NOTTINGHAM CLINICAL TRIALS UNIT

Annual Report 2015

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1 WELCOME

Reflecting on 2015, this may well prove to have been a year of transition for the unit. A growing number of our clinical trials are completing and submitting their results for publication. For example the STOP GAP trial compared the two most commonly used treatments, ciclosporin and prednisolone, for a painful, ulcerating skin disease called pyoderma gangrenosum. Results published in the BMJ showed no clear differences, and recommended that treatment decisions for individual patients may be guided by the different side effect profiles of the two drugs and the patient's own preference. Another landmark publication is the protocol for the ASAP trial, Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza. This trial is now set up with full regulatory approvals in place and is hibernated, ready to be activated in the event of an influenza pandemic. Once activated the trial aims to recruit 2200 participants within six weeks during the first wave of the pandemic, so results would inform clinical practice and health policy during the second wave. We think this is the first multicentre clinical trial that has been set up in readiness for rapid activation at the onset of a pandemic, and it is a model for the development of other 'off-the-shelf' trials as part of preparedness planning for public health emergencies.

Another key development over the last year has been closer engagement with clinical academics. For example, in August Alexia Karantana was appointed as Clinical Associate Professor in Hand Surgery, to lead in establishing a Centre for Evidence-based Hand Surgery in Nottingham. The post is a joint appointment between the Division of Rheumatology, Orthopaedics & Dermatology and the unit, and is partly funded by the British Society for Surgery of the Hand. To find out more about the centre and its work, go to https://www.nottingham.ac.uk/research/groups/cebhs/index.aspx.

In April, the 'Review to enhance Clinical and Health Services Research at Nottingham' presented to the University Executive Board was released. One of the main conclusions of this report was that there is insufficient methodological expertise in clinical trials and clinical trials unit capacity in Nottingham, and a Task and Finish Group was established to consider these issues. With strong support from the School of Medicine, the School of Health Sciences, the Faculty of Medicine and Health Sciences and the Nottingham University Hospitals NHS Trust, this then led to the unit submitting a proposal to the University's Strategic Development Fund for significant investment in new academic staff, and in a short course programme in clinical trials. I am delighted to say that early in 2016 we heard that this proposal has been successful. We look forward to recruiting some of the best researchers in clinical trials to Nottingham.

Lelia Duley
Director, Nottingham Clinical Trials Unit

2 RANDOMISED TRIALS

2.1 Cancer

POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy. A randomised trial in women with early stage breast cancer (POSNOC)

Chief Investigator: **Amit Goyal,** Derby Teaching Hospitals NHS Foundation Trust

Each year over 48,000 women are diagnosed with breast cancer in the UK. Currently women having surgical treatment for their breast cancer also have the first one or two lymph glands (sentinel nodes) in their armpit (axilla) removed, a procedure called sentinel node biopsy. For about a quarter of women, the breast cancer has spread to these sentinel nodes. Currently, these women are offered axillary treatment. This is either a second operation to remove all the axillary lymph glands (axillary node clearance) or axillary radiotherapy. The women also receive adjuvant therapy (chemotherapy, hormone therapy, radiotherapy or breast of chest wall). Outcome is now very good following adjuvant therapy, and so routine axillary treatment may no longer be needed. Axillary treatment is associated with lymphoedema and other long term complications such as numbness, pain and shoulder stiffness. These problems can be upsetting and difficult to cope with.

This trial aims to assess whether adjuvant therapy alone is no worse than (non-inferior to) adjuvant therapy plus axillary treatment for women with early stage breast cancer who have macrometastases in one or two axillary lymph nodes. The primary outcome is axillary recurrence within 5 years. The planned sample size is 1900 women. Recruitment began in the UK in July 2014. Sites in Australia and New Zealand will open to recruitment from February 2016.

Contact: Shabina Sadiq
Funding: NIHR Health Technology Assessment, National Health and Medical Research Council (Australia)
Status: Recruiting
Publications: 2012-18

2.2 Eyes

A randomised controlled Trial of standard and low dose Avastin® for Neovascular macular Degeneration in the East Midlands (TANDEM)

Chief Investigator: **Alexander Foss**, Nottingham University Hospitals NHS Trust

Wet, or neovascular age-related, macular degeneration causes severe sight loss in older people. It is a common condition, with about 25,000 newly affected people each year in the UK. Treatment with Lucentis® (Ranibizumab) or Eyelea® (Aflibercept) is now recommended best practice. Although they prevent sight loss in 90% of patients with wet macular degeneration when given as injections into the eye, Lucentis® and Eyelea® are both quite expensive. Another drug, which has similar properties to Lucentis® is Avastin® (Bevacizumab). Avastin® is currently licensed for colorectal cancer therapy but can also be used for wet macular degeneration, and is a cheaper alternative to Lucentis®.

This is a factorial trial comparing standard versus low-dose Avastin®, and monthly versus two-monthly review intervals. The estimated sample size is 1200 participants. The primary outcome is time to treatment failure.

Contact: Beki Haydock
Funding: NHS England and Care Commissioning Groups
Status: Recruiting
Publications: 2015-5

2.3 Infection

Gentamicin in the Treatment Of Gonorrhoea (G-TOG)

Chief Investigator: **Jonathan Ross,** University Hospitals Birmingham NHS Foundation Trust

Currently the antibiotic ceftriaxone is used to treat gonorrhoea, but there is increasing evidence that this antibiotic is becoming less effective over time and will stop curing patients with gonorrhoea within the next few years.

Many currently available antibiotics do not work against gonorrhoea, and there is an urgent need to find an alternative treatment which is effective and safe. Gentamicin was used in the past in the UK to treat gonorrhoea, and laboratory testing suggests that it remains effective against gonorrhoea. It is currently being used as a treatment in some developing countries.

