Welcome to the 2014 annual report for the Nottingham Clinical Trials Unit. This was a landmark year for the unit; with publication of results from one of our early trials, experiencing our first inspection by the Medicines and Healthcare Products Regulatory Agency (MHRA), the launch of our new quality management system, and welcoming National Institute for Health Research (NIHR) fellows.

The ‘Getting out of the House’ trial recruited 568 people who had had a stroke in the last six weeks to assess whether rehabilitation aimed at improving outdoor mobility helped them get out more, and improved their quality of life and wellbeing. The outdoor mobility rehabilitation was provided for up to 12 sessions over four months. Participants in both treatment groups were offered advice and a personalised pack of information leaflets about public transport, and were asked to keep a monthly travel diary. There were no clear clinically important differences between the allocated groups. However, offering advice and information tailored to individual needs, and keep a monthly diary appeared to improve satisfaction with outdoor mobility.

Last year it was not Santa Claus who visited us in December, but the MHRA. This was the unit’s first inspection, and it was a superb team effort to prepare for inspection and then to work with the inspectors during their three day visit. Heartfelt thanks to Diane Whitham for her leadership, expertise and commitment in preparing us all. Thanks also to the MHRA task force who worked with Diane; Gill Bumphrey, Charlotte Curnow, Alex Erven and Dan Simpkins and to everyone in the unit who contributed to the preparation and to the inspection.

New projects in 2014 included a trial to determine the clinical and cost effectiveness of cognitive rehabilitation groups for people with multiple sclerosis, and a feasibility study for a large randomised trial comparing two surgical approaches for the treatment of Dupuytren’s contractures of the fingers. We also welcomed new NIHR fellows: Peter Godolphin who was appointed to a Research Methods Fellowship, a joint appointment with Stroke Trials Unit (STU); and Philip Whitehead who was awarded a Clinical Trials Fellowship which he will take up at the start of 2016.

Reflecting the unit’s rapid growth in workload and staff numbers, a key and welcome development has been Charlotte Curnow’s promotion to Unit Co-ordinator. Charlotte is now working closely with Matthew Leighton, our Unit Manager, to ensure the high quality ‘behind the scenes’ support essential for a successful high quality clinical trials unit is in place.

Finally, if you would like to join in our monthly journal club discussions on twitter, just go to #nctujc.

Leila Duley
Director, Nottingham Clinical Trials Unit
## RANDOMISED TRIALS

### 2.1 Cancer

**POsitive Sentinel NOdes: 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 arm pit (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 macro metastases in one or two axillary lymph nodes. The primary outcome is axillary recurrence within 5 years. The planned sample size is 1800 women, recruited from 50 sites in the UK. Recruitment began in July 2014.

**Contact:** Shabina Sadiq  
**Funding:** NIHR Health Technology Assessment  
**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) is now recommended best practice. Although it prevents sight loss in 90% of patients with wet macular degeneration when given an injections into the eye, Lucentis is very expensive. Another drug, which has similar properties is Avastin® (Bevacizumab) is currently licensed for colorectal cancer therapy but can also be used for nAMD 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:** Margo Childs  
**Funding:** NHS England and Care Commissioning Groups  
**Status:** Recruiting

### 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. This primary outcome is clearance of Neisseriagonorhoeae at all infected sites confirmed by a negative Nucleic Acid Amplification Test (NAAT) 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 trial (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:** Recruiting  
**Publications:** 2013-1; 2013-17; 2013-18
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 least. This has led to a range of therapies for acute attacks and control of 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 as effective and cost-effective compared with usual general practitioner led care. Estimated sample size is 724 participants. The primary outcome is serum uric acid within the therapeutic range (<360 μmol/L) at two years. Recruitment began in March 2013.

Contact: Lesia Duley
Funding: Arthritis Research UK
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 853 participants. The primary outcome is serum uric acid within the therapeutic range (<360 μmol/L) at two years. Recruitment began in 2013-6.

Contact: Kirsty Sprange
Funding: NIHR Efficacy and Mechanism Evaluation
Status: Recruiting
Publications: 2013-6

“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 180 participants. The primary outcome is relapse at 12 weeks.

Contact: Nafisa Boota
Funding: NIHR Research for Patient Benefit
Status: Recruiting
Publications: 2013-2

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 is 650 women, who are being recruited from 12 sites.

