Designing and reporting surgical trials to influence practice:

Recognising the complexity of surgical interventions

Specialist workshop report for the MRC Hubs for Trial Methodology Network

27th and 28th June 2013

The Royal College of Surgeons of England (RCSEng)

Rationale

The use of a pragmatic trial design is recommended to examine whether interventions can work in clinical practice. Currently, however, there is a lack of well designed and conducted pragmatic trials in surgery which is partly due to the methodological challenges associated with evaluating surgical interventions, which are complex. This complexity relates to a) the intervention and its constituent components, b) pre-, peri- or post-operative interventions (and their constituent components), c) the skill and attributes of surgeons and other team members, and d) the variable contexts in which the interventions are delivered. The degree of 'control' required over each of these factors also requires consideration, in terms of how they are described, standardised and monitored within the RCT. Failure to do so may lead to difficulties in assessing which parts of the intervention are responsible for any observed effect, and cause problems when attempts are made to replicate the intervention in routine clinical practice. To date, there is a lack of methods and guidance for designing pragmatic trials in surgery which take these issues into account.

Aims

This two-day specialist workshop aimed to bring together individuals with interests in surgical trial design, conduct and analysis, and methodological innovation in order to:

1. Consider the complexity of surgical interventions, and terminology in this area
2. Consider the challenges this creates in the design, conduct and analysis of RCTs in surgery
3. Summarise the issues relating to this complexity in terms of the design, delivery and monitoring of surgical interventions within RCTs

General meeting details

The workshop was held at the Royal College of Surgeons of England (RCSEng), London, from 27th-28th June 2013 and was attended by 38 delegates. Participants were selected to represent a broad mix of surgeons and methodologists from a wide range of surgical specialties (Appendix 1). There were 16 surgeons (13 consultants and 3 trainees) and 20 methodologists in attendance and representatives from the British Medical Journal and the Health Technology and Assessment Clinical Trials and Evaluation Board.

Since applying for Hub Network funding for this workshop in 2012, five surgical trials centres have been developed throughout England, supported by the RCSEng (Bristol, Birmingham, London, Liverpool and Oxford). The Directors of each centre, as well as affiliated

methodologists, were invited to attend this workshop. Surgical Specialty Leads (SSLs) representing each surgical subspecialty, appointed by the RCSEng, were also approached. Representatives from surgical trainee collaboratives - regional networks aiming to promote collaboration amongst trainees - were invited to participate. Further delegates were identified through their previous experience with surgical trials. Specific funding was provided for two members of each Hub to attend.

The workshop agenda was finalised during several conference calls between the workshop convenors, and is provided in Appendix 2. Some delegates were invited to deliver presentations addressing the main issues associated with the complexity of surgery (intervention description, monitoring and expertise). Others were asked to present short vignettes to describe their experience of these issues within previous or current surgical RCTs (Appendix 3).

Key issues

Discussion firstly considered how the design of surgical interventions in trials requires identification of the elements contributing to the surgical intervention, the key components of concomitant interventions, and contextual factors. The way in which each of these elements needs to be (or not be) controlled can then be agreed in terms of: a) description, and b) standardisation, c) monitoring (fidelity) and d) the level of expertise necessary to deliver them. Lastly, the amount of control required for each factor may depend on: (i) the scope of the RCT, (ii) the nature of interventions in each trial arm, (iii) the stage of development of the interventions, and (iv) the level of complexity of the interventions. Consideration should be given to these issues at the outset of trial design and continue through to protocol development, trial conduct and follow-up. Despite this, the need to balance rigour and practicality was emphasised, such that consideration of these issues does not result in over-burdening of surgeons, methodologists and statisticians.

A summary of each stage is provided below.

Stage One: Identification of the elements contributing to the surgical interventions under investigation

Surgical interventions

Surgical interventions can be defined as those that cut or physically alter a patient's tissues (whether using a scalpel, stapler, laser or another instrument or device) and involve the use

of a sterile environment, anaesthesia, antiseptic conditions and suturing or stapling. They are made up of multiple component parts and within these, individual steps. Many components are common across surgical interventions, and examples include incision, dissection, resection and reconstruction; however, individual steps within components usually differ according to the operation in question. Some components (or steps) are thought to be 'critical', in that they influence outcomes.

Further work: A classification framework for describing and monitoring surgical interventions is under development.

Concomitant interventions

Concomitant interventions are particularly important in surgical RCTs because blinding is often difficult to achieve. Concomitant interventions can be defined as those naturally accompanying or are associated with the main surgical intervention. They may occur before, during or after the main intervention and may be surgical or non-surgical. Examples include pre-operative assessments, intra-operative anaesthesia and medications, post-operative recovery and rehabilitation. Similar to surgical interventions, concomitant interventions are comprised of components and steps, which may or may not be 'critical'.