This randomised trial is comparing gentamicin with the current standard treatment ceftriaxone to assess whether gentamicin is a safe and effective alternative treatment for gonorrhoea. Recruitment commenced in October 2014 and is taking place in eight sexual health centres in the UK. It will continue for 26 months with an estimated sample size of 720 participants. The primary outcome is clearance of gonorrhoea at all infected sites confirmed by swab testing two weeks after treatment.

Contact: Clare Brittain
Funding: NIHR Health Technology Assessment
Status: Recruiting
Publications: 2014-33

2.4 Mental Health

Psycho-Education and Problem Solving therapy for adults with personality disorder (PEPS trial)

Chief Investigator: **Mary McMurran,** The University of Nottingham

Personality disorders are conditions in which an individual experiences difficulties in terms of how they think, perceive, feel or relate to others. People with personality disorder may have problems which can include negative feelings such as distress, anxiety, worthlessness or anger; avoiding other people and feeling emotionally disconnected; having difficulty managing negative feelings without self-harming (for example, abusing drugs and alcohol or taking overdoses), and having difficulty maintaining stable and close relationships. Social problem-solving therapy is a potential strategy that may benefit people with personality disorders.

This study evaluated the effectiveness of Psycho-Education and Problem Solving (PEPS) therapy compared with usual care for adults with personality disorder. The primary outcome was social functioning at 72 weeks, assessed by the Social Functioning Questionnaire. The trial completed in October 2014. The results indicate that PEPS therapy plus usual treatment was no more effective than usual treatment alone on the primary outcome or any secondary outcomes.

Contact: Florence Day
Funding: NIHR Health Technology Assessment
Status: Main report in press
Publications: 2011-1

2.4 Mental Health *Cont*

Lamotrigine versus inert placebo in the treatment of borderline personality disorder: the LABILE trial

Chief Investigator: **Mike Crawford,** Imperial College London

People with borderline personality disorder experience rapid and distressing changes in mood, poor social functioning and have high rates of suicidal behaviour. Several small scale studies suggest that mood stabilizers may produce short-term reductions in the symptoms of borderline personality disorder. These studies have not been large enough to reliably assess clinical and cost-effectiveness.

The aim of this trial is to investigate the effect of adding lamotrigine to usual care for people with borderline personality disorder on their mental health, social functioning, and quality of life. The study will also assess the effect on suicidal behaviour, prescribing of anti-psychotic and other psychotropic medication, and side effects of lamotrigine. The trial includes an economic evaluation.

Contact: Alan Montgomery
Funding: NIHR Health Technology Assessment
Status: Follow up
Publications: 2015-16

Expanding care for perinatal women with depression (EXPONATE trial)

Chief Investigator: **Oye Gureje,** University of Ibadan, Nigeria

Depression is common among women during the perinatal period and is associated with long-term adverse consequences for the mother and infant. In Nigeria, as in many other low- and-middle-income countries, perinatal depression usually goes unrecognized and untreated.

The aim of EXPONATE is to test the effectiveness and cost-effectiveness of an intervention package for perinatal depression delivered by community midwives in primary maternal care in which physician support and enhanced patient compliance are implemented using mobile phones.

Contact: Alan Montgomery
Funding: Grand Challenges Canada
Status: Analysis and reporting

A stepped care intervention for depression in primary care (STEPCARE trial)

Chief Investigator: **Oye Gureje,** University of Ibadan, Nigeria

Depression constitutes a significant public health burden and is associated with a high level of individual suffering. Insufficient human and material resources impede the provision of adequate care for people with depression in low- and middle-income countries. To bridge this treatment gap, it is essential to integrate the treatment of depression into the primary health care system.

The aim of this study is to evaluate the clinical and cost effectiveness of a care package for care delivered mainly by non-medical Primary Health Care workers with supervision and support from physicians and specialists.

Contact: Alan Montgomery
Funding: MRC/DFID/Welcome Trust Joint Global Health Trials scheme
Status: Follow up
Publications: 2015-26; 2015-49

2.5 Musculoskeletal

Nottingham Gout Treatment Trial Phase 2: trial of a nurse-lead package of care

Chief Investigator: **Michael Doherty,** The University of Nottingham

Gout is often said to be the most painful form of arthritis. Symptoms include intensely painful, red, hot and swollen joints. Gout is most common in men and rarely affects women before the menopause. Prevalence increases with age. Of all the forms of arthritis, gout is understood the best. This has led to a range of therapies to treat acute attacks and control the condition. People with gout are usually managed in primary care, but their care is not always optimal.

This trial to assess whether, for patients with untreated or under-treated gout, nurse led care is effective and cost-effective compared with usual general practitioner-led care. Estimated sample size is initially 724 participants, but this was subsequently revised to 512 participants. The primary outcome is serum uric acid within the therapeutic range (<360 µmol/L) at two years. Recruitment was from March 2013 to October 2014, in total 517 participants were recruited.

Contact: Lelia Duley
Funding: Arthritis Research UK
Status: Follow up

Needle fasciotomy versus limited fasciectomy for treatment of Dupuytren's contractures of the fingers: a feasibility study to investigate the acceptability and design of a multicentre randomised trial (HAND-1)

Chief Investigator: **Tim Davis,** Nottingham University Hospitals NHS Trust

Dupuytren's contractures are fibrous cords under the skin in the palm of the hand. These contractures are painless but cause one or more fingers to gradually and irreversibly curl into the palm, resulting in loss of hand function. Standard treatment is surgery to either remove or divide the contractures, allowing the finger to straighten again. The most common operation is to remove the contracture (limited fasciectomy): the fibrous cords preventing the finger(s) from straightening are cut out through a long skin incision in the hand. The alternative procedure is to divide the contracture with a needle (needle fasciotomy): a needle is put through the skin and sawing movements used to divide the fibrous cords. There is no clear evidence of the comparative benefits and risks of these two quite different surgical procedures for Dupuytren's contractures.