Contact: Jim Thornton
Funding: NIHR Research for Patient Benefit
Status: Recruiting
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 260 women/baby pairs were recruited at eight sites (in Aberdeen, Bradford, Leicester, Liverpool, London, Nottingham and Wolverhampton). Follow up for women is at one year, and for children at age two years (corrected for gestation at birth).

Contact: Angela Puspone-Rajah
Funding: NIHR Programme Grants for Applied Research
Status: Follow up
Publications: 2011-3; 2012-14; 2013-1; 2014-3; 2014-17
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

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 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.

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

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 group cognitive rehabilitation programme plus usual care is associated with reduced impact of MS on quality of life, compared to usual care alone. Estimated sample size is 400 participants. The primary outcome is the psychological impact of MS on everyday life.

Contact: Margo Childs
Funding: NIHR Health Technology Assessment
Status: Set up

2.9 Respiratory

Double-blind randomised controlled 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.

Once the trial is set up, with full regulatory approval, it will be hibernated with annual review to ensure it remains ready to activate in a pandemic. The aim is to activate within four weeks during the first wave of a pandemic, and to complete recruitment in six weeks.

Contact: Clare Brittain
Funding: NIHR Health Technology Assessment
Status: Set up / entering hibernation
Publications: 2019-20

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 2,300 participants. Recruitment is taking place in 10 secondary care sites with a further 93 primary care research GP practices. Currently, 997 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: Andrew Skogg
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 Lendahl, Skane University Hospital; Denmark - Lis Tarnow, Aarhus University

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 at 24 weeks. Recruitment closed in September 2014 having reached target accrual of 509 participants. The study opened to recruitment in August 2013. Recruitment is at 35 sites in the UK, Sweden and Denmark.

Contact: Florence Day
Funding: Reappled
Status: Recruiting
Publications: 2012-8

Bullous pemphigoid steroids and tetracyclines study (BLUSTER)

Chief Investigator: Hywel Williams, The 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 258 patients in September 2013.

Contact: Rob Allen
Funding: NIHR Health Technology Assessment
Status: Analysis and reporting
Publications: 2012-8

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

Chief Investigator: William Jeffcoat, 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. Light-weight 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: 2012-15; 2014-06; 2014-17
2.10 Skin and wound healing

Cont

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

Chief Investigator: Jonathan Batchelor, Derby Teaching 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 steroidointments. Ultraviolet B light therapy (also known as 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 steroids and light therapy) may provide 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 compare the effectiveness and safety of topical corticosteroids (mometasone furoate 0.1% ointment) with (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 appeared or become larger 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 will begin in May 2015.

Contact: Rachel Haines
Funding: NIHR Health Technology Assessment
Status: Set up

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 turning, varied practice of walking and turning 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 is 60 participants.

Contact: Diane Whitham
Funding: NIHR Research for Patient Benefit
Status: Analysis and reporting
Publications: 2013 - 35

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

Efficacy of Nitric Oxide in Stroke (ENOS)

Chief Investigator: Philip Bath, The University of Nottingham

At the time of acute stroke, three-quarters of patients have high blood pressure, which is independently associated with a poor outcome. Lowering blood pressure immediately after the stroke may aid recovery. The aim of this trial was to assess the effects of glyceryl trinitrate patches compared with placebo, and of continuing or temporarily stopping prior antihypertensive medication for patients with acute ischaemic or haemorrhagic stroke.

Recruitment closed in October 2013, with 4,011 participants recruited in 23 countries. The primary outcome was function, assessed with the modified Rankin Scale at 90 days. Transdermal glyceryl trinitrate lowered blood pressure and had acceptable safety but did not improve functional outcome. There was no evidence to support continuing prestroke antihypertensive drugs in patients in the first few days after acute stroke (see http://dx.doi.org/10.1016/S0140-6736(14)61121-1). The trial was funded by the Medical Research Council.

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. Funding is from the NIHR Health Technology Assessment programme.

