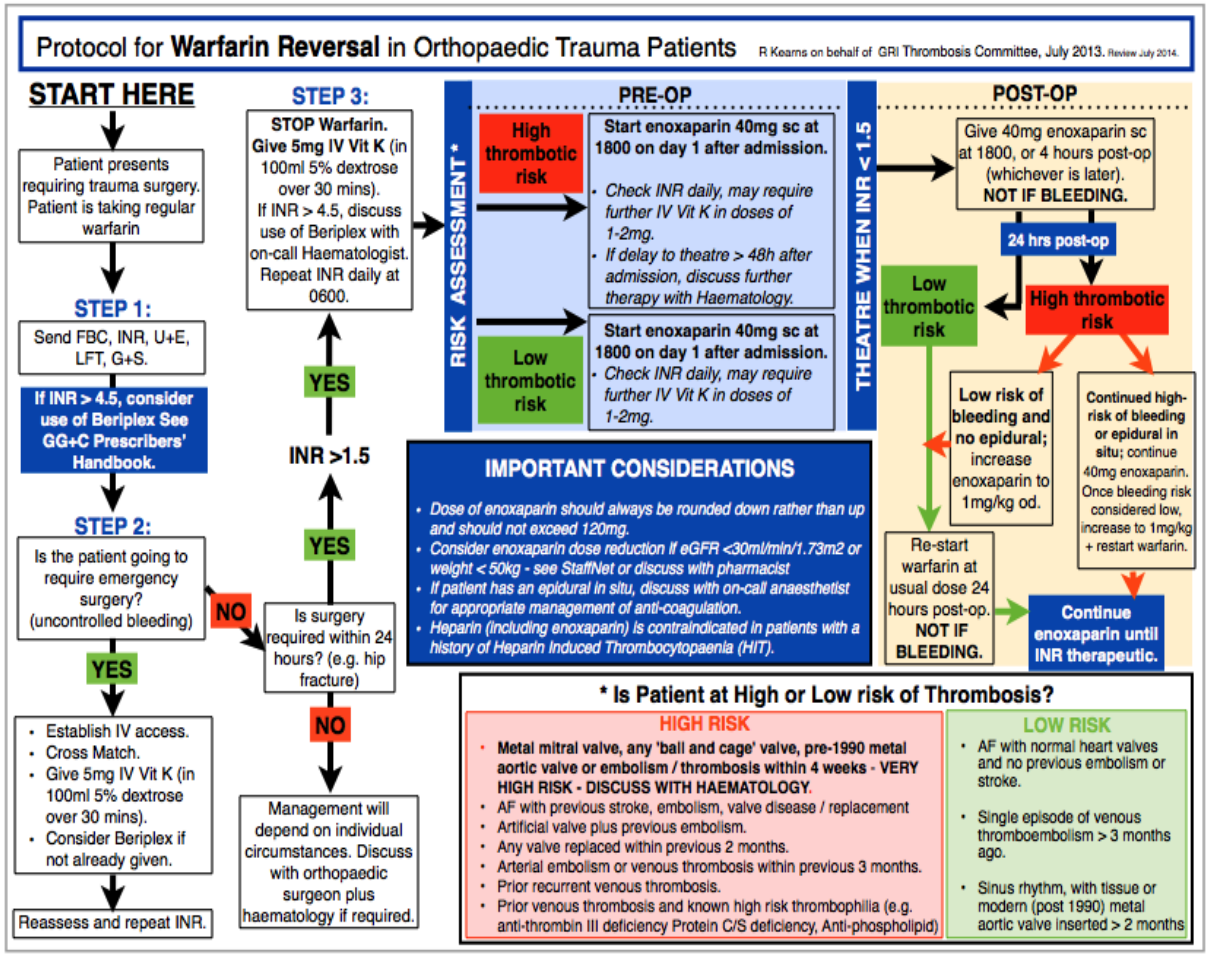


Figure 6.4-1 - Protocol for the management of warfarin in patients admitted with fractured neck of femur.

6.4.1 Re-audit results

There were 28 patients identified as taking warfarin over the 18 month period 1st October 2013 and 31st May 2015.

	Pre-protocol	Post-protocol	P value
Patients (N)	**13**	**28**	
Warfarin indication (N,%):			
AF	**7 (58.3%)**	**AF 20 (80%)**	
AVR	**1 (8.3%)**	**AF + MVR 1 (3.5%)**	
CVA + PE	**1 (8.3%)**	**AF + TIA 1 (3.5%)**	
AF + DVT	**1 (8.3%)**	**AF + CVA 1 (3.5%)**	
AF + CVA	**1 (8.3%)**	**MVR/CABG 1 (3.5%)**	
SVCO	**1 (8.3%)**	**CVA 2 (7%)**	
		DVT 1 (3.5%)	
		TIA 1 (3.5%)	
Admission INR (median, IQR)	**2.2 (1.7-2.8)**	**2.5 (2.2-3.5)**	**0.38**
Hrs post admission to INR<1.6 (mean, SD)	**31.3 (17.7)**	**29 (16)**	**0.43**
Intervention:			
Warfarin stopped	**2 (16.7%)**	**0**	
FFP	**1 (8.3%)**	**0**	
Vit K	**9 (75%)**	**28 (100%)**	**0.04**
Dose of Vit K (median, range)	**2 (0.5-13)**	**5 (0-10)** **(23/28 got 5mg as their initial dose, 1 also got Beriplex)**	**0.24**
Patients going to theatre within 48 hours (N, %)	**7 (58.3%)**	**20 (71.4%)**	**0.66**
Time to theatre / hrs	**45 (34-68.63)**	**40 (23.4-51.9)**	**0.44**

(median, IQR)			
INR on day of surgery **(median, IQR)**	**1.55 (1.17-1.6)**	**1.35 (1.2-1.5)**	**0.31**
Patients restarted on warfarin by 24 hrs (N, %)	**4 (33.3%)**	**9 (32.1%)**	**1**
Time to restart warfarin / hrs (median, IQR)	**66.5 (24-149.5)**	**28 (24-46)**	**0.32**
Time from starting warfarin to INR therapeutic (mean, SD) normal	**80 (42.4-109.2)**	**120 (65-163.3)**	**0.43**
Thromboprophylaxis administered pre-op (N, %)	**10 (83.3%)** **(3 IV heparin, 6 clexane 40mg, 1 clexane 20mg,**	**18 (64.2%)** **(10 clexane 40mg)**	**0.41**
Thromboprophylaxis administered post-op (N, %)	**7 (58.3%)** **(5 clexane 40mg, 1 clexane 130mg, 1 fondaparinux 2.5mg for 3 das then clexane 40mg)**	**27 (96.4%)** **(15 clexane 40mg, 2 clexane 20mg)**	**0.009**
Length of stay (median, IQR)	**20 (11.7-33.7)**	**20 (14.4-33.6)**	**0.38**

Table 6.4-1 - Comparison of data before and after introduction of warfarin protocol

From these data, the following points were noted:

- The protocol has standardised the method and dose of warfarin revrersal.
- The protocol has standardised the prescription of post-operative thromboprophylaxis.

- Reversal of INR was consistently achieved with a standardised dose of vitamin K.

- There was a trend toward more rapid reversal of INR and lower INR on day of surgery though this was not statistically significant.

- There was a trend towards increased number of patients going to theatre within 48 hours.

- There was a trend towards a reduction in the median time to restart warfarin.

- There was a trend towards an increased mean time to reach therapeutic INR. This did not reach statistical significance (p=0.43), though the numbers for comparison were small. We hypothesise that this may be due to the larger dose of vitamin K resulting in a period of relative warfarin resistance. However, this dod not affect length of stay and as such, was felt to be acceptable by the GRI Thrombosis Committee.

- There was a trend towards increased length of stay in the post-protocol group. Again this did not reach statistical significance (p=0.38). This may have been due to the increased time taken to achieve therapeutic INR though reasons for delay to discharge are often multi-factorial.

- There were no thromboembolic complications noted.

- The data were difficult to interpret in view of the low numbers of subjects.

- Ongoing data collection has seen an improvement in the availability of necessary data now that the electronic patient record is more established.

These data have been under ongoing review by the GRI Thrombosis Committee. It has been recommended that the protocol be introduced on a city-wide basis and work is currently ongoing to achieve this.

Chapter 6 Summary

- Data collection for patients taking warfarin and admitted with hip fracture was incomplete in that only 13/19 sets of case notes were available for review. This is unacceptable if accurate data are to be collected and quality is to be maintained. It is likely that this was affected by the transition between a paper-based and electronic patient record which occurred around the same time. This should be taken into consideration when interpreting the results presented prior to the introduction of the protocol.

- Ongoing data collection as part of a quality improvement initiative to assess the performance of the protocol has seen an improvement in the availability of necessary data now that the electronic patient record is more established. A local (or potentially national) database designed specifically to collect real-time information on patients undergoing hip fracture repair would be beneficial in ensuring accurate data collection, quality control and reliability of information.

- Management of patients in GRI suffering hip fracture and taking warfarin was variable and inconsistent.

- In light of our results and a lack of national and local guidance, a quality improvement venture into the peri-operative management of warfarin was commenced.

- A new hospital protocol has been produced. This has undergone consultation by a multi-disciplinary group and has been approved by the Glasgow Royal Infirmary Thrombosis Committee.

- The protocol has been implemented and is subject to ongoing audit with the ultimate aim of improving patient outcomes.

PART 2

Chapter 7

Elective total hip arthroplasty - evidence to date

7.1 Total Hip Athroplasty

7.1.1 Epidemiology and burden of disease

Total Hip Arthroplasty (THA) is a surgical procedure which is performed to relieve pain and improve function in patients with disorders such as degenerative or inflammatory arthritis. In Scotland, 7168 primary THA were performed during the period 2008 – 2009 (193), an increase from a mean of 6486 procedures per annum in the period 2005-2008. In England and Wales, 71,672 primary THA were performed in 2011 (37).

Whilst the number of procedures continues to increase, there has been a reduction in the median length of in-patient stay which has decreased from 10.3 days in 2001 to 6.2 days in 2009 in the Scottish population (193). In addition, same day admissions have increased from 2% in 2001 to 35% in 2009 (193). These improvements are in part due to fast-track admission pathways and peri-operative care packages including early mobilisation and physiotherapy (193). Despite improvements in patient throughput, the performance of primary THA remains a major expenditure within the NHS. The insertion of an artificial hip joint is an expensive treatment with components alone costing between £400 and £2000. Data collated by NHS Scotland's Information Services Division calculates the total cost of THA to lie in the region of £8000 and £14,000 depending on the complexity of the surgery and presence of post-operative complications (194). The performance of THA remains a high volume intervention associated with significant financial outlay.

The median age of a Scottish patient undergoing hip replacement is 68 years and this is considered likely to rise as the population ages (193;195). This elderly patient group commonly suffers co-morbidities such as ischaemic heart disease, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus and peripheral vascular disease. Such co-morbidities are associated with increased peri-operative risk and post-operative complications

resulting in a necessity for careful, well planned anaesthesia and peri-operative care (196-198).

Surprisingly, UK-wide data collected by the UK National Joint Registry shows that the mean age of a patient undergoing THA has actually remained fairly constant at around 67 years since 2003. Similarly stable are the numbers of patients in the over 80 category (14%) and under 50 category (6%) (37). Over the past 8 years, patient body mass index (BMI) has increased from 27.4 to 28.5 and there has been an increase in the number of patients with a BMI of between 30 and 39. In addition, the number of patients deemed to be "fit and healthy" according to the American Society of Anaesthesiologists' (ASA) criteria has decreased. According to the ASA grading system, only 15% of patients undergoing a primary hip replacement in 2011 were considered to be Grade 1 or "fit and healthy" pre-operatively, compared with 37% in 2003. The proportion of fit patients undergoing THA is notably higher in independent, when compared with NHS, hospitals (12% graded as ASA 1 in NHS hospitals compared with 23% in independent hospital). As the percentage of patients within each age bracket has not changed significantly since 2003, this suggests that the reduction in fitness and increase in BMI is not solely attributable to an ageing patient cohort (37).

Retrospective data for over 2 million patients collected via the USA National Hospital Discharge Survey (NHDS) from 1990 to 2004 reports that the highest proportional increase in THA procedures was seen in the 45 – 64 year age group (199). These patients were found to have increasing levels of morbidity including obesity, hypertension and ischaemic heart disease (199). In comparison with Scottish data, the mean length of stay in the US population undergoing THA fell to a mean of 4.5 days in the most recent time period (199). However, the number of patients discharged home was found to be in decline with increasing numbers of patients being discharged to "skilled care", a more economical way of providing ongoing care outwith the acute hospital setting. Data from both the UK and US demonstrate increasing rates of THA performance, alongside increasing levels of co-morbidity and obesity. While US data highlights the increased performance of THA in a younger population, this change is not yet apparent in the UK population.

7.1.2 Surgical procedure

The performance of THA essentially involves replacing both parts of the hip joint (acetabulum and femoral head) with prosthetic implants (cup, head and stem) in order to allow a full range of motion in multiple planes. The “head” replaces the femoral head while the “cup” replaces the bony hip socket. More than sixty different hip prostheses, produced by 19 companies are currently available for THA (200). Prostheses may be cemented, cementless, or “hybrid” (uncemented socket, cemented stem). Of the 71,672 primary THA performed in England and Wales in 2011, 38% were cemented THA, 41% were cementless and 19% were hybrid with the remainder classified as resurfacing procedures. This reveals a trend towards an increasing use of cementless prostheses as well as a reduction in metal on metal devices following a Medical Device Alert from the Medicines and Healthcare products Regulatory Agency (MHRA) (200;201). This alert highlighted that metal on metal devices over 36mm in size were associated with increased wear and consequent need for revision surgery when compared with other devices. There were further concerns that such “wear” could also result in traces of metal being found in the systemic circulation. The MHRA now recommend that patients with these implants are reviewed yearly on a lifelong basis (201).

A number of techniques for total hip arthroplasty have been described with the current most prevalent techniques being the posterior and lateral approaches. In a Cochrane review update published in 2006, investigators compared lateral and posterior approaches for primary THA. The review concluded there was insufficient quantity and quality of evidence to recommend one approach over another and no firm conclusions were able to be drawn (202).

7.1.3 Outcomes in total hip arthroplasty

While the success of operations such as THA were traditionally judged using measures such as morbidity, mortality and post-operative complication rates, the focus has now shifted toward an evaluation of patient-centred outcomes. The assessment of health-related quality of life using validated scoring systems can provide a useful insight into multiple domains of patient experience (203).

As well as the obvious physical changes of having this surgery, psychological and social effects upon the patient's daily life are also considered.

A 2004 systematic review of 74 papers published between 1980 and 2003 and performed by the WHO Collaborating Centre for Public Health Aspects of Osteoarticular Diseases examined quality of life indices after hip or knee replacement. The majority of the studies reported outcomes within 6 to 12 months (though follow up varied from 7 days to 7 years). All studies, using a variety of tools, showed improvements in physical parameters such as pain and mobility after joint replacement surgery. Age was not found to be an obstacle to effective surgery and patients seemed to derive more benefit when undergoing hip rather than knee arthroplasty (203). Psychological and social effects were more variable but were generally more favourable when compared with patients who had not undergone surgery. Patients with poorer pre-operative health related quality of life were also more likely to derive benefit (203).

A further Italian study published in 2011 examined 250 patients who were under 70 years of age and had undergone primary THA over an 11 year period (1985 to 1996). The study aimed to establish functionality and quality of life after THA and identify possible related outcome predictors. This study followed up patients for a mean period of 16 years. This longer term follow up was felt to be important as many THA are now being performed in younger patients with corresponding longer life expectancies. The main finding was that of worsened indices of hip functionality and physical quality of life compared with age-matched healthy controls, and increased indices of functionality and quality of life compared with individuals who had similar pathologies but had not undergone operative intervention. Levels of surgical satisfaction were found to be high (204).

It has also been proposed that timely performance of THA may lengthen lifespan in comparison to patients in whom the procedure is delayed (205). In a study of 28,469 Medicare patients with OA and Rheumatoid arthritis (RA) undergoing THA in 1996, six year survival was improved in the operative group compared with matched controls. However, this benefit was not seen in the first three post-

operative months (in which mortality was higher in the operative group). Protective effects of THA were diminished at five years when the groups appeared to converge. The operative group were generally fitter with 30% less prevalence of co-morbid disease than the control group, but despite controlling for this and other relevant variables (age, sex, socioeconomic group), the protective effects of operative intervention were still present (205).

Similarly, a large study published in 2011 examined 44,558 Danish patients undergoing THA in the 11 year period 1995 – 2006 and compared their mortality rates with matched members of the general population (1:3 ratio, n=133,674) (206). A slightly increased mortality rate was detected in the first 30 days post-operatively (adjusted mortality rate ratio 1.4 [95% CI 1.2 to 1.7]) with a subsequent reduction to a lower risk at the 90 day time point (adjusted mortality rate ratio 0.8 [95% CI 0.7 to 0.9]). Patients undergoing THA had a higher incidence of death related to myocardial infarction and venous thromboembolism than control patients at 90 days, indicating that thromboprophylaxis plays an important role in the peri-operative period. There was a reduced mortality risk in the longer term (up to 12.7 years), though the authors recognised that his may partly be due to the selection bias inherent in the identification of appropriate patients for surgery. Younger patients and patients without co-morbidity had an increase in short-term mortality, although the absolute risk among these patients was small compared with older, less fit patients. This indicates that although THA is a relatively low risk procedure which is associated with short and long term mortality benefits in most, the risks may appear comparatively heightened in individuals who are otherwise “low risk” in terms of their age and co-morbidity status (206).

7.1.4 Cost effectiveness of total hip arthroplasty

While generally considered to be one of the most successful operations performed within the NHS, there is little information about the cost-effectiveness of THA. This was addressed in a recent report from the Exeter Primary Outcomes Study (EPOS). This longitudinal study examined 1589 patients who underwent THA with an Exeter implant during the period 1999 – 2002. Patients were followed up for a ten year period with the reported cost-

effectiveness analysis occurring at the five year time point. Patients were compared with “no surgery” controls in terms of costs of care and quality of life (9).

The SF-36 tool was used to evaluate patient outcomes in this study. SF-36 is a multipurpose health survey of 36 questions that yields an eight-scale profile of functional health and well-being, as well as measures of physical and mental health. Patient outcome scores (SF-36) were collected annually and the difference between pre-operative scores and those collected at five years, was calculated. The gain in Quality Adjusted Life Years (QALY) was estimated using the patients’ own individual SF-36 score as an estimate of what their quality of life (QoL) would have been without surgery. Clearly this has some limitations in that a person’s QoL may have improved, or indeed decreased, for any of a wide number of reasons whether surgery had been performed or not. Analysis was performed for only 938 patients due to incomplete datasets. This study found that each patient gained a mean of 0.8 QALYs over 5 years after undergoing THA, while the mean cost of hospital stay was around £5000. Cost per QALY was found to be around £7000 with older patients incurring higher costs. This was still deemed to be cost-effective when compared with NICE thresholds which currently sit at around £20,000 - £30,000 per QALY gained, though this is currently undergoing further analysis and consideration (207;208).

THA is a commonly performed procedure which can result in improved quality of life as well as other long term outcomes. The optimisation of care provided during THA is therefore of interest to both patients and health care professionals. The role of the anaesthetist is to provide optimal anaesthesia during surgery and analgesia in the post-operative period whilst minimising adverse effects. We wished to investigate methods of providing pain control in patients undergoing THA by comparing a method in common use (spinal morphine) with a technique which has not been fully investigated in this setting (ultrasound guided fascia iliaca block.

7.2 Chapter 7 Summary

- Total hip arthroplasty is increasing in frequency.
- Length of stay associated with total hip arthroplasty is decreasing.
- The number of patients with high BMI and other co-morbidities is increasing, leading to increasing challenges in the peri-operative period.
- Total hip replacement may result in improved quality of life and long-term outcomes.
- Total hip arthroplasty is considered to be a cost-effective intervention.
- The role of the anaesthetist is to provide optimal anaesthesia and post-operative analgesia whilst minimising sde-effects.

Chapter 8

Anaesthesia for Total Hip Arthroplasty

Anaesthesia for THA is commonly performed using general anaesthesia (GA), regional anaesthesia (RA) or a combination of the two. The aim is to provide adequate anaesthesia and optimal analgesia whilst minimising side effects, thus facilitating rapid mobilisation and recovery.

8.1 Subarachnoid block

Subarachnoid blockade (SAB) is a form of RA which can be used to provide both anaesthesia and post-operative analgesia in patients undergoing THA. This involves the injection of local anaesthetic into the cerebrospinal fluid via a specially designed needle under strict aseptic conditions. Opioid drugs are frequently added to the spinal or "intrathecal" injection of local anaesthetic (LA) in order to prolong post-operative pain relief.

8.1.1 Spinal opioids

Spinal opioids have been used since 1979 to provide pain control after surgery. In a 17 nation European survey, morphine was the most commonly used spinal opioid in all countries except the UK (209). Due to its widespread international use, spinal morphine has been extensively investigated. Spinal morphine with post-operative PCA morphine is a commonly used regime for many surgical procedures.

Morphine is more hydrophobic than other opioids and hence has a greater degree of rostral spread and a longer duration of action (171). This is beneficial in terms of producing long-lasting, effective analgesia but has the associated disadvantage of an increased potential for adverse events including respiratory depression. Other side-effects of spinal morphine include: nausea, vomiting, pruritus, urinary retention and sedation. These may be uncomfortable for the patient and delay mobilisation, recovery and eventual discharge (210;211).

There are three recent meta-analyses examining the use of spinal morphine:

A meta-analysis published by Meylan *et al* in 2009 examined 27 studies (1205 patients) published from 1985 - 2007 in which patients received a general anaesthetic accompanied by spinal morphine at doses ranging from 100 - 4000μg (without local anaesthetic) (212). The primary aim was to quantify the analgesic effect with secondary objectives stated as quantification of the harmful effects of spinal morphine and an evaluation of dose-responsiveness. Group sizes ranged from 10 to 47 patients and the mean quality score of the studies was 3/7 using a modified Oxford Score (a seven-point scale evaluating randomisation, concealment, blinding and drop-outs) (213). Surgical procedures were cardiac (13 studies), abdominal (five studies), hysterectomy (four studies), spine (three studies), thoracic (one study) or cardiac and thoracic (one study).

When all trials were combined, there was a significant reduction in post-operative 24 hours morphine consumption (weighted mean difference [WMD] -16.9mg, 95% CI -23.7 to -10.1; eleven RCTs). Intrathecal morphine significantly reduced pain intensity at rest at four hours after surgery (WMD -1.9cm, 95% CI -2.9 to -0.8; five RCTs), at 12 hours after surgery (WMD -0.8cm, 95% CI -1.4 to -0.1; seven RCTs) and at 24 hours post surgery (WMD -1.0cm, 95% CI -1.7 to -0.4; eight RCTs). There were also significant reductions in pain intensity on movement at 12 hours after surgery (WMD -2.0cm, 95% CI -3.1 to -1.0; four RCTs) and at 24 hours after surgery (WMD -1.7cm, 95% CI -2.7 to -0.8; four RCTs). Spinal morphine was associated with a significant reduction in the duration of hospital stay (WMD -0.49 day, 95% CI -0.89 to -0.09; eight RCTs). There was a statistically significant reduction in the incidence of post-operative respiratory complications such as pneumonia. Six cases of respiratory depression (using a variety of definitions) were reported in three trials, occurring only in patients who had received spinal morphine at doses of between 300μg and 4000 μg. The authors concluded that the risk of respiratory depression was significantly increased in patients receiving spinal morphine (OR 7.86, 95% CI 1.54–40.3). When all studies analysing respiratory depression as an outcome were combined, the number needed to harm (NNH) was calculated to be 84. The incidence of pruritus and urinary retention was increased in patients receiving spinal morphine, though sedation and nausea and vomiting occurred only with the same frequency as that seen in controls (212).

Surprisingly, there was no demonstrable statistically significant relationship between adverse effects and dose leading Meylan and colleagues to state:

> *"The published literature does not allow the establishment of a dose–response relationship with confidence, and hence the minimal effective dose of intrathecal morphine when used alone in patients undergoing major surgery remains unknown."*

Meylan *et al* suggested that lower doses of spinal morphine should be further investigated. They also stated that due to uncertainty surrounding the optimal dose, risks of respiratory depression and requirements for post-operative monitoring that there were:

> *"..important logistic and financial issues. These are likely to challenge the use of intrathecal morphine in settings where limited resources do not allow for appropriate postoperative surveillance."*

They further concluded that:

> *"In view of all these caveats, the most radical, and perhaps most appropriate, conclusion would be that this analgesic intervention that reduces postoperative morphine consumption but not morphine-related adverse effects, that only slightly improves postoperative pain intensity, that significantly increases the risk of pruritus, and that is associated with a finite risk of respiratory depression should be abandoned."*

It is of note that this meta-analysis concentrated only on patients who received lone spinal opiate (without local anaesthetic), and who also received a general anaesthetic. Studies of patients undergoing total hip arthroplasty were not included for review in this meta-analysis.

A further meta-analysis of 28 RCTs (1314 patients) was also published in 2009 (214). This meta-analysis exhibited no overlap with the previously described work by Meylan *et al* due to the different inclusion criteria (Meylan *et al* included only trials examining the use of spinal opioids without local anaesthetic) (212). Gehling *et al* investigated the use of spinal morphine in doses ranging from 25 - 2500μg co-administered with local anaesthetic in patients undergoing spinal anaesthesia without general anaesthesia in order to

assess the frequency of side-effects (214). A wide variety of surgeries, including orthopaedic procedures, were included (22 studies). Methodological quality was assessed using the recommendations of McQuay and Moore, a method scored on a 1 to 5 scale derived using appraisals of randomisation, blinding and withdrawals. A score of 5 points indicated a high quality trial. In the assessment of methodological quality, 25 trials (89%) recorded a score of 3 or higher with six trials recording the maximum score of 5 points.

Compared with placebo, patients receiving spinal morphine had a higher incidence of nausea (RR 1.3, 95% CI 1.1-1.5; 24 RCTs), vomiting (RR = 1.6, 95% CI 1.1–2.2; 19 RCTs) and pruritus (RR = 2.0, 95% CI 1.6–1.2.4; 25 RCTs), though they found no difference in rates of urinary retention. Spinal morphine at doses of <300μg did not have a significant impact on the risk of respiratory depression (risk difference $RD_{< 300\mu g}$ = -0.005, 95% CI -0.034 to 0.023). Therefore, in patients receiving a dose of spinal morphine of less than 300μg, the incidence of respiratory depression was not increased when compared with placebo. Higher doses of spinal morphine (>300μg) were associated with a trend towards an increased incidence of respiratory depression, though this was not statistically significant. This meta-analysis was limited to an examination of side-effects and did not evaluate analgesic efficacy (214).

A more recent meta-analysis published in 2012 by Popping *et al*, evaluated the effects of spinal opioid at doses of 50 - 2000μg (administered in combination with local anaesthetic) in patients undergoing surgery, again without general anaesthesia (215). A total of 65 randomised controlled trials (3338 patients) examining both analgesic efficacy and adverse effects of spinal opioids were included. The studies were published over the period 1983 to 2010. Twelve of these were also included in the Gehling meta-analysis (214), though none overlapped with the studies included in the meta-analysis by Meylan (212). Almost half of these studies involved patients undergoing orthopaedic procedures and the median quality score was 3/7 using the Modified Oxford Scale. Again, unpublished work was excluded leaving room for publication bias though no language restrictions were imposed.

The authors concluded that spinal morphine in doses of 50 - 1000μg, significantly reduced 24 hour post-operative morphine consumption (WMD -12 mg, 95% CI -18

to -5; 7 RCTs). Duration of analgesia was also increased though there was no evidence of a dose-response relationship. Respiratory depression was more common in patients receiving spinal morphine with a calculated Number Needed to Harm (NNH) of between 38 and 59 depending on which definition of respiratory depression was used. Spinal morphine increased the risk of: nausea (NNH 9.9), vomiting (NNH 10), urinary retention (NNH 6.5) and pruritus (NNH 4.4), although again, there was no dose-response relationship elicited. While a dose-response effect was not detected during the meta-analysis process, the authors commented that this may be due to other confounders which were not accounted for. When trials evaluating dose-responsiveness as an outcome were evaluated independently, a relationship between dose and response was identified in some of the reported outcomes. However, these studies were generally small, containing a total of only 338 patients (216-219).

In one such dose-finding study by Rathmell *et al*, the use of spinal morphine for hip and knee surgery was examined. There was no increased incidence of respiratory depression or hypoxaemia in patients receiving up to 0.3mg of spinal morphine. This included elderly patients who had also received "significant doses of PCA morphine (219)." A further prospective, randomised controlled trial performed in elderly patients (>65 years) undergoing THA, compared doses of 0 - 200μg of spinal morphine. The authors concluded that 100 μg was the optimal dose as it provided effective analgesia while minimising side effects (218).

Unfortunately, studies investigating the use of spinal opioids are generally inadequately powered to detect the incidence of respiratory depression. As respiratory depression is rare, an accurate estimate of its incidence of would necessitate the design of a trial containing very large numbers of patients and would be difficult and impractical to undertake. Despite this, it would seem reasonable to consider that a lower dose of spinal morphine may increase the chance of avoiding respiratory depression (214;218-222). Equally, it would also seem reasonable to state that there is no effective dose of spinal morphine that can completely and with absolute certainty, preclude the occurrence of respiratory depression. Further research on the minimal effective dose of spinal morphine is merited in order to try and clarify this issue further. In view of the rare yet significant risk of respiratory depression, patients receiving spinal

opioids usually receive intensive monitoring and supplemental oxygen in the post-operative period. This has implications relating to adequate staffing levels, education and training and associated costs.

8.2 Peripheral Nerve Blockade

Peripheral nerve blockade is another form of regional anaesthesia technique which is growing in popularity for the provision of post-operative pain relief. This technique has the advantage of providing targeted analgesia to the operative limb as well as avoiding the sympathetic block, associated hypotension and documented side-effects of spinal anaesthesia (223). In THA, peripheral nerve blockade improves pain scores and reduces morphine consumption (224). This may have advantages in the post-operative period.

The femoral, obturator and sciatic (via the nerve to quadratus femoris) nerves are generally thought of as providing the majority of innervation to the hip joint. The lateral cutaneous nerve of thigh provides cutaneous innervation of the skin overlying the incision site on the lateral thigh. There is also variable innervation received from the sacral plexus as well as cutaneous innervations from the ilioinguinal, iliohypogastric and genitofemoral nerves. In order to provide complete analgesia after hip surgery one must, in theory, block all of these nerves. However, there is no consensus that one nerve block in particular is largely superior to others for analgesia after hip arthroplasty (225).

A review of the pertinent anatomy and nerve localisation techniques is included for each of the relevant nerve blocks. A systematic literature review of studies examining each of these nerve blocks is performed in turn.

8.3 Femoral Nerve Block and “3 in 1 block”

The femoral triangle is an area occupying the upper, medial part of the anterior thigh. The femoral triangle is bordered by the inguinal ligament proximally, the sartorius muscle laterally and the lateral edge of the adductor longus muscle

medially. The fascia lata forms the roof of the triangle with the floor comprised of the iliopsoas and pectineus muscles. The femoral triangle houses the femoral vein, femoral artery and femoral nerve alongside the deep inguinal lymph nodes (83).

The femoral nerve is the largest branch of the lumbar plexus and is comprised of the nerve roots L2, L3 and L4. It enters the thigh beneath the inguinal ligament and lies on the iliopsoas muscle, lateral and deep to the femoral sheath which contains the femoral vessels. At the femoral crease, the nerve is covered by the fascia iliaca and separated from the femoral artery by part of the psoas muscle. It then divides into superficial and deep branches early in its course through the femoral triangle. Superficial branches include the intermediate and medial cutaneous nerves of the thigh as well as nerves to the sartorius and pectineus muscles. Deep branches of the femoral nerve include those supplying the rectus femoris and the vasti muscle groups as well as the saphenous nerve (83). The performance of a femoral nerve block therefore results in anaesthesia of the anterior thigh and most of the femur and knee joint. The block also supplies anaesthesia to the skin on the medial aspect of the leg below the knee joint as a result of the distribution of the saphenous nerve.

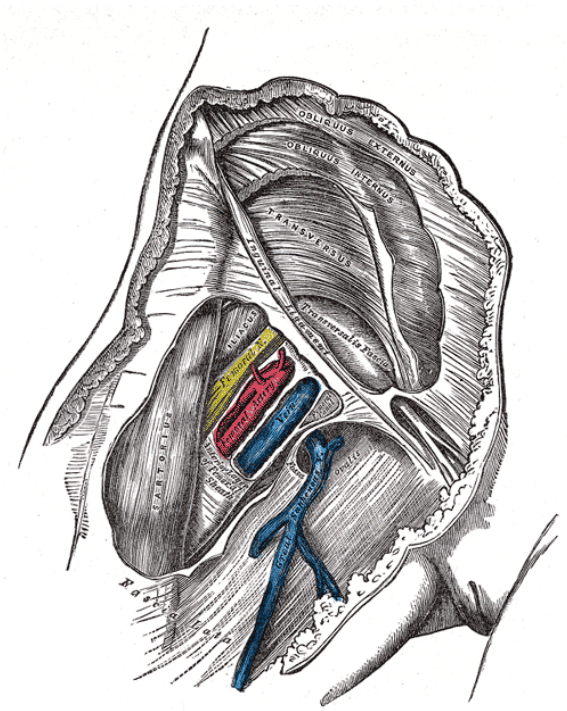


Figure 8.3-1 - Anatomy of the femoral triangle.

Reproduced from Gray's Anatomy, 20th Edition ((84).

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8.3.1 Femoral Nerve Block – Technique using peripheral nerve stimulation

The femoral nerve can be blocked in the following way: the patient is positioned supine with their legs extended and intravenous access is obtained. Aseptic precautions are employed and the patient is attached to routine monitoring in accordance with standards set by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) (226). The skin is prepared with antiseptic solution and the skin anaesthetised with 1-2ml of a short-acting local anaesthetic such as lignocaine 1%. The femoral crease is identified at a point 1-2 cm distal to the inguinal ligament and the femoral pulse palpated. A stimulating needle connected to a peripheral nerve stimulator (PNS) is inserted slightly laterally to the pulse and advanced in a sagittal and cephalad plane. The PNS is initially set to 1mA at a 2 Hz frequency until quadriceps contraction in elicited. The stimulation current is subsequently reduced until the quadriceps contraction ceases. Values > 0.3mA are generally accepted as being adequate (though it is now recognised that values over 0.2mA do not always exclude intraneural injection) (227). Local anaesthetic is subsequently injected with frequent aspirations to detect intravascular needle placement (228).

8.3.2 Femoral Nerve Block – Ultrasound Guided technique

The use of ultrasound to locate peripheral nerves has grown in popularity over recent years and is now a well established and accepted method of nerve localisation. The advantages of this technique include: real time visualisation of the nerve, needle and local anaesthetic injection (229;230). Ultrasound also allows the operator to detect abnormal anatomy, potentially further increasing the success and safety of this technique (231;232). Compared to nerve stimulation or landmark techniques of nerve localisation, ultrasound has been shown to increase success rates, reduce block onset time, increase block duration, reduce volumes of local anaesthetic and increase patient satisfaction (233-238).

Femoral nerve block may be performed using ultrasound guidance (USG) in place of peripheral nerve stimulation. The patient is prepared in the same way as

described for the landmark technique and an 8-14 Hertz (Hz) ultrasound probe is placed in the femoral crease. The nerve fibres are seen lying inferiorly to the fascia iliaca and lateral to the femoral artery. They are commonly visualised as forming a “pennant” shape with the base of the pennant abutting the femoral artery medially, and the tip extending laterally.

The femoral nerve is not a single nerve at this point, and is comprised of multiple nerve fibres. The femoral bundle may be approached using both in-plane and out of plane techniques. Using the in-plane approach, the needle is inserted in a direction along the long-axis of the ultrasound probe and is visualised longitudinally as it approaches the nerve. In the out of plane technique, the needle is inserted perpendicularly to the long axis of the ultrasound probe and is visualised only as a “dot” or by the detection of tissue disturbance. Local anaesthetic is injected in the same way as described previously (239).

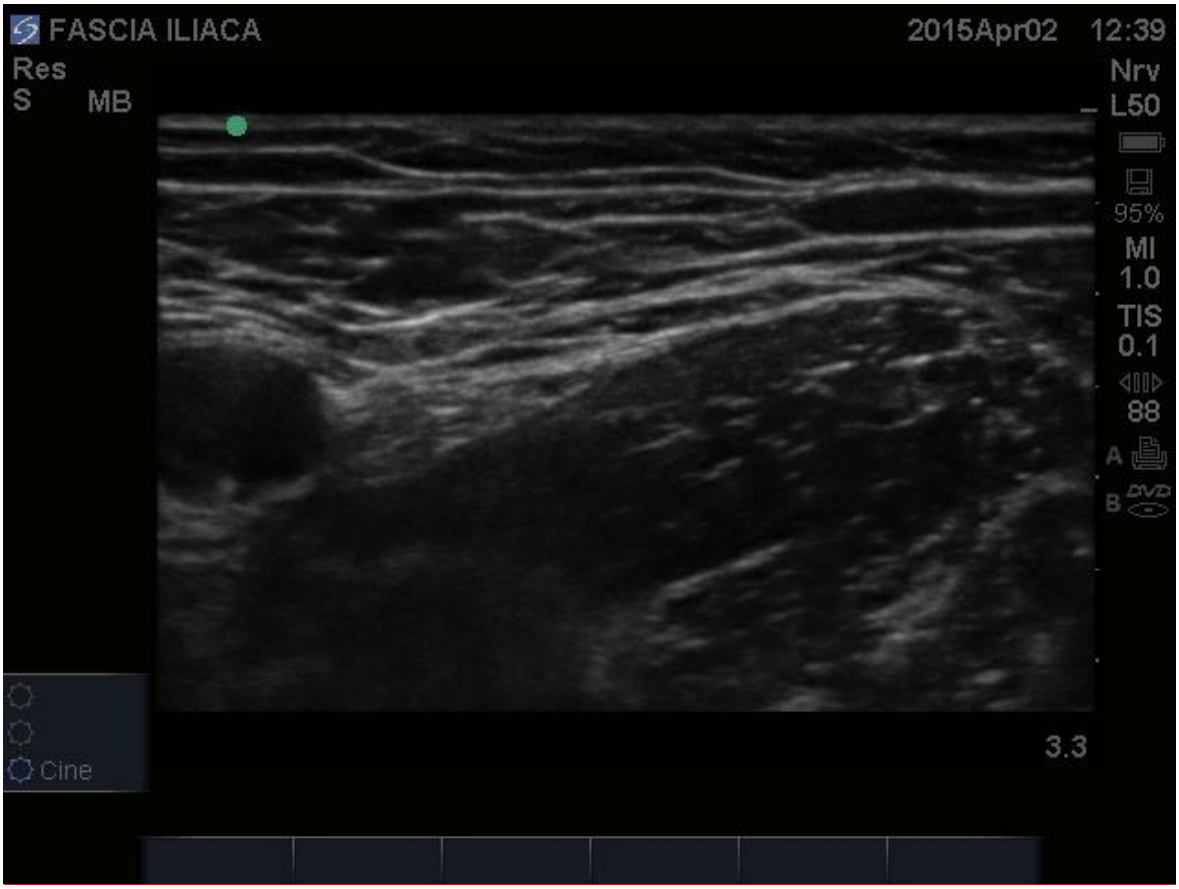

Figure 8.3-2 - Sonographic image of femoral nerve, femoral artery and fascia iliaca

Continuous FNB using a perineural catheter is a development of the traditional single-shot FNB. This can be achieved by locating the femoral nerve using either PNS or USG, and advancing a specially designed catheter to lie adjacent to the nerve. This is usually preferred to lie along the long axis of the nerve. A local anaesthetic infusion can then be infused during the post-operative period.