The HAND-1 study aims to assess the feasibility and acceptability to patients and clinicians of conducting a large randomised trial assessing the comparative clinical and cost effectiveness of needle fasciotomy versus limited fasciectomy for Dupuytren's contractures of fingers. Recruitment is from November 2015 to September 2016 at three sites, and the total sample size is 50 to 85 participants.

Contact: Ellie Harrison
Funding: NIHR Research for Patient Benefit
Status: Recruiting

2.6 Oral and Gastrointestinal

Systematic Evaluation of Aspirin and Fish Oil polyp prevention trial (seAfOod)

Chief Investigator: **Mark Hull,** University of Leeds

Colorectal cancer develops over a number of years from tumour initiation and benign adenoma (or polyp) growth, followed by transformation into malignant adenocarcinoma. Currently colorectal cancer prevention is aimed at detection and removal of asymptomatic colorectal polyps. Polyp removal does reduce bowel cancer risk, but does not prevent all cases of bowel cancer.

This factorial trial is assessing the effects of eicosapentaenoic acid (fish oil) and / or aspirin for people with colorectal polyps attending for colonoscopic surveillance in the NHS Bowel Cancer Screening Programme. Estimated sample size is 755 participants. The primary outcome is recurrent polyp/s at surveillance colonoscopy. Recruitment is due to close in June 2016.

Contact: Sarah Fahy
Funding: NIHR Efficacy and Mechanism Evaluation
Status: Recruiting
Publications: 2013-6; 2015-48

"Follow-on" rifaximin for the prevention of relapse of clostridium-associated diarrhoea: a randomised trial (RAPID)

Chief Investigator: **Robin Spiller,** The University of Nottingham

Clostridium difficile infection is the main cause of antibiotic associated diarrhoea. It mainly affects frail and elderly hospitalised patients, although more recently a rising incidence of a more virulent strain has been associated with infection in younger patients and those in the community. It is characterised by a high incidence of recurrent infection, which can have debilitating consequences for already weakened patients. There are few well designed randomised trials in this condition, and treatment is largely based on experience and consensus opinion.

This trial is comparing rifaximin with placebo for people who have had successful treatment of clostridium difficile. Estimated sample size is 144 participants; with a recruitment target of 180 participants to allow for withdrawal. The primary outcome is relapse at 12 weeks. Recruitment is due to close in March 2016.

Contact: Nafisa Boota
Funding: NIHR Research for Patient Benefit
Status: Recruiting

Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (MIBS trial)

Chief Investigator: **Robin Spiller,** The University of Nottingham

Irritable bowel syndrome is a heterogeneous condition common in both primary and secondary care in the UK, where it accounts for 3% and 40% of all consultations respectively. This condition impacts on patients' quality of life, and their performance at work and home. Irritable bowel syndrome with diarrhoea may develop after inflammation due to bacterial gastroenteritis (post infectious Irritable bowel syndrome) and the immune response can be prolonged. Recent studies have shown 'immune activation' in the mucosa of patients with Irritable bowel syndrome with diarrhoea that does not have an infectious origin, and anti-inflammatory treatment might be beneficial.

The aim of this study was to assess the effect of mesalazine compared with placebo for treatment of irritable bowel syndrome with diarrhoea, and to assess its impact on mast cell numbers and mediator release in an attempt to predict treatment response. 136 patients were randomised; follow up was at 12 weeks. Results do not support any clinically meaningful benefit or harm of mesalazine compared with placebo in unselected patients with IBS-D irritable bowel syndrome with diarrhoea.

Contact: Matthew Leighton
Funding: NIHR Efficacy and Mechanism Evaluation
Status: Published
Publications: 2013-2; 2015-6

2.7 Pregnancy and Childbirth

Induction of labour at 39 weeks versus expectant management for nulliparous women over 35 years of age (35/39 Trial)

Chief Investigator: **Jim Thornton,** The University of Nottingham

In the UK, the average age at childbirth is increasing, with 20% of women now giving birth over 35 years of age. These women are at higher risk of perinatal death, and of pregnancy complications. Obstetric intervention increases with maternal age. Thirty eight per cent of nulliparous women over 35 years give birth by Caesarean section, rising to 50% for women over 40 years.

This trial is comparing a policy of induction of labour at 39 weeks gestation for women aged over 35 years with a policy of awaiting spontaneous onset of labour. The primary outcome is Caesarean section. The study is also assessing the feasibility of conducting a larger trial to assess the comparative effects on perinatal mortality and serious neonatal morbidity. Estimated sample size was 630 women. Overall, 619 women participated. There were no significant differences between groups in the proportion of women who had caesarean section, or the proportion with short-term adverse maternal or neonatal outcome.

Contact: Jim Thornton
Funding: NIHR Research for Patient Benefit
Status: Main report in press
Publications: 2012-17

Immediate versus deferred cord clamping for preterm birth before 32 weeks gestation, a pilot randomized trial (Cord Pilot Trial)

Chief Investigator: **Lelia Duley**, The University of Nottingham

Preterm birth is the most important single determinant of adverse outcome in terms of survival, quality of life, psychosocial and emotional impact on the family, and costs for health services. In the UK one in every 70 babies is born before 32 weeks gestation (very preterm). For very preterm infants, the umbilical cord is usually clamped immediately at birth and the baby taken to a resuscitaire at the side of the room. Deferring cord clamping will allow blood flow between the placenta and baby to continue for a few minutes after birth. The net flow is known as 'placental transfusion'. If cord clamping is deferred, initial care and stabilisation of the baby will be at the bedside. There is promising evidence that deferring cord clamping at very preterm birth may be beneficial, but stronger evidence is needed about the effects on serious morbidity, mortality and disability-free survival.