Contextual factors

Context can be defined as the distinctive features of an intervention's setting, participants and delivery. In surgery, this may include the type of hospital and department, as well as features of the surgical teams, operating theatre environment and available equipment.

Further work: How to describe context and how to assess what elements of context, if any, have an important influence on the potential intervention effect.

Stage Two: Consider the ways in which each element might need to be controlled

Description and standardisation of the interventions

Identification of 'critical' and 'non-critical' components or steps of surgical and concomitant interventions is important, as it is thought that the former are those that influence outcomes. Trialists and surgeons should gain agreement on these key elements prior to undertaking the full RCT in order to establish the level of detail and standardization required for the main trial. This should be considered for both trial arms, as a similar amount of detail

is likely to be required in each. The level of detail and standardization is likely to depend upon the factors described below (stage 3).

Intervention monitoring (fidelity)

Fidelity can be defined as "the extent to which the intervention was delivered as intended". The degree of fidelity required is likely to depend on whether a critical or non-critical component or step is being monitored, as well as other factors (below). Structured assessments of fidelity might take the form of realist evaluation, qualitative research or self-reported descriptions depending on individual study circumstances. Additionally, fidelity might need to be incorporated into analyses, or alternatively a descriptive summary may suffice.

Further work: A classification framework for monitoring interventions within RCTs is under development.

Expertise

Expertise can relate to either the technical skill of those undertaking the surgical intervention or concomitant intervention, or their non-technical skills. It was acknowledged that non-technical skills are difficult to measure and in the context of RCTs, technical expertise is usually considered to be more influential. A formal definition of expertise has yet to be agreed. In order to determine the level of expertise required within a particular trial, all relevant personnel requiring expertise should be established (for example, the surgeon, assistant surgeon and/or wider surgical team) and how specialist this expertise needs to be. Additionally, the degree of dependency of the intervention on expertise should be ascertained. Lastly, the amount of control over expertise thought to be achievable should be determined. All these aforementioned considerations will help to determine the level of expertise required, or the amount to which it should be accounted for in analysis. This might include enforcement of trial entry criteria, statistical consideration of the learning curve or clustering, or formal expertise-based trial designs.

Stage 3: Consider the factors contributing to the level of control

Scope of the study

The PRECIS (pragmatic-explanatory continuum indicator summary) tool can be used in order to consider whether a study is predominantly pragmatic or explanatory in design, and help trialists to judge how closely their proposed design fits with the trial's stated purpose. It is

hypothesised that explanatory trials are more likely to require tighter control compared with those of a more pragmatic nature.

The nature of interventions in each trial arm

According to an existing classification system, interventions within surgical trials can be categorised as 'surgical *vs* medical', 'surgical interventions that differ in a major way' and 'surgical interventions that differ in a minor way' (Cook, 2009). This is likely to have an impact on the level of control required over interventions, and it was also recognised that the same level of control would usually be required in each trial arm.

Further work: The existing classification has several limitations and development of an updated version is now underway. This comprehensive system will include all non-surgical interventions (i.e. not just medical), distinguish between 'major' and 'minor differences, and account for trials in which the interventions are identical in each arm (for example, differing time points or contexts).

The stage of development of the intervention(s)

The stage of innovation of surgical procedures under investigation can be established using the IDEAL (Idea, Development, Exploration, Assessment, Long term study) framework. Greater control may be required over innovative procedures (i.e. those in earlier IDEAL stages) than those representing 'standard practice'. Although the new method may have been deemed to be sufficiently evolved to warrant full evaluation in a RCT, this does not mean that it will not evolve further during this process. Detailed descriptions of any modifications should therefore also be provided.

The complexity of the intervention

In addition to complex interventions, 'complex complex' interventions also exist and in the context of surgery these might represent more technically challenging operations, or a requirement for multifaceted pre-, peri- and post-operative care. It is likely, therefore, that interventions deemed to be more straightforward might require less description, standardisation and monitoring.