8.3.3 "3 in 1" Block

The "3 in 1" block is a modification of the femoral nerve block and was first described by Winnie in 1973 (240). In this technique, a larger volume of injectate is used and pressure is applied distal to the needle insertion point in order to encourage proximal spread via the fascial conduit containing the femoral, obturator and lateral cutaneous nerve of thigh (all of which arise from the lumbar plexus). Although previously claimed to force solution cranially to the lumbar plexus, this technique can be inconsistent in providing anaesthesia of the three nerves arising from the lumbar plexus (86;241).

8.4 Femoral and "3 in 1 nerve blocks" – literature review

A systematic literature review of femoral and "3 in 1" nerve blocks was performed by a single author (RK). Studies were identified using the following methodology; MEDLINE, EMBASE and the Cochrane Register of Controlled Clinical Trials were searched using the search strategy displayed in Figure 8.4-1. Inclusion criteria were: randomised controlled trials (RCTs) published between 1990-2013, performed in human adults, undergoing total hip arthroplasty and published in the English language. At least one of the following outcomes required to be recorded for a study to be included: pain scores, analgesia consumption, or adverse effects. Studies were excluded if they examined patients undergoing hip and knee arthroplasty as one group with no separation of results. References of retrieved articles were for searched for other articles of relevance not identified in the original search.

The potential performance of a Cochrane Review was discussed with a senior academic clinician within the University of Glasgow. It was felt that this would

not be appropriate to undertake as part of a higher degree in view of the requirement to commit to ongoing review and updating of results.

1. exp Arthroplasty, Replacement, Hip/

2. exp Nerve Block/

3. exp Femoral nerve/

4. 2 AND 3

5. (continuous adj femoral).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

6. (three adj one).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

7. 4 OR 5 OR 6

7. 1 AND 7

Figure 8.4-1 – Search strategy

8.4.1 Quality Scoring

Quality scoring was performed by a single reviewer (RK) using the Jadad scoring system (242). This is a 3 question, 5 point system with superior validity and reliability evidence compared with other scoring systems (243). The Jadad score assigns one point for each of the following basic questions:

- Was the study described as being randomised?
- Was the study described as being double blind?

- Was there a description of withdrawals and dropouts? (The article should describe the number of withdrawals and dropouts, in each of the study groups, and any reasons given).

Additional points are given if:

- The method of randomisation was described in the paper, and was appropriate.
- The method of blinding was described, and was appropriate.

Points are deducted if:

- The method of randomisation was described, but was inappropriate.
- The method of blinding was described, but was inappropriate.

The maximum score using this system is 5, with scores of 3 or more considered to represent studies with satisfactory methodological quality.

8.4.2 Results

58 citations were identified of which eight met inclusion criteria (Figure 8.4-2). Study characteristics and outcomes are displayed in Table 8.4-1. The methodological quality of the studies was generally poor with only one study achieving a Jadad score of 4 and none scoring the full 5 points. Studies were generally from Europe or the USA (One study from each of France, Switzerland, Turkey, Denmark, Belgium [2 studies], and USA [2 studies]). All studies had been approved by the relevant Institutional Review Boards or Local Research Ethics Committees. The trials reviewed included a total of 656 patients.

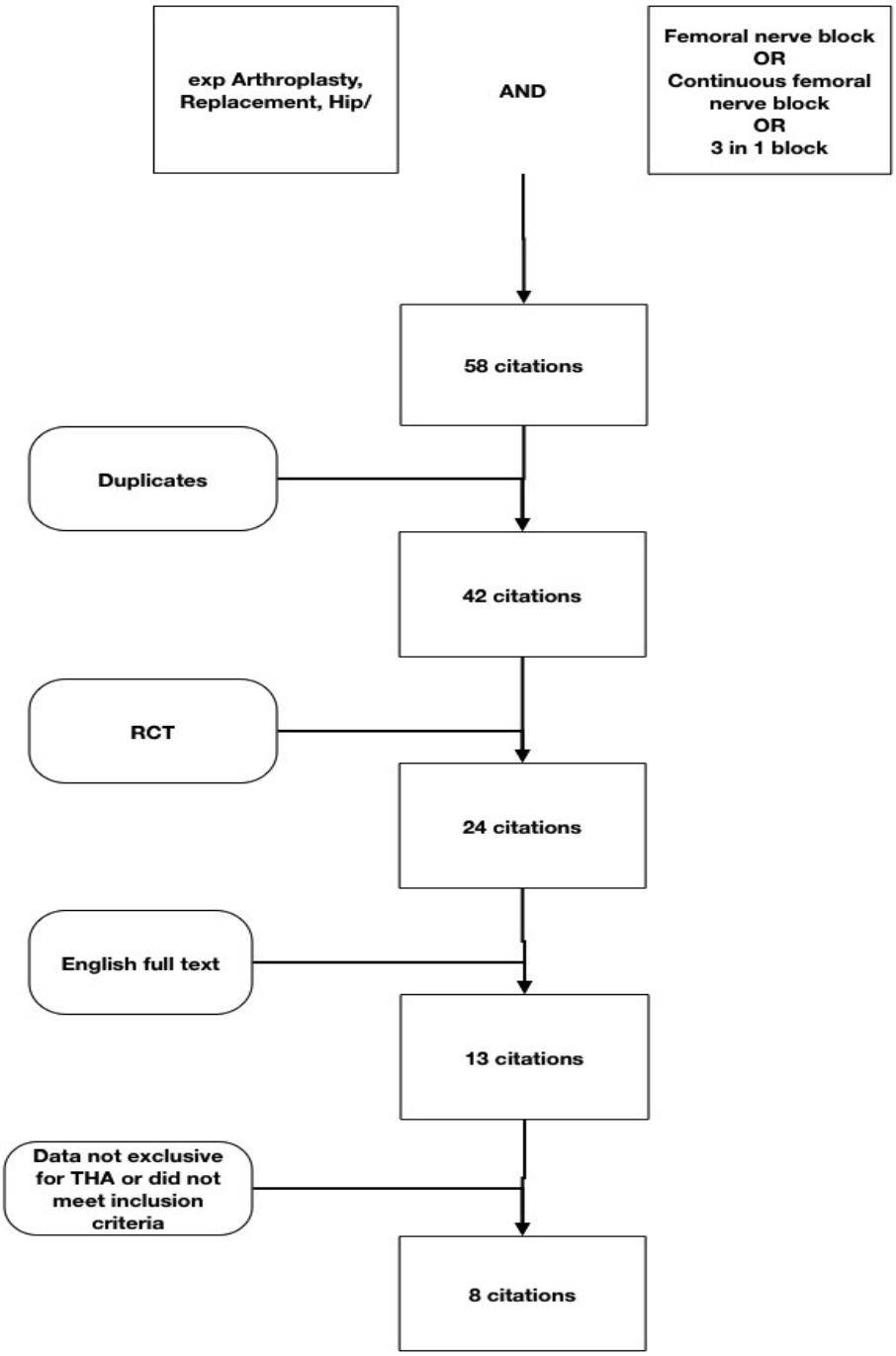

Figure 8.4-2 - Consort diagram of included studies

First author, year (ref)	Type of study	n	Anaesthesia	Analgesic techniques	Nerve localisation technique	Jadad score	Results / comments
Biboulet, 2004(244)	RCT	15 15 15	GA GA GA	FNB (2mg/kg bupivacaine +2µ/kg clonidine). LPB (2mg/kg bupivacaine +2µ/kg clonidine). PCA morphine.	PNS PNS N/A	11001 (3)	Blocks performed at the end of surgery. Pain scores and morphine consumption were lower in the first 4 post-operative hours only. No reduction in post-operative pain scores at rest or movement at 48 hours. Median (range) 24 hour morphine consumption was 15mg (0-32mg) in PCA group, 18mg (1-87mg) in FNB group and 8mg (0-21mg) in LPB group. No difference in level of mobility, post-operative nausea, sedation, or length of stay. LPB group noted to have more complete sensory block in proximal thigh and accompanying lower pain scores in first 4 hours. This was postulated to be due to the innervation provided by the more proximal ilioinguinal,

							iliohypogastric and genitofemoral nerves which would be covered by a more proximal approach to the lumbar plexus and missed by the more distal FNB. Epidural diffusion of LA occurred in 4 out of 15 cases in the LPB group. The authors concluded that neither FNB nor LPB should be used routinely for THA.
Fournier, 1998(245)	RCT	20 20	GA GA	Sham block. 3 in 1 block (40ml 0.5% L-Bupivacaine + 1 in 200,000 adrenaline).	N/A PNS	11001 (3)	Prolonged time to first analgesia in the “3 in 1” group. Mean (SD) 24 hour morphine consumption 8.6mg (±7.7) in sham block group and 7mg (±6.2) in block group. Patients in both groups also received significant amounts of IV fentanyl peri-operatively (mean 235µg). Pain scores and analgesic consumption not significantly different between groups.

Koruglu, 2008(246)	RCT	15 15	GA GA	Sham block. 3 in 1 block (40ml 0.25% L-Bupivacaine).	N/A PNS	11010, -1 (2)	Improved pain scores and reduced analgesic consumption in the “3 in 1” group. Tramadol used for post-operative analgesia – results not clear over what time period the reported amount was administered. Poor methodological quality.
Singelyn, 2005(247)	RCT	15 15 15	GA GA GA	CFNB (40ml 0.25% L-Bupivacaine + 1 in 200,000 adrenaline then 10ml/hr of 0.125% L-Bupivacaine). CEA (lumbar). PCA morphine.	PNS N/A N/A	10010 (2)	Both CFNB and CEA continued for 48 hours. No significant differences between analgesia, rehabilitation or length of hospital stay, though there was a trend towards improved analgesia in both regional anaesthetic groups. PCA group used mean 30mg (SD ± 9mg) IV morphine in 24 hours. Other groups received IV propacetamol and IM piritramide. Continuous FNB associated with fewest side effects prompting the authors to recommend this technique. It was not clear how this study was powered and the authors

							conceded that a larger study may have yielded statistically significant results.
Marino, 2009(248)	RCT	75 75 75	SAB SAB SAB	CFNB (0.6ml/kg ropivacaine then 0.2% ropivacaine at 0.15ml/kg/hr for 48 hrs). CLPB (local anaesthetic regime as for CFNB group). PCA hydromorphone.	PNS PNS + contrast	10110 (3)	Continuous FNB significantly inferior to continuous LPB when compared for: pain scores during physiotherapy (though not at rest), opioid related side effects, post-operative ambulatory distance and patient satisfaction. Continuous FNB only slightly superior to the group receiving PCA opioids alone though it was noted that both regional anaesthetic techniques were associated with a reduced level of post-operative delirium. Hydromorphone used for post-op analgesia – median (95% CI) 6mg (5-7mg) in CFNB group, 4.3mg (3.3-5.3mg) in CLPB group and 9.4mg (1.1-7.7mg) in PCA group. This equates to anywhere between 28mg - 60mg IV morphine in 24 hours.

Ilfeld, 2011(249)	RCT	25 22	GA GA	CFNB (20ml 1.5% mepivacaine +2.5µg/ml adrenaline bolus then 0.2% ropivacaine 6ml/hr infusion with 4ml bolus and 30 min lockout). Block inserted post-operatively. CLPB (local anaesthetic regime as for CFNB). Block inserted post-operatively.	USG USG	10110 (3)	CFNB provided non-inferior analgesia when compared with CLPB. However, CFNB resulted in greater quadriceps muscle weakness and adversely affected patients' ability to ambulate. This has implications in terms of the reduction in functional ability to perform post-operative physiotherapy and may predispose to falls.(250;251) Patients in this study received Oxycontin 10mg bd in addition to oral paracetamol and celecoxib during the study period. It is possible that this may have "blunted" any differences between the groups. In addition to this regular analgesia, patients in the CFNB group received median (10-90th percentile) IV hydromorphone of 2.8mg (1-7.4) and 2.2 (1.2-7.6) in the CLPB group. This equates to approximately 14.6-18.6mg IV morphine. This must be added to the regular oxycontin received which would equate

							to 30mg morphine daily if a conversion factor of 1.5 is used (252).
Singelyn, 2001 (253)	RCT	15 15 15	GA GA GA	CFNB (0.125% bupivacaine with clonidine 1 µg/mL and sufentanil 0.1 µg/ml) continuous infusion of 10ml/hr . CFNB (0.125% bupivacaine with clonidine 1 µ/mL and sufentanil 0.1 µg/ml) plus patient controlled bolus of 10ml, lockout time 60 mins. CFNB (0.125% bupivacaine with	PNS PNS PNS	11011 (4)	At 48 hours, pain relief on movement was significantly better in the 5ml patient controlled bolus group than in the continuous infusion group (p=0.01). Pain scores at rest and at other time points were not significantly different between the 3 groups. Bupivacaine consumption was significantly less in the patient controlled groups than in the continuous infusion group (p<0.001). Side effects were comparable in the three groups. Satisfaction scores were significantly higher in the 5ml patient controlled group than in the other groups (p<0.01). IV propacetamol and IM piritramide used for post op analgesia.

				clonidine 1 µg/mL and sufentanil 0.1 µg/ml) plus patient controlled bolus of 5ml, lockout time 30 mins.			
Uhrbrand B, 1992 (254)	RCT	89 90	GA GA	Nicomorphine 0.1mg prn "3 in 1" block + lateral cutaneous nerve of thigh block (20ml 0.5% bupivacaine and 20ml 2% lignocaine with epinephrine + 5ml 1% lignocaine for LCNT block)	N/A PNS	10100 (2)	Post-operative analgesic consumption was just statistically significantly superior in the "3 in 1" block group (p=0.049). Nicomorphine was used for analgesia. The difference was small and was not felt to be clinically significant. The addition of the lateral cutaneous nerve of thigh block may have had an effect on the results. This study was of poor methodological quality.

Table 8.4-1 - Study characteristics and outcomes – Femoral Nerve Block

CEA = continuous epidural analgesia, CFNB= continuous femoral nerve block, CLPB = continuous lumbar plexus block, FNB = femoral nerve block, , GA = general anaesthesia, IT morphine = intrathecal morphine, LA = local anaesthetic, LCNT = lateral cutaneous nerve of thigh block, LPB = lumbar plexus block, PACU = post-anaesthesia care unit, PCA = patient controlled analgesia, PNS = peripheral nerve stimulator, RCT = randomised controlled trial, SAB = subarachnoid block, THA = total hip arthroplasty.

8.4.3 Discussion – femoral nerve block and "3 in 1" block

Single shot femoral nerve block in isolation is not useful after hip arthroplasty. This may be because the approach is too distal to provide clinically useful anaesthesia of the relevant nerves (244). Continuous femoral nerve block catheters, whilst a promising concept, have not achieved superior analgesia when compared with: continuous epidural analgesia or PCA morphine (247) and continuous lumbar plexus block (248;249). Continuous femoral nerve block (CFNB) catheters may also result in a greater degree of quadriceps weakness and ability to ambulate (249). One study suggested a preferable analgesia profile at 48 hours and decreased use of local anaesthetic using a patient controlled CFNB bolus of 5 ml with 30 minutes lockout than with a basal infusion technique (253). However, other studies have been unable to find a clinically relevant difference between the use of different methods of local anaesthetic administration (255).

8.5 Lumbar (or Psoas) Plexus Block

The lumbar plexus is formed from the ventral rami of L1-L4 with contributions from T12 and L5. Peripheral nerves arising from the plexus are: iliohypogatric, ilioinguinal, lateral femoral cutaneous, femoral and obturator nerves. However, the exact location of the lumbar plexus remains controversial. Some authors believe that the plexus lies between the psoas and quadratus lumborum muscles (256). Further studies on the lumbar plexus place it within the psoas muscle (257;258). A posterior approach is commonly used to block the nerves of the lumbar plexus. The femoral, lateral cutaneous nerve of thigh and obturator nerves can be blocked successfully using this approach. This is therefore a useful technique for patients undergoing hip arthroplasty. As the plexus sits near or within the psoas muscle, it is considered a "deep plexus" block. Consequently, needle placement occurs in a non-compressible area of the body and hence, any bleeding caused during block performance may result in retroperitoneal haematoma. Other potential adverse events include: epidural, intrathecal injection, intravascular injection and renal trauma.

8.5.1 Lumbar plexus block – Technique using peripheral nerve stimulation

The lumbar plexus block is traditionally performed with the patient in the lateral position. A line is drawn across the superior aspect of the iliac crest and the point at which this line is found to intersect a line drawn superiorly from the posterior superior iliac spine, is the point of needle insertion. This is approximately 5cm lateral from the midline. The depth of needle insertion is aided by contact with the L4 transverse process, and whilst this varies between individuals, the distance from this point to successful stimulation of the lumbar plexus is relatively consistent at less than 2cm. On contacting the L4 transverse process, the needle should be walked off caudally and in a slightly medial direction (256). Successful needle placement is determined by quadriceps femoris twitch (i.e. stimulation of the femoral nerve).

More recently a refinement of the above approach, as originally described by Winnie, was suggested by Capdevilla *et al* using a slight modification of the traditional landmarks (257). Patients are again placed in the lateral position with the operative side uppermost. The needle is inserted at the junction of the lateral and medial two thirds of a line between the spinous process of L4 and a line parallel to the spinal column passing through the posterior superior iliac spine. This was determined from results obtained in the CT imaging study performed by Capdevilla *et al* where the lumbar plexus was found to lie at this distance consistently and independently of sex or BMI (257). The needle is then advanced perpendicular to the skin until contact with the transverse process of L4 is obtained. The needle is withdrawn 0.2 cm and advanced under the transverse process until quadriceps femoris muscle twitches are elicited. It was noted in the same imaging study that the depth at which the lumbar plexus was found is higher in males and with increasing BMI. The authors postulated that the perpendicular (rather than medial) direction of the injection reduces the risk of spinal or epidural injection, whilst injecting at a point more medially than in the original technique, reduces the chance of failure (257).

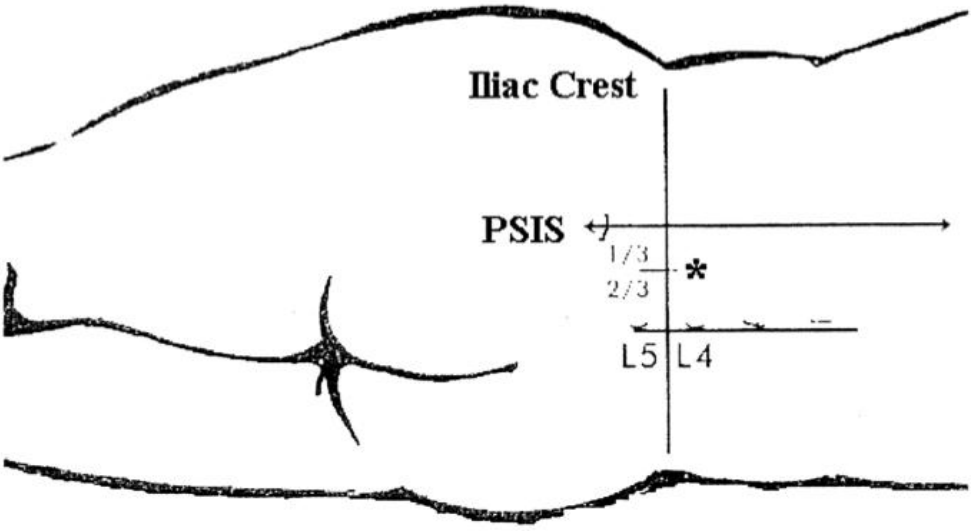

Figure 8.5-1 - Estimation of the point of puncture of continuous psoas compartment block by using the preliminary computed tomography studies. PSIS = posterior superior iliac spine. *Point of puncture (257).

In a prospective, randomised, controlled study of 60 patients the Winnie technique was compared with the newer Capdevila technique with the nerve blocks performed by a single, experienced operator (259). A second operator, who was blinded to the block technique, assessed sensory and motor function at time intervals up to 45 minutes after block insertion. No differences were found in block procedure time, pain scores, 24 hour morphine consumption or time to first morphine analgesia. Bilateral anaesthesia indicating epidural spread was found in 10 patients in the Capdevila group and 12 patients in the Winnie group ($p=0.8$), with block heights reaching T4 at their highest. Seven patients also suffered associated haemodynamic instability. This was a higher incidence than previously reported. The authors concluded that the newer technique proposed by Capdevila *et al* did not offer superior efficacy or safety and that bilateral anaesthesia may in fact be due to spread of local anaesthetic from the psoas muscle rather than direct epidural injection (259).

It is possible to use ultrasound guidance in the performance of the lumbar plexus block, though this is technically difficult due to the depth at which the nerves are found.

8.5.2 Lumbar (psoas) plexus block – literature review

Studies were identified using the following methodology; PUBMED, EMBASE and the Cochrane Register of Controlled Clinical Trials were searched using the search strategy as detailed in Figure 8.5-2. Inclusion criteria were: RCTs published between 1990-2013, performed in human adults, undergoing total hip arthroplasty and published in the English language. At least one of the following outcomes required to be recorded for a study to be included: pain score, analgesia consumption or adverse effects. Studies were excluded if they examined patients undergoing hip and knee arthroplasty as one group with no separation of results. References of retrieved articles were for searched for other articles of relevance not identified in the original search.

1. exp Arthroplasty, Replacement, Hip/

2. exp Nerve Block/

3. (lumbar adj plexus).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

4. (psoas adj compartment).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

5. 2 AND 3

6. 2 AND 4

7. (continuous adj lumbar).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

8. (continuous adj psoas).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

9. 5 OR 6 OR 7 OR 8

10. 1 AND 9

Figure 8.5-2 - Search strategy

8.5.3 Results

90 citations were identified, of which 14 met inclusion criteria (Figure 8.5.3) Study characteristics and outcomes are displayed in Table 8.5.1

The methodological quality of the studies was generally good with only two studies achieving a Jadad score under 3, and three scoring the full 5 points. Studies were from USA (6 studies), Brasil (2 studies), Italy (2 studies), France (2 studies), India (1 study) and Switzerland (1 study). All studies had been approved by the relevant Institutional Review Boards or Local Research Ethics Committees. The included trials reviewed a total of 831 patients.

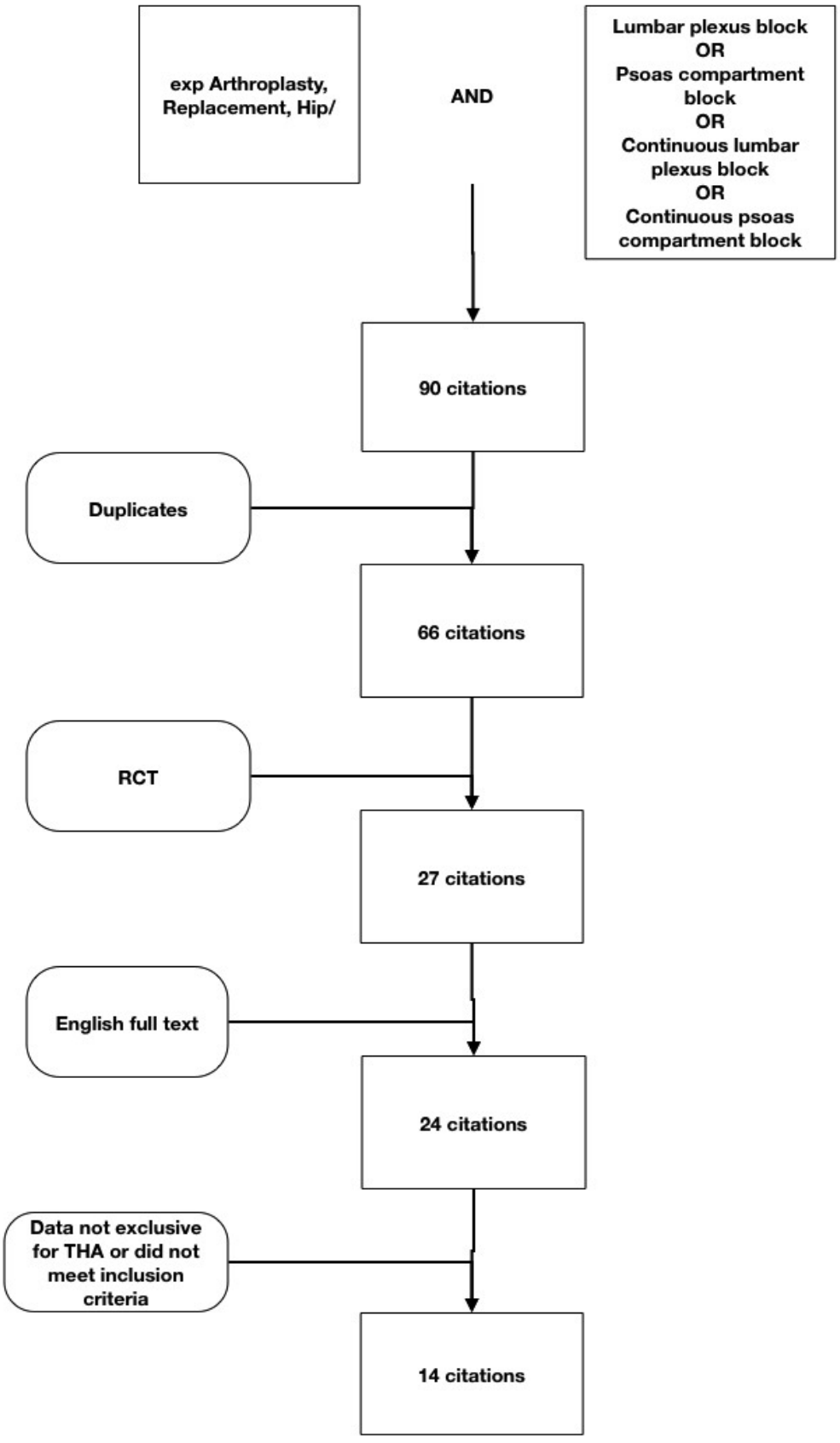

Figure 8.5-3 - Consort diagram of included studies

First author, year (ref)	Type of study	n	Anaesthesia	Analgesic techniques	Nerve localisation technique	Jadad score	Results / comments
Ilfeld 2011(249)	RCT	25 22	GA GA	CFNB (20ml 1.5% mepivacaine +2.5µg/ml adrenaline bolus then 0.2% ropivacaine 6ml/hr infusion with 4ml bolus and 30 min lockout) CLPB (local anaesthetic regime as for CFNB)	USG USG	10110 (3)	CFNB provided non-inferior analgesia when compared with CLPB. However, CFNB resulted in greater quadriceps muscle weakness and adversely affected patients' ability to ambulate. This has implications in terms of the reduction in functional ability to perform post-operative physiotherapy, and may predispose to falls (250;251). Patients in this study received Oxycontin 10mg bd during the study period. It is possible that this may have "blunted" any differences between the groups.
Ilfeld 2010(260)	RCT	26	GA	CLPB - 15ml of 2% mepivacaine with epinephrine (5 µg/ml) bolus then 0.1%	PNS	10110 (3)	This study found that varying the volume and concentration (though not the dose) of local anaesthetic had no effect on

		24	GA	ropivacaine infusion at 12ml/hr plus bolus of 4ml (4mg) ropivacaine, lockout 30 mins CLPB - 15ml of 2% mepivacaine with epinephrine (5 µg/ml) bolus, then 0.4% ropivacaine infusion at 3ml/hr plus bolus of 1ml (4mg) ropivacaine, lockout 30 mins N.B. oxycodone or IV morphine administered for breakthrough pain in both groups	PNS		quadriceps muscle strength at 1 day post-op (primary outcome). Secondary outcomes including abductor and hip flexor strength, and breakthrough opioid requirements were also equivalent. No patients sustained a fall during the study period. The authors concluded that dose rather than volume or concentration of local anaesthetic is the primary determinant of effect with peri-neural catheter infusions.
Duarte 2009(261)	RCT	20	GA	CEA – 10-15ml 0.5% ropivacaine bolus	N/A	10110 (3)	The authors concluded that intra-operative nociceptive blockade was more effective with epidural than lumbar plexus block. This was assessed by examination of

		21	GA	CLPB – 0.4ml/kg 0.5% ropivacaine bolus	PNS		haemodynamics during surgery rather than a clinical assessment of neural blockade or by pain scores / analgesia consumption. Although both groups of patients had catheters inserted for ongoing local anaesthetic infusion, the regimes used were not described, neither was the post-operative systemic analgesic regime. The authors found that both techniques were associated with similar technical difficulties, hemodynamic stability during the surgery and volume of blood loss. Post-operative analgesia and rehabilitation were not assessed.
Ilfeld 2009(262)	RCT	24	GA	CLPB - Ropivacaine, 0.2%, infusion (8 mL/h basal; 4 mL patient-controlled bolus; 30-min lockout) from surgery until post-operative day	PNS	11111 (5)	This study examined longer term outcomes (up to 12 months) after THA with a focus on health related quality of life as described by self-reported WOMAC scores (263). Whilst

				4.			not powered for this outcome (this was a subsequent report of a study designed to assess shorter term outcomes after CLPB for THA), the authors concluded that the extension of CLPB for 4 days post-operatively did not affect longer term health related quality of life.
		23	GA	CLPB - Ropivacaine, 0.2%, infusion (8 mL/h basal; 4 mL patient-controlled bolus; 30-min lockout) from surgery until 36 hours post-operatively. Perineural saline infusion until post-operative day 4.	PNS		
Marino, 2009(248)	RCT	75	SAB	CFNB (0.6ml/kg ropivacaine then 0.2% ropivacaine at 0.15ml/kg/hr for 48 hrs).	PNS	10110 (3)	Continuous FNB was significantly inferior to continuous LPB when compared for: pain scores during physiotherapy (though not at rest), opioid related side effects, post-operative ambulatory distance and patient satisfaction. Continuous FNB was only slightly superior to the group receiving PCA opioids alone though it was noted that both regional anaesthetic techniques were associated
		75	SAB	CLPB (local anaesthetic regime as for CFNB group).	PNS + contrast		

		75	SAB	PCA hydromorphone.	N/A		with a reduced level of post-operative delirium.
Duarte 2009(264)	RCT	20 19	GA GA	LPB with 0.4ml/kg Bupivacaine 0.5% with 1 in 200,000 adrenaline. LPB with 0.4ml/kg 0.5% Ropivacaine.	PNS PNS	11111 (5)	This study showed that ropivacaine may be associated with slightly lower pain scores than bupivacaine, though this was not clinically significant. Morphine consumption and adverse events were not different between groups. The study was not powered to assess the risks of LA toxicity.
Kumar 2009(265)	RCT	15	SAB	CLPB with 0.4 mL/kg (loading dose) of 0.25% bupivacaine, followed by continuous infusion of 0.25% bupivacaine at 0.15 mL/kg/hour for 24 hours.	PNS + contrast	11111 (5)	The addition of tramadol to 0.25% bupivacaine in CLPB after THA neither improves the quality nor the duration of post-operative analgesia. Time to first-dose rescue analgesic, total rescue analgesic requirements, nausea,

		15	SAB	CLPB with 1.5 mg/kg of tramadol added to 0.4 mL/kg loading dose of 0.25% bupivacaine, followed by continuous infusion of 0.15 mg/kg tramadol (50 mg/mL) added to 0.25% bupivacaine at 0.15 mL/kg/hour for 24 hours.	PNS + contrast		vomiting and patient satisfaction were not significantly different between groups.
Ilfeld 2008(266)	RCT	23	GA	CLPB – 15ml mepivacaine, 2%, with 5 µg/ml epinephrine, then 10 ml ropivacaine, 0.5%, with 25 µg epinephrine in those with successful block. 0.2% Ropivacaine infusion at 8 ml/hr plus patient controlled bolus dose of 4 ml, lockout 30 min til post-op day 4.	PNS	11011 (4)	The three primary outcomes related to readiness-for-discharge; (i) adequate analgesia (numeric rating pain score), (ii) independence from intravenous opioids in the previous 12 h, and (iii) ambulation of at least 30 m without a time limit. The distance walked in 6 minutes on the afternoon following surgery (6 minute walk test) was also a primary outcome. Patients given 4 days of perineural ropivacaine attained all three discharge criteria in a

		24	GA	CLPB – 15ml mepivacaine, 2%, with 5 µg/ml epinephrine, then 10 ml ropivacaine, 0.5%, with 25 µg epinephrine in those with successful block. 0.2% Ropivacaine infusion at 8 ml/hr plus patient controlled bolus dose of 4 ml lockout 30 min for 24 hours post-op. Normal saline infusion at 8 ml/hr plus patient controlled bolus dose of 4 ml, lockout 30 min til post-op day 4.	PNS		median of 29 hours, compared with 51 hours for those of the control group (reduction of 38%). Patients assigned to receive ropivacaine mobilised a median of 34m (9 –55m) in 6 min compared with 20 m for those receiving normal saline, though this was not statistically significant. Ten patients receiving the ropivacaine infusion required to have their infusion rates halved due to quadriceps weakness and three patients receiving ropivacaine infusion suffered a fall.
Frassanito 2008 (267)	RCT	20 20	GA GA	Spinal with hyperbaric bupivacaine 15 mg, fentanyl 15µg and morphine 100 µg. LPB with 0.4 ml/kg of ropivacaine 0.5%.	N/A PNS	10001 (2)	This small, single blinded study showed no significant difference between spinal opioid and LPB in terms of analgesia, nausea and vomiting and urinary retention in patients undergoing THA. The incidence of itch was significantly higher in the spinal opioid group. This study was of poor

							methodological quality.
Becchi 2008(268)	RCT	37 36	SAB SAB	CLPB with 3% lignocaine with 1 in 200,000 adrenaline test dose, then 0.75% ropivacaine (0.4 mL/kg) via the catheter over 2 min. Thereafter, continuous infusion of 0.2% ropivacaine at 10 ml/h for 48 h. Sham IV infusion with saline. Continuous infusion of morphine 0.1% and ketorolac 0.12% at a rate of 2mL/h for 48 h. Sham CLPB infusion catheter taped to patient skin.	PNS + contrast N/A	11100 (3)	This study was only single blind (investigators not blinded). Pain scores were lower over the 48 hour post-operative period in the CLPB group though analgesic consumption was only less in first 24 hours. The authors went on to question the value of continuing the infusion past this point. The incidence of nausea was significantly lower in the CLPB group.
Biboulet, 2004(244)	RCT	15	GA	FNB (2mg/kg bupivacaine +2µ/kg clonidine)	PNS	11001 (3)	Pain scores and morphine consumption were lower in the first 4 post-operative hours only in the LPB group. There was no reduction in post-operative pain scores at rest or movement for other time points up to 48 hours. There

		15 15	GA GA	LPB (2mg/kg bupivacaine +2µ/kg clonidine) PCA morphine	PNS N/A		was no difference in level of mobility, post-operative nausea, sedation or length of stay between the three groups. Patients in the LPB group were noted to have a more complete sensory block in the proximal thigh and accompanying lower pain scores in first 4 hours than those in the FNB group. This was postulated to be due to the innervation provided by the more proximal ilioinguinal, iliohypogastric and genitofemoral nerves which would be covered by a more proximal approach to the lumbar plexus and missed by the more distal FNB. Epidural diffusion of LA occurred in 4 out of 15 cases in LPB group. The authors concluded that neither FNB nor LPB should be used routinely for THA.
Siddiqui 2007(269)	RCT	17	GA	CLPB - Test dose 3ml 2% lignocaine with epinephrine. Bolus of 20 ml 0.25% bupivacaine in	PNS	10110 (3)	Only 53% of patients receiving CLPB had blockade of all 3 nerves (femoral, obturator and lateral cutaneous nerve of

				5 ml increments via catheter followed by infusion of bupivacaine 0.125% at 10 ml/h for 36 hours. Catheter removed at 36 hours. PCA morphine as below.			thigh). Despite this, patients in the CLPB group used less morphine, had less nausea and had higher patient satisfaction scores (all statistically significant). This study was not double blind.
		17	GA	PCA morphine 1mg bolus dose, lockout 6 minutes, 4-hour limit of 30 mg.	N/A		
Souron 2003(222)	RCT	27	GA	IT morphine 0.1mg in 1ml 0.9% saline	N/A	10010 (2)	Morphine consumption was statistically significantly lower in patients receiving IT morphine both in the PACU and at 24 and 48 hours post-op. Higher rates of urinary retention were noted in the IT morphine group though there was no increase in itch or PONV and satisfaction scores were generally high and similar between the two groups. Respiratory depression did not occur in either group. There were no
		26	GA	LPB with 25ml 0.475% Ropivacaine	PNS		

							episodes of epidural spread of LA in the LPB group. This study was not double blind.
Stevens 2000(270)	RCT	30 30	GA GA	LPB with 0.4ml/kg bupivacaine and 1 in 200,000 adrenaline. PCA morphine. Skin perforation only at lumbar plexus injection site, no placebo injection. PCA morphine.	PNS N/A	11101 (4)	Pain scores and morphine consumption were statistically significantly less in the LPB up to the 6 hour time point, though not thereafter. Post-operative, though not intra-operative blood loss was also lower in the LPB group though the actual difference was only in the order of 166ml and therefore was not necessarily clinically significant. Epidural extension of LPB occurred in 3 patients.

Table 8.5-1 - Study characteristics and outcomes – Lumbar Plexus Block

CEA = continuous epidural analgesia, CFNB= continuous femoral nerve block, CLPB = continuous lumbar plexus block, FNB = femoral nerve block, , GA = general anaesthesia, h = hours, IT morphine = intrathecal morphine, LA = local anaesthetic, LCNT = lateral cutaneous nerve of thigh block, LPB = lumbar plexus block, m = metres, PACU = post-anaesthesia care unit, PCA = patient controlled analgesia, PNS = peripheral nerve stimulator, RCT = randomised controlled trial, SAB = subarachnoid block, THA = total hip arthroplasty.

8.5.4 Lumbar plexus block - discussion

Use of a single shot lumbar plexus block provides better short term analgesia (4-6 hours post-operatively) in patients who have undergone THA compared with systemic analgesia (244;270). However when compared with spinal opioid, single shot lumbar plexus block was not superior (222;267). Continuous lumbar plexus block has been shown to provide good analgesia following THA when compared with CFNB, PCA morphine and systemic morphine infusion (248;249) (266;268;269). However, this was not associated with improved health related quality of life at 12 months (262). The dose of local anaesthetic rather than the volume or concentration were found to be the most important determinant of efficacy (260), and the addition of tramadol did not improve analgesia (265). Lumbar plexus block may be associated with significant complications including intrathecal and epidural placement, psoas haematoma or abscess, renal trauma and systemic LA toxicity. The performance of this technique requires considerable expertise and may be time-consuming to perform hence limiting its use.

8.6 Sciatic Nerve Block

The sciatic nerve supplies motor and sensory innervation to the posterior aspect of the thigh and most of the lower leg and therefore can provide analgesia after hip surgery when used in combination with a lumbar plexus nerve block. The sciatic nerve is formed from the anterior rami of L4 – S3, and is the largest nerve in the body, forming most of the sacral plexus (L4–S4). The sciatic nerve is actually formed of two nerves in close proximity, the tibial and common peroneal nerves. These nerves usually separate in the mid-thigh, although separation as proximally as the pelvis occurs in a minority of patients. The sciatic nerve leaves the pelvis via the greater sciatic foramen, commonly under the pririformis muscle, before travelling under the gluteus maximus and continuing distally between the greater trochanter and ischial tuberosity. It supplies motor innervation to the muscles of the posterior thigh as well as all muscles of the leg and foot. It provides sensory innervation to the skin of the lateral aspect of the leg (anterolateral and posterolateral), and almost all of the

foot (with the exception of the medial part of the foot which is innervated by saphenous nerve). Injury to the sciatic nerve typically produces: complete motor loss of the muscles of the posterior thigh, leg and foot and sensory loss over the territories described above (83).