This pilot trial is comparing cord clamping within 20 seconds with clamping after at least two minutes, for births before 32 weeks gestation. The aim is to assess the feasibility of conducting a large randomised trial in the UK. Recruitment was from March 2013 to February 2015. Overall 261 women/baby pairs were recruited at eight sites. Follow up for women is at one year, and for children at age two years (corrected for gestation at birth).

Contact: Lindsay Armstrong-Buisseret
Funding: NIHR Programme Grants for Applied Research
Status: Follow up
Publications: 2011-3; 2012-12; 2013-13; 2013-14; 2014-13; 2014-17; 2015-13; 2015-17; 2015-50

2.7 Pregnancy and Childbirth *Cont*

Feasibility of conducting a randomised trial evaluating timing of cord clamping for preterm births in low and middle income countries (i-cord)

Chief Investigator: **Lelia Duley,** The University of Nottingham

An estimated 15 million babies are born before preterm (before 37 gestation weeks) each year, of whom more than 1 million die following complications of being born too early. Preterm birth is more common in low and middle income countries. Almost two thirds of preterm births occur in sub-Saharan Africa and South Asia. Inequalities in survival around the world are stark. For example, of infants born at 28 to 32 weeks gestation in high income countries 95% survive, compared with 30% in low income countries.

This study aims to assess feasibility of a large randomised trial comparing alternative policies for timing of cord clamping for births between 28 and 34 weeks gestation (or 1–2 kg birthweight). A prospective audit of births at five hospitals in Uganda (2 sites), Kenya, India and Pakistan is assessing current practice for timing of cord clamping and for neonatal care in the delivery room, and the proportion of births which can be correctly identified as being at this gestation. A separate study in India is assessing the volume and duration of umbilical flow at preterm birth if the umbilical cord in not clamped immediately. Finally, potential barriers to recruitment in a randomised trial are being explored in a qualitative study in Uganda.

Contact: Lelia Duley
Funding: MRC/DFID/Wellcome Trust Joint Global Health Trials scheme
Status: Analysis and reporting

Do tests of placental function improve outcome for women with reduced fetal movements at 36 weeks gestation, or later? The REMIT-2 trial

Chief Investigator: **Alexander Heazell,** University of Manchester

In the UK, 1 in 220 babies are stillborn (born with no signs of life after 24 weeks of pregnancy). This is a higher proportion than in many other high income countries. Forty percent of babies who are stillborn die after 36 weeks of pregnancy and have no lethal structural abnormality. These deaths are tragedies for the families. If babies at risk of stillbirth could be identified and delivered early, lives could be saved.

An association between the mother noticing reduced fetal movements and subsequent stillbirth has been documented for over 40 years. For women reporting reduced fetal movements at 36 weeks or later, standard care varies but usually includes assessment of the fetal heart rate with cardiotocography, and assessment of fetal growth and wellbeing by ultrasound scan and umbilical artery doppler. The aims of this trial are to assess whether using tests to measure placental function may improve pregnancy outcome, compared with standard care for women at or near term (at least 36 weeks gestation); and if so to assess the feasibility of a large multicentre trial. The primary outcome is a composite measure which includes perinatal death, fetal growth restriction, umbilical artery pH <7.1 or admission to the neonatal intensive care unit for at least 48 hours. The sample size is 750 women.

Contact: Lindsay Armstrong-Buisseret
Funding: NIHR Clinician Scientist Fellowship
Status: Set up
Publications: 2015-38

2.8 Rehabilitation

Community in-reach and care transition (CIRACT trial)

Chief Investigator: **Opinder Sahota,** Nottingham University Hospitals NHS Trust

This trial aims to reduce the length of hospital stay and re-admission and to improve health-related quality of life for unplanned hospital admission for people over the age of 70 years by delivery of the Community in-reach and care transition (CIRACT) service as compared to traditional hospital based rehabilitation. The primary outcome measure is hospital length of stay from admission to discharge from the general medical elderly care ward. Follow up of participants is to day 91 post discharge date. Embedded within the study are health economics and mechanism and action sub- studies. The planned sample size was 240 participants; which was achieved in July 2014.

Contact: Margo Childs
Funding: NIHR Health Services and Delivery Research
Status: Analysis and reporting
Publications: 2015-11

Rehabilitation of memory following traumatic brain injury: a randomised trial (ReMemBrin trial)

Chief Investigator: **Roshan das Nair,** Nottingham University Hospitals NHS Trust

Memory problems are common following traumatic brain injury. These can not only be persistent, but may be debilitating and difficult to treat. The effectiveness of cognitive rehabilitation following brain injury has been assessed in randomised trials, which have mainly focused on attention, executive functions, and visual neglect. Memory rehabilitation has not been sufficiently researched, however.

This trial is evaluating a group memory rehabilitation programme for adults, including military personnel, who have had a traumatic brain injury. The study is comparing group based memory rehabilitation plus usual care with usual care alone. Estimated sample size is 312 participants. The primary outcome is an assessment of memory at six months. Recruitment closed at the end of December 2015.

Contact: Amy Evans
Funding: NIHR Health Technology Assessment
Status: Follow up
Publications: 2015-2

Cognitive Rehabilitation for Attention and Memory for people with Multiple Sclerosis (CRAMMS)

Chief Investigator: **Nadina Lincoln,** The University of Nottingham

Around two thirds of people with Multiple Sclerosis experience difficulties paying attention, learning, remembering new things and planning tasks. This can be distressing for the individual and their families and friends. Small scale trials suggest that cognitive rehabilitation may be effective to improve memory in people with MS. However, large randomised controlled trials have not been performed.