Safety and efficacy of intensive versus guideline antplatelet 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

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. Funding is from the British Heart Foundation and NIHR Health Technology Assessment programme.
## 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 topic covered by these Cochrane Reviews include prevention and treatment of hypertensive disorders of pregnancy, care during childbirth, and diagnosis of gestational diabetes.

| Contacts: | Lelia Duley |
| Status: | Ongoing |

### 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 comprehension, 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. Following a systematic search, this review will produce a narrative review of the ethical issues. 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 |

### 3.2 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 trials, 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 first collaborators’ meeting for trials is scheduled for April 2015. The project is a collaboration with Lisa Askie, William Tarnow-Mordi and John Simes, at the University of Sydney.

| Contacts: | 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 genuine 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 |
| Publication: | 2013-16 |

### 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 |
| Publication: | 2013 |

### 4.3 Recruitment and retention

In collaboration with the University of Manchester, we are undertaking two embedded randomised trials of a multi-media website intervention to enhance recruitment into the safAFOod 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 |
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 Meegan (University of Leeds); Sam Odle (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 Ysella (Liverpool Women’s Hospital NHS Trust).

Contacts: Lelia Duley, Virginia Portillo
Funding: NIHR Programme Grants for Applied Research
Current Status: Ongoing


2014-30: Wilman E, Megone C, Oliver S, Duley L, Gyte G, Wright PC. Ethical issues regarding consent to trials involving preterm or sick infants: a systematic review (framework synthesis). Arch Dis Child Fetal Neonatal Ed. 2014;00:00:00:00. DOI:10.1136/archdischild-2014-306576.220


### Nottingham Clinical Trials Advisory Group

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>Philip Bath</td>
<td>Stroke Association Professor of Stroke Medicine</td>
</tr>
<tr>
<td>Professor</td>
<td>Mike Clarke</td>
<td>All Ireland Hub for Trials Methodology Research</td>
</tr>
<tr>
<td>Emeritus</td>
<td>Janet Darbyshire</td>
<td>Professor of Epidemiology, University College London</td>
</tr>
<tr>
<td>Director</td>
<td>Sarah Armstrong</td>
<td>Director of Research Design Service, East Midlands</td>
</tr>
<tr>
<td>Professor</td>
<td>Tony Avery</td>
<td>Professor of Primary Health Care</td>
</tr>
<tr>
<td>Chair</td>
<td>Richard Deeley</td>
<td>Head of Commercial Finance</td>
</tr>
<tr>
<td>Professor</td>
<td>Avril Drummond</td>
<td>Professor of Healthcare Research</td>
</tr>
<tr>
<td>Consultant</td>
<td>Frances Game</td>
<td>Consultant Diabetologist and Clinical Director of R&amp;D, Derby Teaching Hops NHS Foundation Trust</td>
</tr>
</tbody>
</table>