8.6.1 Sciatic nerve block – Technique using peripheral nerve stimulation

The sciatic nerve can be blocked from several different locations along the lower extremity. Labat's sciatic nerve block is a classic approach which targets the nerve in the gluteal region. Other approaches to sciatic nerve blockade include the anterior and lateral approaches (which allow the patient to remain supine), and the parasacral and prone approaches. The Raj sub-gluteal approach is performed in the supine position with the hip flexed.

In the Labat approach, the patient is placed in the lateral position (operative side up), and the leg is flexed at the knee. A line is drawn between the greater trochanter and the posterior superior iliac spine (PSIS). A second line is then drawn from the greater trochanter to the patient's sacral hiatus. The point of needle insertion is found by drawing a line perpendicular from the midpoint of the first line to its intersection with the second line.

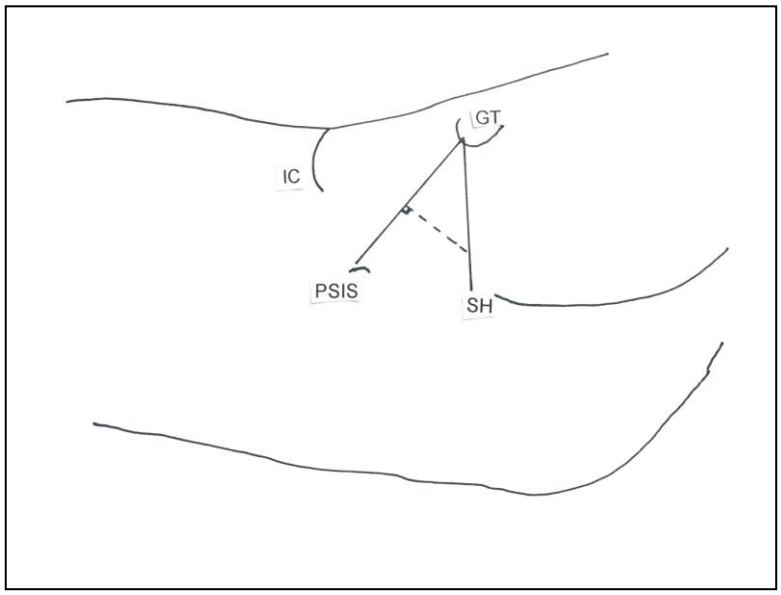

Figure 8.6-1 - The Labat approach to the sciatic nerve

GT = Greater trochanter, IC = Iliac Crest, PSIS = posterior superior iliac spine, SH = sacral hiatus.

The anterior approach to the sciatic nerve is performed with the patient lying supine. This may be an advantage in patients in whom changing position will be associated with pain. A line is drawn from the pubic tubercle to the anterior superior iliac spine (ASIS). A second parallel line is then drawn from the greater trochanter. A perpendicular line is drawn at the junction of the medial and lateral two thirds, to intersect the second line. This is the point of needle insertion.

The lateral approach to the sciatic nerve can again be performed with the patient in the supine position. A line is drawn from the posterior edge of the greater trochanter along the length of the femur. The needle is then inserted along this line at a point half way between the knee and greater trochanter. Blocking the sciatic nerve at this level will miss the posterior cutaneous nerve of thigh and will therefore not prevent tourniquet pain.

The Raj approach is again performed supine but with the patient's leg held in a flexed position at the knee and hip to 90°. A line is drawn connecting the greater trochanter to the ischial tuberosity. The point of needle insertion is around half way along this line in the groove formed by the hamstring and adductor muscles (271).

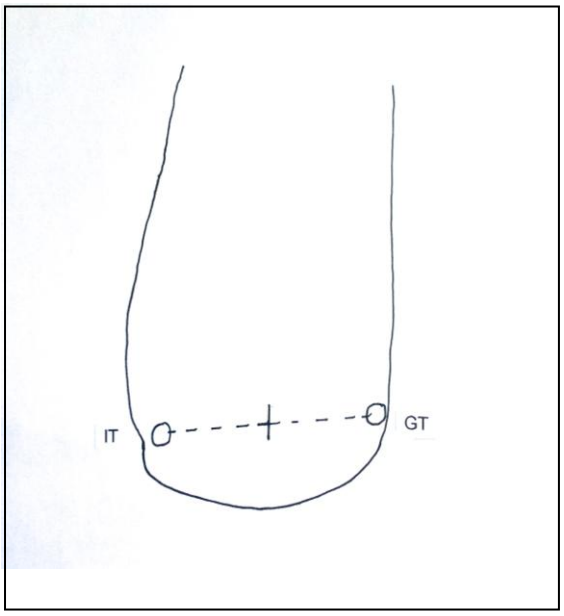

Figure 8.6-2 - The Raj approach to the sciatic nerve.

GT = Greater Trochanter, IT = Ischial Tuberosity

8.6.2 Sciatic nerve block – ultrasound guided technique

The sciatic nerve can be blocked both in the sub-gluteal region and anteriorly using ultrasound guidance. To perform the block from the sub-gluteal position, the patient must lie in the lateral position with the operative leg uppermost. A line is drawn between the greater trochanter and ishcial tubserosity and the sciatic nerve presumed to lie half way down this line. A 5Hz curvelinear ultrasound transducer is then applied in a parallel position with the depth set to around 7cm. The bony structures can then be identified, and the sciatic nerve visualised below he gluteus maximus muscle. The nerve is often seen as a thin, wide, lip-shaped structure in this area. The nerve can then be anaesthetised using an in- or out of plane technique (272).

To perform a sciatic nerve block from the anterior approach, the sciatic nerve is accessed at the level of the greater trochanter posterior to the femur. The nerve sits at the posterior border of adductor magnus and behind biceps femoris. The patient is positioned with the hip and knee slightly flexed and the hip externally rotated to 45°. A low frequency (2-5MHz) transducer is then placed on the thigh approximately 8cm distal to the inguinal crease. The femur and sciatic nerve can then be viewed and local anaesthetic infiltrated.

8.6.3 Literature review – sciatic nerve block

Studies were identified using the following methodology: MEDLINE, EMBASE and the Cochrane Register of Controlled Clinical Trials were searched using the search strategy displayed in Figure 8.6-3. Inclusion criteria were: RCTs published between 1990 - 2013, performed in human adults, undergoing total hip arthroplasty and published in the English language. At least one of the following outcomes required to be recorded for a study to be included: pain score, analgesia consumption or adverse effects. Studies were excluded if they examined patients undergoing hip and knee arthroplasty as one group with no separation of results. References of retrieved articles were for searched for other articles of relevance not identified in the original search.

1. exp Arthroplasty, Replacement, Hip/
2. exp Nerve Block/
3. exp Sciatic Nerve/
4. (continuous adj sciatic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 2 AND 3
6. 4 OR 5
7. 1 AND 6

Figure 8.6-3 - Search strategy

8.6.4 Results

Ten citations were identified, of which only one met inclusion criteria (Figure 8.6-4). Study characteristics and outcomes are displayed in Table 8.6-1. The methodological quality of the included Dutch study was good with a Jadad score of 4. This study had been approved by the relevant Institutional Review Board or local ethics committee. The study included 45 patients.

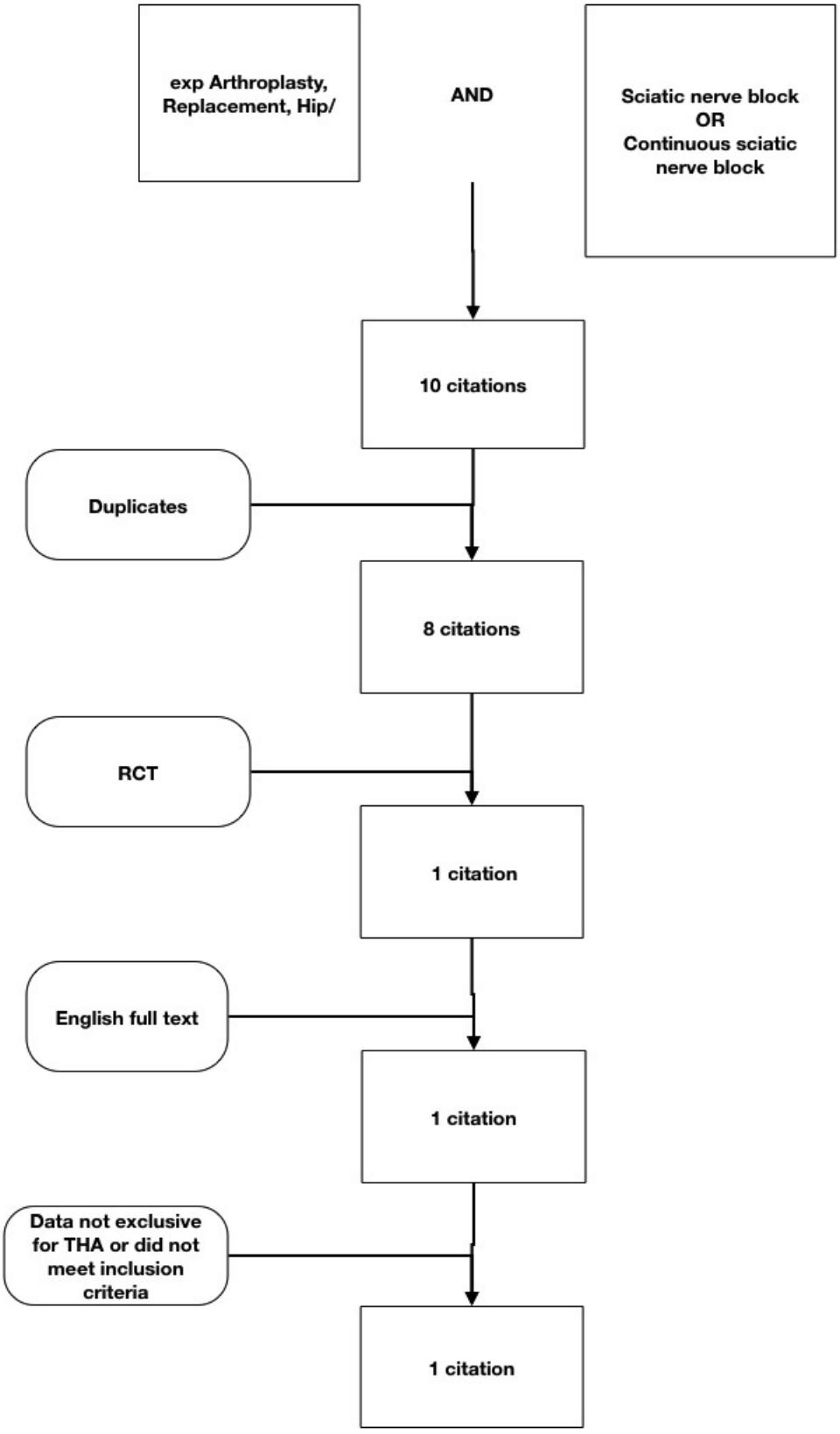

Figure 8.6-4 - Consort diagram of included studies

First author, year (ref)	Type of study	n	Anaesthesia	Analgesic techniques	Nerve localisation technique	Jadad score	Results / comments
De Leeuw M(273)	RCT	15	GA	Sciatic (10ml) and LPB (40ml) with total 50 mL levobupivacaine 3 mg/mL with 1 in 200,000 adrenaline.	PNS	11110	Patients generally had low pain scores and opiate use though there was no significant difference between groups. The duration of motor blockade was found to be longest in the Bupivacaine group. Epidural spread of LA was noted in 1 patient.
		15	GA	Sciatic (10ml) and LPB (40ml) with total 50 mL ropivacaine 4.5 mg/mL with 1 in 200,000 adrenaline.	PNS		
		15	GA	Sciatic (10ml) and LPB (40ml) with total 50 mL bupivacaine 3 mg/mL with 1 in 200,000 adrenaline.	PNS		

Table 8.6-1- Study characteristics and outcomes – Sciatic Nerve Block

GA = general anaesthesia, LPB = lumbar plexus block, PNS = peripheral nerve stimulator, RCT = randomised controlled trial, THA = total hip arthroplasty.

8.6.5 Discussion

There is a lack of high quality, published evidence examining the use of sciatic nerve blockade in total hip replacement. Consequently, there is at present no clear evidence to support the routine performance of a sciatic nerve block for hip replacement surgery. While it is not possible to provide complete analgesia of the hip joint after hip replacement surgery without a sciatic nerve block, this is not commonly practiced due to concerns about reduced post-operative mobility.

8.7 Fascia iliaca block

The fascia iliaca block may be considered an anterior approach to the lumbar plexus which relies on proximal spread of local anaesthetic beneath the fascia iliaca. The fascia iliaca is a fascial layer which connects laterally to the whole length of the inner lip of the iliac crest and medially to the linea terminalis of the lesser pelvis where it is continuous with periosteum. It is connected to the posterior margin of the inguinal ligament and is continuous with the transversalis fascia. The fascia iliaca covers the iliacus (a large, triangular shaped muscle which fills the ilium) and the psoas muscle (together referred to as the iliopsoas). The external iliac vessels lie anterior to the fascia while the nerves of the lumbar plexus lie posteriorly. The fascia iliaca passes behind the femoral vessels which are encased within the femoral sheath.

The femoral nerve descends through the fibres of the psoas major to exit at the lower portion of the lateral border of the psoas muscle. It then passes distally between the psoas and iliacus muscle, deep to the fascia iliaca. The femoral nerve exits the pelvis into the upper thigh, enclosed in the fascia iliaca and sits on top of the iliopsoas muscle and lateral to the femoral vessels.

The lateral cutaneous nerve of thigh is a purely sensory nerve arising from the L2 and L3 nerve roots that provides sensation from the iliac crest down the lateral portion of the thigh. This nerve also emerges from the lumbar plexus and travels downward lateral to the psoas muscle, crossing the iliacus muscle deep

to the fascia iliaca. The obturator nerve innervates a portion of the distal, medial thigh and is predominantly a motor nerve. It arises from the L2-4 nerve roots and crosses the iliacus muscle, deep to the fascia, in the medial thigh. Therefore, injection of local anaesthetic beneath the fascia iliaca should result in anaesthesia of all three of these nerves.

In addition, two other lumbar plexus nerves contribute sensory fibers to the upper part of the anterior aspect of the thigh. These are the ilioinguinal nerve and the gentiofemoral nerve. The ilioinguinal nerve emerges at the lateral border of the psoas muscle, before crossing the quadratus lumbarum muscle obliquely. It lies immediately posterior to its covering fascia until it pierces the transversus abdominis and oblique muscles in the direction of the spermatic cord or the round ligament of the uterus. The genitofemoral nerve perforates the psoas muscle, then runs on its anterior aspect posterior to the fascia iliaca. The fascia iliaca block may therefore also result in anaesthesia of the genitofemoral nerve.

8.7.1 Fascia ilaca block – landmark technique

The landmarks for this block are the anterior superior iliac spine, pubic tubercle and inguinal ligament. The fascia iliaca block is performed in the following way: The patient is positioned in the supine position and a line drawn on the skin connecting the anterior superior iliac spine to the pubic tubercle. This is then divided into thirds. At the junction of the lateral and medial two thirds, a second line is drawn perpendicular to and intersecting the line joining the anterior superior iliac spine and pubic tubercle. The insertion point is 1cm along this second line. A block needle is then inserted perpendicular to the skin at this point. A “pop” or give is felt as the needle passes through the fascia lata, and a second “pop” felt as it passes through the fascia iliaca. The local anesthetic should inject without resistance. Large volumes of local anaesthetic are generally used as the fascia iliaca block is a field block in which no individual nerve is targeted.

The fascia iliaca block was first described by Dalens et al in 1989 after a randomised study comparing it with the “3 in 1” block in 120 children ranging in

age from 0.7 to 17 years and from 7.3 to 79kg (86). Blockade of all 3 nerves was found in over 90% of patients receiving fascia iliaca block compared with levels of between 13% (obturator) and 100% (femoral) seen with the "3 in 1" technique. This was further investigated in 100 fit adults by Capdevila et al in 1998 (241). In this study, the fascia iliaca block was found to provide more reliable blockade of both femoral and lateral cutaneous nerve of thigh than the "3 in 1" block. However, neither block produced full sensory anaesthesia in any more than 38% of patients and spread of local anaesthetic was variable and unpredictable (241).

8.7.2 Fascia iliaca block – ultrasound guided technique

The use of ultrasound to perform fascia iliaca block has recently been investigated with the hypothesis that direct visualisation of the needle and injectate would result in more accurate placement of local anaesthetic and subsequent higher success rates (10). In this study of 80 patients undergoing total hip or knee replacement, patients were randomised to receive a fascia iliaca block performed using either a landmark or ultrasound guided technique. As well as sensory blockade, motor blockade of both femoral and obturator nerves was assessed. Patients receiving a landmark technique fascia iliaca block had successful blockade of all 3 nerves in 47% of cases. This compares favourably with the 34% described in the study by Capdevila et al (241). In the patients in whom ultrasound guidance was used for block placement, a higher rate of sensory block in the medial thigh (95% vs 60%, p=0.001) was seen. Complete blockade of all three nerves was seen in 82% of patients (p=0.001).

While this data is encouraging, the potential clinical benefits of this have not been fully investigated.

8.7.3 Literature review – Fascia iliaca block

Studies were identified using the following methodology; PUBMED, EMBASE and the Cochrane Register of Controlled Clinical Trials were searched using the search strategy as detailed in Figure 8.7-1. Inclusion criteria were: RCTs published between 1990-2013, performed in human adults, undergoing total hip

arthroplasty and published in the English language. At least one of the following outcomes required to be recorded for a study to be included: pain score, analgesia consumption or adverse effects. Studies were excluded if they examined patients undergoing hip and knee arthroplasty as one group with no separation of results. References of retrieved articles were searched for other articles of relevance not identified in the original search.

1. exp Arthroplasty, Replacement, Hip/
2. exp Nerve Block/
3. fascia iliaca block.mp.
4. ilacus fascia.mp.
5. 3 OR 4
6. 2 AND 5
7. 1 AND 6

Figure 8.7-1 - Search strategy

8.7.4 Results

3 citations were identified, of which only one met inclusion criteria. This was an Australian study of 44 patients. Study characteristics and outcomes are displayed in Table 8.7-1. The methodological quality of the included study was good with a Jadad score of 4. This study had been approved by the relevant Institutional Review Boards or Local Research Ethics Committee.

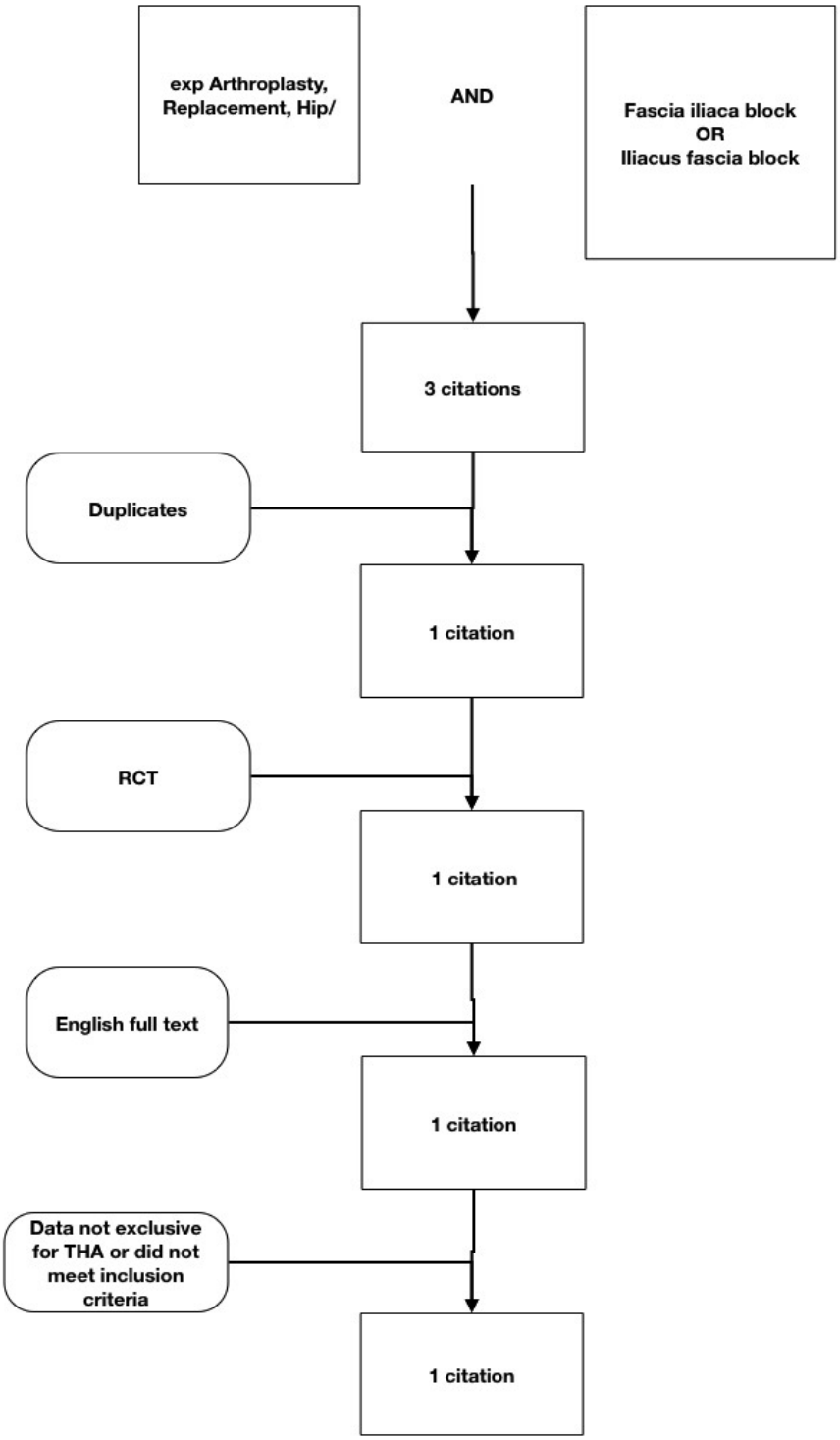

Figure 8.7-2 - Consort diagram of included studies

First author, year (ref)	Type of study	n	Anaesthesia	Analgesic techniques	Nerve localisation technique	Jadad score	Results / comments
Stevens 2007(274)	RCT	22	SAB	Modified fascia iliaca block with 30ml 0.5% bupivacaine with 1 in 200,000 adrenaline plus 150µg clonidine and 9ml normal saline (total volume 40ml). SAB with 2.5-3.5ml of 0.5% bupivacaine and 10-15µg fentanyl. PCA morphine.	Landmark	11110 (4)	The authors hypothesised that making the point of needle insertion 1cm above the inguinal ligament (rather than 0.5cm below) would result in a more proximal spread of LA and more reliable block of the nerves derived from L1 and L2. While no difference in morphine consumption was noted at 3 or 6 hour time points, a statistically significant decrease in morphine use was seen at 12 hours (median 10mg vs 26mg, $p<0.01$), and at 24 hours (22.5mg vs 37.5mg, $p<0.001$). This was thought to be due to improved LA spread to reach the nerves formed by the L1-2 roots (ilioinguinal, iliohypogastric and genitofemoral nerves). Pain scores were not different between groups though this can be explained by the fact that patients titrated their own
		22	SAB	Modified fascia iliaca block with 40ml normal saline. SAB with 2.5-3.5ml of 0.5% bupivacaine and 10-15µg fentanyl. PCA morphine.	Landmark		

							analgesia to effect. The incidence of PONV was also not different between groups. It should be noted that the group receiving the active block received not only LA but clonidine within the injectate and it is possible that this may have resulted in systemic effects and affected the morphine consumption.

Table 8.7-1- Study characteristics and outcomes – Fascia Iliaca Block

PCA = patient controlled analgesia, THA = total hip arthroplasty, LA = local anaesthetic, RCT = randomised controlled trial, SAB = subarachnoid block.

8.7.5 Discussion – fascia iliaca block

There is a lack of published evidence relating to the use of the fascia iliaca block for analgesia after total hip replacement. While some promising results have been seen with the fascia iliaca block performed using a landmark technique, the potential benefits of an ultrasound guided approach have not yet been fully examined and merit further investigation.

We hypothesise that by increasing the success rate of the fascia iliaca block with ultrasound, it will be possible to achieve superior analgesia post-operatively. Our aim is to assess whether the use of the ultrasound guided fascia iliaca block is non-inferior to intrathecal morphine in the provision of post-operative analgesia for primary hip arthroplasty. If this is the case, opioid could be removed from the spinal anaesthetic. This could, in theory, have significant safety benefits, whilst also reducing side effects.

8.8 Chapter 8 Summary

- There are a number of regional anaesthesia techniques which can be used for total hip arthroplasty. Each has advantages and disadvantages.

- Spinal morphine is a well established technique used for anaesthesia and analgesia in total hip replacement.

- Ultrasound guided fascia iliaca block has not yet been investigated in the clinical setting as a means of providing analgesia after total hip arthroplasty.

Chapter 9

Spinal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty: study protocol for a randomised, blinded, non-inferiority controlled trial

The following chapter forms the basis for the study protocol which was published in the journal Trials; 2011:12;51.

9.1 Background

Hip surgery is increasingly being performed, often in elderly patients with significant co-morbidity (275). Whilst the optimal anaesthetic technique is yet to be established (225), it is important that adverse effects are minimised to optimise patient safety, comfort and recovery and to facilitate rehabilitation. The main options for anaesthesia are general anaesthesia (GA) and regional anaesthesia (RA) or a combination of the two. In a recent systematic review, regional anaesthesia (RA) was demonstrated to reduce post-operative pain, morphine consumption and post-operative nausea and vomiting compared to systemic analgesia (224).

Spinal anaesthesia is a RA technique commonly used in many patients undergoing total hip arthroplasty (THA) (276). Opioids are commonly added to the spinal anaesthetic in order to prolong and improve post-operative pain relief (277) and are associated with reduced post-operative opioid requirements in patients undergoing hip arthroplasty (218;219;221). However, spinal opioids are associated with side effects including urinary retention, nausea and vomiting, itch and rarely, but most seriously, respiratory depression (199). Such adverse effects can be uncomfortable for the patient, delay mobilisation, recovery and eventual discharge and occasionally be dangerous (210;211).

In patients undergoing THA, peripheral nerve blockade has been shown to improve pain scores and reduce opioid consumption (224). The fascia iliaca nerve block can provide sensory blockade of the main nerves which supply pain to the hip: the femoral nerve, obturator nerve and lateral cutaneous nerve of thigh (86;274). However, clinical success rates of this block when performed 'blindly' using traditional landmark techniques are variable (241). Using ultrasound to locate nerves during peripheral nerve blockade has repeatedly been shown to increase success rates, reduce block onset time, increase block duration, reduce volumes of local anaesthetic required and increase patient satisfaction compared to traditional techniques (233-238;278). Use of

ultrasound guidance in the performance of fascia iliaca block has been shown to increase success rates compared with the landmark technique (10). In this study, the clinical benefits of this increased success were not further investigated.

Ultrasound guided fascia iliaca block has not yet been evaluated clinically as a method of providing post-operative analgesia following primary THA. We hypothesise that by increasing the success rate of the fascia iliaca block with ultrasound, it will be possible to achieve superior and more reliable analgesia than that obtained using the landmark based technique. The aim of this study is to assess whether the ultrasound guided fascia iliaca block can provide comparable post-operative analgesia to spinal morphine for primary THA. If this is the case, spinal opioid could be removed from the spinal anaesthetic. This could potentially reduce opioid related side effects, have safety benefits and reduce nursing workload in terms of post-operative monitoring requirements. The further investigation of this technique will provide a valuable contribution to existing knowledge and could profoundly change current practice.

9.2 Methods / Design

9.2.1 Overview

This is a single centre, randomised, double-blinded, placebo-controlled, non-inferiority study (279). This study has been approved by the West of Scotland Research Ethics Committee 4 (reference no. 10/S0704/43) and is registered with the ClinicalTrials.gov database (reference no. NCT01217294). This study will be performed in keeping with the requirements of the Declaration of Helsinki.

9.2.2 Hypothesis

Ultrasound guided fascia iliaca plane block provides post-operative analgesia which is not inferior to that obtained with spinal morphine in patients undergoing primary total hip arthroplasty.

9.2.3 Objectives

This study aims to compare the efficacy and safety of ultrasound guided fascia iliaca block with spinal morphine in the provision of post-operative analgesia after primary hip arthroplasty.

9.2.4 Primary outcome

The primary outcome measure is post-operative intravenous morphine consumption in a 24 hour period as self administered using a patient controlled analgesia (PCA) pump.

Patients will receive “step-down” opioid analgesics after the PCA is discontinued at 24 hours post-operatively. These step down analgesics will be converted to intravenous morphine equivalent when calculating 48 hour morphine consumption in the secondary outcomes. This will not affect the Primary Outcome of 24 hour morphine consumption.

9.2.5 Secondary outcomes

Secondary outcomes include:

- Pain scores at 3, 6, 12 and 24, 36 and 48 hours at rest and on movement as recorded post-operatively on the PCA chart where time zero is the end of the operation (numerical pain rating score 0 – 10 where 0 is no pain and 10 is worst pain imaginable).

- Time to first morphine administration in minutes from time zero.

- Morphine consumption at 3, 6, 12, 36 and 48 hours (morphine equivalent will be reported at 48 hours due to the use of step-down opioid analgesia).

- Episodes of respiratory depression defined as respiratory rate < 8/min or requiring naloxone administration in the first 48 hours post-operatively.

- Incidence of hypotension as defined by systolic blood pressure < 80mmHg or a drop of >25% from baseline systolic pressure, or requiring vasopressor in the first 48 hours post-operatively from time zero.

- Incidence of post-operative nausea and vomiting as defined by nausea score of greater than or equal to 2 (on a PONV scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe nausea and 4 = patient vomiting) or requiring the administration of an anti-emetic agent in the first 48 hours post-operatively.

- Incidence of pruritus as defined by itch felt to be distressing by the patient on questioning after the first 48 hour period post-operatively or requiring treatment with naloxone.

- Incidence of sedation as defined by sedation score of greater than or equal to 2 (where 0 = awake, S = normal sleep, 1 = drowsy but easy to rouse, 2 = sedated and difficult to rouse, and 3 = unconscious) or requiring naloxone administration in the first 48 hours post-operatively.

- Incidence of urinary retention as defined by the requirement for urinary catheterisation due to failure to pass urine in the first 48 hours post-operatively.

- Time to first mobilisation as defined by patient able to mobilise from bed to chair in hours from time zero as recorded by physiotherapy staff.

- Quadriceps strength as graded by the MRC assessment of power on the first post-operative day as recorded by the physiotherapist.

- Patient satisfaction as measured using a visual analogue scale (VAS) from 0 – 100mm where 0 is absolutely not satisfied and 100 is completely satisfied.

9.2.6 Study centre

Our centre is a tertiary referral facility for orthopaedics and trauma surgery with the necessary type and volume of clinical cases required for this study. There is a wealth of experience on the use of ultrasound guidance for regional anaesthetic techniques, including fascia iliaca block (10), within the department.

9.2.7 Patients and enrolment

Patients scheduled to undergo unilateral primary hip arthroplasty will be invited to participate in the study during their routine pre-operative assessment visit performed in advance of surgery. Inclusion criteria are: ASA physical status I - III, 18 - 85 years of age, weight between 50-110 kg, and competence to consent. Exclusion criteria are: contraindications to fascia iliaca block or spinal anaesthesia such as coagulopathy, malignancy or infection in the inguinal area, preference for general anaesthesia, allergy to opioids, significant peripheral neuropathy or neurological disorder affecting the lower extremity, pregnancy, history of alcohol or drug dependency, history of long term strong opioid intake (i.e. WHO step 3 analgesics) and history of significant psychiatric conditions that may affect patient assessment.

All suitable patients will be given a patient information sheet approved by the West of Scotland Ethics Committee. They will be given an opportunity to review this before written informed consent is obtained prior to surgery.

9.2.8 Consent

The process of consent will be in accordance with the Declaration of Helsinki. Patients will be fully informed that they are being asked to participate in a research study. The procedures involved in the study and the chances of being assigned randomly to one of two groups will be explained in person and via an information sheet. Patients will be made aware that they may receive a placebo injection in their groin and that this would have no clinical benefit to them. A signed consent form will be obtained from each patient and retained by the investigators. Patients will be made aware that their case notes may be accessed

by relevant research staff as well as NHS ward staff and independent research monitors who may wish to inspect documentation. All parties reviewing the patient's records will treat the information in the strictest of confidence and patient confidentiality will be maintained at all times. Patients will be made aware of their right to withdraw from the study at any time without adverse effects on their clinical care.

9.2.9 Randomisation

A computer generated allocation sequence (in permuted blocks) will be created by an independent operator who is not directly involved with the study. Once created, the allocation sequence will be kept in a secure locked drawer making it inaccessible to all study personnel. Allocation concealment will be achieved using sequentially numbered sealed envelopes which are opaque when held up to the light. When a patient is enrolled in the study, an administrator working within the Glasgow University Academic Unit of Anaesthesia will be contacted and asked to give the next numbered envelope to the anaesthetist who will make up the medications used in the study. The administrator will record the patient's details and the number of the envelope assigned to that patient. The allocation sequence will be accessed only when study data collection is complete or in any instance where unblinding of the study is thought to be essential in the provision of appropriate patient care.

Patients in the Ultrasound Guided Fascia Iliaca Group will receive: spinal anaesthesia with hyperbaric bupivacaine at a dose between 10 and 15 mg, adjusted based on patient height and weight at the discretion of the attending anaesthetist, with no spinal morphine. Ultrasound guided fascia iliaca block using 2 mg/kg of levobupivacaine diluted to a total of 40 ml with sterile saline.

Post-operative analgesia will include Paracetamol 1 g four times daily and patient controlled analgesia (PCA) with morphine (1 mg bolus, 5 minute lockout period). Patients will continue on any analgesics they were taking pre-operatively.

Patients in the Spinal Morphine Group will receive: spinal anaesthesia with hyperbaric bupivacaine as above, and with the addition of spinal morphine 100

micrograms (0.1 ml). “Sham” ultrasound guided fascia iliaca injection with 40 ml of sterile saline. Post-operative analgesia as previously described.

9.2.10 Blinding

This is a double blind study as both patient and investigator are blinded to the treatment allocation. The injectates for the nerve blocks will be prepared by an independent anaesthetist who has no involvement with study design, data collection or analysis. This same independent anaesthetist will prepare and perform the spinal injections and look after the patient in theatre. The use of sedation with target controlled infusion propofol and the administration of fluid will be at the discretion of the independent anaesthetist. Anti-emetic drugs will not be given in theatre unless felt to be necessary by this anaesthetist. This anaesthetist, who has no ongoing role within the study, will be the only person who is aware of the treatment allocation.

A separate study anaesthetist will perform the ultrasound guided fascia iliaca blocks in a blinded fashion using the pre-prepared injectate. The patient, surgeon, study anaesthetist performing the ultrasound guided fascia-iliaca blocks, ward staff, and research nursing staff who collect and record the outcome data will all be blinded to the study intervention. In the very rare event that a member of research nursing staff can not perform data collection, a study anaesthetist will be asked to perform this task. The study anaesthetist will be blinded to the treatment allocation in all cases.

The study will be unblinded only after all patients had been recruited and the study is declared closed to the relevant authorities. All study data will be kept entirely separate from the treatment allocation key until the time of unblinding and analysis of results. No member of the study team will have access to the allocation key at any point as this will be kept securely by a member of University of Glasgow secretarial staff.

9.2.11 Intra-operative management

The anaesthetist looking after the patient in theatre will play no part in data analysis and will record the intra-operative proceedings as normal. The patient's participation in this study and the two possible anaesthetics that may have been administered will be documented on the anaesthetic chart. The randomisation code may be accessed if deemed necessary in the provision of optimal patient care. The patient may receive sedation if requested and as directed by the anaesthetic doctor. Fluid administration and the use of vasopressors will again be at the discretion of the anaesthetic doctor. All medications, with the exception of the medications used to perform the spinal or fascia iliaca block, will be detailed in the anaesthetic record. No anti-emetic will be administered peri-operatively unless specifically indicated.

9.2.12 Postoperative management

After surgery, patients will be taken to the recovery room and monitored according to standard hospital policy. Pain will be treated, if required, with intravenous morphine every 5 - 10 min as directed by nursing staff. Patients will be familiarised with the Patient Controlled Analagesia (PCA) device and discharged once recovery room discharge criteria have been met. Patients will remain on oxygen for at least 24 hours and whilst receiving PCA morphine as is routine protocol in our unit.

Naloxone will be prescribed for sedation or respiratory depression as specified on the PCA protocol. After a 48 hour period, data regarding pain scores, nausea, itch, sedation and hypotension will cease being collected as detailed in the primary and secondary outcomes. The investigator who collects the data (research nurse) will be blinded as to the nature of the anaesthetic administered. The time to first mobilisation will be assessed and the patient will continue to be monitored by physiotherapy staff until discharge. Any serious adverse events will prompt follow up. Patients will be seen routinely following discharge by the arthroplasty specialist nurse. Symptoms of nerve damage will be actively sought at this consultation. Patients will be asked to rate their level of satisfaction with post-operative analgesia at both 48 hour and 3 month time points.

9.2.13 Criteria for discontinuation

Every effort will be made to retain patients in the trial and to minimise withdrawals. Patients may request to be withdrawn from this study at any time. Intention to treat and “as treated” analyses will be performed.

9.2.14 Data Collection

Data will be obtained from copies of the anaesthetic record, recovery room observation chart, PCA chart, ward observation chart and drug prescription chart. These charts will be reviewed after the first 48 hour post-operative period by an independent research nurse. The research nurse will be blinded to the anaesthetic technique used. All documentation relating to the study will be stored in an anonymised case report file unique to each patient. These case report files will be archived in a locked facility for a period of 10 years.

9.2.15 Sample Size and Statistical Considerations

In the comparison of ultrasound guided fascia iliaca block with spinal opioid in patients undergoing primary hip replacement, we intend to compare an established technique in widespread practice (spinal morphine) with the less well investigated technique of ultrasound guided fascia iliaca block. The primary outcome of the study is 24 hour morphine consumption. This outcome is used commonly in trials of spinal opioid for hip arthroplasty surgery. Mean 24 hour morphine consumption after hip arthroplasty is reported to lie within the range 10 mg (221) to 30 mg (219) when using 0.1 mg intrathecal morphine. From our own audit data of patients receiving spinal opioid for hip arthroplasty over an 8 month period, mean 24 hour post-operative morphine consumption was 24.6mg (SD 17.6mg) which lies within the reported range described above (219;221).

In order to calculate sample size, we used a method suggested for non-inferiority trials (279;280). For this we made the following assumptions. Type 1 error (α) was set at 0.05; Type 2 error (β) at 0.2; and Z numbers based on one-tailed testing. We considered a difference between groups (δ) of greater than 10 mg of morphine to be clinically significant. 10 mg of morphine equates to one

subcutaneous dose of morphine commonly used in post-operative analgesia pain protocols (281).

The expected difference between the Control (spinal morphine) and Treatment (ultrasound guided fascia iliaca) groups (δ) is more difficult to estimate. To date, there is only one published trial looking at 24 hour post-operative morphine consumption after fascia iliaca block for hip arthroplasty, although this was performed with the landmark technique alone and did not employ ultrasound (274). In this study, mean 24 hour post-operative morphine consumption in the fascia iliaca group was 23 mg. Therefore, there is a 1.6 mg difference between the mean 24 hour morphine consumption obtained from our audit data of patients receiving spinal morphine, and that obtained in a study looking at patients receiving fascia iliaca block for hip arthroplasty (274). Thus, the number of patients required to adequately power this study is 108.