This trial is assessing whether a group cognitive rehabilitation programme plus usual care is associated with reduced impact of MS on quality of life, compared to usual care alone. The primary outcome is the psychological impact of MS on everyday life 12 months after randomisation. Estimated sample size is 400 participants, to be recruited from 4 sites. Recruitment opened in March 2015.

Contact: Amy Evans
Funding: NIHR Health Technology Assessment
Status: Recruiting

2.9 Respiratory

Double-blinded randomised trial of early low dose steroids in patients admitted to hospital with influenza infection during a pandemic (ASAP)

Chief Investigator: **Wei Shen Lim,** Nottingham University Hospitals NHS Trust

An influenza pandemic occurs when a new strain of influenza virus emerges which is different from other currently circulating strains of the virus. This means that few people have any protection against the new virus, and so the virus can infect people easily. The virus therefore spreads on a worldwide scale and infects a large proportion of the population. In contrast to the regular seasonal epidemics of influenza, these pandemics occur irregularly, with the 1918 Spanish flu the most serious pandemic in recent history. There are currently no markers that will predict the pathogenicity or spread of a potential pandemic strain. Therefore, any plans for a future pandemic need to be flexible and take account of different possible scenarios from mild to severe.

Corticosteroid use in influenza is widespread, non-systematic and controversial. During the last pandemic in 2009, corticosteroid use during hospital admission was reported in various cohort studies and non-randomised studies but there are no randomised trials of the use of corticosteroids for patients with pandemic, avian or seasonal influenza infection.

This trial will assess the effects of adding a five-day course of dexamethasone (a corticosteroid), started within 24 hours of hospital admission, to standard care. Participants will be adults hospitalised with an influenza-like illness during the pandemic. Estimated sample size is 2,200 participants. The primary outcome is admission to intensive care unit or death, within 30 days of hospital admission. During a pandemic, the aim is to activate the trial within four weeks during the first wave of the pandemic, and to complete recruitment in six weeks. Results would then inform clinical practice and health policy during the second wave.

The trial is now set up, with full regulatory approval, and has been hibernated. During hibernation the trial will be reviewed annually to ensure it remains ready to activate rapidly when required.

Contact: Clare Brittain
Funding: NIHR Health Technology Assessment
Status: Hibernation
Publications: 2013-20; 2015-7; 2015-53

Clinical and cost-effectiveness of temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations: a pragmatic randomised trial (FAST)

Chief Investigator: **Tim Harrison,** The University of Nottingham

Asthma is a common chronic condition. Acute exacerbations of asthma cause considerable morbidity, and account for a large component of the NHS-associated costs of asthma as they lead to high levels of emergency healthcare use. Asthma self-management plans could potentially improve asthma control, reducing exacerbations requiring oral corticosteroids and emergency healthcare as well as time away from work.

Although written self-management plans are recommended for all patients with asthma, many patients are not provided with one. Reasons for this include a lack of time and confusion about what to include in the plan when asthma control is deteriorating but before the need for oral corticosteroids.

This trial will compare a self-management plan which includes a temporary fourfold increase in inhaled corticosteroid with the same plan without an increase in inhaled corticosteroid when the participants' asthma control deteriorates. Estimated sample size is between 1774 and 1850 with recruitment due to end on 31st January 2016. Recruitment is taking place in 11 secondary care sites with a further 195 primary care research GP practices. Currently, 1700 participants have been recruited. The primary outcome is the time to first asthma exacerbation, requiring the use of oral steroids or an unscheduled healthcare consultation for asthma.

Contact: Richard Swinden
Funding: NIHR Health Technology Assessment
Status: Recruiting

2.10 Skin and wound healing

LeucoPatch® in the management of hard to heal diabetic foot ulcers

Chief Investigators: UK - **Frances Game,** Derby Teaching Hospitals NHS Foundation Trust;
Sweden - **Magnus Löndahl,** Skane University Hospital;
Denmark - **Lise Tarnow,** Nordsjaellands Hospital

Diabetic foot ulcer is a common and severe complication of diabetes mellitus and despite improved outcomes remains the dominating reason for non-traumatic leg amputations in most western countries. LeucoPatch® is produced from patient's own venous blood by centrifugation, the final product comprising of a thin circular plug composed predominantly of fibrin with living platelets and leucocytes. The number of plugs used is determined by the size of the individual wound.

This trial sets out to demonstrate whether the application of LeucoPatch® used in conjunction with usual care is superior to usual care alone. The primary outcome will be percentage of ulcers healed within 20 weeks. Estimated sample size of 250 participants. The study opened to recruitment in August 2013. Recruitment is at 35 sites in the UK, Sweden and Denmark.

Contact: Florence Day
Funding: Reapplix
Status: Recruiting

Bullous pemphigoid steroids and tetracyclines study (BLISTER)

Chief Investigator: **Hywel Williams,** University of Nottingham

Bullous pemphigoid is an autoimmune skin disorder characterised by large blisters, which can cause considerable pain and distress. It may be acute or chronic, and is most common in people over 70 years of age.

This study is comparing the antibiotic doxycycline (a tetracycline) with prednisolone (a corticosteroid) for treatment of bullous pemphigoid. Both drugs are given as a single daily oral dose. The primary outcomes are blister control at six weeks, and severe or life threatening events at one year. The trial recruited from 57 sites, 50 in the UK and 7 in Germany. Recruitment closed having reached target accrual of 256 patients in September 2013.