### Nottingham Clinical Trials Steering Group

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>Jonathan Hollands</td>
<td>Research Manager, School of Medicine</td>
</tr>
<tr>
<td>Researcher</td>
<td>Chris Huke</td>
<td>School Manager, School of Medicine</td>
</tr>
<tr>
<td>Researcher</td>
<td>Sheila O'Malley</td>
<td>Lead Research Management &amp; Governance (RM&amp;G) Manager, Clinical Research Network, East Midlands</td>
</tr>
<tr>
<td>Professor</td>
<td>Kim Thomas</td>
<td>Professor of Applied Dermatology Research</td>
</tr>
<tr>
<td>Consultant</td>
<td>Wei Shen Lin</td>
<td>Consultant Respiratory Medicine</td>
</tr>
<tr>
<td>Professor</td>
<td>Hywel Williams</td>
<td>Professor of Dermato-Epidemiology, University of Nottingham</td>
</tr>
<tr>
<td>Professor</td>
<td>Tony Avery</td>
<td>Professor of Primary Health Care, University of Nottingham, and Director of Research for the School of Medicine</td>
</tr>
<tr>
<td>Professor</td>
<td>Philip Bath</td>
<td>Stroke Association Professor of Stroke Medicine</td>
</tr>
<tr>
<td>Clinical Trials Coordinator</td>
<td>Aimee Tooley</td>
<td>Data Coordinator</td>
</tr>
<tr>
<td>Trial Coordinator</td>
<td>Aisha Shafayat</td>
<td></td>
</tr>
<tr>
<td>Professor of Medical Statistics and Clinical Trials/ Deputy Director of NCTU</td>
<td>Alan Montgomery</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials Facilitator</td>
<td>Alex Erven</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Amy Moody</td>
<td></td>
</tr>
<tr>
<td>Trial Coordinator</td>
<td>Andrew Jadowski</td>
<td></td>
</tr>
<tr>
<td>Trial Administrator</td>
<td>Andrew Skeggs</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Angela Pushpa-Rajah</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Amarnya Chatterjee</td>
<td></td>
</tr>
<tr>
<td>Data Coordinator</td>
<td>Brian Barnes</td>
<td></td>
</tr>
<tr>
<td>Data Coordinator</td>
<td>Cecilia Piri</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials Monitor</td>
<td>Charlotte Curnow</td>
<td></td>
</tr>
<tr>
<td>Unit Coordinator</td>
<td>Charlotte Lloyd</td>
<td></td>
</tr>
<tr>
<td>NHS Programme Manager</td>
<td>Chris Rumsey</td>
<td></td>
</tr>
<tr>
<td>Database System Developer</td>
<td>Clare Britain</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Dan Simpkins</td>
<td></td>
</tr>
<tr>
<td>IT and Data Manager</td>
<td>Dawn Coleby</td>
<td></td>
</tr>
<tr>
<td>Research Fellow</td>
<td>Desmond Dorrainjajo</td>
<td></td>
</tr>
<tr>
<td>Trial Administrator</td>
<td>Diane Whitham</td>
<td>Research Manager/ Deputy Director of NCTU</td>
</tr>
<tr>
<td>Trial Coordinator</td>
<td>Ellie Harrison</td>
<td></td>
</tr>
<tr>
<td>Senior Trial Manager</td>
<td>Eleanor Mitchell</td>
<td></td>
</tr>
<tr>
<td>Data Entry Clerk</td>
<td>Elise Gray</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Florence Day</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Garry Meakin</td>
<td></td>
</tr>
<tr>
<td>Trial Coordinator</td>
<td>Gill Bumphrey</td>
<td></td>
</tr>
<tr>
<td>Trial Administrator</td>
<td>Jennifer McDermott</td>
<td></td>
</tr>
<tr>
<td>Trial Administrator</td>
<td>Jennifer White</td>
<td></td>
</tr>
<tr>
<td>Trial Administrator</td>
<td>Julie Jones</td>
<td></td>
</tr>
<tr>
<td>Database System Developer</td>
<td>Kirsty Sprange</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Leila Dukey</td>
<td>Professor of Clinical Trials Research, and Director of NCTU</td>
</tr>
<tr>
<td>Professor of Clinical Trials Research, and Director of NCTU</td>
<td>Lisa Charlesworth</td>
<td>Trial Manager</td>
</tr>
<tr>
<td>Data Entry Clerk</td>
<td>Lisa Gregory</td>
<td></td>
</tr>
<tr>
<td>Data Manager</td>
<td>Lucinda Murphy</td>
<td></td>
</tr>
<tr>
<td>Data Manager</td>
<td>Lucy Bradshaw</td>
<td>Medical Statistician</td>
</tr>
<tr>
<td>Senior Trial Manager</td>
<td>Margo Childs</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Margherita Carucci</td>
<td>Trial Coordinator</td>
</tr>
<tr>
<td>Research Manager</td>
<td>Mat Leighton</td>
<td></td>
</tr>
<tr>
<td>Clinical Research Facilitator</td>
<td>Nafisa Boots</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Pat Morris</td>
<td></td>
</tr>
<tr>
<td>Trial Administrator</td>
<td>Rachel Haines</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Rob Atkin</td>
<td></td>
</tr>
<tr>
<td>Trial Coordinator</td>
<td>Ruth Fletcher</td>
<td></td>
</tr>
<tr>
<td>Unit/NHS Programme Administrator</td>
<td>Sandip Stapleton</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Sarah Smith</td>
<td></td>
</tr>
<tr>
<td>NHS Programme Administrator</td>
<td>Sarah Walker</td>
<td></td>
</tr>
<tr>
<td>Senior Data Co-ordinator</td>
<td>Shabina Sadiq</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Sharon Eltender</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials Monitor</td>
<td>Trish Houghton</td>
<td></td>
</tr>
<tr>
<td>Clinical Research Facilitator</td>
<td>Virginia Portrait</td>
<td></td>
</tr>
<tr>
<td>NHS Programme Manager</td>
<td>Viv Turtle-Savage</td>
<td></td>
</tr>
<tr>
<td>Trial Manager</td>
<td>Wei Tan</td>
<td>Medical Statistician</td>
</tr>
</tbody>
</table>