The null Hypothesis (H_0) for this non-inferiority study is that the experimental treatment (ultrasound guided fascia iliaca block) is not non-inferior to the established treatment (spinal morphine) by more than the clinically significant amount (δ). If H_0 is rejected, the alternative hypothesis is that ultrasound guided fascia iliaca block is non-inferior to spinal opioid.

The study will be performed using both intention to treat and “as treated” analyses. In the intention to treat analysis, patients will be considered failures if they require general anaesthesia or were unable to receive randomised treatment for any other reason. In the “as treated” analysis, only data from patients completing randomised treatment will be analysed.

Secondary data analyses will be carried out on all secondary outcomes. These will be compared between groups using t-test, and Mann-Whitney, or Chi-squared tests as appropriate.

It is anticipated that recruitment for this study will take between 12 and 18 months to complete if 1 to 2 patients are enrolled each week, using one surgeon to reduce surgical variability. Data collection for each patient will occur during the first 48 hours post-operatively and at a routine follow up appointment. No

further follow up will be routinely arranged. Any patients requiring specific follow up will have this arranged on an individual basis.

We recognise that while this study is powered for the primary outcome, it is not powered for the secondary outcomes. However, the data we collect in this study will provide useful information for further studies looking specifically at these outcomes.

9.2.16 Adverse Event Reporting and Safety

Definitions:

Adverse Event (AE) - Any untoward medical occurrence that a patient experiences whilst participating in the study. This includes occurrences which are not necessarily caused by or related to the trial treatment.

Serious Adverse Event (SAE) – A Serious Adverse Event is defined as an untoward occurrence that:

a. results in death
b. is life threatening (at the time of the event)*
c. requires hospitalisation or prolongation of existing hospitalisation**
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect.
f. is otherwise considered medically significant by the investigator

*Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

**Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an adverse event.

Full details of all AEs will be recorded in the subject's medical records and on the study record forms. Adverse Events will be monitored and followed up until satisfactory resolution or stabilisation.

All adverse events must be assessed for seriousness, causality, expectedness and severity. This assessment is the responsibility of the Chief Investigator.

An SAE occurring to a research participant should be reported to the main Research Ethics Committee and Sponsor where in the opinion of the Chief Investigator the event was:

● Related – resulted from administration of any of the research procedures.

● Unexpected – type of event is not listed in the protocol as an expected occurrence.

The Principal Investigators shall report any SAE arising during the study to the Chief Investigator and Sponsor as soon as reasonably practicable.

Serious Adverse Events will be reported using the National Research Ethics Service SAE report form. This will thereafter be forwarded both to the Sponsor and to the Research Ethics Committee for review and assessment.

9.3 Discussion

9.3.1 Risk Benefit Assessment

We expect that all patients will benefit from this study in view of the high level of post-operative monitoring and follow up which will be employed. In order to achieve blinding and improve the validity of the study, a “sham” ultrasound guided fascia iliaca block will be performed in patients in the Spinal Morphine Group. These patients will therefore receive an injection of an inactive substance (sterile saline) into the groin. As no local anaesthetic is being used in the sham block, potential risks will include: discomfort on injection, bleeding or bruising at the puncture site and nerve damage. Nerve damage is rare with fascia iliaca blocks as the needle is not directed towards the nerves themselves, but rather to lie in a plane between muscle layers. In the patients receiving fascia iliaca block with local anaesthetic, the risks are as before with the addition of local anaesthetic toxicity, although a pre-determined safe dose of local anaesthetic is being used.

Patients in the Spinal Morphine Group will receive spinal morphine in combination with local anaesthetic in the spinal injection. Spinal opioids have

been used since 1979 to provide pain control after surgery (282). Due to its widespread international use, spinal morphine has been extensively investigated in this setting and spinal morphine in combination with systemic morphine is a commonly used post-operative regime for many surgical procedures including hip arthroplasty (209;222;283). Low dose spinal morphine can provide adequate analgesia whilst minimising side-effects (218;219;221). Such side-effects include: delayed respiratory depression, pruritus, post- operative nausea and vomiting and urinary retention (277;284-286). Although respiratory depression is rare with low doses of intrathecal morphine (286), it is potentially life-threatening. Furthermore, the concomitant use of systemic opioids for post-operative analgesia may add to this risk. Previous research has concluded that 100 micrograms of intrathecal morphine combines analgesic efficacy whilst minimising the side effect profile (218;221). Reassuringly, in a dose-finding study of intrathecal morphine for hip and knee surgery, there was no increased incidence of respiratory depression or hypoxaemia in patients receiving up to 0.3 mg of intrathecal morphine. This included elderly patients who had also received *"significant doses of PCA morphine"* (219).

A recent meta-analysis of 1300 patients was unable to define whether the use of spinal morphine increased the risk of respiratory depression (214). Studies investigating the use of intrathecal opioid are generally not adequately powered to detect the incidence of respiratory depression. However, it is believed that lower doses result in a reduced risk (214;218-222). A recent trial of 1915 patients receiving 0.15 mg of intrathecal morphine for Caesarean section found the incidence of a respiratory rate of less than 10 breaths per minute to be 0.26% and the need for naloxone 0.052% (220). However, there is no evidence that there is an effective dose of spinal morphine that would completely preclude the occurrence of respiratory depression. An accurate estimate of the incidence of this complication would therefore require a trial containing very large numbers of patients and is impractical to undertake. In keeping with other investigators, we cannot accurately predict the incidence of respiratory depression that may occur after the use of low dose spinal opioid and PCA morphine.

In the planning of this study, a number of measures have been employed to reduce this potential risk. These include: the utilisation of the lowest dose of

spinal morphine thought to be effective (0.1 mg), the use of specific monitoring charts to ensure that the patient is monitored on an hourly basis, delivery of supplemental oxygen whilst receiving morphine via the PCA device, routine prescription of naloxone and the use of clear protocols to be followed by nursing staff in the management of adverse events. All nursing staff involved in post-operative patient care are competent and experienced in the management of patients who have received spinal and systemic morphine, and are trained in the necessary monitoring procedures.

Both spinal anaesthesia and peripheral nerve blockade are commonly performed for hip arthroplasty in the United Kingdom. Any possible risks must be weighed up against the risks of a general anaesthetic. Any adverse events relating to each of the procedures will be recorded by staff performing the study and any necessary investigations, treatment or follow up arranged thereafter.

Chapter 10

Statistical considerations

10.1 Non-inferiority

This study was originally designed as a traditional superiority study. After editorial review by the editors of the *Trials* journal, it was considered optimal to adopt a non-inferiority design (11). A non-inferiority study aims to determine whether a new treatment is no worse than a standard or reference treatment (279). In order to meaningfully use this concept in the clinical setting, a margin of non-inferiority (a margin between the groups which is felt to be clinically significant) is sought (δ). This is because trying to prove that two treatments are exactly the same is extremely difficult if not impossible. Non-inferiority trials aim to show that a new treatment is at least as effective as the established treatment, or that it is worse by an amount less than δ (i.e. less than the amount considered clinically significant). Therefore, even if a new treatment is found to be no better than a more established treatment, it may have other important advantages such as lower invasiveness, or fewer side effects.(279) It follows that the question of non-inferiority is non-symmetrical in that the new treatment is not of interest if it is in fact worse than the established treatment (by greater than δ).

10.1.1 Hypotheses in a non-inferiority trial

A non-inferiority trial is different to the more traditional superiority trial in a number of ways. One of the most fundamental differences lies within the null hypothesis for the study. In a superiority study, the null hypothesis states that there is no difference between the two treatments and rejection of the null hypothesis means that the two treatments differ. A type I error in this scenario occurs when the null hypothesis is rejected erroneously (i.e. a difference is found where there is none). A type II error occurs when there is a difference between the two treatments but this is not detected.

Conversely, in a non-inferiority study, the null hypothesis states that one treatment is *not* non-inferior (or *is* unacceptably worse than) the other. The alternative hypothesis is that the difference between the two treatments is less than δ and that the new treatment is therefore non-inferior to the traditional treatment. Thus the null hypothesis appears to be reversed in a sense as the null

hypothesis is not "null" at all. In this situation, a type I error exists if a genuinely inferior new treatment is accepted as being non-inferior and a type II error occurs when a non-inferior treatment is rejected erroneously. The use of the clinically significant amount (δ) is used not only in the analysis of a non-inferiority study but in the calculation of sample size(163;279).

10.1.2 Study design

In order to perform a non-inferiority trial, it is necessary that the reference treatment's efficacy is well established and is in common use, as is the case with spinal morphine. This makes an alternative study design with a comparison made to a placebo or untreated control group unethical (279). In addition, outcome measures and patient population should be similar to those in studies looking at the reference treatment. Sample size should be calculated using the following equation:

Z = multiple for standard deviation (SD) to convert to confidence intervals (CI)

SD^2 = variance

$$n = 2 \times ((z(1 - \alpha) + z(1 - \beta)) / (\delta))^2 \times SD^2 \quad (287)$$

Equation 10.1-1 - sample size calculation for non-inferiority study with continuous outcome variable

A pre-stated margin of non-inferiority is often chosen as the smallest value that would result in a clinically important effect (288). The value used for δ should generally be smaller than the difference used in a superiority trial of a similar outcome. This means that non-inferiority studies often require increased numbers of participants in order to be adequately powered (279). As with all studies, minimising drop-out and non-adherence to treatment is of high importance if accurate results are to be achieved.

10.1.3 Analysis

Intention to treat (ITT) analysis is generally recommended for a standard superiority study:

ITT *"Includes all randomised patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol (289)."*

In non-inferiority studies, ITT analysis can increase the risk of a type I error (falsely declaring non-inferiority when in fact there is a clinically important difference between the two groups) (290). For example, if two groups of patients randomised to different treatments in a poorly designed trial were to cross-over to a large extent, it would result in two groups in which large numbers of participants received each of the treatments. In a superiority study, this would (correctly) be likely to produce a result in which there was no difference found between the groups. However, in a non-inferiority study, if the groups were to become "blended" by significant cross-over, this might result in non-inferiority being erroneously declared (type I error). Therefore, in a non-inferiority study, the more poorly run the trial, the more likely an ITT analysis will show non-inferiority (290). For this reason, non-ITT analyses are often considered more appropriate for non-inferiority studies as they reduce the chance of a type I error. Such analyses use participants who received and completed allocated treatment. The term "as treated" means that when the data are analysed, the treatment assignment is based on the actual treatment the patients received, not the treatment the patients are supposed to have received (i.e. the treatment to which they were randomised).

To this end, the FDA's Guidance for Industry Non-Inferiority Clinical Trials, suggests using an 'as-treated' analysis for the primary outcome (291):

> *"Intent-to-treat (ITT) analyses in superiority trials are nonetheless preferred because they protect against the kinds of bias that might be associated with early departure from the study. In non-inferiority trials, many kinds of problems fatal to a superiority trial, such as non-adherence, misclassification of the primary endpoint, or measurement problems more generally (i.e., "noise"), or many dropouts who must be assessed as part of the treated group, can bias toward no treatment difference (success) and undermine the validity of the trial, creating apparent non-inferiority where it did not really exist. Although an "as-treated" analysis is therefore often suggested*

> *as the primary analysis for NI studies, there are also significant concerns with the possibility of informative censoring in an as-treated analysis. It is therefore important to conduct both ITT and as-treated analyses in NI studies. Differences in results using the two analyses will need close examination."*

This is reinforced by the authors of the extension to the CONSORT statement for non-inferiority and equivalence studies who state (279):

> *"In non-inferiority and equivalence trials, non-ITT analyses might be desirable as a protection from ITT's increase of type I error risk (falsely concluding non-inferiority). There is greater confidence in results when the conclusions are consistent."*

The concerns outlined above regarding the sole use of an "as treated" analysis for non-inferiority studies include that of 'informative censoring", and there is an argument that in a non-inferiority study, there is an even greater need to ensure that the study is well designed and carefully monitored. The use of both ITT and "as treated" analyses is suggested by European and US authorities (291;292).

10.1.4 Interpretation of results

Non-inferiority is most easily assessed using a confidence interval (CI) approach. Firstly, a non-inferiority margin is specified (δ). This is the maximum difference tolerated between the groups before the new treatment is considered inferior. If the 95% confidence interval for the difference between treatment means lies within this margin, then non-inferiority is deemed to have been established. In order to interpret confidence intervals in non-inferiority studies, the following statements are true:

- When the entire CI is greater than δ, the treatment is inferior.
- When the upper limit of the CI is less than δ, the treatment is non-inferior.
- When the upper limit of the CI is greater than δ, the result is inconclusive.

This can be represented graphically as seen in Figure 11.1-1:

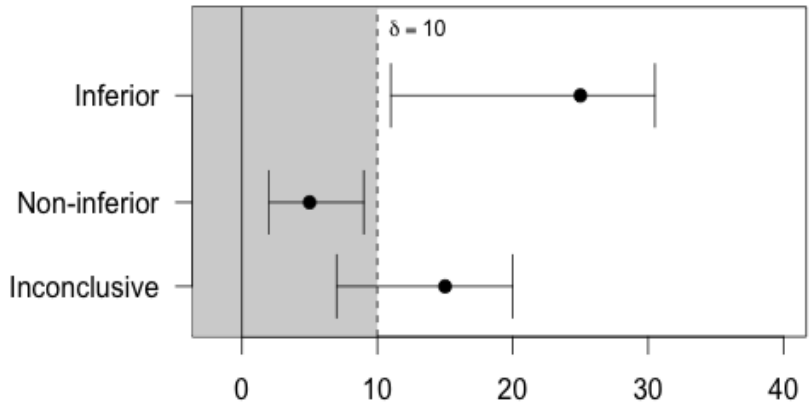

Figure 10.1-1- Interpretation of confidence intervals for non-inferiority studies

Advantages	Disadvantages
Useful when placebo control is inappropriate.	Must meet specific design and analysis parameters to be useful.
Not limited to pharmaceutical therapy	Requirements appear to be poorly understood by investigators.
Can be used for risk-benefit analyses	Not recommended when the reference treatment is not well established, or is inconsistent when compared with placebo.
Appropriate for comparing a specific intervention to itself (dose vs dose or formulation vs formulation).	An appropriate sample size for non-inferiority trials is usually larger than that required for superiority trials.
	Type I error may occur resulting in falsely declaring a treatment non-inferior. As there is commonly no placebo arm (in contrast with a superiority study), there is no way of telling whether the new treatment is any better than no treatment.

Table 10.1-1 - Advantages and disadvantages of non-inferiority studies

10.1.5 Statistical software 'R studio'

Statistics for this study were performed using R studio software. R is a computer language and environmental platform for statistical computing. It is based on the older computer language "S" and provides a wide variety of statistical and graphical techniques. R is freely available under the terms of the Free Software Foundation's GNU General Public License in source code form and can be run on a wide variety of UNIX platforms. It is compatible with Windows and MacOS. R is a modular system which employs a highly effective data handling and storage facility. It also has a large number of coherent, integrated tools for data analysis as well as sophisticated graphical facilities useful for data analysis and subsequent publication purposes.

Further reasons to use R for statistical analysis include:

- It is the main statistical environment used by researchers in areas such as statistics and computational mathematics. This means that the newest statistical and analytic techniques will be implemented on it first.
- It is extremely flexible and can be used for both simple and highly complex analyses.
- It is freely available and costs nothing to install and use.

10.1.6 Statistical considerations for the study: Spinal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty: a randomised, blinded, non-inferiority controlled trial.

The primary outcome of this trial was 24 hour post-operative morphine consumption. We hypothesised that there would not be a clinically meaningful difference between the two groups, therefore, we planned this trial with a non-inferiority design. From our own experience, and from examining other similar studies, we considered that up to a 10mg increase in morphine consumption in the first 24 hours post-operatively would be an acceptable clinical difference in establishing non-inferiority and this was therefore chosen as the non-inferiority

margin (δ). A priori statistical considerations including sample size calculation and planned analyses are outlined in Chapter 10 and have been published in a journal of trial methodology (11).

Statistical analysis for this study was performed using R studio Version 0.98.953 – © 2009-2013 RStudio, Inc. Data were transferred to R studio from Microsoft Access and Excel programmes using appropriate import scripts. All data sources were combined with the study allocation key and data were transformed to be readable by R, i.e. information such as dates and times were changed to the appropriate format where necessary. ITT and "as treated" groups were separated to allow independent analysis of both groups. All data were assessed for normality using a Shapiro test and by displaying graphically in the form of a histogram. These distributions informed the way in which the data were reported as well as the performance of further statistical analysis.

10.1.6.1 Primary outcome

The primary outcome (24 hour morphine consumption), was calculated using the difference between the medians and confidence intervals between the two groups. We planned to declare non-inferiority of the ultrasound guided fascia iliaca group with respect to the spinal morphine group if the upper bound of the 2-sided 95% confidence interval (CI) of the difference in medians in 24-hour opioid consumption between groups (ultrasound guided fascia iliaca group – spinal morphine group) was <10 mg. The use of confidence intervals in reporting the results of research has increased over the past several years as this provides a greater amount of information than p-values alone. This practice is now recommended by many editors of scientific journals (293).

Because of the right-skewed distribution of the median 24-hour opioid consumption (see Figure 11.1-2), CI construction was done without distribution assumptions by using a bias-corrected bootstrapping technique (with 10,000 replications) (294;295). Bootstrapping is a statistical technique requiring intensive computational input which can allow a researcher to make inferences from their data without making strong distributional assumptions. In other words, bootstrapping can provide information on the shape of the sampling

distribution of the outcome in question. This can then be used to calculate improved confidence intervals if the sampling distribution is not normal. Due to the non-inferiority design, the primary outcome analysis was performed using both ITT and “as treated” populations.

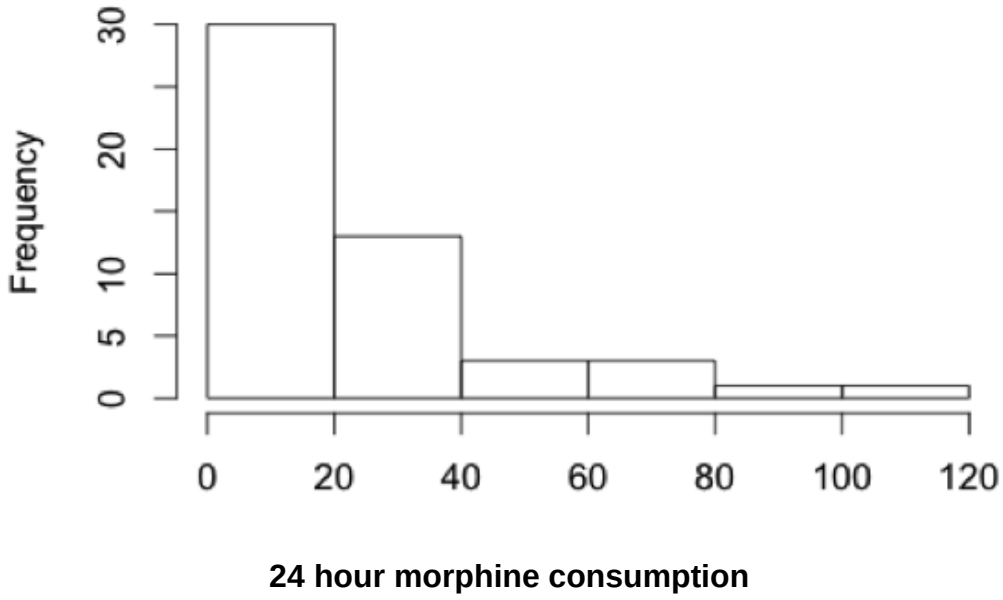

Figure 10.1-2 - Histogram showing right skew of data for primary outcome - 24 hour morphine consumption

10.1.6.2 Demographic variables and secondary outcomes

Descriptive statistics were calculated for demographic variables. Z tests of two proportions were used for data relating to gender and pre-operative administration of paracetamol as these were simple count data. Student’s t tests were used for normally distributed demographic variables such as weight, height, pre-operative heart rate, pre-operative systolic BP (SBP), pre-operative diastolic BP (DBP) and pre-operative SpO2. These data were expressed as means and standard deviations (SD).

As PCA morphine was generally removed at 24 hours post-operatively, patients received oral opioids from this point onward if required. Oxynorm was originally the oral opioid of choice though this changed to oral morphine after the study had been running for 4 months due to a change in hospital prescribing policy.

Oxynorm was converted to oral morphine by multiplying it by 1.5 (252). Oral morphine was then converted to IV morphine by dividing by 3 (252). This was added to the 48 hour morphine consumption for all patients to give a figure for total 48 hour systemic opioid consumption.

Wilcoxon rank sum tests were used for non-normally distributed data which included: body mass index (BMI), fascia iliaca block time, surgery time, blood loss during surgery, time to first administration of morphine, morphine consumption at 3, 6, 12, 24, 36, 48 hours, pain scores at rest and movement at 3, 6, 12, 24, 36, 48 hours, time to first mobilisation, quadriceps power grade prior to first mobilisation and patient satisfaction at 48 hours. These data were expressed using median and inter-quartile range (IQR). Again, Z tests of two proportions were used for data involving counts, which were: paraesthesia during fascia iliaca block, paraesthesia during spinal injection, intra-operative administration of anti-emetic, number of patients suffering respiratory depression, number of doses of naloxone administered for respiratory depression, number of patients with episodes of SBP < 80mmHg, number of patients with episodes of SBP > 25% below baseline, number of patients given post-operative vasopressor, urinary retention requiring catheterisation, number of patients with PONV scores >2, number of patients requiring post-operative anti-emetic, number of patients requiring treatment for pruritus, number of patients with distressing pruritus, number of patients with sedation score > 2, mobilisation at first attempt, number of adverse events and number of serious adverse events. The tests were two sided and a p value of <0.05 was considered statistically significant.

10.1.7 Linear regression

Linear regression is a statistical tool used to model the dependence of a variable (y) on one or more predictor variables (x). In simple linear regression, we aim to predict one variable from a second variable. In the case of simple linear regression, the prediction of the dependent variable (y) when plotted as a function of the predictor variable (x) forms a straight line. Linear regression calculates an equation that minimises the distance between the fitted line and all of the data points (the residuals). This can be denoted as $y = a + bx$ (i.e. the

equation for a straight line where ‘b’ represents the slope of the line [or regression coefficient], and ‘a’ represents the point at which the y axis is crossed [or regression constant]). The regression coefficient represents the change in the dependent variable which is associated with a change of one unit in the predictor variable (i.e. the slope of the regression line).

In multiple linear regression, the dependent variable is predicted by two or more predictor variables. This allows the investigation of the effects of a number of different predictor variables on the dependent variable. Multiple linear regression analysis may be used to;

- Identify factors which may affect the variable of interest (y) in order to improve understanding of the process.
- Determine the extent to which the explanatory variables are linearly related to the dependent variable after adjusting for other variables.
- Allow prediction of the dependent variables from explanatory variables.

R^2 is a statistical measure which represents the amount of variation in the data that is explained by the regression. R^2 has a value between 0 and 100%. An R^2 of 0% indicates that the model explains none of the variability of the response data around its mean. An R^2 of 100% means that the model explains all of the variability of the response data around its mean. For example, if the R^2 value is 0.88, this means that 88% of the variation in the dependent variable is explained by variation in the predictor variable(s). R^2 is also known as the coefficient of determination, or the coefficient of multiple determination for multiple linear regression.

While R^2 provides useful information, it does not always give the full picture and has a number of limitations. Firstly, every time a predictor variable is added to a model, the R^2 increases, even if this is due to chance alone. R^2 never decreases in this situation. It therefore follows that a model with more terms may appear to have a better fit simply because it contains more predictor variables. Secondly, if a model has too many predictors, it can begin to model the random

noise in the data. This is known as “over-fitting” the model and it can result in falsely high R^2 values and a decreased ability to make predictions (296).

In order to address some of these issues, the adjusted R^2 can be used. This is adjusted for the number of predictor variables in the model and will allow an increase in the adjusted R^2 only if the new predictor variable improves the model more than would be expected by chance alone. The adjusted R^2 is therefore always lower than R^2. The adjusted R^2 is used when quoting results for linear regression in this study.

It should be noted that regression models should not be used to make predictions outwith the range of the original data.

10.1.7.1 Linear regression for primary outcome

A linear regression analysis was performed for the primary outcome of 24 hour morphine consumption as this is a continuous variable. The regression analysis was performed using both forward and backward step-wise approaches in order to try and find the optimal model. The coefficient of determination, R^2, was calculated as an indicator of the proportion of variability explained by each model. AIC values were also calculated in order to assess the quality of the model.

A note on Akaike's Information Criterion (AIC)

AIC stands for Akaike's Information Criterion. This is a measure of the relative quality of a statistical model for a given set of data. AIC trades off the “goodness of fit” of the model with the complexity of the model offering a relative estimate of the information lost when a given model is used to represent the process that generates the data. As such, AIC provides a means for model selection. When comparing models fitted by maximum likelihood to the same data, the smaller the AIC, the better the fit.

10.1.8 Logistic regression

Logistic regression is used when the outcome variable of interest is binary or dichotomous (e.g. the presence or absence of a symptom, alive versus dead etc). The goal of logistic regression is to find the best fitting (yet biologically plausible) model to describe the relationship between the dependent (or outcome) variable and the independent (predictor or explanatory) variables. This process allows us to look at the fit of the model as well as at the significance of the relationships (between dependent and independent variables) that are being modelled. Logistic regression estimates the probability of an event occurring. Therefore, rather than being able to predict a precise numerical value of a dependent variable from independent variables, the probability of an event occurring rather than an event not occurring is calculated. The odds ratio (OR) is used to describe this concept and is defined as (296);

"The ratio of the odds of an event occurring to it not occurring".

A logistic regression analysis was performed for selected dichotomous secondary outcomes.

10.2 Chapter 10 Summary

- A non-inferiority study aims to determine whether a new treatment is no worse than a standard or reference treatment.

- In a non-inferiority study, the null hypothesis states that one treatment is *not* non-inferior (or is unacceptably worse than) the other.

- Linear and logistic regression are statistical tools which can be used respectively to model; the dependence of a variable (y) on one or more predictor variables (x) and the probability of an event occurring.

- Both intention to treat and ‘as treated’ analyses should be performed when analysing a non-inferiority study.

Chapter 11

Results

I am indebted to Dr Gilda Piaggio PhD (Honorary Professor Medical Statistics Department, London School of Hygiene and Tropical Medicine London, UK) and Dr Janet Wittes PhD (Statistics Collaborative, Inc., Washington DC) for their expert advice in the interpretation of the analyses pertaining to the Primary Outcome of 24 hour morphine consumption.

11.1 Results

From May 2011 to April 2014, 108 patients were recruited and randomised to either of the two study treatments. Two patients did not undergo study intervention and subsequent surgery. The first was found to have cellulitis near the operative site and was cancelled by the operating surgeon. The second was cancelled due to lack of time on the operating list. Both of these patients were withdrawn from the "as treated" analysis. Three patients required general anaesthesia and were also withdrawn from the study as directed by the study protocol (11). 108 patients were analysed in the intention to treat (ITT) analysis and 103 in the 'as treated' analysis.

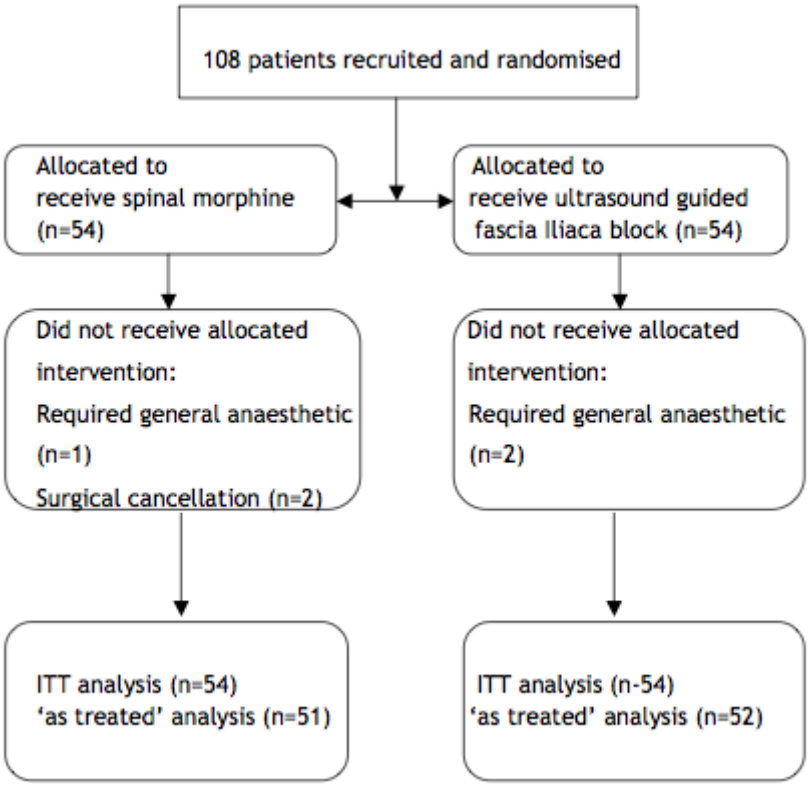

Figure 11.1-1- Consort diagram for study participants

Patient demographics were similar between groups and are displayed in Table 11.1-1. As the study was randomised, any detected differences should be attributable to chance alone.

	Spinal Morphine (n=54)	**USG Fascia Iliaca Block (n=54)**	**No data**
Age / years Median (IQR)	63.5 (55-72.75)	67 (56.25-74.75)	0
Sex = male (N, %)	22 (40.7%)	31 (57.4%)	0
Weight / kg, Mean (SD)	80.15 (13.46)	79.91 (14.29)	0
Height / cm Mean (SD)	163.8 (8.80)	165.9 (8.22)	0
BMI Median (IQR)	29.5 (27.25-32)	29(26-32.75)	0
Pre-op HR Mean (SD)	74.2 (12.39)	67.89 (10.07)	0
Pre-op SBP / mmHg Mean (SD)	135.3(14.21)	134(16.00)	0
Pre-op DBP / mmHg Mean (SD)	76.98 (10.17)	75.7 (8.92)	0
Pre-op SpO2 /% Median (IQR)	97 (96-98)	97(96-98)	2

Table 11.1-1 - Patient demographics (intention to treat)

BMI = body mass index, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, IQR = inter-quartile range, SD = standard deviation, SpO2 = peripheral capillary oxygen saturation.

11.1.1 Primary outcome

For the ‘as treated’ analysis, the medians for 24 hour morphine consumption were calculated for each group.

	Spinal morphine (n = 51)	Fascia Iliaca Block (n = 52)	P value
24 hour morphine consumption / mg median (IQR)	14 (4.5 - 32.5)	39 (18 - 49.5)	<0.001

Table 11.1-2 - Primary outcome (as treated)

The difference between the two medians was then calculated as described in chapter 11 (median with 95% confidence intervals - bias correcting bootstrapping technique with 10,000 replications). The difference between the medians was 25mg (95% CI 9.0 - 30.5mg). The median is greater than the pre-specified non-inferiority margin (δ = 10mg) though the lower end of the confidence interval crosses δ. The same analysis was performed for the ITT group giving a similar difference between medians of 24mg (95% CI 14 – 29mg). The 95% CI in this case lies completely to the right of δ. This is displayed graphically in Figure 11.1-2.

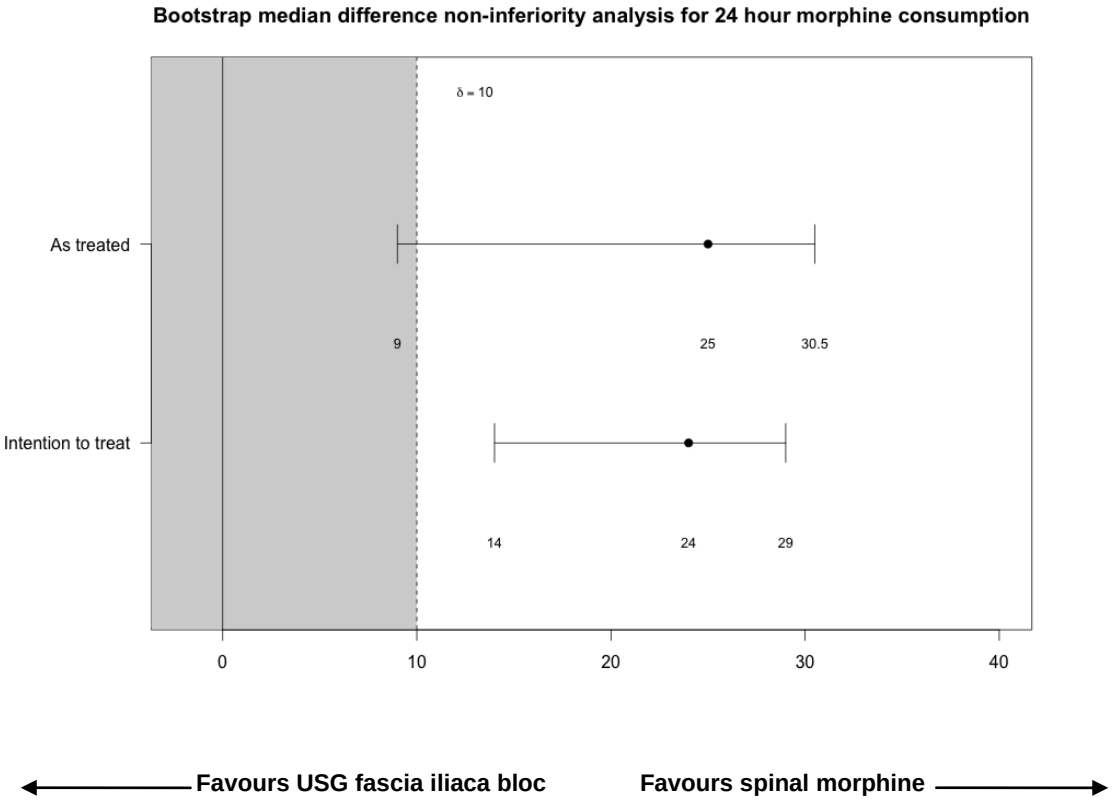

Figure 11.1-2 - As treated and ITT analyses for 24 hour morphine consumption (primary outcome).

For the ITT analysis, as the 95% CI for the difference between the medians lies fully outwith δ, it can be concluded that ultrasound guided fascia iliaca block is not non-inferior (or is inferior) to spinal morphine in providing analgesia after total hip arthroplasty. Therefore the null hypothesis is accepted.

In the "as treated analysis", the CI includes δ but is still wholly to the right of zero. The difference is therefore statistically significant but the result is technically inconclusive regarding possible inferiority of magnitude δ or worse (279).

As the results of the ITT and "as treated" analyses differed slightly, we sought further statistical advice from two experts in the analysis of non-inferiority study. The first was the primary author of the CONSORT extension statement on reporting of non-inferiority studies (279). Dr Piaggio gave the following interpretation of the Primary Outcome results:

> *"The results of the two analyses are consistent, in that the point estimate is to the right of δ. The ITT analysis clearly shows inferiority of ultrasound guided fascia iliaca block with respect to spinal morphine. The "as treated" analysis includes fewer subjects, therefore has less power to show inferiority, but still it shows that the new treatment is significantly worse than spinal morphine. From this data, I would not recommend to replace spinal morphine by USG fascia iliaca block".*

Further advice was received from the author of a paper on non-inferiority methodology published in a journal of trial design (290). Dr Wittes gave the following interpretation of the primary outcome result:

> *"The conventional rule for declaring non-inferiority is that the 95% confidence intervals for both the ITT and the as-treated analyses must be fully contained in the gray area. In other words, the "bad" end of the confidence interval must satisfy the non-inferiority bound.*
>
> *Your study shows:*
>
> *ITT: the entire confidence interval is above 0, showing a statistically significant benefit for spinal morphine.*
>
> *As treated: again, the entire confidence interval is above 0, showing a statistically significant benefit for spinal morphine. The fact that the left end of the CI is within the non-inferiority bound does not change that conclusion. To have concluded non-inferiority, the right end of the CI would have had to have been below the NI bound. So, in your case, both analyses lead to the same conclusion."*

11.1.2 Secondary outcomes

Secondary outcomes were analysed on an 'as treated' basis and statistically significant values are tabulated in Table 11.1-3 and 11.1-4. There were no statistically significant differences between the study groups for: ultrasound guided fascia iliaca block or spinal performance and associated adverse events, duration of surgery, blood loss during surgery, administration of pre-operative paracetamol, administration of intra-operative anti-emetic, time to first

administration of morphine, rest visual analogue pain scores (VAS) at 3, 24, 36 and 48 hours, VAS pain scores on movement at 3, 24, 36 and 48 hours, respiratory depression, hypotension, sedation, nausea, vomiting, urinary retention, pruritus, mobilisation at 1st attempt, power grade before mobilisation, patient satisfaction or adverse events.

Outcomes reaching statistical significance ($p < 0.05$) were: morphine consumption at all time points (3, 6, 12, 24, 36, and 48 hours), pain scores (VAS) at rest and movement at 6 and 12 hours and time to first mobilisation. Tables related to other secondary outcomes can be found in Appendix 12.

	Spinal morphine (n=51)	Ultrasound guided Fascia Iliaca Block (n=52)	p value	Missing data
Time 1st morphine / mins **Median (IQR)**	129(55-228)	130·5(60-240)	0·93	6
Morphine consumption at 3 hours / mg **Median (IQR)**	1(0-3)	3(0-11)	0·007	1
Morphine consumption at 6 hours / mg **Median (IQR)**	4(2-9)	13.5(5·75-20·75)	<0·001	0
Morphine consumption at 12 hours / mg **Median (IQR)**	10(2·5-22·5)	24(14-35·5)	<0·001	0
Morphine consumption at 24 hours / mg **Median (IQR)**	14(4·5-32·5)	39(18-49·5)	<0·001	0
Morphine consumption at 36 hours / mg **Median (IQR)**	15(5-32·5)	39.5(18-55)	<0·001	0
Morphine consumption at 48 hours – corrected / mg **Median (IQR)**	19(11-38·67)	42.33(20·25-55·08)	0·003	0

Table 11.1-3 - Morphine consumption (as treated)

	Spinal morphine (n=51)	Ultrasound guided Fascia Iliaca Block (n=52)	p value	Missing data
VAS 3 hrs at rest Median (IQR)	0 (0-1)	0 (0-4)	0·151	5
VAS 6 hrs at rest Median (IQR)	0 (0-2)	3 (0-5)	<0·001	4
VAS 12 hrs at rest Median (IQR)	0 (0-2)	2 (0-3)	0·004	4
VAS 24 hrs at rest (median, IQR)	0 (0-4)	0.5 (0-3·75)	0·83	8
VAS 36 hrs at rest Median, IQR)	0 (0-1)	0 (0-4·75)	0·52	67
VAS 48 hrs at rest (median (IQR)	1 (0-4)	1(0-2)	0·26	15
VAS 3 hrs on movement Median (IQR)	0(0-2)	0(0-4)	0·95	0
VAS 6 hrs on movement Median (IQR)	0(0-3·5)	3(0-5·25)	0·03	8
VAS 12 hrs on movement Median (IQR)	0(0-2)	2(0-4)	0·03	9
VAS 24 hrs on movement Median (IQR)	2(0-6)	2(0-4)	0·51	12
VAS 36 hrs on movement Median (IQR)	0(0-2·5)	0(0-4)	0·67	68
VAS 48 hrs on movement Median (IQR)	4(3-7)	4(2-6)	0·58	16

Table 11.1-4 - VAS pain scores (as treated)

11.1.2.1 Adverse events

There were no episodes of respiratory depression in either group. There was no statistically significant difference between groups for: patients experiencing hypotension (both SBP < 80mmHg and SBP < 25% under baseline reading), urinary retention requiring catheterisation, patients requiring an anti-emetic, patients experiencing pruritus requiring treatment, patients with pruritus considered to be distressing, ability to mobilise at first attempt, quadriceps power grade prior to first mobilisation attempt, patient satisfaction scores at 48 hours, presence of residual paraesthesia at 48 hours, occurrence of adverse events (AE) and occurrence of serious adverse events (SAE).