Contact: Beki Haydock
Funding: NIHR Health Technology Assessment
Status: In press
Publications: 2012-7

Fibreglass casts in the management of ulcers of the heel in diabetes (HEELS)

Chief Investigator: **William Jeffcoate,** Nottingham University Hospitals NHS Trust

Up to 15% of people with diabetes develop chronic ulceration of their foot, and this is most common among the elderly. Two-thirds of foot ulcers heal within 12 months, but of these 40% will recur within 12 months. Lightweight fibreglass heel casts are used for heel ulcers in the belief that they improve healing and reduce pain and discomfort. These casts take 15 minutes to mould to the heel, are applied over the primary wound dressing, and held in place with an outer dressing. They can be worn inside shoes, and need to be replaced on average every three weeks.

This trial is comparing usual care plus fibreglass heel casts with usual care alone for the management of ulcers of the heel in diabetes. The primary outcome is ulcer healing at 24 weeks. Recruitment closed in September 2014 having reached target accrual of 509 participants.

Contact: Viv Turtle-Savage
Funding: NIHR Health Technology Assessment
Status: Analysis and reporting
Publications: 2012-14; 2014-6

2.10 Skin and wound healing *Cont*

Randomised controlled trial of silk therapeutic clothing for the long-term management of eczema in children (CLOTHES)

Chief Investigator: **Kim Thomas,** The University of Nottingham

Eczema is a chronic, inflammatory skin condition that impacts on the quality of life of patients and their families. Some types of clothing can cause irritation to the skin, and current guidelines recommend the use of loose cotton clothing, and the avoidance of wool and other rough fibres next to the skin. In response to this need, new clothing products have become available in recent years, and these are now marketed as having beneficial effects in the treatment of eczema.

The therapeutic silk garments included in this trial are available on prescription through the NHS, but the trial evidence supporting their use is currently limited. The trial objectives are to: 1) assess whether silk therapeutic clothing, when used in addition to standard eczema care, reduces eczema severity in children over a period of six months, 2) estimate the within trial cost-effectiveness of silk therapeutic clothing with standard care, compared to standard care alone, from an NHS and a family perspective. The primary outcome is eczema severity, as assessed by research nurses who are blinded to participant group allocation.

Recruitment took place from November 2013 to May 2015. 300 children with moderate to severe eczema were recruited from five sites, and follow-up was completed in December 2015.

Contact: Rachel Haines / Ellie Harrison
Funding: NIHR Health Technology Assessment
Status: Analysis and reporting
Publications: 2015-14

Barrier Enhancement for Eczema Prevention (BEEP)

Chief Investigator: **Hywel Williams,** The University of Nottingham

Eczema is a common skin problem affecting 16% to 30% of children in the UK, and around 20% worldwide. The onset of eczema usually occurs in infancy, and generally dry skin is one of the first abnormalities in babies who eventually develop the condition. It is thought that skin barrier dysfunction (dry skin and increased trans-epidermal water loss) could be a primary event in the development of eczema and atopy. Emollient therapy has been shown to improve skin barrier function by providing lipids to the stratum corneum (the outermost layer of skin), in turn improving skin hydration by trapping in water. Early and regular use of emollient could lead to a potential improvement in skin barrier function.

The primary objective of this trial is to determine whether advising parents to apply emollient to their child's skin daily for the first year of life, in addition to best practice infant skin care advice, can prevent or delay the onset of eczema in high-risk children, when compared with a control group who are given the best practice infant skin care advice only. Recruitment began in November 2014. The aim is to recruit 1282 families over 2 years, at 16 sites.

Contact: Sandip Stapleton
Funding: NIHR Health Technology Assessment
Status: Recruiting

2.10 Skin and wound healing *Cont*

Home Interventions and Light Therapy for the Treatment of Vitiligo (HI-Light)

Chief Investigator: **Jonathan Batchelor,** Derby Hospitals NHS Foundation Trust and The University of Nottingham

Vitiligo causes loss of pigment on the skin and white patches appear in the affected areas. This condition affects around 1% of the population worldwide, and patients with vitiligo can experience problems such as shame, depression, and low self-esteem due to the appearance of their skin. There is no cure for vitiligo, as the cause of the condition is not understood. Treatment options for small areas of vitiligo are limited; small patches are sometimes treated with topical corticosteroid ointments. Narrowband Ultraviolet B light therapy (NB-UVB) may also be offered as a treatment, but it involves frequent visits to hospital and is mainly used for widespread vitiligo. Hand-held NB-UVB light units are available to use in the home on small patches of vitiligo, though these are not available on the NHS. Previous vitiligo research suggests that combination therapies (topical steroid and light therapy) may prove more effective in the treatment of the condition than either therapy alone, though the efficacy of these combined treatments has yet to be established.

The objective of this trial is to provide information on the comparative effectiveness and safety of topical corticosteroids (mometasone furoate 0.1% ointment) versus (i) home-based NB-UVB light, and (ii) the combination of topical corticosteroids and home-based NB-UVB light for early and limited vitiligo in adults and children. The trial aims to recruit 440 adults and children over the age of 5 across the UK who have non-segmental vitiligo, and at least one patch of vitiligo which has shown to be active in the past 12 months. Participants will be asked to treat their vitiligo patches with ointment and a light therapy unit at home, for a period of 9 months. Recruitment began in May 2015.

Contact: Garry Meakin
Funding: NIHR Health Technology Assessment
Status: Recruiting

2.11 Stroke

Visual Cue Training to improve walking and turning after stroke: a pilot study (VCT trial)

Chief Investigator: **Kristen Holland,** University of Salford

Following stroke, a major goal of rehabilitation is retraining in walking. Even if the ability to walk is regained, problems with slow speed and lack of balance are common. Up to half of stroke survivors discharged into the community will fall, and a large proportion of these falls occur during walking and turning. Given the importance of vision in the control of walking and evidence indicating varied practice of walking improves mobility outcomes, this study aims to examine the feasibility and preliminary efficacy of varied walking practice in response to visual cues, for the rehabilitation of walking following stroke.

This three arm pilot trial is comparing (i) visual cue training plus standard rehabilitation with walking and turning practice; (ii) treadmill based visual cue training; and (iii) standard rehabilitation alone. The sample size was 60 participants. Fifty six participants took part, and thirty four completed treatment and follow-up assessments. Adherence to the treatments was good with 16 treatments being provided over a median of 8.4, 7.5 and 9 weeks for T-VCT, O-VCT, and UC respectively. No adverse events were reported. Post treatment improvements in walking speed, symmetry, balance and functional mobility were seen in all treatment arms.

Contact: Diane Whitham
Funding: NIHR Research for Patient Benefit
Status: Published
Publications: 2013-35; 2015-55

2.12 Trials Co-ordinated by the Nottingham Stroke Trials Unit

Nottingham Clinical Trials Unit collaborates with the Nottingham Stroke Trials Unit, led by Philip Bath, on several large multicentre trials.

Safety and efficacy of intensive versus guideline antiplatelet therapy in high-risk patients with recent ischaemic stroke or transient ischaemic attack: a randomised trial (TARDIS)

Chief Investigator: **Philip Bath,** The University of Nottingham

Nottingham Clinical Trials Unit collaborates with the Nottingham Stroke Trials Unit, led by Philip Bath, on several large multicentre trials.

The highest risk time for recurrence is immediately after stroke or transient ischaemic attack. Existing prevention strategies (such as antithrombotic drugs, lowering lipids or blood pressure lowering, and carotid endarterectomy) reduce, but do not abolish, further events. Dual antiplatelet therapy is superior to aspirin monotherapy. Triple antiplatelet therapy has already been shown to improve outcome for patients with coronary disease.

This international trial compares triple therapy (aspirin, dipyridamole and clopidogrel) with guideline antiplatelet therapy (combined aspirin and dipyridamole or clopidogrel) given for one month. Target sample size is 4,100 patients. The primary outcome is stroke severity at 90 days assessed using the modified Rankin Scale.

Contact: Lelia Duley
Funding: British Heart Foundation and NIHR Health Technology Assessment
Status: Recruiting
Publications: 2015-42

Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH 2)

Chief Investigator: **Nikola Sprigg,** The University of Nottingham

There is currently no effective treatment for stroke associated with intracerebral haemorrhage. Tranexamic acid is an antifibrinolytic drug, which reduces mortality in trauma patients who are bleeding, and is most effective if given early.

This trial is comparing intravenous tranexamic acid with placebo for patients who are within eight hours of acute primary intracerebral haemorrhagic stroke. Estimated sample size is 2,000 participants. Recruitment opened in March 2013.

Contact: Lelia Duley
Funding: NIHR Health Technology Assessment
Status: Recruiting

Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2)

Chief Investigator: **Philip Bath,** The University of Nottingham

This trial is assessing the safety and efficacy of transdermal glyceryl trinitrate, a nitric oxide donor, and of the feasibility of a multicentre ambulance-based stroke trial. Total sample size is 850 participants. Recruitment opened in September 2015. The primary outcome is death/dependence/independence: 7-level modified Rankin Scale (mRS) 90 days after stroke.

Contact: Alan Montgomery
Funding: British Heart Foundation
Status: Recruiting

3 SYSTEMATIC REVIEWS

3.1 Contribution to the Cochrane Pregnancy and Childbirth Group

The Cochrane Pregnancy and Childbirth Group was the first review group within the Cochrane Collaboration, and remains the largest with over 600 published reviews and protocols. The unit contributes to this group as Editor (Lelia Duley), and Review Author (Lelia Duley, Jim Thornton) for over 30 reviews. The topics covered by these Cochrane Reviews include prevention and treatment of hypertensive disorders of pregnancy, care during childbirth, and diagnosis of gestational diabetes.

Contact: Lelia Duley
Status: Ongoing
Publications: 2009-8, 2011-4 2011-8, 2012-2, 2012-5, 2012-6, 2012-12; 2012-16; 2013-3, 2013-4; 2013-8, 2013-9, 2013-15, 2014-13; 2014-31; 2014-32; 2015-3; 2015-38; 2015-46;

3.2 Ethics issues in recruitment of sick and preterm infants to randomised trials

Recruitment of preterm or sick infants to trials requires approaching parents at a particularly difficult time, often with a tight timescale for making a decision. This raises challenges for obtaining informed consent to such research, especially issues regarding competence, understanding, time and voluntariness for parents reaching a decision. On the other hand if the problem of consent is not successfully addressed, this risks becoming an 'orphan' area of research. The review is relatively novel, combining approaches across the disciplinary divide between philosophy and social science. The aim is to identify the ethical challenges and potential solutions, in order to inform the design and conduct of future trials. The project is led by Chris Megone (University of Leeds).

Contact: Lelia Duley
Funding: NIHR Programme Grants for Applied Research
Status: Analysis and reporting
Publications: 2014-30; 2015-40

3.3 Prospective meta-analysis of alternative strategies for placental transfusion at very preterm birth

Internationally, the meta-register of controlled trials lists a growing number of planned or ongoing trials of timing of cord clamping that include preterm births. This project has formed a collaborative group of these trialists, which has developed and agreed the protocol for a prospective meta-analysis. The review has been registered with Prospero (CRD42013004405) the international prospective register of systematic reviews (see http://www.crd.york.ac.uk/prospero/). As the trials scheduled to be part of this meta-analysis are due to be completed at different times, the analysis plan will include at least two cycles of analysis. The project is in collaboration with Lisa Askie, William Tarnow-Mordi and John Simes, at the University of Sydney.