The nature of all Adverse events and Serious Adverse Events are tabulated below:

Nature of AE	Study Group
Post-operative pyrexia	Block
Post-operative lower respiratory tract infection	Opiate
Prolonged quadriceps motor weakness > 48 hours but resolving within one week	Block
Post-operative vasovagal episode	Opiate
Post-operative blood transfusion	Opiate
Post-operative atrial fibrillation (AF) in a patient with known paroxysmal AF	Block

Table 11.1-5- Adverse events (AE)

Nature of SAE	Study Group
Pulmonary embolism	Opiate
Pulmonary embolism	Block
Multiple pulmonary emboli	Block
Wound infection resulting in multi-organ failure	Opiate
Femoral nerve palsy (resolved completely within 3 months)	Block
Late wound infection, hyponatraemia and confusion	Block

Table 11.1-6- Serious adverse events (SAE)

All AEs and SAEs were reported to the West of Scotland Research Ethics Committee and NHS Greater Glasgow and Clyde Research and Development Department for review. Each of these incidents was discussed by the appropriate parties. No further actions were deemed necessary.

11.2 Linear regression analysis

11.2.1 Forward approach to linear regression analysis from all possible variables

Linear regression analysis was performed for the primary outcome of 24 hour morphine consumption using both forward and backward stepwise methodologies. An initial model was created by analysing each predictor variable separately against the primary outcome (24 hour morphine consumption) in a univariate unadjusted regression analysis. Only one time point for variables within a time series (i.e. morphine consumption and pain scores) was used. The time point of 12 hours was chosen for these variables as it

reached the greatest level of significance on unadjusted testing. Any variables reaching statistical significance ($p<0.05$) in these unadjusted analyses were extracted and combined to create an adjusted regression model. Factors reaching statistical significance on unadjusted analysis were: age, height, group, morphine consumption at 12 hours, pain score at rest at 12 hours, urinary retention requiring catheterisation, pruritus found to be distressing and quadriceps power grade before first mobilisation. The coefficient of determination and AIC values were calculated for the adjusted regression model using these co-variates ($R^2 = 0.897$, AIC 678).

Variable	**Unadjusted univariate analysis for all variables**		**Adjusted analysis for all variables**	
	Estimate	P value	Estimate	P value
Age	-0.99	<0.001	-0.10	0.34
Weight	0.17	0.39	-	-
Height	1.03	0.002	0.12	0.34
BMI	-0.16	0.79	-	-
Male gender	9.92	0.07	-	-
Group opiate	-16.96	0.002	1.71	0.433
Pre-op HR	-0.26	0.29	-	-
Pre-op SBP	-0.28	0.12	-	-
Pre-op DBP	-0.08	0.78	-	-
Pre-op SpO_2	-2.15	0.37	-	-

Surgery duration	-0.08	0.51	-	-
Surgical blood loss	0.03	0.11	-	-
Time first morphine administered	-0.021	0.09	-	-
Morphine consumption at 12 hours	1.55	<0.001	1.45	< 0.001
Pre-operative paracetamol administered	10.18	0.10	-	-
Intra-op anti-emetic administered	-19.37	0.18	-	-
VAS at rest at 12 hours	6.15	<0.001	0.49	0.36
No. episodes resp depression	NA	NA	-	-
No. doses naloxone	17.55	0.54	-	-
No. episodes SBP<80mmHg	4.25	0.21	-	-
No. episodes SBP>25% under baseline	-0.57	0.27	-	-

No. of post-op vasopressor doses	-4.25	0.66	-	-
Urine retention requiring catheterisation	-11.72	0.046	0.70	0.74
No. of episodes of PONV score>2	0.58	0.90	-	-
No. of post-op anti-emetic doses	-1.03	0.65	-	-
Episodes of pruritus requiring treatment	24.08	0.15	-	-
Pruritus found to be distressing	21.36	0.03	-0.71	0.84
No. episodes sedation score >2	9.47	0.74	-	-
Sedation requiring treatment	NA	NA	-	-

Time to first mobilisation	0.31	0.21	-	-
Mobilisation at first attempt	-8.91	0.20	-	-
Power grade before first mobilisation	-8.01	0.01	-1.54	0.19
Patient satisfaction at 48 hours	0.063	0.62	-	-

Table 11.2-1 – Unadjusted univariate and adjusted multi-variate linear regression models using all possible co-variates for the primary outcome (24 hour morphine consumption).

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PONV = post-operative nausea and vomiting. P values reaching statistical significance ($p<0.05$) are highlighted in yellow.

11.2.1.1 Adjusted model from all possible variables

All study variables were then combined in a full multi-variate analysis. The R^2 for this full adjusted model was 0.899 and the AIC was 546. However, a model with a large number of covariates is not desirable. Co-variates found to be statistically significant in this model were extracted and used to create a new model. The co-variates which reached statistical significance in this full adjusted analysis were: age, pre-operative SpO_2, morphine consumption at 12 hours and number of episodes of PONV score > 2. Using these as the predictor variables in a new adjusted model resulted in an R^2 of 0.903 and AIC of 733. A backward stepwise linear regression could not be performed using all variables as there was insufficient information for some of the variables.

Variable	Full adjusted analysis including all variables		Adjusted analysis including only statistically significant variables	
	Estimate	P value	Estimate	P value
Age	-0.36	0.02	-0.21	0.02
Weight	-0.01	0.99	-	-
Height	0.07	0.85	-	-
BMI	-1.01	0.21	-	-
Male gender	-4.36	0.23	-	-
Group opiate	2.012	0.42	-	-
Pre-op HR	0.023	0.80	-	-
Pre-op SBP	0.09	0.33	-	-
Pre-op DBP	-0.09	0.58	-	-
Pre-op SpO_2	-2.87	0.006	-0.49	0.52
Surgery duration	0.06	0.37	-	-
Surgical blood loss	-0.01	0.19	-	-
Time first morphine administered	0.003	0.53	-	-

Morphine consumption at 12 hours	1.48	< 0.001	1.52	<0.001
Pre-operative paracetamol administered	-0.85	0.74	-	-
Intra-op anti-emetic administered	4.75	0.99	-	-
VAS at rest at 12 hours	-0.38	0.57	-	-
No. episodes resp depression	NA	NA	-	-
No. doses naloxone	17.23	0.18	-	-
No. episodes SBP<80mmHg	-0.45	0.87	-	-
No. episodes SBP>25% under baseline	-0.41	0.12	-	-
No. of post-op vasopressor doses	-1.02	0.73	-	-

Urine retention requiring catheterisation	1.09	0.68	-	-
No. of episodes of PONV score>2	-4.67	0.03	-4.18	0.006
No. of post-op anti-emetic doses	-0.08	0.94	-	-
Episodes of pruritus requiring treatment	-3.31	0.64	-	-
Pruritus found to be distressing	0.93	0.82	-	-
No. episodes sedation score >2	NA	NA	-	-
Sedation requiring treatment	NA	NA	-	-
Time to first mobilisation	0.13	0.29	-	-
Mobilisation at first attempt	-1.42	0.74	-	-

Power grade before first mobilisation	-1.94	0.15	-	-
Patient satisfaction at 48 hours	-0.05	0.35	-	-

Table 11.2-2 - Backward approach adjusted multi-variable linear regression models using all possible co-variates for the primary outcome (24 hour morphine consumption).

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PONV = post-operative nausea and vomiting. P values reaching statistical significance ($p<0.05$) are highlighted in yellow.

11.2.1.2 Unadjusted and adjusted analyses of variables available before 24 hours

A further univariate unadjusted analysis was performed using only variables that would be available to a clinician prior to the outcome of interest being available (24 hour morphine consumption). The included variables were: age, weight, height, BMI, sex, study group, pre-operative heart rate, pre-operative systolic and diastolic blood pressure, pre-operative SpO_2, surgery duration, surgical blood loss, time first morphine administered, VAS pain score at rest at 12 hours, morphine consumption at 12 hours, intra-operative anti-emetic and pre-operative paracetamol administered. These will be known as the "initial 24 hour factors". This was considered to be more useful if a prediction tool was to be used in clinical practice. Co-variates found to be significant in this univariate unadjusted analysis (group, age, height, VAS at rest at 12 hours and morphine consumption at 12 hours) were then combined to create a new adjusted model (R2 0.896 AIC 728).

Variable	Univariate unadjusted analyses for initial 24 hour variables		Adjusted analysis for initial 24 hour variables	
	Estimate	P value	Estimate	P value
Age	-0.99	<0.001	-0.14	0.18
Weight	0.17	0.39	-	-
Height	1.03	0.002	0.07	0.53
BMI	-0.16	0.79	-	-
Male gender	9.92	0.07	-	-
Group opiate	-16.96	0.002	0.93	0.65
Pre-op HR	-0.26	0.29	-	-
Pre-op SBP	-0.28	0.12	-	-
Pre-op DBP	-0.08	0.78	-	-
Pre-op SpO_2	-2.15	0.37	-	-
Surgery duration	-0.08	0.51	-	-
Surgical blood loss	0.03	0.11	-	-
Time first morphine administered	-0.021	0.09	-	-

Morphine consumption at 12 hours	1.55	<0.001	22.81	< 0.001
Pre-operative paracetamol administered	10.18	0.10	-	-
Intra-op anti-emetic administered	-19.37	0.18	-	-
VAS at rest at 12 hours	6.15	<0.001	0.57	0.57

Table 11.2-3 - Unadjusted and adjusted linear regression models for co-variates available in the first 24 hours for the primary outcome (24 hour morphine consumption).

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PONV = post-operative nausea and vomiting. P values reaching statistical significance ($p<0.05$) are highlighted in yellow.

11.2.1.3 Adjusted model for variables available before 24 hours

An adjusted model containing all of the "initial 24 hour factors" (age, weight, height, BMI, sex, study group, pre-op heart rate, pre-op systolic and diastolic blood pressure, pre-op SpO_2, surgery duration, surgical blood loss, time first morphine administered, VAS score at rest at 12 hours, morphine consumption at 12 hours, intra-operative anti-emetic and pre-operative paracetamol administered) was then created (R2 0.908 AIC 644). Factors which were found to be significant in this adjusted model (age, surgery duration and 12 hour morphine consumption) were analysed to give a model with an R^2 of 0.898 and AIC of 751.

Variable	Adjusted analysis for initial 24 hour variables		Adjusted analysis for initial 24 hour variables reaching significance	
	Estimate	P value	Estimate	P value
Age	-0.24	0.04	-0.17	0.054
Weight	-0.23	0.22	-	-
Height	10.27	0.29	-	-
BMI	-0.40	0.46	-	-
Male gender	-4.53	0.11	-	-
Group opiate	1.6	0.43	-	-
Pre-op HR	-0.06	0.49	-	-
Pre-op SBP	-1.01	0.94	-	-
Pre-op DBP	0.04	0.73	-	-
Pre-op SpO_2	-2.15	0.37	-	-
Surgery duration	0.11	0.03	0.03	0.41
Surgical blood loss	0.01	0.07	-	-
Time first morphine administered	0.01	0.06	-	-

Morphine consumption at 12 hours	1.55	<0.001	1.52	<0.001
Pre-operative paracetamol administered	-0.16	0.94	-	-
Intra-op anti-emetic administered	-2.11	0.64	-	-
VAS at rest at 12 hours	-0.02	0.97	-	-

Table 11.2-4 - Multivariate adjusted linear regression model for co-variates available in the first 24 hours for the primary outcome (24 hour morphine consumption).

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PONV = post-operative nausea and vomiting. P values reaching statistical significance ($p<0.05$) are highlighted in yellow.

11.2.1.4 Backward stepwise linear regression from variables available before 24 hours

A backward stepwise linear regression was then performed on all of the "initial 24 hour" covariates. The co-variates found to create the best model fit using this approach were: age, height, weight, sex, pre-operative SpO_2, surgical time, surgical blood loss, time first morphine administered and morphine consumption at 12 hours. The R^2 for this model was 0.916 and the AIC was 642. This was considered to be the best fit from all the models tested.

Variable	Adjusted analysis for initial 24 hour variables	
	Estimate	P value
Age	-0.25	0.006
Weight	-	-
Height	10.27	0.009
BMI	-	-
Male gender	-4.54	0.07
Group opiate	-	-
Pre-op HR	-	-
Pre-op SBP	-	-
Pre-op DBP	-	-
Pre-op SpO_2	-1.5	0.049
Surgery time	0.11	0.01
Surgical blood loss	0.01	0.06
Time first morphine administered	0.01	0.04
Morphine consumption at 12 hours	1.54	<0.001

Pre-operative paracetamol administered	-	-
Intra-op anti-emetic administered	-	-
VAS at rest at 12 hours	-	-

Table 11.2-5 - Backward stepwise regression approach for co-variates available in the first 24 hours for the primary outcome (24 hour morphine consumption).

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PONV = post-operative nausea and vomiting. P values reaching statistical significance ($p<0.05$) are highlighted in yellow.

11.3 Logistic regression analysis

Logistic regression analysis was performed on dichotomous outcomes which were felt to be of greatest clinical significance (i.e. those outcomes felt to relate most closely to a patient's recovery and post-operative experience).

11.3.1.1 Hypotension - SBP > 25% below baseline

Unadjusted univariate logistic regression was performed for variables which were suspected clinically to have a potential effect on episodes of SBP > 25% under baseline. Neither being in the spinal morphine group ($p=0.49$), gender ($p=0.14$), nor 3 hour morphine consumption ($p=0.48$) had an effect on the number of episodes of SBP >25% below baseline in the post-operative period.

Morphine consumption at 6 hours was associated with decreased episodes of SBP >25% below baseline ($p = 0.03$). OR = 0.96 (95% CI 0.92 to 0.99). Therefore for every 1mg increase in morphine in a 24 hr period, the odds of having a hypotensive episode were reduced by 4%. Group did not influence this ($p= 0.09$)

Similarly, morphine consumption at 12 hours (p = 0.02, OR = 0.97 [95% CI 0.95 to 0.99]), 24 hours (p=0.009, OR = 0.98 [95% CI 0.96 to 0.99]), and 48 hours (p=0.008, OR = 0.98 [95% CI = 0.96 - 0.99]) were associated with decreased numbers of SBP >25% under baseline. Therefore for every 1mg increase in morphine in 24 hr period, the odds of having a hypotensive episode were reduced by 2%. Group did not influence this (p= 0.098 and 0.086 respectively).

Age was associated with an increase in the numbers of episodes of SBP>25% under baseline (p= 0.008). The Odds Ratio (OR) was 1.05 (95% CI 1.02 to 1.10). Therefore for every 1 year increase in age, the odds of having a hypotensive episode were increased by 5%.

Pre-operative SBP was also associated with episodes of post-operative hypotension >25% under baseline (p = 0.0002, OR 1.06 [95% CI 1.03 to 1.10]). Therefore for every 1mmHg increase in pre-operative SBP, the odds of an episode of hypotension increased by 6%

11.3.1.2 Urinary retention requiring catheterisation

Factors which were considered to pose a theoretical risk of increased likelihood of urinary retention requiring catheterisation were analysed. Neither study group (p=0.27), age (p=0.14), gender (p=0.33), BMI (p=0.09), weight (p=0.18), surgical blood loss (p=0.94), post-operative hypotension (SBP >25% under baseline, p=0.23), nor pain score at rest at 12 hours (p=0.4334) increased the odds of requiring catheterisation. 24 hour morphine consumption almost reached statistical significance with a p value of 0.052 (OR 0.98, [95% CI 0.96 to 0.99]).

11.3.1.3 Post-operative nausea and vomiting

The odds of developing post-operative nausea and vomiting as defined by nausea score > 2 were not affected by: age (p=0.15), gender (p=0.62) weight (p=0.29), height (p=0.41), pre-operative systolic blood pressure (p=0.16), study group

(p=0.62), 24 hour morphine consumption (p=0.84), hypotension (SBP > 25% under baseline, p=0.45), surgical time (p= 0.52) or surgical blood loss (p=0.22).

Increasing BMI increased the odds of experiencing PONV (p= 0.04, OR 1.13 [95% CI 1.01 to 1.28]). Therefore for every 1 unit increase in BMI, the odds of a patient suffering PONV increased by 13%. VAS pain score at rest at 12 hours also reached statistical significance (p=0.049, OR 1.25 [95% CI 0.99 to 1.58]). Therefore for every 1 unit increase in the VAS pain score at rest at 12 hours, the odds of experiencing an episode of PONV was increased by 25%.

11.3.1.4 Mobilisation

Mobilisation at first attempt was unaffected by: age (p=0.29), sex (p=0.21), BMI (p=0.43), weight (p=0.72), height (p= 0.99), study group (p=0.1), pre-operative systolic blood pressure (p=0.2), PONV (p=0.62), urinary catheterisation (p=0.11), 24 hour morphine consumption (p=0.20), pain scores at rest at 12 hours (p=0.85) and surgical time (p=0.21).

The odds of mobilising at the first attempt was affected by the amount of blood lost peri-operatively (p=0.02, OR 0.99 [95% CI 0.99 to 0.99]). Therefore for every 1ml additional blood loss, there was a 0.3% decreased chance of the patient mobilising at the first attempt. Similarly for post-operative hypotension as defined by SBP > 25% below baseline (p=0.05, OR 0.92, [95% CI 0.85 to 0.99]. Having an episode of post-operative hypotension reduced the odds of mobilising successfully on the first attempt by approximately 8%.

11.4 Chapter 11 Summary

- For the primary outcome of 24 hour morphine consumption, the ITT analysis clearly shows inferiority of ultrasound guided fascia iliaca block with respect to spinal morphine. The “as treated” analysis includes fewer subjects, therefore has less power to show inferiority, but still shows that the new treatment is significantly worse than spinal morphine. From this data, we would not recommend to replace spinal morphine by USG fascia iliaca block”.

- Secondary outcomes reaching statistical significance ($p < 0.05$) in favour of spinal morphine were: morphine consumption at all time points (3, 6, 12, 24, 36, and 48 hours), pain scores (VAS) at rest and movement at 6 and 12 hours and time to first mobilisation.

- The factors found to create the best model for predicting 24 hour morphine consumption were: age, BMI, surgical time, surgical blood loss, time first morphine administered and morphine consumption at 12 hours.

Chapter 12

Discussion

12.1 Discussion

12.1.1 Study design and methodological considerations

This study was designed following the publication by Dolan *et al* which showed the impoved reliability of fascia iliaca block when performed using ultrasound guidance (10). The effects upon analgesia were not examined in this study and we were interested to investigate this in the setting of total hip replacement. In the only study examining the use of fascia iliaca block for THA, Stevens *et al* compared a modified landmark technique fascia iliaca block with placebo block in patients undergoing THA (274). They noted a morphine sparing effect in the fascia iliaca block group at 24 hours which they hypothesised may have been due to increased proximal spread of local anaesthetic resulting in improved anaesthesia in the upper third of the thigh, The duration of analgesia provided by ultrasound guided fascia iliaca block has not been investigated, though in a systematic review and meta-analysis of peripheral nerve blocks performed with peripheral nerve stimulation or ultrasound guidance, blocks performed using ultrasound were found to last around 25% longer (278). We hypothesised that using ultrasound guidance to place the fascia iliaca block would result in more reliable placement of anaesthetic and allow for a greater degree of proximal spread and potentially longer duration of effect. As ultrasound guided fascia iliaca block had not yet been investigated as an analgesic modality for primary THA, we felt it important to investigate this in the first instance.

It could be argued that the use of a fascia iliaca catheter with infusion of local anaesthetic might have had even greater potential for long lasting analgesia and would have been a suitable comparison for spinal morphine. As this is a more invasive technique, we felt that it was important to investigate the less invasive option in the first instance.

The study was initially designed as a traditional superiority study. On submission of the protocol to the *Trials* journal (a journal of trial methodology edited by the authors of the CONSORT statements), we were advised that a non-inferiority

design was more appropriate. This was because we did not think that ultrasound guided fascia iliaca block was likely to be superior to spinal morphine in the provision of analgesia after THA. Our initial hypothesis was that ultrasound guided fascia iliaca block would provide analgesia which was comparable to spinal morphine in the provision of analgesia after THA. We were encouraged by the results of both Dolan et al and Stevens et al that ultrasound guided fascia iliaca block had the potential to provide more reliable and prolonged analgesia than a standard fascia iliaca block. If the ultrasound guided block was associated with fewer adverse effects than spinal morphine, then it could be considered as a preferable option. The non-inferiority design encompasses these principles in that if a new treatment option is found to be non-inferior to a more established treatment option, then it may be preferred if it has some other advantage. The results of the study are clear in that ultrasound guided fascia iliaca block is inferior to spinal morphine in the provision of analgesia after THA. However, we could not have known this at the time of study design.

Spinal morphine (rather than spinal diamorphine) was utilised in this study as it is more widely used internationally and was therefore felt to be of greater relevance to the international anaesthetic community.

12.1.2 Primary outcome

Twenty four hour morphine consumption was chosen as the primary outcome in this study as analgesic consumption can be used as a marker for patients' experience of pain. Pain scores themselves are difficult to interpret and while providing some interesting information, are highly subjective and subject to inter- and intra-individual variation.

In this randomised, controlled, double blind, non-inferiority study the median value for 24 hour morphine consumption was 14mg (IQR 4.5 - 32.5mg) in the spinal morphine group and 39mg (IQR 18 – 49.5mg) in the ultrasound guided fascia iliaca block group ($p<0.001$). The difference between the two medians was calculated as described in chapter 11 (median with 95% confidence intervals - bias correcting bootstrapping technique with 10,000 replications). The difference between the medians for the 'as treated' group was 25mg (95% CI 9.0

- 30.5mg). The same analysis performed in the ITT analysis gave a difference between medians of 24mg (95% CI 14 – 29mg) which is greater than the pre-specified non-inferiority margin (δ = 10mg).

For the ITT analysis, it can be concluded that ultrasound guided fascia iliaca block is inferior to spinal morphine in providing analgesia after total hip arthroplasty. In the "as treated analysis", the CI includes δ but is still to the right of zero. Statistical advice from two separate experts in non-inferiority trial methodology was sought (see Chapter 12). The conclusion of both authors was that ultrasound fascia iliaca block was not non-inferior to spinal morphine in the provision of analgesia after THA and could not be recommended as a replacement for spinal morphine.

The values for morphine consumption seen in our study are within a similar range to the findings of an earlier study of 44 patients which compared a modified landmark-based fascia iliaca block with placebo block in patients receiving a spinal with fentanyl for total hip replacement (274). In this study, patients who received the fascia iliaca block with local anaesthetic used a median of 23mg morphine in 24 hours, whereas the group receiving the placebo block (with 0.9% saline) received 37.5mg ($p<0.001$). This may indicate that the fascia iliaca blocks in our study were no better than placebo, though it should be noted that the patients in the study by Stevens *et al* also received fentanyl in their spinal injection which may have yielded some additional analgesic effects (274). In addition, patients in the intervention arm of this study received 150mcg of clonidine as part of the injectate used to perform the fascia iliaca block. This may also have influenced analgesic requirements in this group as clonidine has analgesic as well as sedating effects (244;297). In a spinal morphine dose finding study by Rathmell *et al*, patients receiving lone spinal anaesthesia with no spinal opioid required around 75mg of intravenous morphine in the first 24 hours post-operatively (226). This is significantly more than was required by patients receiving the ultrasound guided fascia iliaca block in this study and would indicate that patients were likely to have received some analgesia from the block.

In other studies examining femoral and “3 in 1” nerve blocks for THR (see Table 9.4-1), 24 hour post-operative consumption of intravenous morphine (or its equivalent when other opioids were used) ranged from 7mg to 60mg. However, these studies were very heterogeneous and mainly randomised patients to receive general anaesthesia in addition to nerve block or control intervention making direct comparison difficult (244;245;248;249;253). When administering 0.1mg of spinal morphine to patients undergoing THR, mean IV morphine consumption in 24 hours is reported to lie anywhere between 10 and 30mg (219;221). Our median consumption of 14mg in the spinal morphine group would therefore be in keeping with this range.

Unfortunately, not all patients received pre-operative paracetamol despite this being prescribed for all patients. Reasons for this were due to availabaility of nursing staff to give the medication in a timely fashion. The ward nurses who were responsible for administering the paracetamol had no knowledge of the treatment allocation and therefore any omissions were entirely random and should have affected each group equally. In the spinal morphine group, 64.7% of patients received pre-operative paracetamol while in the fascia ililaca group, this was slightly greater at 78.8% (p 0.17). All patients were prescribed regular paracetamol post-operatively. While more patients in the fascia iliaca group received paracetamol pre-operatively, it seems unlikely that this one off dose of simple analgesia would have significantly altered the results of the study. As patients in the fascia iliaca group had inferior analgesia despite the above theoretical advantage, this reinforces the result of the primary outcome further.

One of the limitations of our study relates to the fact that the efficacy of the ultrasound guided fascia iliaca block was not confirmed prior to the administration of spinal anaesthesia. This was omitted on a pragmatic level in view of the practicalities of undertaking this study within an NHS setting. It would not have been possible to assess the efficacy of the block without significantly delaying the progress of the operating list due to lack of personnel and facilities. This would have made the continuation and completion of the study extremely difficult due to the significant pressures already on the orthopaedic service. It would also not have been possible to assess block efficacy without unblinding the investigator. As pre-operative assessment of the

effects of fascia iliaca block would not normally be performed prior to the induction of anaesthesia in patients undergoing elective THR, we considered that the omission of this assessment was more representative of “real life” practice.

Our department is a tertiary referral centre for trauma and orthopaedic surgery and has significant expertise in the field of regional anaesthesia (10;224). This includes a study comparing the efficacy of ultrasound guided versus the landmark technique for the performance of fascia iliaca blocks. This study concluded that the ultrasound guided method was more effective in achieving sensory loss in the anterior, medial, and lateral aspects of the thigh from 47% to 82% ($p<0.001$) as well as improving both femoral ($p=0.006$) and obturator motor block ($p=0.033$) (10). Study investigators were trained by experts within the department in order to ensure that they were proficient in performing ultrasound guided fascia iliaca blocks. The majority of the blocks were performed by RJK (75/108, 69.4%) with other investigators performing the remainder of the blocks (AG = 13/108, PH = 7/108, KP 7/108, AM = 6/108).

Reasons for poorer analgesia in the ultrasound guided fascia iliaca block group can be explained by the innervation of the hip joint. Even if a fascia iliaca block was entirely successful in anaesthetising the lateral cutaneous nerve of thigh, femoral and obturator nerves, it would still be unlikely to provide complete anaesthesia and hence analgesia, due to the variable innervation received from the sacral plexus as well as the ilioinguinal, iliohypogastric and genitofemoral nerves. Sciatic nerve block is not routinely performed for total hip replacement due to concerns about poor post-operative mobility as well as a lack of published evidence.

The paper by Stevens *et al* examining a landmark based fascia iliaca block postulated that the reason for the improved analgesia seen with their fascia iliaca block was due to the modified approach whereby the point of needle insertion was 1cm above the inguinal ligament (274). It was hypothesised that this may have aided the spread of local anaesthetic towards the lumbar plexus hence improving the chance of anaesthetising the ilioinguinal, iliohypogastric and genitofemoral nerves in addition to the femoral, obturator and lateral cutaneous nerve of thigh. This method of block performance is unsuitable for

patients with previous mesh inguinal hernia repair and may carry an increased risk of bowel perforation or inferior gastric artery puncture. This was a study of 44 patients and there is no description within the paper of the methodology used to calculate sample size. It is therefore unclear whether this study is adequately powered. There have been no other trials to date which confirm the results of this study.

12.1.2.1 A discussion of intention to treat and 'as treated' analyses in non-inferiority studies

The use of an ITT analysis in a non-inferiority study would normally be expected to generate a greater risk of a type I error (declaring non-inferiority when this is not the case) than the "as treated" analysis. This is why the "as treated" analysis has been traditionally preferred for this type of trial (279;291). This is the opposite of what might be expected in a traditional superiority study where the ITT analysis penalises the poorly conducted trial and is considered to be at less risk of producing a type I error. The erroneous rejection of the null hypothesis in a non-inferiority ITT analysis can thus be indicative of a poorly designed and / or run study and is an inherent problem with the non-inferiority design. Despite these concerns, there is an argument that the ITT analysis is still the most valid to utilise, even in a non-inferiority study. This is on the basis that any trial should be conducted using rigorous methodology regardless of whether it is of superiority or non-inferiority design, as well as the fact that utilisation of ITT maintains the virtues of randomisation. It is therefore considered important to apply both types of analyses to a non-inferiority study in order to prevent any "informative censoring" and in the recognition that both types of analyses have inherent strengths and weaknesses.

There is a further argument that a third placebo arm should be utilised to ensure that any new treatment is in fact superior to placebo and that there is some within-trial validation of the value used for δ. This is due to the phenomenon of "biocreep" whereby an inferior treatment, wrongly labelled as being non-inferior in a poorly conducted non-inferiority study, erroneously becomes accepted as a control for other studies. This can result in new treatments being compared to a treatment which may be no better than placebo (292). It was felt

inappropriate to include a placebo arm in this study as this would have resulted in patients having no analgesia in place for when the spinal anaesthetic wore off. This was felt to be unethical and unnecessary given the strength of evidence surrounding the established efficacy of spinal morphine (215;298).

The value of δ clearly influences the results (as well as the sample size) in a non-inferiority study. The calculation of δ is difficult and there are a number of accepted methods for doing so. The value chosen for δ needs to justified by statistical and clinical reasoning as well as being tailored to the particular clinical context. As such, it is extremely difficult to define a rule that adequately covers all clinical situations. For this reason, it is vital that the nature of the study (be it non-inferiority or superiority) as well as the value chosen for δ is defined *a priori*. Without this, a value for δ can easily be declared retrospectively in order to influence results in favour of non-inferiority. The protocol for this study, including a thorough description of trial methodology and statistical considerations including the calculation of δ, was published in a journal of trial methodology prior to embarking upon recruitment (11). This journal is edited by the authors of the Consolidated Standards of Reporting Trials (CONSORT) statements (299). The CONSORT statements are an evidence-based, minimum set of recommendations for reporting randomised studies. They offer a standardised way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting and aiding critical appraisal and interpretation. The CONSORT statements are endorsed by prominent general medical journals, many specialty medical journals and leading editorial organisations.

In this study, we have demonstrated a result which is in direct opposition to the methodological concerns highlighted above. In the ITT analysis, non-inferiority has been rejected (i.e. the null hypothesis has been acccepted) and we can conclude that the ultrasound guided fascia iliaca block is in fact inferior to spinal morphine. The “as treated” analysis result is technically inconclusive (and has fewer subjects and hence slightly less power) although again shows that the ultrasound guided fascia iliaca block is “significantly worse” than spinal morphine. Neither type I error nor type II error (i.e. falsely rejecting a truly non-inferior treatment) seem likely in this situation.

12.1.2.2 Study withdrawals

In reviewing the result of the primary outcome, it is of interest to consider why five patients (4.6%) were removed from the analysis. This non-completion rate is considered to be low when compared to other RCTs (300). Two patients were removed due to having surgery cancelled (one for cellulitis at the operative site and one due to lack of operating time). Both of these patients were in the spinal morphine group. The reasons for cancellation and resultant withdrawal were entirely independent of study involvement and the surgeon making these decisions had no knowledge of study group allocation. Neither patient received any intervention relating to the study other than randomisation. No data other than demographics were available for these patients. A further three patients (one from the spinal morphine group and two from the fascia iliaca group) were withdrawn from the analysis due to the fact they required a general anaesthetic (GA). This was a pre-determined reason for withdrawal as published in the study protocol. In all cases of general anaesthesia being administered, the patient had received the ultrasound guided fascia iliaca block (either with local anaesthetic or saline). In one case, the spinal was not able to be administered by the anaesthetist and was therefore abandoned in favour of a GA. In the other two cases, the spinal was administered, however one patient had no demonstrable motor block and the other developed myoclonic jerking during surgery (for which no sinister cause could be found) and both patients required a GA to facilitate surgery. Therefore, in only one of the three cases, was there any certainty that the full spinal drug dose had been administered. In addition, the drugs involved in the administration of a GA may have impacted upon the results and it was felt necessary to remove these patients from the “as treated” analysis. As the study was double blind, neither patient nor investigator knew which treatment had been administered prior to the GA being administered. In addition, the person making the decision to perform a GA was the usual anaesthetist for the theatre list who had no ongoing involvement with data collection and was not part of the study personnel. These factors aimed to minimise bias as far as possible.

12.1.2.3 Linear regression modeling for the primary outcome

The linear regression analysis found to result in the best model fit was a backward stepwise approach using co-variates which would be available to the clinician within the first 24 hours post-operatively. This approach was investigated as a model using factors which were available to a clinician within the first 24 hours was considered more useful if a prediction tool was to be used in clinical practice. The co-variates found to create the best predictive model for 24 hour morphine consumption were: age, height, weight, sex, pre-operative SpO_2, surgical time, surgical blood loss, time first morphine administered and morphine consumption at 12 hours. The R^2 for this model was 0.916 and the AIC was 642.

Age is a well established predictor of analgesic requirements in the acute post-operative setting and is negatively correlated with the dose of analgesia required (301;302). While weight and BMI are thought to have some influence on analgesic requirements, this is thought to be clinically insignificant compared with overall inter-individual variability (301;303). In keeping with the findings of others, we found surgical factors such as longer operating time may have an influence on post-operative analgesia (304;305). Prolonged surgery and/or greater levels of blood loss may be indicative of more difficult surgery requiring greater tissue manipulation and is plausible as an influencing factor on analgesia consumption post-operatively. Early analgesia consumption has also been found to correlate with later analgesic requirements in adolescents undergoing scoliosis surgery (306). An interesting systematic review of 48 studies examined predictors of post-operative pain and analgesic requirements after surgery. Factors found to be predictive of post-operative pain were: pre-existing pain, anxiety (or other psychological distress), age and type of surgery. Factors predictive of post-operative analgesic consumption were: type of surgery, age and psychological distress (including anxiety). Major orthopaedic surgery was found to be a risk factor for post-operative pain. Many of the patients in our study would have had pre-existing pain which has precipitated the surgery and therefore have two inherent predictive factors for the development of pain and requirement for analgesia before any other considerations are made. An assessment of pre-operative pain and psychological distress was not performed

as part of this study, though patients on strong opioid analgesia or with a diagnosis of chronic pain pre-operatively were excluded. While potentially useful as a predictive tool, this model requires further validation before being employed in the clinical setting.

12.1.3 Secondary outcomes

We hypothesised that if an ultrasound guided fascia ilaca block was non-inferior compared with spinal morphine in the provision of analgesia after THA, that it may actually be advantageous if it reduced the incidence of side effects commonly associated with spinal morphine. These include: nausea and vomiting, pruritus, urinary retention, sedation and most seriously, respiratory depression. It should be noted that the study was not powered for all secondary outcomes.

Secondary outcomes reaching statistical significance ($p < 0.05$) were: morphine consumption at all time points (3, 6, 12, 24, 36, and 48 hours), pain scores (VAS) at rest and movement at 6 and 12 hours and time to first mobilisation. Pain scores at both rest and movement were not statistically significantly different at 3 hours (when the effects of the spinal anaesthetic would be expected to be providing at least some analgesia) nor at 24 and 48 hours. Morphine consumption has been discussed in detail under “Primary outcome”. The other secondary outcomes reaching statistical significance will be discussed in turn. Further outcomes of interest will then be discussed (PONV, pruritus, and hypotension).

12.1.3.1 VAS Pain scores

The fact that pain scores were not significantly different after 12 hours could be attributable to the fact that the patients titrated their own analgesia to effect and is one of the reasons why pain scores can be difficult to interpret. The fact that this took 12 - 24 hours to achieve may be explained by the fact that there is a learning curve in managing to use a patient controlled analgesia (PCA) device and that patients in the ultrasound guided fascia iliaca group may have had to

"catch up" with analgesia requirements if their pain relief was inadequate when the spinal anaesthetic wore off. Whilst there was a statistically significant difference in VAS pain scores at 6 and 12 hours, the clinical significance of this is debatable. The distinction between statistically significant and clinically significant differences in VAS pain scores has not been extensively studied in the post-operative population (307). Pain scores were generally low (highest median score 3/10). This makes differences in pain scores (when scores are generally within the "mild" category) difficult to quantify. It may be that while differences reached statistical significance, that there was no clinically significant difference between groups. On comparing patient satisfaction scores at 48 hours, it would seem that there was no difference between the groups and this may back up the assertion that there was no clinically significant difference in pain scores between the groups. The subject of clinical significance between pain scores in the post-operative setting is one where further research is required.

The first 24 hours after THR are considered to be the most painful with analgesic requirements reducing substantially from this point (222). This was evident in our study where the majority of the morphine consumption (including oral morphine given once the PCA was removed) was consumed within the first 24 hours.

12.1.3.2 Mobilisation

Mobilisation is a highly important aspect of the patient's recovery and improved mobility is ultimately one of the main goals of THR surgery. In this study, we looked at three different factors relating to post-operative mobilisation: time to first mobilisation, power grade of straight leg raise, and mobilisation at first attempt. We defined mobilisation as the ability to mobilise from bed to chair as this is the initial assessment used by physiotherapy staff in our institution. Time to first mobilsation in hours was statistically significantly shorter in the opioid group when compared to the fascia iliaca group: median 23 hours (IQR 19-25.5) vs 25 hours (20-42), p=0.04. Mobility at the first attempt was slightly higher in the opioid group (44, 86.3%) compared with the USG fascia iliaca block group (38, 73%) though this was not statistically significant (p=0.16). Power grade for

knee extension was assessed using the MRC scale. This was found to be the same between groups; median 4 (IQR 4 – 5). This would go against the theory that any differences in the ability to mobilise could be attributed to the ongoing effects of the nerve block.

0	No movement
1	Flicker is perceptible in the muscle
2	Movement only if gravity eliminated
3	Can move limb against gravity
4	Can move against gravity & some resistance exerted by examiner
5	Normal power

Table 12.1-1 - MRC power grade scale

Comparison with other studies is difficult for this outcome due to the variety of ways in which mobility can be assessed. For example, in a study of 45 patients undergoing THR and randomised to either PCA, CFNB or epidural, day of first ambulation with a walker was (3.9 ± 1 vs 3.2 ± 0.7 vs 3.5 ± 0.7 days ($p = 0.09$), respectively (247). In a study of 47 patients comparing CFNB and CLPB, distance of ambulation was assessed as a measure of mobility. This was found to be significantly poorer in the CFNB group (266). In a larger study of 225 patients randomised to receive either PCA, CFNB or CLPB, all patients managed to ambulate on the first post-operative day. However, the number of patients who were able to walk > 12 metres at forty-eight hours was significantly greater in the CLPB group compared with both the CFNB group and the PCA group (14.7%, 1.3%, and 1.3%, respectively; $p < 0.003$) (248).

On performing logistic regression analysis, mobilisation at first attempt was unaffected by: age ($p=0.29$), sex ($p=0.21$), BMI ($p=0.43$), weight ($p=0.72$), height

(p= 0.99), study group (p=0.1), pre-operative systolic blood pressure (p=0.2), PONV (p=0.62), urinary catheterisation (p=0.11), 24 hour morphine consumption (p=0.20), pain scores at rest at 12 hours (p=0.85), and surgical time (p=0.21).