Contact: Lelia Duley
Funding: NIHR Programme Grants for Applied Research
Status: Set up

4 IMPROVING THE QUALITY AND EFFICIENCY OF TRIALS

4.1 Site identification and selection

Careful site selection methods and tools, such as questionnaires, have evolved to become "best" practice in the commercial and non-commercial clinical trials setting. However, there is little evidence of the value of such strategies, and there is no generally accepted model or tool to use when identifying potential sites and deciding which to include in a trial.

The Nottingham Clinical Trials Unit developed a simple template site selection questionnaire in 2010. This includes both generic questions about research experience and capacity and study specific questions based on requirements of the trial protocol. These questionnaires have been piloted in four multi-centre trials in the UK. This pilot project is assessing how well the questionnaire predicts performance against pre-specified recruitment targets at each site.

To describe strategies in current use for identifying and selecting trial sites for randomised trials, we have also conducted a survey of Chief Investigators for trials funded by the National Institute for Health Research, and of UK Trial Managers' Network members.

Contact: Diane Whitham
Status: Ongoing
Publications: 2013-16; 2015- 54; 2015-56

4.2 Consent for emergency trials

Offering participation in a randomised trial during a clinical emergency can be challenging for both clinicians and patients. We developed an oral assent two stage pathway to offer participation in the Cord Pilot Trial to women having a very preterm birth. This was for use when birth was imminent, and was used for almost one third of women recruited to the trial. In collaboration with Susan Ayers, City University, we have conducted qualitative interviews to assess the views and experiences of clinicians and women of the two consent pathways in this trial.

Contact: Lelia Duley
Funding: NIHR Programme Grants for Applied Research
Status: Analysis and reporting

4.3 Recruitment and retention

In collaboration with the University of Manchester, we are conducting two embedded randomised trials of a multi-media website intervention to enhance recruitment into the seAFOod and HiLight trials. These embedded trials are both part of the MRC-funded Systematic Techniques for Assisting Recruitment to trials (START) study.

A further study embedded in the BEEP trial is evaluating two interventions to enhance retention of participants and collection of outcome data at follow up. This study has a factorial design, and will assess the effects of SMS notification before sending questionnaires and of timing of a voucher payment.

Contact: Alan Montgomery
Status: Ongoing

4.4 Adjudication in clinical trials

Adjudication in stroke trials

Central adjudication in clinical trials involves a committee of independent assessors re-evaluating data reported by onsite trial staff in order to standardise outcome assessment and reduce bias. However, this procedure can be time consuming and expensive, and may or may not alter the classification of site-reported events. Currently there is a lack of evidence to guide when an adjudication committee should be used in a clinical trial.

Working in collaboration with the Stroke Trials Unit, we conducted secondary analyses of a large stroke trial to investigate the impact adjudication had on the trial results. Statistical simulations were used to establish how the effect of adjudication would change if the accuracy of site diagnosis varied. Further work is being developed to establish when adjudication may or may not be important to include in a clinical trial.

Contact: Pete Godolphin
Funding: NIHR Research Methods Fellowship
Status: Ongoing

Adjudication of neonatal cranial ultrasound scans

There is substantial variation between individuals in reporting the findings of cranial ultrasound scans. This could have important implications for clinical trials that use diagnoses assessed by cranial ultrasound as an outcome measure. Trials of timing of cord clamping at very preterm birth have suggested there may be an effect on intraventricular haemorrhage, which in these trial was a diagnosis based on cranial ultrasound scan. However, these trials have not reported clearly how the ultrasound data were collected and assessed. Often a mix of people will conduct and report the scans, and both the quality of the scans and their interpretation is variable in clinical practice.

This study aimed to provide standardised, independent adjudication of the cranial ultrasound scans for babies recruited to the Cord Pilot Trial, and to allow assessment of the intra-and inter-observer reliability of the scan interpretation.

Contact: Lucy Bradshaw
Funding: NIHR Programme Grants for Applied Research
Status: Analysis and reporting

5 OTHER RESEARCH

5.1 Improving quality of care and outcome at very preterm birth

Chief Investigator: **Lelia Duley,** The University of Nottingham

This five-year programme includes five work packages, with 10 projects. These projects include a James Lind Alliance Priority Setting Partnership for Preterm Birth, qualitative work exploring the experiences of parents at the time of preterm birth, developing and evaluating a new trolley to support providing initial neonatal care at the bedside, a systematic review of ethics issues in recruitment of preterm and sick infants to randomised trials, the Cord Pilot Trial, and a prospective meta-analysis.

The programme was developed by, and is being conducted by, partners from a wide range of institutions, including: Jane Abbott and Zoe Chilvers (Bliss); Susan Ayers (University of Sussex); Jon Dorling and Jim Thornton (University of Nottingham); David Field (University of Leicester); Gill Gyte (National Childbirth Trust); William McGuire (University of York); Chris Megone (University of Leeds); Sam Oddie (Bradford Teaching Hospitals NHS Foundation Trust); Sandy Oliver (Institute of Education, University of London); John Simes (University of Sydney); Andrew Weeks (University of Liverpool); and Bill Yoxall (Liverpool Women's Hospital NHS Trust).

Contact:	Lelia Duley
Funding:	NIHR Programme Grants for Applied Research
Status:	Ongoing
Publications:	2012-12; 2013-1; 2013-7; 2013-8; 2013-9; 2013-10; 2013-11; 2013-12; 2014-17; 2014-21; 2014-22; 2014-29; 2014-30; 2015-12; 2015-13; 2015-17;2015-31; 2015-40; 2015-43.

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7 GROUPS

7.1 Nottingham Clinical Trials Advisory Group

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