The odds of mobilising at the first attempt were affected by the amount of blood lost peri-operatively (p=0.02, OR 0.997 [95% CI 0.994 to 0.999]). Therefore for every 1ml additional blood loss, there was a 0.3% decreased chance of the patient mobilising at the first attempt. Similarly for post-operative hypotension as defined by SBP > 25% below baseline (p=0.05, OR 0.92, [95% CI 0.85 to 0.99]. Having an episode of post-operative hypotension therefore reduced the odds of mobilising successfully on the first attempt by approximately 8%.

12.1.3.3 Nausea and vomiting

While not statistically significantly different between groups, the incidence of nausea requiring anti-emetics was relatively high in this study. When examining these outcomes, it is worth noting exactly what definition of each outcome is being used. For example, in this study post-operative nausea and vomiting PONV) as defined by a PONV score > 2 (moderate nausea) occurred in 7 patients (13.7%) in the spinal morphine group and 9 (17.3%) in the USG fascia iliaca group. If defining nausea as the requirement for an anti-emetic to be administered, then the incidence of nausea was higher at 25 patients (49%) in the spinal morphine group, and 24 (46%) in the USG fascia iliaca group.

0	**None**
1	Mild nausea
2	Moderate nausea
3	Severe nausea
4	Patient vomiting

Table 12.1-2 – PONV Score

Many of the studies analysed in the systematic literature review in Chapter 9 involved the patients being given nerve blocks in addition to general anaesthesia. It is difficult to compare the outcome of nausea between patients receiving spinal and general anaesthesia as this would be a significant confounding factor.

Two meta-analyses of intrathecal morphine can be used for comparison. In a 2009 meta-analysis of 28 RCTs (1314 patients) by Gehling *et al*, the incidence of nausea was 28% in the control group (no spinal morphine) with a relative risk (RR) of 1.3 in the spinal morphine group (214). In a more recent meta-analysis of 65 RCTs (3338 patients) by Popping *et al* (215), the incidence of nausea was 16.5% in the control group and 31.9% in the spinal morphine group. While both studies included a high proportion of orthopaedic studies, it should be noted that they compared wide ranges of spinal morphine (25-2500mcg). The incidence of PONV in our study therefore depends upon the definition used. While examining reported PONV scores, the incidence appears to be within an acceptable and expected range. However, the administration of anti-emetics is high indicating that PONV was either under-reported in terms of the performance of PONV scoring, or over-treated by staff eager to prevent nausea. Rates may also be higher than expected due to the systemic morphine administered via PCA post-operatively.

We further compared our results to more specific studies involving spinal anaesthesia ± nerve block for THA. In a spinal morphine dose-finding study performed in 60 patients > 65 years of age, patients were randomised to receive, 0, 50, 100 or 200 mcg of spinal morphine. The incidence of nausea as defined by patient request for anti-emetic was 1/15 (6.7%), 5/15 (33.3%), 6/15 (40%) and 6/15 (40%) respectively (218). Another spinal morphine dose-finding study including 143 patients found the rate of PONV to be > 60% in all groups (spinal morphine dose 0.025mg, 0.05mg. 0.1mg, 0.2mg) (221). In a comparison of landmark based modified fascia iliaca block with placebo in patients receiving spinal anaesthesia with local anaesthetic and fentanyl, Stevens *et al* recorded a nausea rate of 5/22 (22.7%) in each study group (274). In a large study of 225 patients by Marino *et al* (248), patients were randomised to receive either CLPB plus PCA, CFNB plus PCA or PCA alone. The incidence of nausea (again definition

not specified) was reported as 9 (12%) in the CLPB group, 34 (45.9%) in the CFNB group, and 48 (64.9%) in the PCA group. This was despite the administration of metoclopramide 10mg pre-operatively. A study by Becchi *et al* reported an incidence of nausea (as defined by patient complaint) as 25/35 (71.4%) in the group receiving morphine and ketorolac infusion compared with 4/35 patients (11.4%) in the group who received CLPB (p<0.001) (268). Rates of PONV therefore vary significantly and are dependent upon the definition used.

After performing logistic regression analysis on our data, the odds of developing post-operative nausea and vomiting as defined by nausea score > 2 were not affected by: age (p=0.15), gender (p=0.62) weight (p=0.29), height (p=0.41), pre-op systolic blood pressure (p=0.16), study group (p=0.62), 24 hour morphine consumption (p=0.84), hypotension (SBP > 25% under baseline, p=0.45), surgical time (p= 0.52), or surgical blood loss (p=0.22).

Increasing BMI increased the odds of experiencing PONV (p= 0.04, OR 1.13 [95% CI 1.01 to 1.28]). Therefore for every 1 unit increase in BMI, the odds of a patient suffering PONV increase by 13%. VAS pain score at rest at 12 hours also reached statistical significance (p=0.05, OR 1.25 [95% CI 0.99 to 1.58]). Therefore for every 1 unit increase in the VAS pain score at rest at 12 hours, the odds of experiencing an episode of PONV was increased by 25%.

12.1.3.4 Pruritus

Pruritus is considered to be major side effect of spinal opioids, can contribute to patient discomfort and can be difficult to treat. Dose finding studies have reported a dose-related increase in pruritus with increasing doses of spinal morphine. 0.1mg is considered to be a dose which combines analgesic efficacy with an acceptable side-effect profile (218;221).

The incidence of pruritus was not statistically significantly different between study groups. The number of patients requiring treatment for itch was 2 (3.9%) in the opioid group and 1 (1.9%) is the USG fascia ililaca group. This was lower than the number of patients who reported itch when they were asked about it directly by study personnel (6[11.8%] vs 3[5.8%]). The incidence of pruritus is

lower than seen in other studies. For example, Slappendel *et al* reported an incidence of around 38%, and Rathmell *et al* and Murphy *et al* reported a rate of 40% in patients receiving 0.1mg of spinal morphine (218;219;221). In a large meta-analysis examining the effects of a wide range of dose of spinal morphine, the incidence was reported as 12% in the control group and 37% in the spinal morphine group (214). A further larger meta-analysis reported a rate of 4.4% in the control group and 29.2% in the spinal morphine group (215). A dose-response relationship was illicited in both meta-analyses.

12.1.3.5 Hypotension

The incidence of hypotension as defined by SBP < 80mmHg and SBP > 25% under baseline reading was not statistically significantly different between study groups. Hypotension is a common side effect of spinal anaesthesia and results from pre-ganglionic sympathetic blockade. Following surgery, hypotension can be due to a number of factors including: hypovolaemia, ongoing haemorrhage and sepsis and so any patient exhibiting hypotension requires medical review in order to make a proper assessment. In our study, the incidence of severe hypotension (defined as SBP < 80mmHg) was low at 1 (1.9%) in the spinal opioid group and 6(1.5%) in the fascia iliaca block group. Hypotension of SBP > 25% below baseline was common occurring in around half of all patients. On examining the other studies in which patients received spinal anaesthesia ± nerve block for THR, the incidence of hypotension is not reported and therefore comparison is difficult. Definitions of hypotension vary and again this makes any attempt at comparison difficult. Hypotension was not reported in either of the meta-analyses of spinal morphine (214;215). Despite this, only one patient required any vasopressors and the majority of patients in our study were able to mobilise at the first attempt.

From logistic regression analysis, both age and pre-operative SBP were found to be predictive of post-operative hypotension. For every 1 year increase in age, the odds of having a hypotensive episode were increased by 5%, and for every 1mmHg increase in pre-operative SBP, the odds of an episode of hypotension

increased by 6%. Morphine consumption decreased the chances of developing post-operative hypotension. This is difficult to explain as one would expect increasing opioid consumption to have had the opposite effect.

12.1.3.6 Respiratory depression

Thankfully there were no episodes of respiratory depression or sedation requiring treatment in this study. This is reassuring as respiratory depression is one of the most feared complications of spinal opioids. It should be noted that this study was not powered for this outcome (nor any of the other secondary outcomes) and that detecting any difference between study groups would have required a far higher number of patients.

12.1.3.7 Urinary retention

Rates of urinary retention requiring catheterisation were 20 (39.2%) in the spinal opioid group and 15 (28.9%) in the USG fascia iliaca block group. Slappendel *et al* reported rates of around 70% in their spinal morphine dose finding study (221) while Murphy *et al* reported rates of 10-25% (218). In a meta-analysis of 65 RCTs, Popping et al found the risk of ureteric catheterisation to be 16.5% in the control group and 39.1% in the spinal morphine group (7 studies, wide range of spinal morphine doses) (215). In the meta-analysis of 28 RCTs by Gehling et al, the incidence was found to be 17% in controls with no increased risk noted in the spinal morphine patients (214). Only 8 studies could be included in this analysis however and the authors noted that a type II error could not be excluded.

On logistic regression analysis, neither study group (p=0.27), age (p=0.14), gender (p=0.33), BMI (p=0.09), weight (p=0.18), surgical blood loss (p=0.94), post-operative hypotension (SBP >25% under baseline, p=0.23), nor pain score at rest at 12 hours (p=0.4334) increased the odds of requiring catheterisation. 24 hour morphine consumption almost reached statistical significance with a p value of 0.052 (OR 0.98, [95% CI 0.96 to 0.99]).

Ultrasound guided fascia iliaca block is not only inferior in the provision of analgesia after THA but confers no advantage in reducing the side-effect profile.

We do not recommend replacing spinal morphine with ultrasound guided fascia iliaca block for THA.

12.1.4 Examination of Adverse Events and Serious Adverse Events

After discussion with the operating surgeon in each case, none of the AEs or SAEs were felt to be directly related to the study intervention

12.1.4.1 Femoral nerve palsy

Symptoms and signs of femoral neuropathy vary depending on the severity and location of the injury. Typical characteristics of a femoral nerve injury include groin or thigh pain, weakness of the iliopsoas, paralysis of the quadriceps femoris, loss of the knee jerk and sensory loss over the anteromedial aspect of the lower extremity. There may also be swelling or haematoma noted in the wound or inguinal region. Patients are usually able to walk on the flat using mobility assist devices, however climbing stairs is found difficult and may not be possible.

In the two instances of prolonged quadriceps motor weakness reported as an AE or SAE in this study, it was not possible to definitively state the nature of the injury as both surgery and fascia iliaca block are associated with a potential risk of nerve damage.

While femoral nerve block is a theoretical complication of fascia iliaca block, the actual incidence is difficult to estimate as it is so uncommon. The incidence of neuropathy following any peripheral nerve block was assessed in a large French study which found 4 cases of neurological injury and 4 cases of radiculopathy amongst 21,278 peripheral nerve block (0.04%) (308). All cases of radiculopathy were associated either with paraesthesia during insertion or pain during injection, neither of which occurred in our patients. There have been only two reported cases of neurological injury following fascia iliaca block. The first was in a 78 year old female who had a hip replacement performed under

spinal anaesthesia. The block was performed without the use of ultrasound guidance and at the end of the surgery (while the spinal block was still effective). The patient suffered reduced sensation and weakness in the anterior thigh which had fully resolved by day 8 (309). The second case occurred in a 15 year old girl who received a fascia iliaca block without ultrasound guidance whilst under general anaesthesia for knee arthroscopy. She had reduced sensation and mild weakness post-operatively and also complained of pain. These symptoms had resolved fully by 8 months (310).

Neurological injury secondary to regional anaesthesia is thought to be related either to needle trauma, high pressure injection of fluid into the nerve, direct neurotoxicity of injected drugs or nerve ischaemia. In the performance of the blocks in our patients we tried to minimise these risks as far as possible. Firstly, we performed the block prior to spinal anaesthesia so that any discomfort experienced could be reported. We also used ultrasound guidance to allow direct visualisation of the needle and to ensure that the injectate was deposited at a point distant to the nerve. The injectate contained only local anaesthetic or normal saline and contained no potentially neurotoxic additives.

Femoral nerve palsy is also a recognised concentration of hip arthroplasty. A systematic review published in 2012 reported an incidence of femoral nerve palsy of 0.1-2.4% with a mean of 0.8%. Treatment is mainly conservative and recovery can continue up to one year after the injury (311). In our study, one patient's neurological function had returned to normal within one week, with the other recovering after three months.

12.1.4.2 Pulmonary embolism

Three patients in this study developed pulmonary embolism post-operatively.

Whilst this was unexpected, both deep venous thrombosis (DVT) and pulmonary embolism (PE) are well recognised complications of lower limb orthopaedic surgery. Prior to the routine prescription of post-operative thromboprophylaxis, up to 60% of patients undergoing major orthopaedic surgery developed a DVT. Following the advent of routine thromboprophylaxis, the incidence of venous

thromboembolism has decreased. However, it is still considered a risk of surgery and as such, is included in surgical consent discussions (312).

In reporting these SAEs in our study, we did not feel that the occurrence of PE was related to the anaesthetic technique used (i.e. the study intervention). Both groups in our study receive spinal anaesthesia which is known to decrease the incidence of DVT (and which is routinely performed in patients undergoing hip replacement). From reviewing the notes and the case report file, the patients mobilised within an acceptable timeframe for this type of operation and received standard DVT prophylaxis according to hospital guidelines. There were no other complications.

12.1.4.3 Wound infection

The incidence of wound infection after total hip replacement is around 1% (313). The operating surgeon therefore discusses this potential complication with patients prior to consent being obtained. The potential for post-operative infection, along with other post-operative complications, is also highlighted on patient centred websites such as “NHS choices” (314). The incidence of infection has decreased over the last few decades with the routine use of chlorhexidine skin disinfectant, laminar flow theatres, prophylactic antibiotics, occlusive drapes, occlusive surgical gowns and cuffed theatre attire. All of these measures were employed by the surgical team involved with this study.

The SAEs reported in this study were discussed in detail with the operating surgeon. The patients’ involvement with the study was not thought to be causative of the infection nor have any bearing on their post-operative course. These incidents were felt to be due to complications of the surgical procedure, and not related to the study intervention in any way.

12.1.5 Study strengths and limitations

The strengths of this study lie in its *a priori* publication in a journal of trial methodology and the excellent peer review from renowned world experts in trial design that this entailed (11). Peer review was also received from experts in regional anaesthesia representing the European Society of Regional Anaesthesia and Pain Medicine (ESRA) in the review and awarding of our grant funding. The study methodology was judged to have scored highly on their scoring system and was unanimously voted as being successful (see Appendix 4).

The calculation of the powering required for this study has been described in detail and we are confident that this study included sufficient patients to allow meaningful conclusions to be reached.

This study was randomised using a computer generated allocation system (in permuted blocks). Demographics for both groups were similar indicating successful randomisation. Allocation concealment was ensured by using system of sealed envelopes. The study was double blind as all patients received both a spinal anaesthetic and ultrasound guided fascia iliaca block injection. The anaesthetist who was a trial investigator was unaware of the contents of the injectates and so was also blinded to the study allocation. The only person aware of the treatment allocation was the anaesthetist who routinely anaesthetised for the operating list. This anaesthetist was tasked with making up the fascia iliaca and spinal injectates, inserting the spinal anaesthetic and looking after the patient in theatre. This anaesthetist had no involvement with study data collection or reporting.

Any withdrawals or dropouts from the study were noted and any reasons for withdrawal described in detail.

Both ITT and “as treated” analyses were performed and the pros and cons of each approach examined. We received validation of our interpretation of the primary outcome result from two separate leading experts in the field of non-inferiority methodology.

Limitations of the study mainly relate to the fact that it was performed in a non-research setting within the NHS system. This made it extremely difficult to ensure that collect all intended data were collected. For example, data collected for 36 hour pain scores was limited (68 not recorded) as it was usually late at night and patients were generally asleep. Nursing staff on the ward were informed of the study and given relevant information. However, the large number of nurses on the ward and frequent changes of shift meant that some nurses may have been more vigilant in recording data than others. We made every effort to ensure that nursing and physiotherapy staff were not asked to perform any additional duties as a result of the study, as the majority of the outcomes assessed are routinely monitored after THA in our hospital. The study was powered for the primary outcome but not the secondary outcomes.

A further limitation of the study relates to the fact that ultrasound guided fascia iliaca block efficacy was not assessed prior to administering the spinal anaesthetic. This could result in the argument that the fascia iliaca block group had higher analgesic requirements due to the fact that the blocks did not work. This is clearly a possibility though is made less likely by the fact that all study investigators were trained in the technique and have a high level of experience in performing the block within their own clinical practice. This notwithstanding, it is possible that some of the blocks did not work and this may clearly have affected the results.

The reasons for not checking block efficacy were mainly pragmatic. We did not have available facilities to allow the safe insertion of a nerve block outwith the operating theatre and in advance of the patient going to theatre. If we had done this, it would have necessitated the presence of an additional anaesthetic nurse and this was not possible due to staffing levels. If we had simply performed the block and then waited to assess the effects before proceeding to administer the spinal anaesthetic, this would have resulted in a significant delay between patients. This was again not possible due to pressures on theatre time. In addition, any assessment of the efficacy of the block would have unblinded the study anaesthetist and would have required an independent anaesthetist to perform if this was to be avoided. Any demonstrable leg weakness would also have alerted the patient to their study allocation and hence the study would not

have been double blind. Finally, we aimed to perform a study which would be representative to and relevant to usual clinical practice. It is not our usual practice to check the effects of a nerve block prior to administering spinal or general anaesthesia and as such, it was felt appropriate that the study be performed in this way.

12.1.6 A discussion of the use of a placebo block

The use of placebos in RCTs is controversial and is an issue which was discussed at length with the West of Scotland Research and Ethics Committee prior to the finalisation of the study protocol and commencement of recruitment. The committee concluded that the advantages of using a placebo ultrasound guided fascia iliaca block to ensure the internal validity of the study outweighed the potential risks of harm. Placebo can be defined as:

> *"an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (315)."*

An alternative definition is:

> *"A substance or procedure that has no inherent power to produce an effect that is sought or expected (316)."*

Disadvantages of using a placebo block in this study can be thought of as following:

Any neuropraxia occurring post-operatively may have been caused by a procedure which was of no benefit to the patient. In this study, this eventuality did not occur as both episodes of neuropraxia occurred in patients allocated to receive the fascia iliaca block with local anaesthetic. Neuropraxia may also have been caused by the surgery. The exact aetiology of femoral neuropraxia after THA is often difficult to ascertain and is usually managed conservatively (317).

Any adverse effects noted in the groups may have been related to either the spinal anaesthetic or the USG fascia iliaca block. While the injectates for each were different between groups, the fact that both interventions were performed in all patients makes assessment of adverse effects less clear.

It is possible that the injection of saline in the fascia iliaca space may have exerted an effect upon the nerves via the application of pressure or the disruption of tissues (318).

Use of a placebo is considered to be acceptable in certain circumstances under Provision 33 of the Declaration of Helsinki. This states that:

> *"The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option (319)".*

We considered the use of placebo in this study to have scientific merit as there was no other way of ensuring that the study was truly double blind. The option of simply performing a sonographic examination of the femoral area with the ultrasound probe was proposed as an option but it was felt that the patient was likely to realise that a block had not been performed. The performance of a subcutaneous injection was also considered, but this (as with the previous suggestion) would also have unblinded the operator who was involved in data analysis. The risk to the patient from an ultrasound guided fascia iliaca block with normal saline was felt to be low. As fascia iliaca block is a field block and does not direct the injectate directly towards the nerve, this was felt to present a low risk for neuropraxia. Blocks were performed using a sterile technique to minimise any infective risk. Patients were fully informed of the possibility that

they may receive a placebo nerve block and were given the opportunity to ask questions regarding this. Consent was obtained and it was emphasised to patients that they were entirely free to refuse study involvement in the knowledge that this would not impact on their care in any way. Patients were also aware that they could drop out of the study at any time without having to give a reason.

It has been suggested that the use of a placebo block be evaluated using the "SHAM tool" which aims to establish the risk of harm to the patient. This tool was first published in 2011, and was therefore not available at the time of our study being designed and undergoing ethical review (October 2010) (320). The SHAM scale suggests that the use of placebo injection for femoral nerve block is considered to be of moderate risk and should prompt an alternative approach by study designers. We consider that fascia iliaca block is of lower risk than a femoral nerve block as the needle and injectate are not directed towards the nerve. We were reassured that our trial design was acceptable in view of the advice received from the West of Scotland Research Ethics Committee and by the favourable peer review and feedback received from the European Society of Regional Anaesthesia and Pain Medicine and by the editors of the Trials journal.

12.2 Conclusion

This is an adequately powered and methodologically robust study which has shown that ultrasound guided fascia iliaca block is not non-inferior to spinal morphine in the provision of analgesia after total hip replacement. Ultrasound guided fascia iliaca block is not only inferior in the provision of analgesia after THA but may confer no advantage in reducing the side-effect profile (although the study was not powered for the secondary outcomes). The incidence of adverse effects often attributed to spinal morphine was not different between groups and reassuringly, there were no incidences of respiratory depression. This has clear implications for practice and would suggest that spinal morphine remains an effective analgesic agent in this patient group. The effect of an ultrasound guided fascia iliaca block administered in addition to spinal morphine

was not investigated in this study but would be of interest as this may result in morphine sparing in the post-operative period.

12.3 Chapter 12 Summary

- This study has clear implications for practice. Ultrasound guided fascia iliaca block is not recommended as a replacement for spinal morphine inpatient undergoing primary total hip arthroplasty.

- Strengths of this study include: its *a priori* publication and validation of trial methodology, strength of peer review, expert statistical advice and representation of real life practice. Limitations relate to the use of placebo block, the lack of checking blocks for efficacy and the restrictions of doing research within an NHS setting.

Chapter 13

Summary and future directions

13.1 Summary and future directions

In this work, I have examined the epidemiology and pathophysiology of ageing recognising the challenges that this may bring to the future of healthcare provision. In particular, the increasing prevalence of morbidity relating to musculoskeletal disease and the corresponding burden on health and social resources is a burgeoning problem and an area where research must be targeted if improvements are to be made.

Patients admitted with fractured hip account for a large proportion of patients requiring emergency surgery in hospital. This patient group is particularly frail with high levels of morbidity, mortality and ongoing dependence. I have examined the reasons why this patient cohort represents a management challenge to the healthcare team, exploring the concept of frailty and the scoring systems that can be used to help stratify peri-operative risk. I have analysed guidelines relating to the management of these patients and compared them for different common clinical scenarios such as the presence of anaemia or a heart murmur. This work provides a useful guide to clinicians who can often be overwhelmed by the large volume of information available. The use of clinical guidelines in general has been examined and their benefits and potential disadvantages discussed.

The role of large volume data collection in the form of national hip fracture audits has been reviewed. These data have allowed a comparison between our own practice and national standards. A detailed audit of all patients admitted with fractured hip over a one year period in Glasgow Royal Infirmary was performed and data compared with that obtained from national databases. This allowed us to benchmark our data against accepted standards of care and to identify areas for potential improvement. The results of this audit showed our outcomes to compare favourably against those seen nationally. We then examined sub-populations identified by staff members as representing specific management challenges. These were patients admitted to ICU and patients taking warfarin. The results of these sub-group analyses indicate that although

only a small proportion of patients suffering hip fracture are admitted to critical care, that this number is rising. One could make an argument that a far larger proportion of this frail patient group could benefit from an enhanced level of post-operative care, though this has clear implications for resources and is beyond the scope of this thesis. The results of this work were communicated to anaesthetic, critical care and orthopaedic departments for further consultation.

Patients taking warfarin and admitted with hip fracture were found to be a group where management was variable and inconsistent and where guidance was lacking. This prompted a quality improvement initiative in the form of a protocol to guide management. This was formulated in a multi-disciplinary setting and approved by the local Thrombosis Committee and is under ongoing review. This work encouraged me to found the Glasgow Royal Infirmary Theatre Improvement Group. This group includes interested staff members who are encouraged to propose areas where they feel care may be improved. Using a collaborative approach, we aim to tackle these issues and improve patient care and ultimately, outcomes. So far, projects undertaken by the group have included a surgical sign-out for patients undergoing emergency laparotomy and an intervention to prevent undetected post-operative anaemia in patients having surgery for hip fracture. Feedback from other disciplines has been positive and some of our interventions have been translated into other areas of care by surgical staff. This theatre improvement group has prompted the institution of similar groups both in the obstetric service and in critical care. I hope that this culture of quality improvement will continue to prosper and result in meaningful improvements in care.

The performance of elective orthopaedic surgery also accounts for a large proportion of surgical workload with total hip replacements being one of the most commonly performed and generally successful surgical procedures. Methods of anaesthesia for total hip replacement have been examined and a systematic review of the different types of peripheral nerve blocks performed. This detailed literature review allows a comprehensive comparison of the available techniques and highlights the lack of research performed on ultrasound guided fascia iliaca blocks. I hypothesised that an ultrasound guided fascia iliaca block may provide analgesia which was non-inferior to that provided by

spinal morphine (a popular and commonly performed technique in this patient population). If this was the case, the removal of spinal morphine from the injectate could potentially result in a reduction in unpleasant side-effects such as nausea, itch and potentially dangerous respiratory depression as well as having implications for nursing workload. We performed a randomised, controlled, double blind trial of 108 patients to examine this hypothesis. The trial was adequately powered and the study protocol was published *a priori* in a journal of trial methodology. The results showed that ultrasound guided fascia iliaca block was not non-inferior to spinal morphine and supports the use of 0.1mg spinal morphine as providing adequate analgesia after total hip replacement.

Following on from this work, I was interested to explore the role of regional anaesthesia in another surgical setting. The use of regional anaesthetic techniques to improve flow and potentially patency and lifespan of arteriovenous fistulae is an area I find interesting and I have therefore embarked upon a collaborative project with the Department of Vascular Surgery at the Western infirmary, Glasgow. This is a further randomised controlled trial for which I designed the protocol with input from the vascular team. The protocol has been published in a journal of trial methodology and recruitment is now underway (321).

Appendices

Appendix 1: IRAS forms (REC and R&D)

Appendix 2: West of Scotland Research Ethics Committee approval letter

Appendix 3: NHS Greater Glasgow and Clyde Research and Development approval letter

Appendix 4: Trials journal feedback

Appendix 5: Trials journal acceptance letter

Appendix 6: ESRA Grant award letter

Appendix 7: Study patient information letter

Appendix 8: Study GP information letter

Appendix 9: Study consent form

Appendix 10: Study data collection proforma

Appendix 11: End of study declaration form

Appendix 12: Secondary outcome results tables

Appendix 1

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Intrathecal opiate vs fascia iliaca block. Version 1. 1/8/10

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial or clinical investigation

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples, other human biological samples and/or data *(specific project only)*

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

[ ] England
[x] Scotland
[ ] Wales
[ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

( ) England

(●) Scotland

- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which review bodies are you applying to?

- ☑ NHS/HSC Research and Development offices
- ☑ Research Ethics Committee
- ☐ National Information Governance Board for Health and Social Care (NIGB)
- ☐ Ministry of Justice (MoJ)

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity? *The guidance notes explain how an adult is defined for this purpose.*

○ Yes ◉ No

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service in England or Wales?

○ Yes ◉ No

9. Is the study, or any part of the study, being undertaken as an educational project?

○ Yes ◉ No

10. Is this project financially supported by the United States Department for Health and Human Services?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

NHS
National Patient Safety Agency
National Research Ethics Service

Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Intrathecal opiate vs fascia iliaca block. Version 1. 1/8/10

Please complete these details after you have booked the REC application for review.

REC Name:
West of Scotland Ethics Committee

REC Reference Number:

Submission date:
19/08/2010

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Intrathecal opiate versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	John	Kinsella
Post	Head of Section, Anaesthesia, Pain and Critical Care		
Qualifications	MB BS MD FRCA		
Employer	University of Glasgow		
Work Address	University Section of Anaesthetics, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow		
Post Code	G31 2ER		
Work E-mail	jk19v@clinmed.gla.ac.uk		
* Personal E-mail			
Work Telephone	01412111198		
* Personal Telephone/Mobile			

Fax	01412111191

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Dr	Steven	Burke
Address	Research and Development Department		
	Tennent Institute,		
	38, Church Street, Glasgow		
Post Code	G11 6NT		
E-mail	steven.burke@ggc.scot.nhs.uk		
Telephone	0141 232 9429		
Fax	01412112811		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	GN10AN280
Sponsor's/protocol number:	1
Protocol Version:	1.1
Protocol Date:	01/08/2010
Funder's reference number:	
International Standard Randomised Controlled Trial Number (ISRCTN):	
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	
Project website:	

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

Hip replacement surgery is a commonly performed operation. Pain control after hip surgery is important to ensure patient comfort, allow the patient to be mobile, and to aid a good recovery. Patients having hip replacement surgery

need to have an anaesthetic performed by an anaesthetic doctor. As well as keeping the patient comfortable during the operation, the anaesthetic can help to provide pain control after the operation, particularly in the first 24 hours. There are many different ways of providing anaesthesia and pain control after hip surgery and we currently do not have a clear answer as to which way is best. One of the most common ways to do the anaesthetic is with a spinal injection. This involves an injection in the patient's back which numbs the patient from the waist down and allows surgery to be performed without the need for a full general anaesthetic. Many patients like this technique as it means they feel less drowsy afterwards and can eat and drink sooner than if they had a general anaesthetic. One of the drugs which is often used in the spinal injection is morphine. This is an effective pain killer but may cause side effects such as drowsiness, itch, difficulty passing urine and sickness. Another way of providing pain control is with a nerve block. This involves an injection in the groin and can be done along with a spinal injection. If a nerve block is used, then morphine could be removed from the spinal injection. This should reduce the number of patients having side effects such as itch, difficulty passing urine, sickness and drowsiness. We wish to compare a spinal injection containing morphine with a spinal injection without morphine and a nerve block to see which one provides the best pain control after hip surgery.

A6-2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

The main issues regarding this study are as follows:

1. In group 1, patients will receive an ultrasound guided fascia iliaca block (groin injection using local anaesthetic) and a spinal injection with local anaesthetic but no spinal morphine. In group 2, we propose that patients will receive a "sham" ultrsaound guided fascia iliaca block (groin injection) performed using sterile saline, and a spinal injection containing both local anaesthetic and spinal morphine. The use of a fake or sham block in group 2 means that the patient will receive an injection of an inactive substance into the groin. This will help to guarantee blinding of both patients and investigators thus improving the validity of the study. However, the performance of the sham block may be associated with some risks. As no local anaesthetic is being used in the sham block, the risks will be of discomfort on injection, bleeding or bruising at the puncture site and nerve damage. Nerve damage is rare with fascia iliaca blocks as the needle is not directed towards the nerves themselves, but rather to lie in a plane between muscle layers.

We would be grateful for the advice of the ethics committee as to whether the use of a sham block would be acceptable. The alternative would be to prepare the patients for a nerve block by cleaning the skin, placing an ultrasound probe in the groin area and performing a small injection to numb the skin but not performing the nerve block itself. This would unblind the anaesthetist performing the procedure. It is unlikely that many patients would realise that the full nerve block had not been performed although there may be exceptions.

2. There are certain risks associated with both spinal injections and nerve blocks. Both of the procedures are commonly performed for hip surgery in the United Kingdom and risks of serious side effects are rare. Any possible risks must be weighed up against the risks of a general anaesthetic.

Risks of spinal injection include; lowering of blood pressure, headache, nausea and vomiting, muscle twitching, loss of consciousness, abscess, meningitis, failure of the procedure and nerve damage (this may range from an area of numbness or weakness which resolves in a few days, to permanent paralysis in 1 in 250,000 people). If morphine is added to the anaesthetic mixure, the risks of slowing of breathing, urinary retention and itch are added.

Risks of nerve block include; bleeding and bruising, accidental injection of local anaesthetic into a blood vessel causing fits or heart and blood pressure problems, nerve damage, allergic reaction and failure of the block.

It should be noted that the above risks are very rare and these procedures are carried out very commonly in modern practice.

Each patient will have had the opportunity to read an information sheet which explains the risks of each procedure in detail and to discuss this further with a member of the research team.

Any adverse events relating to each of the procedures will be recorded by staff performing the study and any necessary investigations, treatment or follow up arranged thereafter.

3. If the nerve block is not successful, the patient might experience a higher level of pain after the operation. The patient will be given morphine via a patient controlled infusion pump in order to achieve adequate pain relief post-operatively.

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To determine if performing a nerve block along with a plain spinal injection can provide as good pain relief as a spinal injection containing morphine for hip surgery.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To assess the patient's pain and to observe post-operative events such as nausea, sedation, itch etc which may occur with each of the two anaesthetic techniques.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Regional anaesthesia has several benefits over general anaesthesia for patients undergoing hip replacement surgery. A spinal injection is a commonly used regional anaesthetic technique. If morphine is added to a spinal injection, it can provide effective pain relief but may cause a number of unpleasant and potentially serious side effects. As an alternative, a nerve block can be performed. The nerve block we have discussed is called an ultrasound guided fascia iliac block. This nerve block is performed using an ultrasound machine so that the exact position of the injection can be seen. This technique has been shown to be very effective at producing numbness over the area where the hip surgery is performed. However, no-one has assessed whether this improves pain control after hip surgery. The ultrasound guided fascia iliaca block is considered safe and is associated with few complications. Particularly, as the injection is directed into the tissue layer surrounding the nerve rather than near the nerve itself, the risk of nerve damage may be lower than other nerve blocks. If we can show that ultrasound guided fascia iliaca block provides comparable pain relief with less side effects than spinal injection with morphine, we could remove morphine from the spinal injection and potentially improve patient safety.

A13. Please give a full summary of your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The study is of a double blind, randomised controlled design. All patients will already have been scheduled for hip replacement surgery. Patients will be seen at their routine pre-operative assessment clinic visit. The study will be explained at this point and the patient given an information leaflet to read. The patient may sign the consent form at this point though they will be encouraged to discuss their participation in the study with friends and family before deciding whether to take part or not. The patient will be seen again before their operation. If they wish to take part in the study, and have not already signed a consent form, they will be given the opportunity to sign one at this point. The patient will be aware that they may change their mind at any point, with no need for explanation, without this having any detrimental effect on their care.

On the day of surgery, the patient will be taken to the theatre reception area before their operation as normal. Routine monitoring will be started as is usual(blood pressure, heart monitor, oxygen level). A cannula will be inserted into a vein as is routine for any operation.

The patient will then be randomly assigned (like tossing a coin), into one of two groups.
The first group will receive a nerve block (which involves an injection in the groin of local anaesthetic) and spinal injection (an injection in the back) with no morphine in it.
The second group will receive a spinal injection with morphine in it and an injection in the groin of saline, a solution which does not contain local anesthetic.

An anaesthetist not directly involved with the study will prepare the drugs to be used for both the nerve block and the spinal injection in a sterile manner as directed by the randomisation schedule. This means that neither the anaesthetist performing the procedure nor the patient will know which group the patient is in.

Therefore, in order that the patient does not realise which group he or she is in, all patients will receive both a spinal injection in their back as well as an injection in their groin.

To perform the injection in the groin, patients will undergo the following; The skin in the groin area is cleaned with antiseptic solution. An ultrasound probe is used to visualise the nerves in the groin area. A small injection of local anaesthetic is used to numb the skin. In the patients who are to receive the nerve block, local anaesthetic will be injected in the groin area to surround the nerves. Those who are not meant to receive the nerve block will receive an injection of saline in the groin area. The above will be performed by an anaesthetist experienced in the technique as detailed on the study delegation log.

Patients will then be taken to the anaesthetic room (by the operating theatre) to have a spinal injection performed. In the group who received the nerve block with local anaesthetic, a spinal injection containing only local anaesthetic will

be used. In the group receiving the injection in the groin of saline, a spinal injection containing local anaesthetic and morphine will be used. This will be performed by the anaesthetist assigned to the operating theatre. As the drugs will already have been prepared, this anaesthetist will also be blinded as to which group each patient is in.

The medications used to perform the injection in the groin and spinal injection will not be recorded on the anaesthetic chart. The patient's participation in the study and the 2 possible anaesthetics that may have been received will be documented on the anaesthetic chart using a pre-made sticky label. Documentation of the patient's actual anaesthetic procedure as well as any adverse events will be kept in an opaque sealed envelope in the patient's file. This data will be accessed if deemed necessary in the provision of optimal patient care.

Once the anaesthetic is complete, the patient will receive standard care whilst in theatre. If the patient wishes to sleep throughout the operation, they can be given sedating medicines by the anaesthetist. After the operation, the patient will be taken to the recovery area for a period of observation. This is routine after any operation. The patient will be prescribed regular pain killers as well as a morphine pump which has a button that the patient will be told to press if they have pain. The morphine pump (or PCA device) is used commonly after many types of operations and is a very safe method of pain control.

The patient will then move to the ward where they will continue to be monitored by trial personnel for a 48 hour period. Data regarding the amount of morphine used, pain scores, and any side effects will be recorded and treatment given as necessary. Patients will be reviewed at a routine follow-up appointment at 6 weeks after discharge. If any adverse events occur, further investigations and follow up will be arranged as necessary.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☐ Design of the research
- ☐ Management of the research
- ☐ Undertaking the research
- ☐ Analysis of results
- ☐ Dissemination of findings
- ☑ None of the above

Give details of involvement, or if none please justify the absence of involvement.
The study follows what is considered normal practice as many patients undergoing hip surgery would receive a spinal anaesthetic plus a nerve block. The difference to patients from what might happen normally is therefore small and so it was felt that there was not enough of a departure from what is normal to justify formal consultation

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

- English-speaking
- Competent to give consent
- ASA physical status I - III
- 18-85 years of age, inclusive
- 50-110 kg, inclusive
- Scheduled for unilateral primary hip arthroplasty

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- Contraindications to fascia iliaca plane block (e.g. allergy to local anesthetics)
- Contraindication to spinal anaesthesia (infection at spinal injection site, hypovolaemia, raised intracerebral pressure or deemed unsuitable for spinal anaesthesia by the anaesthetist)
- Coagulopathy, malignancy or infection in the inguinal area
- Patient preference for general anaesthesia
- Allergy to opiates

• Significant peripheral neuropathy or neurologic disorder affecting the lower extremity
• Pregnancy
• History of alcohol or drug dependency / abuse
• History of long term opioid intake (MST, oramorph, oxycontin, oxynorm, sevredol, fentanyl, tramadol)
• History of significant psychiatric conditions that may affect patient assessment

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
seeking consent	1	0	30 minutes	Rachel Kearns, STr or Alan Macfarlane, consultant.or anaesthetic research fellow. Pre-operative assessment clinic and ward
giving patient information sheet	1	0	10 mins	Rachel Kearns, STr or CRF nursing staff, pre-operative assessment clinic

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
fascia iliaca nerve block	1	0	20 minutes	Dr Rachel Kearns or anaesthetic research fellow, theatre reception
Spinal anaesthetic	1	1	20 minutes	Anaesthetist who normally performs the list, anaesthetic room
Propofol sedation	1	1	60 minutes	Anaesthetist who normally performs the list, operating theatre

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

(●) Yes ( ) No

If Yes, please give details, explain the risks and justify the need to withhold the intervention or procedure:

The administration of morphine in the spinal injection will be withheld in one of the study groups. This group will receive a nerve block with local anaesthetic instead.

A21. How long do you expect each participant to be in the study in total?

The period of data collection will last for 48 hours. The patient will be followed up at 6 weeks following discharge at a routine follow up appointment. If any patient requires further follow up, this will be arranged on an individual basis.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

All patients will receive an injection in the groin as well as a spinal injection in the back. Both of these procedures are performed commonly in patients undergoing hip surgery and are usually tolerated well. The main risks of participating in the study relate to these injections. In particular, we propose to perform a "sham" block (groin injection) in group 2. This means that we will be injecting saline instead of local anaesthetic into the fascia iliaca plane. This is being done in order to ensure that the study is properly blinded. We hope that this will improve the validity of the results. However, this means exposing the patient to an injection which will not provide them with any benefit in terms of pain relief. Risks of having such an injection performed with saline include bleeding and bruising at the injection site, discomfort during the procedure and nerve damage.
The risk of nerve damage is very low in this type of injection as the local anesthetic is not directed towards the nerves themselves but rather to lie in a layer surrounding the nerves.

We would be grateful for guidance from the Ethics Committee as to whether this would be acceptable.

The alternative to this would be to prepare the patient for a nerve block by cleaning the skin and placing an ultrasound probe in the groin area. A small injection to numb the skin could then be performed without performing the nerve block itself. However, this would result in unblinding of the anaesthetist and potentially, of the patient.

In terms of what the patient will experience, the performance of the injection in the groin involves having the skin over the groin area (on the side of the hip operation) cleaned with a cleaning solution. This may feel slightly cold but should not be uncomfortable. An ultrasound probe will be placed over the groin area in order to see the relevant nerves. Again, this is not uncomfortable for the patient and is generally not distressing. All patients will have a small amount of local anaesthetic injected into their groin area to numb up the skin where the nerve block is going to be performed. This is slightly uncomfortable (like having an injection to numb your mouth at the dentist). There are no significant risks associated with this. Patients in group 1 will then receive an injection of local anesthetic into the groin. Patients in group 2 will have an injection of saline into their groin. However, if they were having their hip surgery done outwith the trial, they may have had a nerve block performed as a routine part of their anaesthetic.

Performance of a spinal injection involves cleaning the skin on the back with an antiseptic solution before injecting a small amount of local anaesthetic into the skin to numb the area. This makes the spinal injection more comfortable. Patients may experience some tingling in their legs during the spinal injection and are encouraged to report any such sensations to the operator. Spinal injections are performed very commonly and are generally well tolerated.

As with all type of anaesthetic there are risks. Both groups will receive a spinal anaesthetic which is a standard and commonly used anaesthetic for hip operations. This, amongst other things, has the major benefit of avoiding the risks of a general anaesthetic. Spinal anaesthesia is safe but common side effects include feeling sick afterwards. There is also a small chance of a headache. Nerve damage is rare complication of a spinal anaesthetic. The symptoms include numbness or weakness. Most of the time this is short lived and resolves after a few weeks to months. In group 2 the drug added to the spinal anaesthetic (morphine) is widely used. It can however cause itching, feeling sick or very rarely problems with breathing. Group 1 will not receive this drug but instead will receive an injection in the groin of local anaesthetic. Nerve damage, as described above, is also a rare complication of nerve blocks. In this particular block however using ultrasound the needle is not placed near the nerve and we believe that this makes it safer than other nerve blocks as the needle should not be able to damage the nerve. We would not therefore anticipate a significant increase in nerve damage in the nerve block group. In both a spinal and nerve block procedure there may be some pain or bruising at the injection site. The occurrence of any complication will be documented and will include :

Minor complications
o Local bruising
o Pain in the injection site
o Short term numbness or tingling in the leg

Major complications (but uncommon < 1%)
o Seizure / loss of consciousness
o Muscle twitching

o Irregular heart beat
o Breathing problems
o long-term numbness and tingling
o Infection
o Allergy to the local anesthetic (exceedingly rare)

All procedures will be performed by an anaesthetist experienced in the technique. Any adverse events will be documented and any necessary treatment or follow up arranged. Patients will be free to withdraw from the study at any time without their care being affected.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

Participants who receive the nerve block (injection in the groin of local anaesthetic) will not receive morphine in their spinal injection. This has the potential benefit of avoiding side effects such as drowsiness, itch and difficulty passing urine. All patients will receive a morphine pump after their operation meaning that they are in control of the pain relief they receive. Patients having this type of operation usually have pain relief administered by a member of nursing staff. The ability to be in control of pain relief is seen as advantageous by many patients. Patients will also be monitored very closely by the research team and any adverse events followed up appropriately.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

All patients will be followed up 6 weeks after discharge. Any patient who has experienced an adverse event which requires further investigation or treatment will be followed up accordingly.

A26. What are the potential risks for the researchers themselves? *(if any)*

none.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified from orthopaedic theatre lists. Theatre lists are compiled by the orthopaedic surgeon after patients have been seen in clinic.

Patients will attend the pre-operative assessment clinic as is routine. One of the research team will explain the trial to suitable patients at this point. Patients will be given an information leaflet describing the trial in more detail. They will be encouraged to discuss their involvement in the trial with friends and family prior to making a decision. Patients will be reviewed before surgery and consent will be sought at this point.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◉ Yes ○ No

Please give details below:
The identification of participants will be by the usual clinical team. This would involve knowledge of identifying information which would need to be known anyway for the provision of clinical care.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The presence of a study will be highlighted by the anaesthetist at the pre-operative assessment clinic. Patients will be asked if they would be willing to see a member of research staff (either CRF nurse or Dr Rachel Kearns) in order to receive a patient information sheet about the study.
If there were no initial objections at clinic then potential participants will be approached by one of the research team on the night before surgery. The study will be explained, a patient information leaflet provided if this has not been done already, and consent obtained if the patient wishes to do so.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

A patient information leaflet will be provided and informed, written consent obtained as above.

All patients should be able to provide consent and inablility to consent is an exclusion criteria

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

The study will be described at the pre-operative assessment clinic approximately two weeks before the planned operation. An information leaflet will be given to the patient and they will be encouraged to discuss their participation with friends and family prior to making a decision.

Consent for the study will be obtained in the 24 hour period before surgery.

All potential participants will be informed of their right to change their mind at any point.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- ○ Yes
- ◉ No
- ○ Not Known

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters)*

Inability to be able to give informed consent and inability to speak English are exclusion criteria. No arrangements have therefore been made to provide interpreters.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The research period extends for a 6 week period only and therefore it is unlikely that any such information will become available in this short time period.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ◉ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files including X−rays

- [ ] NHS computers
- [ ] Home or other personal computers
- [x] University computers
- [ ] Private company computers
- [ ] Laptop computers

Further details:

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All personal data will be anonymised and kept in accordance with the NHS confidentiality policy.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The team of health care professionals who will be providing care in the peri-operative period will have access to the clinical notes as is routine in any patient undergoing in-patient care. Members of the research team will have access to the patients' case notes. The request for access to the notes will be detailed in the consent form.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

- ( ) Less than 3 months
- ( ) 3 – 6 months
- ( ) 6 – 12 months
- ( ) 12 months – 3 years
- (•) Over 3 years

If longer than 12 months, please justify:
All data will be kept in a secure locked facility for a period of 15 years. Data will have had all patient identifiers removed and will be kept in a secure locked facility. Patient identification data will be stored in a separate locked, secure facility.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

( ) Yes (•) No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

( ) Yes (•) No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

◉ Yes ○ No

Please give details, or justify if not registering the research.
Application for registration on the Clinicaltrials.gov database is underway.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☐ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A53. Will you inform participants of the results?

○ Yes ◉ No

Please give details of how you will inform participants or justify if not doing so.
The results should not have any long term implications for the patient. If any patient suffers a serious problem during the course of the study, any relevant data would be made available to them.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- ☑ Independent external review
- ☐ Review within a company

- ☐ Review within a multi−centre research group
- ☑ Review within the Chief Investigator's institution or host organisation
- ☑ Review within the research team
- ☐ Review by educational supervisor
- ☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
External peer review as part of grant application process (Chief Scietist Office small grant application). We plan to submit the protocol to the "Trials" journal. This will again provide an independent, external review.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☑ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor
- ☑ Other review by individual with relevant statistical expertise
- ☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	ms	Michele	Robertson
Department	Department of statistics, Robertson Centre for Biostatistics		
Institution	Glasgow University		
Work Address	Boyd Orr Building,		
	University of Glasgow		
Post Code	G128QQ		
Telephone	01413304744		
Fax			
Mobile			
E-mail	michele@stats.gla.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Morphine consumption in the first 24 hours post-operatively

A58. What are the secondary outcome measures? *(if any)*

• Pain scores at 3, 6, 12, 24, 36 and 48 hours as recorded post-operatively on the PCA chart where time zero is the

end of the operation (numerical pain rating score 0 – 10 where 0 is no pain and 10 is worst pain imaginable).
• Time to 1st morphine administration in minutes from time zero.
• Episodes of respiratory depression defined as respiratory rate < 8/min or requiring naloxone administration in the first 48 hours post-operatively.
• Incidence of hypotension as defined by systolic blood pressure < 80mmHg or a drop of >25% from baseline systolic pressure, or requiring vasopressor in the first 48 hours post-operatively.
• Incidence of post-operative nausea and vomiting as defined by nausea score of greater than or equal to 2 (on a PONV scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe nausea and 4 = patient vomiting) or requiring the administration of an anti-emetic agent in the first 48 hours post-operatively.
• Incidence of pruritus as defined by itch felt to be distressing by the patient on questioning after the first 48 hour period post-operatively or requiring treatment with naloxone.
• Incidence of sedation as defined by sedation score of greater than or equal to 2 (where 0 = awake, S = normal sleep, 1 = drowsy but easy to rouse, 2 = sedated and difficult to rouse, and 3 = unconscious) or requiring naloxone administration in the first 48 hours post-operatively.
• Incidence of urinary retention as defined by the requirement for urinary catheterisation due to failure to pass urine in the first 48 hours post-operatively.
• Time to first mobilisation as defined by patient able to mobilise from bed to chair in hours from time zero as recorded by physiotherapy staff.
• Patient satisfaction as measured using a visual analogue scale (VAS) from 0 – 100mm where 0 is absolutely not satisfied and 100 is completely satisfied. This will be performed after 48 hours and at a routine follow up appointment 6 weeks after discharge.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	106
Total international sample size (including UK):	106
Total in European Economic Area:	0

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Our primary outcome measure is 24 hour post-operative morphine consumption. We consider a difference of 10mg of morphine between groups in a 24 hour period to be significant clinically. Using a 2 group t test of equal means, a type I error rate of 0.05 and power of 0.80, we calculate that 96 patients are required to detect this difference. We anticipate an attrition rate of approximately 10% due to complications, adverse effects, protocol violations, equipment failure, patient withdrawal, and loss to follow up. In order to achieve the required sample size of 96 patients, we anticipate enrolling 106 patients.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Patients will be randomly assigned to one of two groups using a computer generated randomisation schedule.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Data will be managed on an intention to treat basis. Continuous variables will be summarized as mean values ± SD and categorical variables will be presented as median and range. Statistical significance will be established at a $p<0.05$.

The following analyses will be performed:

1. The main hypothesis of 24 hour morphine consumption (primary outcome measure), will be analysed by students t-test / Mann-Whitney U-test depending on whether data is normally distributed.
2. Secondary data analyses will be carried out on; time to first morphine administration, pain scores, nausea and vomiting scores, pruritus scores, sedation scores, patient satisfaction scores, episodes of hypotension, episodes of urinary retention, episodes of respiratory depression and time to first mobilisation. These will be compared among groups using t-test and Mann-Whitney test as appropriate.
3. Presence or absence of adverse effects (e.g. accidental vascular puncture, intravascular local anesthetic injection, persistent postoperative paresthesia) will be compared using the Chi-Squared test.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Dr	Rachel	Kearns
Post	STr Anaesthetics, Pain and Critical Care Medicine		
Qualifications	MBChB MRCP FRCA		
Employer	NHS Greater Glasgow and Clyde		
Work Address	Department of Anaesthesia, Glasgow Royal Infirmary, 91, Wishart Street Glasgow		
Post Code	G312HT		
Telephone	01412114620		
Fax			
Mobile	07890524153		
Work Email	rkearns@doctors.net.uk		

	Title	Forename/Initials	Surname
	Dr	Alan JR	Macfarlane
Post	Consultant Anaesthetist in Anaesthesia, Pain and Critical Care Medicine		
Qualifications	MBChB BSc MRCP FRCA		
Employer	NHS Greater Glasgow and Clyde		
Work Address	Department of Anaesthesia, Glasgow Royal Infirmary, 91, Wishart Street Glasgow		
Post Code	G312HT		
Telephone	01412114620		
Fax			
Mobile			
Work Email	alan.macfarlane@nhs.net		

	Title	Forename/Initials	Surname
	Dr	Keith J	Anderson
Post	Consultant Anaesthetist in Anaesthesia, Pain and Critical Care Medicine		
Qualifications	MBChB BSc FRCA		
Employer	NHS Greater Glasgow and Clyde		

Work Address	Department of Anaesthesia, Glasgow Royal Infirmary, 91, Wishart Street Glasgow
Post Code	G312HT
Telephone	01412114620
Fax	
Mobile	
Work Email	keithanderson@doctors.org.uk

Title	Forename/Initials	Surname
Mrs	Barbara	Mclaren

Post	Research Nurse Manager
Qualifications	RN
Employer	Clinical Research Facility
Work Address	CRF, Tennent Institute,Western Inf 38, Church Street, Glasgow
Post Code	G11 6NT
Telephone	0141 232 9520
Fax	
Mobile	
Work Email	barbara.mclaren@ggc.scot.nhs.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

If Other, please specify:

Commercial status: Non-Commercial

Contact person

Name of organisation	NHS Greater Glasgow and Clyde
Given name	Dr Steven
Family name	Burke
Address	Tennant Institute, 38, Church Street
Town/city	Glasgow
Post code	G116NT
Country	UNITED KINGDOM
Telephone	0141 232 9429

Fax	0141 211 2811
E-mail	steven.burke@ggc.scot.nhs.uk

Is the sponsor based outside the UK?

○ Yes ◉ No

Where the lead sponsor is not established within the UK, a legal representative in the UK may need to be appointed. Please consult the guidance notes.

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Dr	Steven	Burke
Organisation	Research and Development Management Office		
Address	Tennant Institute, 38 Church Street		
	Western Infirmary,		
	Glasgow,		
Post Code	G11 6NT		
Work Email	steven.burke@ggc.scot.nhs.uk		
Telephone	0141 232 9429		
Fax	0141 211 2811		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 03/01/2011

Planned end date: 05/08/2013

Total duration:

Years: 2 Months: 7 Days:

A71-1. Is this study?

◉ Single centre

○ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

☐ England

- [x] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

[ ] NHS organisations in England	
[ ] NHS organisations in Wales	
[x] NHS organisations in Scotland	1
[ ] HSC organisations in Northern Ireland	
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Social care organisations	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent hospitals	
[ ] Educational establishments	
[ ] Independent research units	
[ ] Other (give details)	

Total UK sites in study: 1

A75-1. Will a data monitoring committee (DMC) be convened?

○ Yes ◉ No

If Yes, please forward details of the membership of the DMC, its standard operating procedures and summary reports of interim analyses to the Research Ethics Committee which gives a favourable opinion of the study (or to GTAC if applicable).

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The trial would be stopped prematurely if there was an unacceptable level of adverse events in either one of the study groups.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- [x] NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- [ ] Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Research site		Investigator/ Collaborator/ Contact	
Institution name	NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary	Title	Professor
Department name	Deaprtment of Anaesthesia	First name/ Initials	John
Street address	91, Wishart Street,	Surname	Kinsella
Town/city	Glasgow		
Post Code	G312HT		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the main REC or the GTAC (as applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the main REC, in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs.
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- [x] Chief Investigator
- [ ] Sponsor
- [ ] Study co-ordinator
- [ ] Student
- [ ] Other – please give details
- [ ] None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

- [x] I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by john kinsella on 09/08/2010 13:28.

Job Title/Post:	Professor of Anaesthesia Pain and Critical Care
Organisation:	Univrsity of Glasgow
Email:	jk19v@clinmed.gla.ac.uk
Signature:	.....
Print Name:	PROFESSOR JOHN KINSELLA
Date:	*(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

This section was signed electronically by Dr Steven Burke on 03/08/2010 09:33.

Job Title/Post:	Research Co-ordinator
Organisation:	NHS Greater Glasgow & Clyde
Email:	steven.burke@ggc.scot.nhs.uk

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Intrathecal opiate vs fascia iliaca block. Version 1. 1/8/10

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(•) Other clinical trial or clinical investigation

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples, other human biological samples and/or data *(specific project only)*

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(•) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(•) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(•) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

[ ] England
[x] Scotland
[ ] Wales
[ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

( ) England

(•) Scotland

- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which review bodies are you applying to?

- ☑ NHS/HSC Research and Development offices
- ☑ Research Ethics Committee
- ☐ National Information Governance Board for Health and Social Care (NIGB)
- ☐ Ministry of Justice (MoJ)

5. Will any research sites in this study be NHS organisations?

● Yes ○ No

6. Do you plan to include any participants who are children?

○ Yes ● No

7. Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity? *The guidance notes explain how an adult is defined for this purpose.*

○ Yes ● No

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service in England or Wales?

○ Yes ● No

9. Is the study, or any part of the study, being undertaken as an educational project?

○ Yes ● No

10. Is this project financially supported by the United States Department for Health and Human Services?

○ Yes ● No

Integrated Research Application System
Application Form for Other clinical trial or investigation

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Intrathecal opiate vs fascia iliaca block. Version 1. 1/8/10

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Intrathecal opiate versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty

A3-1. Chief Investigator:

Title	Forename/Initials	Surname
Professor	John	Kinsella

Post	Head of Section, Anaesthesia, Pain and Critical Care
Qualifications	MB BS MD FRCA
Employer	University of Glasgow
Work Address	University Section of Anaesthetics, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow
Post Code	G31 2ER
Work E-mail	jk19v@clinmed.gla.ac.uk
* Personal E-mail	
Work Telephone	01412111198
* Personal Telephone/Mobile	
Fax	01412111191

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

Title	Forename/Initials	Surname
Dr	Steven	Burke

Address	Research and Development Department Tennent Institute, 38, Church Street, Glasgow
Post Code	G11 6NT
E-mail	steven.burke@ggc.scot.nhs.uk
Telephone	0141 232 9429
Fax	01412112811

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	GN10AN280
Sponsor's/protocol number:	1
Protocol Version:	1.1
Protocol Date:	01/08/2010
Funder's reference number:	
International Standard Randomised Controlled Trial Number (ISRCTN):	
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	
Project website:	

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

Hip replacement surgery is a commonly performed operation. Pain control after hip surgery is important to ensure patient comfort, allow the patient to be mobile, and to aid a good recovery. Patients having hip replacement surgery need to have an anaesthetic performed by an anaesthetic doctor. As well as keeping the patient comfortable during the operation, the anaesthetic can help to provide pain control after the operation, particularly in the first 24 hours. There are many different ways of providing anaesthesia and pain control after hip surgery and we currently do not have a clear answer as to which way is best. One of the most common ways to do the anaesthetic is with a spinal injection. This involves an injection in the patient's back which numbs the patient from the waist down and allows surgery to be performed without the need for a full general anaesthetic. Many patients like this technique as it means they feel less drowsy afterwards and can eat and drink sooner than if they had a general anaesthetic. One of the drugs which is often used in the spinal injection is morphine. This is an effective pain killer but may cause side effects such as drowsiness, itch, difficulty passing urine and sickness. Another way of providing pain control is with a nerve block. This involves an injection in the groin and can be done along with a spinal injection. If a nerve block is used, then morphine could be removed from the spinal injection. This should reduce the number of patients having side effects such as itch, difficulty passing urine, sickness and drowsiness. We wish to compare a spinal injection containing morphine with a spinal injection without morphine and a nerve block to see which one provides the best pain control after hip surgery.

A6-2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

The main issues regarding this study are as follows:

1. In group 1, patients will receive an ultrasound guided fascia iliaca block (groin injection using local anaesthetic) and a spinal injection with local anaesthetic but no spinal morphine. In group 2, we propose that patients will receive a "sham" ultrsaound guided fascia iliaca block (groin injection) performed using sterile saline, and a spinal injection containing both local anaesthetic and spinal morphine. The use of a fake or sham block in group 2 means that the patient will receive an injection of an inactive substance into the groin. This will help to guarantee blinding of both patients and investigators thus improving the validity of the study. However, the performance of the sham block may be associated with some risks. As no local anaesthetic is being used in the sham block, the risks will be of discomfort on injection, bleeding or bruising at the puncture site and nerve damage. Nerve damage is rare with fascia iliaca blocks as the needle is not directed towards the nerves themselves, but rather to lie in a plane between muscle layers.

We would be grateful for the advice of the ethics committee as to whether the use of a sham block would be acceptable. The alternative would be to prepare the patients for a nerve block by cleaning the skin, placing an ultrasound probe in the groin area and performing a small injection to numb the skin but not performing the nerve block itself. This would unblind the anaesthetist performing the procedure. It is unlikely that many patients would realise that the full nerve block had not been performed although there may be exceptions.

2. There are certain risks associated with both spinal injections and nerve blocks. Both of the procedures are commonly performed for hip surgery in the United Kingdom and risks of serious side effects are rare. Any possible risks must be weighed up against the risks of a general anaesthetic.

Risks of spinal injection include; lowering of blood pressure, headache, nausea and vomiting, muscle twitching, loss of consciousness, abscess, meningitis, failure of the procedure and nerve damage (this may range from an area of numbness or weakness which resolves in a few days, to permanent paralysis in 1 in 250,000 people). If morphine is added to the anaesthetic mixure, the risks of slowing of breathing, urinary retention and itch are added.

Risks of nerve block include; bleeding and bruising, accidental injection of local anaesthetic into a blood vessel causing fits or heart and blood pressure problems, nerve damage, allergic reaction and failure of the block.

It should be noted that the above risks are very rare and these procedures are carried out very commonly in modern practice.

Each patient will have had the opportunity to read an information sheet which explains the risks of each procedure in detail and to discuss this further with a member of the research team.

Any adverse events relating to each of the procedures will be recorded by staff performing the study and any necessary investigations, treatment or follow up arranged thereafter.

3. If the nerve block is not successful, the patient might experience a higher level of pain after the operation. The patient will be given morphine via a patient controlled infusion pump in order to achieve adequate pain relief post-operatively.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study

- [ ] Laboratory study
- [ ] Metanalysis
- [ ] Qualitative research
- [ ] Questionnaire, interview or observation study
- [x] Randomised controlled trial
- [ ] Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To determine if performing a nerve block along with a plain spinal injection can provide as good pain relief as a spinal injection containing morphine for hip surgery.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To assess the patient's pain and to observe post-operative events such as nausea, sedation, itch etc which may occur with each of the two anaesthetic techniques.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Regional anaesthesia has several benefits over general anaesthesia for patients undergoing hip replacement surgery. A spinal injection is a commonly used regional anaesthetic technique. If morphine is added to a spinal injection, it can provide effective pain relief but may cause a number of unpleasant and potentially serious side effects. As an alternative, a nerve block can be performed. The nerve block we have discussed is called an ultrasound guided fascia iliac block. This nerve block is performed using an ultrasound machine so that the exact position of the injection can be seen. This technique has been shown to be very effective at producing numbness over the area where the hip surgery is performed. However, no-one has assessed whether this improves pain control after hip surgery. The ultrasound guided fascia iliaca block is considered safe and is associated with few complications. Particularly, as the injection is directed into the tissue layer surrounding the nerve rather than near the nerve itself, the risk of nerve damage may be lower than other nerve blocks. If we can show that ultrasound guided fascia iliaca block provides comparable pain relief with less side effects than spinal injection with morphine, we could remove morphine from the spinal injection and potentially improve patient safety.

A13. Please give a full summary of your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The study is of a double blind, randomised controlled design. All patients will already have been scheduled for hip replacement surgery. Patients will be seen at their routine pre-operative assessment clinic visit. The study will be explained at this point and the patient given an information leaflet to read. The patient may sign the consent form at this point though they will be encouraged to discuss their participation in the study with friends and family before deciding whether to take part or not. The patient will be seen again before their operation. If they wish to take part in the study, and have not already signed a consent form, they will be given the opportunity to sign one at this point. The patient will be aware that they may change their mind at any point, with no need for explanation, without this having any detrimental effect on their care.

On the day of surgery, the patient will be taken to the theatre reception area before their operation as normal. Routine monitoring will be started as is usual(blood pressure, heart monitor, oxygen level). A cannula will be inserted into a vein as is routine for any operation.

The patient will then be randomly assigned (like tossing a coin), into one of two groups.
The first group will receive a nerve block (which involves an injection in the groin of local anaesthetic) and spinal injection (an injection in the back) with no morphine in it.
The second group will receive a spinal injection with morphine in it and an injection in the groin of saline, a solution which does not contain local anesthetic.

An anaesthetist not directly involved with the study will prepare the drugs to be used for both the nerve block and the spinal injection in a sterile manner as directed by the randomisation schedule. This means that neither the anaesthetist performing the procedure nor the patient will know which group the patient is in.

Therefore, in order that the patient does not realise which group he or she is in, all patients will receive both a spinal injection in their back as well as an injection in their groin.

To perform the injection in the groin, patients will undergo the following; The skin in the groin area is cleaned with antiseptic solution. An ultrasound probe is used to visualise the nerves in the groin area. A small injection of local anaesthetic is used to numb the skin. In the patients who are to receive the nerve block, local anaesthetic will be injected in the groin area to surround the nerves. Those who are not meant to receive the nerve block will receive an injection of saline in the groin area. The above will be performed by an anaesthetist experienced in the technique as detailed on the study delegation log.

Patients will then be taken to the anaesthetic room (by the operating theatre) to have a spinal injection performed. In the group who received the nerve block with local anaesthetic, a spinal injection containing only local anaesthetic will be used. In the group receiving the injection in the groin of saline, a spinal injection containing local anaesthetic and morphine will be used. This will be performed by the anaesthetist assigned to the operating theatre. As the drugs will already have been prepared, this anaesthetist will also be blinded as to which group each patient is in.

The medications used to perform the injection in the groin and spinal injection will not be recorded on the anaesthetic chart. The patient's participation in the study and the 2 possible anaesthetics that may have been received will be documented on the anaesthetic chart using a pre-made sticky label. Documentation of the patient's actual anaesthetic procedure as well as any adverse events will be kept in an opaque sealed envelope in the patient's file. This data will be accessed if deemed necessary in the provision of optimal patient care.

Once the anaesthetic is complete, the patient will receive standard care whilst in theatre. If the patient wishes to sleep throughout the operation, they can be given sedating medicines by the anaesthetist. After the operation, the patient will be taken to the recovery area for a period of observation. This is routine after any operation. The patient will be prescribed regular pain killers as well as a morphine pump which has a button that the patient will be told to press if they have pain. The morphine pump (or PCA device) is used commonly after many types of operations and is a very safe method of pain control.

The patient will then move to the ward where they will continue to be monitored by trial personnel for a 48 hour period. Data regarding the amount of morphine used, pain scores, and any side effects will be recorded and treatment given as necessary. Patients will be reviewed at a routine follow-up appointment at 6 weeks after discharge. If any adverse events occur, further investigations and follow up will be arranged as necessary.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☐ Design of the research
- ☐ Management of the research
- ☐ Undertaking the research
- ☐ Analysis of results
- ☐ Dissemination of findings
- ☑ None of the above

Give details of involvement, or if none please justify the absence of involvement.
The study follows what is considered normal practice as many patients undergoing hip surgery would receive a spinal anaesthetic plus a nerve block. The difference to patients from what might happen normally is therefore small and so it was felt that there was not enough of a departure from what is normal to justify formal consultation

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood

- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [x] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit: 85	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

• English-speaking
• Competent to give consent
• ASA physical status I - III
• 18-85 years of age, inclusive
• 50-110 kg, inclusive
• Scheduled for unilateral primary hip arthroplasty

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

• Contraindications to fascia iliaca plane block (e.g. allergy to local anesthetics)
• Contraindication to spinal anaesthesia (infection at spinal injection site, hypovolaemia, raised intracerebral pressure or deemed unsuitable for spinal anaesthesia by the anaesthetist)
• Coagulopathy, malignancy or infection in the inguinal area
• Patient preference for general anaesthesia
• Allergy to opiates
• Significant peripheral neuropathy or neurologic disorder affecting the lower extremity
• Pregnancy
• History of alcohol or drug dependency / abuse
• History of long term opioid intake (MST, oramorph, oxycontin, oxynorm, sevredol, fentanyl, tramadol)
• History of significant psychiatric conditions that may affect patient assessment

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
seeking consent	1	0	30 minutes	Rachel Kearns, STr or Alan Macfarlane, consultant.or anaesthetic research fellow. Pre-operative assessment clinic and ward
giving patient information sheet	1	0	10 mins	Rachel Kearns, STr or CRF nursing staff, pre-operative assessment clinic

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
fascia iliaca nerve block	1	0	20 minutes	Dr Rachel Kearns or anaesthetic research fellow, theatre reception
Spinal anaesthetic	1	1	20 minutes	Anaesthetist who normally performs the list, anaesthetic room
Propofol sedation	1	1	60 minutes	Anaesthetist who normally performs the list, operating theatre

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

(●) Yes ( ) No

If Yes, please give details, explain the risks and justify the need to withhold the intervention or procedure:

The administration of morphine in the spinal injection will be withheld in one of the study groups. This group will receive a nerve block with local anaesthetic instead.

A21. How long do you expect each participant to be in the study in total?

The period of data collection will last for 48 hours. The patient will be followed up at 6 weeks following discharge at a routine follow up appointment. If any patient requires further follow up, this will be arranged on an individual basis.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps

would be taken to minimise risks and burdens as far as possible.

All patients will receive an injection in the groin as well as a spinal injection in the back. Both of these procedures are performed commonly in patients undergoing hip surgery and are usually tolerated well. The main risks of participating in the study relate to these injections. In particular, we propose to perform a "sham" block (groin injection) in group 2. This means that we will be injecting saline instead of local anaesthetic into the fascia iliaca plane. This is being done in order to ensure that the study is properly blinded. We hope that this will improve the validity of the results. However, this means exposing the patient to an injection which will not provide them with any benefit in terms of pain relief. Risks of having such an injection performed with saline include bleeding and bruising at the injection site, discomfort during the procedure and nerve damage.
The risk of nerve damage is very low in this type of injection as the local anesthetic is not directed towards the nerves themselves but rather to lie in a layer surrounding the nerves.

We would be grateful for guidance from the Ethics Committee as to whether this would be acceptable.

The alternative to this would be to prepare the patient for a nerve block by cleaning the skin and placing an ultrasound probe in the groin area. A small injection to numb the skin could then be performed without performing the nerve block itself. However, this would result in unblinding of the anaesthetist and potentially, of the patient.

In terms of what the patient will experience, the performance of the injection in the groin involves having the skin over the groin area (on the side of the hip operation) cleaned with a cleaning solution. This may feel slightly cold but should not be uncomfortable. An ultrasound probe will be placed over the groin area in order to see the relevant nerves. Again, this is not uncomfortable for the patient and is generally not distressing. All patients will have a small amount of local anaesthetic injected into their groin area to numb up the skin where the nerve block is going to be performed. This is slightly uncomfortable (like having an injection to numb your mouth at the dentist). There are no significant risks associated with this. Patients in group 1 will then receive an injection of local anesthetic into the groin. Patients in group 2 will have an injection of saline into their groin. However, if they were having their hip surgery done outwith the trial, they may have had a nerve block performed as a routine part of their anaesthetic.

Performance of a spinal injection involves cleaning the skin on the back with an antiseptic solution before injecting a small amount of local anaesthetic into the skin to numb the area. This makes the spinal injection more comfortable. Patients may experience some tingling in their legs during the spinal injection and are encouraged to report any such sensations to the operator. Spinal injections are performed very commonly and are generally well tolerated.

As with all type of anaesthetic there are risks. Both groups will receive a spinal anaesthetic which is a standard and commonly used anaesthetic for hip operations. This, amongst other things, has the major benefit of avoiding the risks of a general anaesthetic. Spinal anaesthesia is safe but common side effects include feeling sick afterwards. There is also a small chance of a headache. Nerve damage is rare complication of a spinal anaesthetic. The symptoms include numbness or weakness. Most of the time this is short lived and resolves after a few weeks to months. In group 2 the drug added to the spinal anaesthetic (morphine) is widely used. It can however cause itching, feeling sick or very rarely problems with breathing. Group 1 will not receive this drug but instead will receive an injection in the groin of local anaesthetic. Nerve damage, as described above, is also a rare complication of nerve blocks. In this particular block however using ultrasound the needle is not placed near the nerve and we believe that this makes it safer than other nerve blocks as the needle should not be able to damage the nerve. We would not therefore anticipate a significant increase in nerve damage in the nerve block group. In both a spinal and nerve block procedure there may be some pain or bruising at the injection site. The occurrence of any complication will be documented and will include :

Minor complications
o Local bruising
o Pain in the injection site
o Short term numbness or tingling in the leg

Major complications (but uncommon < 1%)
o Seizure / loss of consciousness
o Muscle twitching
o Irregular heart beat
o Breathing problems
o long-term numbness and tingling
o Infection
o Allergy to the local anesthetic (exceedingly rare)

All procedures will be performed by an anaesthetist experienced in the technique. Any adverse events will be documented and any necessary treatment or follow up arranged. Patients will be free to withdraw from the study at

any time without their care being affected.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

Participants who receive the nerve block (injection in the groin of local anaesthetic) will not receive morphine in their spinal injection. This has the potential benefit of avoiding side effects such as drowsiness, itch and difficulty passing urine. All patients will receive a morphine pump after their operation meaning that they are in control of the pain relief they receive. Patients having this type of operation usually have pain relief administered by a member of nursing staff. The ability to be in control of pain relief is seen as advantageous by many patients. Patients will also be monitored very closely by the research team and any adverse events followed up appropriately.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

All patients will be followed up 6 weeks after discharge. Any patient who has experienced an adverse event which requires further investigation or treatment will be followed up accordingly.

A26. What are the potential risks for the researchers themselves? *(if any)*

none.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified from orthopaedic theatre lists. Theatre lists are compiled by the orthopaedic surgeon after patients have been seen in clinic.

Patients will attend the pre-operative assessment clinic as is routine. One of the research team will explain the trial to suitable patients at this point. Patients will be given an information leaflet describing the trial in more detail. They will be encouraged to discuss their involvement in the trial with friends and family prior to making a decision. Patients will be reviewed before surgery and consent will be sought at this point.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◉ Yes ○ No

Please give details below:
The identification of participants will be by the usual clinical team. This would involve knowledge of identifying information which would need to be known anyway for the provision of clinical care.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the*

arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.

Potential participants will be identified during their routine pre-operative clinic appointment by the anaesthetist or surgeon reviewing the patient. Patients will be asked if they would be willing to talk to a member of research staff about potential participation in the study. If the patient agrees, they will be given a patient information sheet by one of the research personnel (either CRF nurse or Dr Rachel Kearns?. Consent will not be obtained at this time bu the patient will be given to ask questions. The patient will be made aware that research staff will have access to their clinical notes should they agree to participate. Confidentiality will be maintained at all times and data will be managed in accordance with The Data Protection Act.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The presence of a study will be highlighted by the anaesthetist at the pre-operative assessment clinic. Patients will be asked if they would be willing to see a member of research staff (either CRF nurse or Dr Rachel Kearns) in order to receive a patient information sheet about the study.
If there were no initial objections at clinic then potential participants will be approached by one of the research team on the night before surgery. The study will be explained, a patient information leaflet provided if this has not been done already, and consent obtained if the patient wishes to do so.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

A patient information leaflet will be provided and informed, written consent obtained as above.

All patients should be able to provide consent and inablility to consent is an exclusion criteria

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

The study will be described at the pre-operative assessment clinic approximately two weeks before the planned operation. An information leaflet will be given to the patient and they will be encouraged to discuss their participation with friends and family prior to making a decision.

Consent for the study will be obtained in the 24 hour period before surgery.

All potential participants will be informed of their right to change their mind at any point.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- ○ Yes
- ◉ No
- ○ Not Known

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Inability to be able to give informed consent and inability to speak English are exclusion criteria. No arrangements have therefore been made to provide interpreters.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The research period extends for a 6 week period only and therefore it is unlikely that any such information will become available in this short time period.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ◉ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents

- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files including X−rays
  - ☐ NHS computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal information will be kept in a locked filing cabinet in a locked room seperate from the research data and will be accessible only by the research team.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All personal data will be anonymised and kept in accordance with the NHS confidentiality policy.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The team of health care professionals who will be providing care in the peri-operative period will have access to the clinical notes as is routine in any patient undergoing in-patient care. Members of the research team will have access to the patients' case notes. The request for access to the notes will be detailed in the consent form.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Analysis of the data will be performed by Dr Rachel Kearns and Professor John Kinsella in the University Department of Anaesthesia, Glasgow Royal Infirmary.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Professor	John	Kinsella
Post	Head of Section: Anaesthesia, Critical care and Pain Medicine		
Qualifications	MB BS MD FRCA		
Work Address	University Department of Anaesthesia, Glasgow Royal Infirmary, Glasgow		
Post Code	G31 2ER		
Work Email	jk19v@clinmed.gla.ac.uk		
Work Telephone	01412111198		
Fax	01412111191		

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
All data will be kept in a secure locked facility for a period of 15 years. Data will have had all patient identifiers removed and will be kept in a secure locked facility. Patient identification data will be stored in a separate locked, secure facility.

A44. For how long will you store research data generated by the study?

Years: 15
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

All data will be kept in a secure locked facility for a period of 15 years. Data will have had any patient identifiers removed. Patient identification data will be stored in a separate locked, secure facility. Electronic data will be stored on a secure university computer. The investigating team may access the data after discussion with the Principle Investigator.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

(●) Yes ( ) No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

(●) Yes ( ) No

Please give details, or justify if not registering the research.
Application for registration on the Clinicaltrials.gov database is underway.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [ ] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

n/a

A53. Will you inform participants of the results?

( ) Yes (●) No

Please give details of how you will inform participants or justify if not doing so.
The results should not have any long term implications for the patient. If any patient suffers a serious problem during the course of the study, any relevant data would be made available to them.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
External peer review as part of grant application process (Chief Scietist Office small grant application). We plan to submit the protocol to the "Trials" journal. This will again provide an independent, external review.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☑ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor
- ☑ Other review by individual with relevant statistical expertise
- ☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	ms	Michele	Robertson
Department	Department of statistics, Robertson Centre for Biostatistics		
Institution	Glasgow University		
Work Address	Boyd Orr Building,		
	University of Glasgow		
Post Code	G128QQ		
Telephone	01413304744		
Fax			
Mobile			
E-mail	michele@stats.gla.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Morphine consumption in the first 24 hours post-operatively

A58. What are the secondary outcome measures? *(if any)*

• Pain scores at 3, 6, 12, 24, 36 and 48 hours as recorded post-operatively on the PCA chart where time zero is the end of the operation (numerical pain rating score 0 – 10 where 0 is no pain and 10 is worst pain imaginable).
• Time to 1st morphine administration in minutes from time zero.
• Episodes of respiratory depression defined as respiratory rate < 8/min or requiring naloxone administration in the first 48 hours post-operatively.
• Incidence of hypotension as defined by systolic blood pressure < 80mmHg or a drop of >25% from baseline systolic pressure, or requiring vasopressor in the first 48 hours post-operatively.
• Incidence of post-operative nausea and vomiting as defined by nausea score of greater than or equal to 2 (on a PONV

scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe nausea and 4 = patient vomiting) or requiring the administration of an anti-emetic agent in the first 48 hours post-operatively.
• Incidence of pruritus as defined by itch felt to be distressing by the patient on questioning after the first 48 hour period post-operatively or requiring treatment with naloxone.
• Incidence of sedation as defined by sedation score of greater than or equal to 2 (where 0 = awake, S = normal sleep, 1 = drowsy but easy to rouse, 2 = sedated and difficult to rouse, and 3 = unconscious) or requiring naloxone administration in the first 48 hours post-operatively.
• Incidence of urinary retention as defined by the requirement for urinary catheterisation due to failure to pass urine in the first 48 hours post-operatively.
• Time to first mobilisation as defined by patient able to mobilise from bed to chair in hours from time zero as recorded by physiotherapy staff.
• Patient satisfaction as measured using a visual analogue scale (VAS) from 0 – 100mm where 0 is absolutely not satisfied and 100 is completely satisfied. This will be performed after 48 hours and at a routine follow up appointment 6 weeks after discharge.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	106
Total international sample size (including UK):	106
Total in European Economic Area:	0

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Our primary outcome measure is 24 hour post-operative morphine consumption. We consider a difference of 10mg of morphine between groups in a 24 hour period to be significant clinically. Using a 2 group t test of equal means, a type I error rate of 0.05 and power of 0.80, we calculate that 96 patients are required to detect this difference. We anticipate an attrition rate of approximately 10% due to complications, adverse effects, protocol violations, equipment failure, patient withdrawal, and loss to follow up. In order to achieve the required sample size of 96 patients, we anticipate enrolling 106 patients.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Patients will be randomly assigned to one of two groups using a computer generated randomisation schedule.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Data will be managed on an intention to treat basis. Continuous variables will be summarized as mean values ± SD and categorical variables will be presented as median and range. Statistical significance will be established at a $p<0.05$.

The following analyses will be performed:

1. The main hypothesis of 24 hour morphine consumption (primary outcome measure), will be analysed by students t-test / Mann-Whitney U-test depending on whether data is normally distributed.
2. Secondary data analyses will be carried out on; time to first morphine administration, pain scores, nausea and vomiting scores, pruritus scores, sedation scores, patient satisfaction scores, episodes of hypotension, episodes of

urinary retention, episodes of respiratory depression and time to first mobilisation. These will be compared among groups using t-test and Mann-Whitney test as appropriate.
3. Presence or absence of adverse effects (e.g. accidental vascular puncture, intravascular local anesthetic injection, persistent postoperative paresthesia) will be compared using the Chi-Squared test.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Dr	Rachel	Kearns
Post	STr Anaesthetics, Pain and Critical Care Medicine		
Qualifications	MBChB MRCP FRCA		
Employer	NHS Greater Glasgow and Clyde		
Work Address	Department of Anaesthesia, Glasgow Royal Infirmary, 91, Wishart Street Glasgow		
Post Code	G312HT		
Telephone	01412114620		
Fax			
Mobile	07890524153		
Work Email	rkearns@doctors.net.uk		

	Title	Forename/Initials	Surname
	Dr	Alan JR	Macfarlane
Post	Consultant Anaesthetist in Anaesthesia, Pain and Critical Care Medicine		
Qualifications	MBChB BSc MRCP FRCA		
Employer	NHS Greater Glasgow and Clyde		
Work Address	Department of Anaesthesia, Glasgow Royal Infirmary, 91, Wishart Street Glasgow		
Post Code	G312HT		
Telephone	01412114620		
Fax			
Mobile			
Work Email	alan.macfarlane@nhs.net		

	Title	Forename/Initials	Surname
	Dr	Keith J	Anderson
Post	Consultant Anaesthetist in Anaesthesia, Pain and Critical Care Medicine		
Qualifications	MBChB BSc FRCA		
Employer	NHS Greater Glasgow and Clyde		
Work Address	Department of Anaesthesia, Glasgow Royal Infirmary, 91, Wishart Street Glasgow		
Post Code	G312HT		
Telephone	01412114620		

Fax	
Mobile	
Work Email	keithanderson@doctors.org.uk

Title	Forename/Initials	Surname
Mrs	Barbara	Mclaren

Post	Research Nurse Manager
Qualifications	RN
Employer	Clinical Research Facility
Work Address	CRF, Tennent Institute,Western Inf 38, Church Street, Glasgow
Post Code	G11 6NT
Telephone	0141 232 9520
Fax	
Mobile	
Work Email	barbara.mclaren@ggc.scot.nhs.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	NHS Greater Glasgow and Clyde
Given name	Dr Steven
Family name	Burke
Address	Tennant Institute, 38, Church Street
Town/city	Glasgow
Post code	G116NT
Country	UNITED KINGDOM
Telephone	0141 232 9429
Fax	0141 211 2811
E-mail	steven.burke@ggc.scot.nhs.uk

Is the sponsor based outside the UK?

○ Yes ◉ No

Where the lead sponsor is not established within the UK, a legal representative in the UK may need to be appointed. Please consult the guidance notes.

A65. Has external funding for the research been secured?

☐ Funding secured from one or more funders
☑ External funding application to one or more funders in progress
☐ No application for external funding will be made

Please give details of funding applications.

Organisation	Chief Scientist Office
Address	Chief Scientist Office, 14, St Andrew's House, Regent Road Edinburgh
Post Code	EH13DG
Telephone	0131 244 2248
Fax	0131 244 2285
Mobile	
Email	nick.gosling@scotland.gsi.gov.uk

Funding Application Status: ○ Secured ◉ In progress

Date Funding decision expected: 30/10/2010

Amount:

Duration

Years: 2

Months:

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

What type of research project is this?

◉ Standalone project
○ Project that is part of a programme grant
○ Project that is part of a fellowship/ personal award/ research training award
○ Other

Other – please state:

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

◉ Yes ○ No

Name: West of Scotland Ethics Committee

Type of organisation:
(●) NHS ( ) Academic ( ) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: Ethical approval

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (●) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Dr	Steven	Burke
Organisation	Research and Development Management Office		
Address	Tennant Institute, 38 Church Street		
	Western Infirmary,		
	Glasgow,		
Post Code	G11 6NT		
Work Email	steven.burke@ggc.scot.nhs.uk		
Telephone	0141 232 9429		
Fax	0141 211 2811		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 03/01/2011
Planned end date: 05/08/2013
Total duration:
Years: 2 Months: 7 Days:

A71-1. Is this study?

(●) Single centre
( ) Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [ ] England
- [x] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

☐ NHS organisations in England	
☐ NHS organisations in Wales	
☑ NHS organisations in Scotland	1
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Social care organisations	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent hospitals	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	

Total UK sites in study: 1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

Any organisations involved only in identification of potential participants are described as "participant identification centres".

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The results will be reviewed by the research team on a monthly basis.
All adverse events will be recorded by the trial investigators. If clinically indicated, the nature of the anaesthetic administered in the study may be revealed should this be necessary in the assessment of an adverse event. All such instances will be discussed with the chief investigator prior to the removal of blinding. All serious adverse events (SAEs) will be referred to the Chief Investigator. After assessment by the Chief Investigator, SAEs and suspected unexpected serious adverse reactions (SUSARs) will be reported to the Pharmacovigilance Office in the Robertson Centre for Biostatistics in Glasgow. All SUSARs will be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) by the pharmacovigilance office at the Robertson Centre for Biostatistics in Glasgow.

A75-1. Will a data monitoring committee (DMC) be convened?

○ Yes ◉ No

If Yes, please forward details of the membership of the DMC, its standard operating procedures and summary reports of interim analyses to the Research Ethics Committee which gives a favourable opinion of the study (or to GTAC if applicable).

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The trial would be stopped prematurely if there was an unacceptable level of adverse events in either one of the study groups.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- [x] NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- [ ] Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

- ○ Yes
- ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

◯ Yes ◉ No ◯ Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Research site		Investigator/ Collaborator/ Contact	
Institution name	NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary	Title	Professor
Department name	Deaprtment of Anaesthesia	First name/ Initials	John
Street address	91, Wishart Street,	Surname	Kinsella
Town/city	Glasgow		
Post Code	G312HT		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the main REC or the GTAC (as applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the main REC, in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs.
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- [x] Chief Investigator
- [ ] Sponsor
- [ ] Study co-ordinator
- [ ] Student
- [ ] Other – please give details
- [ ] None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

- [x] I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by john kinsella on 09/08/2010 13:29.

Job Title/Post:	Professor of Anaesthesia Pain and Critical Care
Organisation:	University of Glasgow
Email:	jk19v@clinmed.gla.ac.uk
Signature:	.....
Print Name:	PROFESSOR JOHN KINSELLA
Date:	12/08/2010 *(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

This section was signed electronically by Dr Steven Burke on 03/08/2010 09:35.

Job Title/Post:	Research Co-ordinator
Organisation:	NHS Greater Glasgow & Clyde
Email:	steven.burke@ggc.scot.nhs.uk

Appendix 2

WoSRES

West of Scotland Research Ethics Service

West of Scotland REC 4
Ground floor, Tennent Institute
Western Infirmary
38 Church Street
Glasgow
G11 6NT
e-mail: evelyn.jackson@ggc.scot.nhs.uk
Telephone: 0141-211-1722
Facsimile: 0141-211-1847

21 October 2010

Professor John Kinsella
Head of Section of Anaesthesia, Pain and Critical Care
University Section of Anaesthetics
Glasgow Royal Infirmary
Level 2, 10 Alexandra Parade
Glasgow
G31 2ER

Dear Professor Kinsella

REC reference number:	**10/S0704/43**
Protocol number:	**1**
Study Title:	**Intrathecal opiate versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty**

Thank you for your letter of 30 September 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, as revised, subject to the conditions specified below.

Ethical Review of Research Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the Favourable Opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved Documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Investigator CV	-	06 August 2010
Protocol	1.1	01 August 2010
Dr K J Anderson's CV	-	-
REC application	-	09 August 2010
Covering Letter	1.1	-
GP/Consultant Information Sheets	1.1	01 August 2010
Participant Information Sheet	1.2	30 September 2010
Response to Request for Further Information		30 September 2010
Participant Consent Form	1.1	01 August 2010
Dr A Macfarlane's CV	-	22 July 2010
Dr R Kearns' CV	-	-

Statement of Compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After Ethical Review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/S0704/43	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

***for* Dr Brian Neilly**
Chair

Enclosures: List of names and professions of members who were present at the meeting
"After ethical review – guidance for researchers"

Copy to: Dr Steven Burke, R&D Office, Tennent Institute, Western Infirmary

West of Scotland REC 4

Attendance at Sub-Committee of the REC meeting on 21 October 2010

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Kenneth James (Chair)	Consultant Anaesthetist	Yes	In correspondence
Dr Grace Lindsay	Nurse Lecturer	Yes	In correspondence

Appendix 3

Coordinator/Administrator: Dr Erica Packard/Ms Elaine O'Donnell
Telephone Number: 0141 211 6208
E-Mail: erica.packard@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

R&D Management Office
Western Infirmary
Tennent Institute
1st Floor 38 Church Street
Glasgow, G11 6NT,

14 April 2011

Prof John Kinsella
University Section of Anaesthesia
Pain & Critical Care Medicine
4th Flr Walton Building
Glasgow Royal Infirmary
Castle Street
Glasgow G31 2HT

NHS GG&C Board Approval

Dear Prof Kinsella,

Study Title:	**Intrathecal opiate versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty**
Principal Investigator:	**Prof John Kinsella**
GG&C HB site	**Glasgow Royal Infirmary**
Sponsor	**NHS Greater Glasgow and Clyde**
R&D reference:	**GN10AN280**
REC reference:	**10/S0704/43**
Protocol no: (including version and date)	**V1.5; 30th Mar 2011**

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004
   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

NHS
Greater Glasgow and Clyde

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a quarterly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial
   d. Notification of Trial/study end including final recruitment figures
   e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

[redacted]

Dr Erica Packard
Research Co-ordinator

Cc: Rachel Harrison

Appendix 4

Title: Study protocol: Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty – a randomised, blinded, non-inferiority trial

MS: 1483554814464143

Response to reviewer's report

Dear Dr Moher,

Thank you for giving us the opportunity to revise and resubmit our manuscript entitled; **"Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty – a randomised controlled trial".**

We have revised our manuscript in response to your helpful suggestions and comments. Below please find an itemised summary of the suggestions, followed by our responses *(in italics)*.

This is a protocol of a randomized trial comparing ultrasound block to no ultrasound block in 96 people receiving primary hip arthroplasty. The primary outcome is 24-hour post operative morphine consumption.
Page numbering, and better still line numbering would greatly facilitate my peer review of the protocol

This has now been addressed. Please see the revised manuscript.

The protocol is registered and the investigators are seeking funds. On this latter point, can the investigators provide a little more detail for readers about the funding request? For

example, are the investigators applying for peer review funding, funding from industry, or a combination?

This aspect has been expanded from line 393. A grant application has been submitted to the Chief Scientist's Office (CSO). The CSO is part of the Scottish Government Health Directorate. Its role is to support research initiated by the research community in Scotland and to advise the Scottish Government on how research contributes to improvements in health and healthcare. Grant applications to the CSO undergo a stringent peer review process prior to any award being made.

A grant application has also been made to the European Society for Regional Anaesthesia and Pain Medicine. Once again, all applications are peer reviewed by experts in the field of regional anaesthesia prior to funds being awarded. These funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The decision regarding any funding awards remains outstanding.

In the covering letter submitted along with the protocol the investigators consider this to be a pragmatic trial. I'm more used to thinking about pragmatic trials as ones involving several hundred participants across many different centres recruiting participants.

The word "pragmatic" has been removed.

In the body of the protocol (hypothesis section) the investigators state their interest in seeing whether ultrasound guided versus non-ultrasound block is "comparable". When I read comparable in the context of a randomised trial I interpret this to mean interest in detecting equivalence or non-inferiority. The investigators need to clarify this point as it impinges upon several other aspects of the proposed trial, particularly the sample size section. Is the trial designed as a superiority trial or an equivalence or non-inferiority trial?

We thank the reviewer for these helpful comments. We have altered the manuscript to clarify that this is a noninferiority trial. As we had not originally categorised the trial in this manner, the statistical calculation to obtain the sample size has been revised (line 259). The number of patients now required has altered very slightly and the statistical derivation of this number is described in the revised manuscript.

First line of the "overview" section: the investigators should delete "prospective" and elsewhere in the text of the protocol.

The word "prospective" has been deleted as advised.

The consent section is rather long at about half a page. Is there something unusual about this trial, in terms of the intervention, safety profile that warrants this amount of space?

The consent process for this trial has been reviewed and approved by the West of Scotland Research Ethics Committee 4. The Research Ethics Committee did not feel that there was anything unusual or concerning about our trial. This section of the article has therefore been shortened accordingly. Please see the revised manuscript (line 166).

The randomisation section needs more clarification for readers. The investigators tell readers about how the generation of their sequence will be generated – computer generated. What's less well described is how allocation concealment is be achieved and how the randomization will be implemented (e.g., Moher et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials. BMJ. 2010 Mar 23;340:c869)?

This section has now been extended to take into account the reviewers comments, many of which were addressed in our protocol but unfortunately omitted from the manuscript. Please see the revised manuscript (line 175).

Would readers find it more helpful if group 1 and group 2 were relabelled 'experimental' and 'control'?

*Group 1 has been renamed **Fascia Iliaca Group** and Group 2, **Spinal Morphine Group**. See line 189.*

In the sample size and statistical considerations section the reader is not provided with information about the anticipated length of time the investigators will take to recruit and enrol the participants – how long will the trial take? Similarly, in this section, there are no details as to whether the investigators plan on establishing a data safety and monitoring committee as part of the trial conduct?

It is anticipated that recruitment for this study will take between one and two years to complete if 1 to 2 patients are enrolled each week. We wish to work only with one surgeon to reduce inter-operator variability. At present he undertakes at least 4 total hip replacements every week. Data collection for each patient will occur during the first 48 hours post-operatively and at a routine 6 week follow up appointment. No further follow up will be routinely arranged. Any patients requiring specific follow up will have this arranged on an individual basis. (Line 306)

We value and respect the reviewer's question on the need for a Data Monitoring Committee. However, we have not proposed to have an independent data monitoring committee. It is our understanding that the need for such committees in certain trials remains under debate. Our understanding is that Data Monitoring Committees are required where the trial meets the definition of 'Randomised trial with mortality or major morbidity endpoints'. Respiratory depression or death are the only serious adverse events we would think worthy of the attention of the suggested additional data monitoring committee. These events are extremely rare and have not occurred in the context of intrathecal opioid use in our hospital in the last 5 years. Death would be picked up routinely by the Scottish Audit of Surgical Mortality. Both would be picked up at follow up in the

first 48 hours by investigators. In addition all serious morbidity or mortality would be independently audited by our institution's cardiac arrest audit, and / or the anaesthetic department's well developed morbidity and mortality review process. In the event of either of these serious events, we would invite the Anaesthetic Clinical Governance Committee to review the results of the study up until that point.

Consistent with good clinical practice, we also intend to conduct monthly safety meetings in order to highlight and discuss any safety concerns. Whilst we appreciate that these will not be independent, all adverse events will be reviewed at these meetings and any serious adverse events (and suspected unexpected serious adverse reactions) communicated to the appropriate authority as detailed in the protocol, namely the Pharmacovigilance Office in the Robertson Centre for Biostatistics in Glasgow.

Yours sincerely,

Dr Rachel Kearns

Dr Alan Macfarlane

Dr Keith Anderson

Professor John Kinsella

Academic Unit of Anaesthesia Pain and Critical Care Medicine, 4th Floor, Walton Building, Glasgow Royal Infirmary, 84 Castle Street, Glasgow, G40SF
Tel: +44 (0)141 2114625
Email: rkearns@doctors.org.uk

Appendix 5

From: David Moher <editorial@trialsjournal.com>
To: Dr Rachel Kearns <rkearns@doctors.org.uk>
Date: 15 Feb 2011 09:58:47 +0000
Subject: Your manuscript is acceptable for publication in principle.
Authors: Rachel J Kearns Dr, Alan JR Macfarlane Dr, Keith J Anderson Dr and John Kinsella Professor
Title : Study Protocol: Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty - a randomised, blinded noninferiority trial.
Journal: Trials
MS : 1483554814464143

Dear Dr Kearns,

Peer review of your manuscript (above) is now complete, and we are delighted, in principle, to accept the manuscript for publication in Trials.

However before acceptance, our editorial production team needs to check the format of your manuscript, to ensure that it conforms to the standards of the journal. They will get in touch with you shortly to request any necessary changes or to confirm that none are needed.

Authors of study protocols published in a BMC Series medical journal or Trials are entitled to a 20% discount (http://www.biomedcentral.com/info/about/apcfaq#discount) on the article processing charge if the results of the trial are submitted and accepted for publication in one of these journals. For more information on this scheme, and to find out whether your protocol can be published with a discount, view the publish your study protocol page at BioMed Central (http://www.biomedcentral.com/info/authors/protocols).

If you have any problems or questions regarding your manuscript, please do get in touch.

Best wishes,

Editors-in-Chief: Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell

Tel: +44 20 3192 2000Facsimile: +44 20 3192 2012
e-mail: editorial@trialsjournal.com
Web: http://www.trialsjournal.com/

Appendix 6

THE EUROPEAN SOCIETY OF REGIONAL ANAESTHESIA & PAIN THERAPY

ESRA Research Grant 2011

March 2011

Dear Dr. Kearns,

It is a pleasure to inform you that your application for the ESRA Research Grant has been successful. Your submission followed the ESRA guidelines and conformed in almost all points to the published ESRA Grant requirements/preferences. The fact that you have not published any original studies on regional anaesthesia in peer-reviewed journals was the only one drawback. The Grant Subcommittee consisting of 3 Board Members with extensive scientific background, scored independently your protocol titled "Intrathecal opioid versus ultrasound-guided fascia iliaca plane block for analgesia after primary THA" giving it 48 out of 60 possible points. During the midterm ESRA Board meeting in Brussels on March 11th, 2011 the Officers of the Board unanimously voted to give your project one of the ESRA Research Grants.

I personally congratulate you and you co-workers on your successful application. ESRA wishes your project all the best and hopes for its timely and effective conduct. As a Chairman of the Research Grant Subcommittee I would like to be informed by e-mail about the progress of your study: the dates of inclusion of the first and the last patient, submission of the manuscript to a peer-reviewed journal and acceptance of the manuscript for publication. The manuscript you submit for publication should state that the study was sponsored by the ESRA Research Grant. Also, please do not forget to mention the support of the ESRA Research Grant, whenever you publicly present the data from your study, either partial or complete.

Concerning the terms and conditions of transfer of Grant's money, please contact via e-mail ESRA Treasurer, Dr. Harald Rettig (hcrettig@hotmail.com).

Kind regards,

Zbigniew J. Koscielniak-Nielsen, MD, PhD, FRCA

Chairman of the ESRA Research Grant Committee

Appendix 7

University Department of Anaesthesia,

Pain & Critical Care Medicine 4th Floor,

Walton Building, Glasgow Royal Infirmary,

91, Wishart Street, Glasgow, G31 2ER

NHS Greater Glasgow and Clyde

Intrathecal opioid versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty

Information Sheet

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by Dr Rachel Kearns, Dr Alan Macfarlane, Dr Keith Anderson and Professor John Kinsella from the Department of Anaesthesia, Pain and Critical Care Medicine in Glasgow Royal Infirmary.

What is the purpose of the study?

This study is being performed in order to investigate the optimal way to provide anaesthesia and pain relief for patients undergoing hip surgery. At present, there are a wide range of acceptable techniques each with their own advantages and disadvantages. We wish to compare two different methods of providing anaesthesia and pain control after the operation to see which provides the best results in terms of pain control with the least side effects.

Why have I been invited?

You have been invited to take part in this study as you have been scheduled to undergo a total hip replacement by your surgeon. This operation is performed commonly in our hospital and requires

an anaesthetic given by an anaesthetic doctor. We propose to use two different anaesthetic techniques to provide anaesthesia and pain control for this operation. Both of these techniques are currently being used by anaesthetic doctors for this type of operation and are known to be safe. However, the two techniques have not been compared before. We hope that by comparing these two techniques directly, we will be able to establish whether one is better than the other for patients undergoing hip surgery.

Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then be given to you. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive or your future treatment. If you do decide to take part, your General Practitioner (GP) will be informed of your involvement.

What does taking part involve?

You will be seen by your surgeon and anaesthetic doctor at the pre-operative assessment clinic as normal. At this visit, a member of staff involved in the performance of this study will give you some information about what participation in the study involves. Any risks and benefits will be discussed with you at this visit. You will be seen again before your operation at which point any further questions you have will be answered. If you decide that you would like to take part in the study, you will be asked to sign a consent form and will be allocated at random into one of two groups (this is like a coin toss).

Patients in both groups will receive two injections; a nerve block (which is an injection in the groin), and a spinal injection (which is an injection in the back). The nature of these injections will differ slightly in each group so that the two different anaesthetic techniques can be compared. As all patients will receive both an injection in the back and an injection in the groin, neither patient nor doctor will know what group they are in. This will make the results of the study more reliable.

Patients in Group 1 will receive a nerve block (injection in the groin) using ultrasound imaging. The nerve block will be performed using local anaesthetic in order to provide pain relief after the surgery. Patients will then receive a spinal anaesthetic (injection in the back) which contains

local anaesthetic but which does not contain any morphine. The spinal injection will make the patient numb from the waist down so that the surgery can be performed.

Patients in Group 2 will again receive a nerve block (injection in the groin) using ultrasound imaging. In this group, saline (salty water) rather than local anaesthetic will be used to perform the nerve block. Patients in this group will again receive a spinal injection (injection in the back) which will make them numb from the waist down. In this group, the spinal injection will also contain morphine to provide post-operative pain relief.

The techniques described are not new and are commonly performed for this type of operation. The techniques described will be performed by an experienced anaesthetic doctor. Patients will be offered medicine (if they wish) which will make them feel sleepy during the operation. This can be discussed with the anaesthetic doctor.

After the operation, both groups of patients will receive pain killers. This will consist of Paracetamol as well as a pump containing morphine. The morphine pump provides you with pain relief when you need it and will give you a dose of pain killer when you press a button on a handset. This is a standard method of giving pain relief after major surgery. You cannot take too much morphine using this pump as there are many safety features which prevent this.

After the operation, you will receive oxygen through an oxygen mask while you are using the morphine pump. This is routine when using this type of pain relief. You will be monitored each hour initially by nursing staff on the ward. The physiotherapy team will do exercises with you with the aim of getting you up onto your feet within 1 day of your operation. Again, this is routine after a hip operation. Information will also be collected by a member of the study team regarding your levels of pain, mobility, satisfaction with the technique and whether any other side effects of the pain relief occurred. This will occur while you are in hospital**.** The surgeon who performed your operation will see you at a clinic 3 months after your operation as is routine for all patients having this type of surgery.

What happens to the information?

Your identity and personal information will be completely confidential and known only to the researchers. The information obtained will remain confidential and stored within a locked filing

cabinet for a period of 10 years. The data are held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people, without your permission.

What are the possible benefits of taking part?

It is hoped that by taking part in this research, you will be providing valuable information regarding the best way to provide pain relief after hip surgery. We hope that we can help to identify the best way to provide pain relief while keeping any side effects to the lowest possible level.

Are there any risks?

As with all type of anaesthetic there are risks. Both groups will receive a spinal anaesthetic which is a standard and commonly used anaesthetic for hip operations. This, amongst other things, has the major benefit of avoiding the risks of a general anaesthetic.

Spinal anaesthesia is safe but common side effects include feeling sick, fall in blood pressure and difficulty passing urine afterwards. There is also a small chance of a headache. Nerve damage is a rare complication of a spinal anaesthetic. The symptoms include numbness or weakness. Most of the time this is short lived and resolves after a few weeks to months. In very rare cases, nerve damage can be permanent. Other rare risks include infection and abscess formation. The risk of permanent damage or paralysis due to spinal anaesthesia is estimated to be around 1 in 50,000 cases). In the patients receiving morphine in the spinal injection, additional risks include drowsiness and breathing problems (very rare) and itch. It should be noted that the incidence of serious side effects is extremely rare and that spinal anaesthesia is currently the technique of choice in this hospital to provide anaesthesia for this patient group.

Nerve damage, as described above, is also a rare complication of a nerve block. In the case of the nerve block being used in this study however, the needle is not placed near the nerve and we believe that this is safer than other nerve blocks as the needle should not be able to damage the nerve. Other risks of a nerve block include pain or bruising at the injection site, failure to be effective, infection, seizures and irregular heart rate (very rare).

Who has reviewed the study?

This study has been reviewed by the West of Scotland Research Ethics Committee 4.

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone **not** closely linked to the study, please contact**;** Dr Malcolm Booth, Consultant in Anaesthesia and Intensive Care Medicine at Glasgow Royal Infirmary, telephone 0141 211 4225

Contacts:

Rachel Kearns, Anaesthetic Registrar, Glasgow Royal Infirmary; telephone 0141 211 4620

Alan Macfarlane, Consultant Anaesthetist, Glasgow Royal Infirmary; telephone 0141 211 4620

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please contact: Margaret Smith, The Complaints Manager, Glasgow Royal Infirmary, telephone 0141 2115112.

Thank you for your time and cooperation

Appendix 8

University Department of Anaesthesia,

Pain & Critical Care Medicine 4th Floor,

Walton Building, Glasgow Royal Infirmary,

91, Wishart Street, Glasgow, G31 2HT

Regarding:……

Dear Doctor,

Your patient named above has agreed to participate in a clinical research trial titled;

Intrathecal opioid versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty

The research is being carried out by Dr Rachel Kearns, Dr Alan Macfarlane, Dr Keith Anderson and Professor John Kinsella from the Department of Anaesthesia, Pain and Critical Care Medicine in Glasgow Royal Infirmary.

This study is being performed to investigate the optimal way to provide anaesthesia and pain relief for patients undergoing hip surgery. We plan to compare a nerve block (ultrasound guided fascia iliaca plane block) and a spinal injection containing only local anaesthetic, with a sham nerve block and a spinal injection containing intrathecal morphine. We hypothesise that ultrasound guided fasca iliaca plane block will provide analgesia equivalent to that of intrathecal morphine for primary hip arthroplasty in the first 48 hours after surgery and will therefore remove the need to use intrathecal opioid. As intrathecal opioids have some significant side effects, this may provide some benefits in susceptible patients.

Participation in this trial will involve undergoing one of the two treatment arms in a blinded fashion and receiving follow up by the research team on the ward for 48 hours post-operatively. Patients will be reviewed 3 months after discharge at the arthroplasty clinic as is routine for all patients undergoing hip surgery.

Risks of participation relate to spinal anaesthesia and peripheral nerve blockade. If a patient who has participated in this trial consults you with any symptoms which you consider may be related to one of the trial procedures, we would be most grateful if you could contact us using the contact details below.

Please do not hesitate to contact us should you require any further information.

Yours sincerely,

Rachel Kearns

ST6 in Anaesthesia

Telephone: 0141 2114620

Email: rkearns@doctors.org.uk

Appendix 9

University Department of Anaesthesia,
Pain & Critical Care Medicine 4th Floor,
Walton Building, Glasgow Royal Infirmary,
91, Wishart Street, Glasgow, G31 2HT

Subject number:

Intrathecal opioid versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty

Consent Form

Please initial the BOX

I confirm that I have read and understand the information sheet dated 26/05/2011 (version 1.4) for the above study and have had the opportunity to ask questions	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records.	☐
I confirm that my General Practitioner may be informed of my involvement in the above study	☐
I agree to take part in the above study	☐

----------	----------	----------
Name of Participant	Date	Signature
----------	----------	----------
Name of Researcher	Date	Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patients' notes


NHS
Greater Glasgow
and Clyde

Appendix 10

PATIENT STUDY NUMBER:	PATIENT INITIALS

University Section of Anaesthesia,
Walton Building, Glasgow Royal Infirmary,
91, Wishart Street, Glasgow, G31 2HT

Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty study.

Patient Data Collection Sheet

Version no.: 1.4 (180411)	Patient study no._____
Researcher; Dr Rachel Kearns	Patient CHI no. _____

Inclusion criteria (all must be present)

English-speaking	□	Competent to give consent	□
ASA physical status I – III	□	18-85 years of age, inclusive	□
50-110kg inclusive	□	For unilateral primary hip arthroplasty	□

Exclusion criteria (none must be present)

Infection at injection site	□	Hypovolaemia	□
Raised intracerebral pressure	□	Coagulopathy	□
Malignancy at injection site	□	Allergy to opioids / LA	□
Pregnancy	□	Alcohol / drug dependency	□
Patient preference for general anaesthesia			□
Peripheral neuropathy or neurologic disorder affecting the lower extremity			□
Long term opioid intake(MST,Oramorph,oxycontin,oxynorm,sevredol,fentanyl)			□
Significant psychiatric conditions that may affect patient assessment			□

Consent

Consent obtained	yes □	no □
Copy of consent form to patient / notes / research file	yes □	no □
Date:		
Signature of personnel obtaining consent _____		

PATIENT STUDY NUMBER:	PATIENT INITIALS

Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty study.

Patient Data Collection Sheet

Version no.: 1.4 (180411) Patient study no._____

Researcher; Dr Rachel Kearns

Demographics

Age	Weight	Height
Sex	BMI	

Pre-op observations

HR	BP (baseline)	SpO2

Fascia Iliaca Block

Time to perform (from skin cleansing to finish): _____minutes

Adverse events:

Vessel puncture	□	Paraesthesia	□
Inability to identify landmarks	□	LA toxicity	□

Other…….....

Spinal injection

Adverse events:

Bloody tap	□	Paraesthesia	□
Local anaesthetic toxicity	□	Pain on injection	□
Failure	□		

Other…….....

Surgeon :
Duration of surgery :
Estimated blood loss :
Time of end of surgery (ie time of leaving theatre = time zero):

Requirement for GA : yes □ no □

Paracetamol 1g administered pre-operatively	yes □	no □	
Anti-emetic administered intra-operatively	yes □	no □	why……..

PATIENT STUDY NUMBER:	PATIENT INITIALS

Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty study.

Patient Data Collection Sheet

Version no.: 1.4 (180411) Patient study no._____

Researcher; Dr Rachel Kearns

Time to first morphine from end of surgery (time zero from page 2) (mins) :

IV PCA Morphine consumption (mg) from end of surgery

3 hours _____	24 hours _____
6 hours _____	(if available)
12 hours _____	48 hours _____ (if available)

**Total dose of oxynorm received by patient in first 48 hour period:_____ (see kardex)

Pain scores (VAS 0 – 10) – document at rest and on movement (R / M) – NB. If PCA discontinued at 24 hours, pain scores etc should be available from obs / MEWS chart

3 hours ___/___	24 hours ____/___
6 hours ___/___	36 hours _____
12 hours ___/___	48 hours ____/___

Respiratory depression in 1st 48 hours post-operatively

Respiratory rate < 8	□ no. of readings ____
Naloxone administered for respiratory depression	□ no. of doses ____

Hypotension in 1st 48 hours post-operatively – Baseline BP is that recorded on pre-op checklist

Systolic BP < 80mmHg	□ no. of readings ____
Systolic BP > 25% less than baseline BP (_____)	□ no. of readings ____
Vasopressors required post-operatively	□ no. of doses ____

Urinary retention in 1st 48 hours post-operatively

Urinary retention requiring catheterisation	□

PONV in 1st 48 hours post-operatively

Nausea score ≥ 2	□ no. of readings ____
Nausea requiring anti-emetic	□ no. of doses ____

Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty study.

Patient Data Collection Sheet

Version no.: 1.4 (180411) Patient study no._____

Researcher; Dr Rachel Kearns

Pruritus in 1st 48 hours post-operatively

Requiring treatment with naloxone	□ no. of doses ____
Itch felt to be distressing to the patient	□

Sedation in 1st 48 hours post-operatively

Sedation score ≥ 2	□ no. of readings ____
Sedation requiring treatment with naloxone	□ no. of doses ____

Time to first mobilisation (bed to chair) from time zero (end of surgery)

Time in hours _____

Did patient achieve mobilisation at first attempt? yes □ no □

Quadriceps strength pre mobilisation as graded by physiotherapists on post-operative day 1 using MRC power assessment scale (0 - 5)

Grade

Patient satisfaction score (VAS 0 - 100mm)

At 48 hours	□
At 6 weeks	□

Adverse event / serious adverse event reported? yes □ no □

Please refer any AE / SAE to Rachel Kearns

Email: rachel.harrison890@gmail.com

Mobile: 07890524153

Tel: 0141 2114620

Appendix 11

NHS
Health Research Authority

DECLARATION OF THE END OF A STUDY

(For all studies except clinical trials of investigational medicinal products)

To be completed in typescript by the Chief Investigator and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC") within 90 days of the conclusion of the study or within 15 days of early termination. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	Professor John Kinsella
Address:	Academic Unit of Anaesthesia, Pain and Critical Care Medicine 2nd floor The new lister building Glasgow Royal Infirmary 10 Alexandra Parade Glasgow G31 2ER
Telephone:	0141 201 8630
Email:	john.kinsella@glasgow.ac.uk
Fax:	No fax machine

2. Details of study

Full title of study:	Intrathecal opiate versus ultrasound guided fascia iliaca block for analgesia after primary hip arthroplasty
Research sponsor:	NHS Greater Glasgow and Clyde
Name of main REC:	West of Scotland REC4
Main REC reference number:	10/S0704/43

3. Study duration

Date study commenced:	23/05/2011
Date study ended:	07/04/2014
Did this study terminate prematurely?	*No* *If yes please complete sections 4, 5 & 6, if no please go direct to section 7.*

4. Recruitment

Number of participants recruited	108
Proposed number of participants to be recruited at the start of the study	108
If different, please state the reason or this	—

5. Circumstances of early termination

What is the justification for this early termination?	—

6. Temporary halt

Is this a temporary halt to the study?	~~Yes~~ / No
If yes, what is the justification for temporarily halting the study? When do you expect the study to re-start?	*e.g. Safety, difficulties recruiting participants, trial has not commenced, other reasons.*

7. Potential implications for research participants

Are there any potential implications for research participants as a result of terminating/halting the study prematurely? Please describe the steps taken to address them.	The study has not stopped prematurely. There will be no consequences to the patients as a consequence of the study coming to an end.

8. Final report on the research

Is a summary of the final report on the research enclosed with this form?	*No* *If no, please forward within 12 months of the end of the study.*

9. Declaration

Signature of Chief Investigator:	[redacted]
Print name:	PROF. SOHN KINSELLA
Date of submission:	29/04/14

Appendix 12

	Spinal morphine (n=51)	Ultrasound guided Fascia Iliaca Block (n=52)	p value	Missing data
FI block time / secs **Median (IQR)**	240 (180·0-292·5)	240 (180-300)	0·67	5
FI vessel puncture **N (%)**	0	0	NA	0
FI paraesthesia on injection **N (%)**	1 (2%)	0	0·99	0
Spinal bloody tap **N (%)**	0	0	NA	0
Spinal paraesthesia on insertion **N (%)**	0	3 (5·77%)	0·23	0
Spinal pain on injection **N (%)**	0	0	NA	0

Table App 12-Error! No text of specified style in document.**-1 - Anaesthetic procedural information (as treated)**

FI = fascia iliaca, NA = not applicable. P values reaching statistical significance ($p<0.05$) are highlighted in yellow

	Spinal morphine (n=51)	Ultrasound guided Fascia Iliaca Block (n=52)	p value	Missing data
Surgery time / mins Median (IQR)	88 (73·5-97)	79 (60 – 91·25)	0·06	0
Surgery blood loss / ml Median (IQR)	300 (200-400)	300 (200-400)	0·84	4
Pre-op paracetamol N (%)	33(64·7%)	41(78·8%)	0·17	0
Intra-op anti-emetic N (%)	3 (2·9%)	1 (1·0%)	0·60	0

Table App 12-2 – Surgical information (as treated)
P values reaching statistical significance (p<0.05) are highlighted in yellow.

	Spinal morphine (n=51)	Ultrasound guided Fascia Iliaca Block (n=52)	p value	Missing data
No. patients with respiratory depression < 8 breaths per min **N (%)**	0	0	NA	0
No. patients with episodes of SBP < 80mmHg **N (%)**	1 (1·96%)	6 (11·54%)	0·12	0
No. patients with episodes of SBP > 25% under baseline N (%)	25 (49·02%)	29 (55·77%)	0·63	0
No. patients given post-operative vasopressor **N (%)**	0	1 (1·92%)	1	0
Urinary retention requiring catheterisation **N (%)**	20 (39·22%)	15 (28·85%)	0·37	0
Patients with PONV score >2 **N (%)**	7 (13·73%)	9 (17·3%)	0·82	0
No. patients requiring anti-emetics, N (%)	25 (49·02%)	24(46·15%)	0·93	0
No. patients with pruritus requiring treatment, N (%)	2 (3·92%)	1 (1·92%)	0·99	0

Pruritus considered to be distressing **N (%)**	6 (11·76%)	3 (5·77%)	0·47	0
Patients with episodes of sedation score > 2 **N (%)**	0 (0)	1 (1·92%)	1	0
Sedation requiring treatment **N (%)**	0	0	NA	0
Time of 1st mobilisation/ hrs Median (IQR)	23 (19-25·5)	25 (20-42)	0·04	3
Mobile on 1st attempt **N (%)**	44 (86·27%)	38 (73·08%)	0·16	0
Power grade at 1st mobilisation attempt **Median (IQR)**	4 (4-5)	4(4-5)	0·06	7
Patient satisfaction at 48 hrs **Median, IQR**	76(59-89)	80(50-89)	0·57	9
Residual paraesthesia at 48hrs **N (%)**	1 (1·96%)	0 (0)	0·99	0
Adverse events **N (%)**	3 (58·82%)	3 (57·69%)	1	0
SAE **N (%)**	2 (3·92%)	4 (7·69%)	0·69	0

Table App 12-3 – Secondary outcomes (as treated)

SBP = systolic blood pressure, PONV = post-operative nausea and vomiting, SAE = serious adverse event, NA = not applicable. P values reaching statistical significance ($p<0.05$) are highlighted in yellow.

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