Feedback

Feedback was obtained from 22 of the 36 participants (61.1%), including 11 surgeons (consultant = 9, trainee = 2), 10 methodologists and the HTA representative. A summary of the findings are provided below:

A. Participants were asked if they agreed or disagreed with the following statements:

	Statement	Number of people in agreement (%)
1	The format of the workshop encouraged networking and discussion with colleagues	21 (95.5)
2	My understanding of the methodological issues around intervention description and measurement of fidelity in surgical trials has increased	22 (100)
3	Were you provided with sufficient information about the content of the workshop beforehand?	20 (90.9)
4	Would you be interested in a future meeting about methodology for RCTs in surgery?	22 (100)

B. Verbatim examples of workshop elements that were considered to be useful:

- Time to reflect on issues and interaction with multidisciplinary panel
- Mix of surgeons & methodologists was great and about the right balance. Mix of longer talks and short vignettes good (though variability in sticking to topic!)
- I enjoyed the vignettes and discussion around expertise and the importance of context
- Made me think about deliver of an intervention and how we might approach developing new treatments
- Work on standardising interventions, pragmatic design and trial design

- Discussion on how to define, record and report complex interventions
- Concomitant interventions discussion
- Classification of surgical interventions
- Clustering
- IDEAL framework
- The progress of qualitative trials in surgery
- Better understanding of expertise trials
- ITT vs per protocol
- Discussion of the importance or not of skill in the intervention
- Discussion of protocolising or not the intervention and control
- Time for discussion
- Round-table structure of the room
- Interdisciplinary interaction
- Mixture of abstract and applied methods
- Hearing from experience of other surgeons
- Insights from surgeons themselves re practical issues and constraints
- Pragmatic vs explanatory discussions
- Vignettes of trials very interesting
- Very useful to talk openly about the pros and cons of different methodological approaches - sometimes we get bogged down in dogma
- Interesting to understand and explore problems faced by colleagues with smaller trials and softer outcome measures

C. Verbatim examples of things that could have been done better:

- Smaller group, more time for discussion, less case studies
- Perhaps more small group work – though maybe more appropriate for later workshops as things develop further
- Not sure how well the vignettes worked. Bit of a race to get through them all.
- Case vignettes could have focused more on the debated issue (i.e. describing interventions)
- Could have clearer statement of expected outputs from beginning
- Wider representation e.g. health economics
- Very little!
- Chairmanship style on Friday did not lend itself to open and exploratory debate (compared to Thursday)
- I just about lasted for the full two days – couldn't cope with any longer!
- Structured discussion to evolve guidance

- I'd have liked to receive the handout in advance
- Maybe a bit more time for small group work (couple of sessions rather than just one)
- Maybe some 'debates' could be helpful in clarifying the issues - just a thought.
- The vignettes were great – more and longer time for discussion?

D. Other comments:

Positive	Negative
Fantastic event, really enjoyed!	Difficult to hear at times, esp. when refreshments arrived
Venue, catering, accommodation all excellent	Venue could be a bit noisy
2 days good duration – tiring but 1 day workshop wouldn't be enough to cover everything adequately	Could avoid bringing in trolleys during sessions
Good venue	Difficult to see screen from all parts of room
Well structured and conducted overall. Enjoyed and learnt from discussions which were friendly and insightful	Difficulty seeing screen
Venue at RCS is great and if possible should be kept for future meetings	Maybe need to cover other parts of the country to encourage others to participate in future meetings
Congratulations for organising such a great and inspiring meeting	Those of us travelling from the provinces often find 10am start more manageable
Excellent meeting – great opportunities to learn and network	
Great facilities Excellent days – well chaired, well done, great location	
Fine – didn't stay overnight so can't comment on accommodation	
Venue and catering very good Small groups worked well despite my antibodies to that sort of thing Good mix of people	
Really good and thought provoking	
Goodenough Club was fantastic!	
All very good!	
All great speakers	

Venue and food great. London good too though somewhere up north would be good too.....	
The location was excellent and the accommodation was also good.	
Really enjoyed the day	

E. Future workshop topics

The most popular topics for future workshops were: surgical *vs* non-surgical RCTs (n=20), outcome assessment and blinding (n=20), optimisation of recruitment (n=17) and resource use issues in surgical RCTs (n=8).

Other suggestions are listed below:

- Early stage evaluation of surgical innovation
- Expertise-based surgical RCTs
- Retention
- Modern methods for analysis (e.g. ordinal analysis, covariate adjustment)
- Methods for minimising impact of crossovers
- Trials in vulnerable adults (e.g. elderly, incapacitated, unconscious)
- Influence of regulation/FDA
- Introduction/testing of implants and devices
- ½ day session on dealing with common problems with funding, referees and R and D departments
- Effective planning and design or surgical RCTs so as to avoid as many predictable barriers/organisational problems to running the RCT or implementing the intervention if found to be effective

Appendix 1: Delegate list

Name	Title and affiliation
Mr Simon Bach	Senior Lecturer, Birmingham University and Consultant Colorectal Surgeon, Queen Elizabeth Hospital, Birmingham RCSEng Surgical Specialty Lead (Colorectal)
Professor David Beard	Professor of Musculoskeletal Science, University of Oxford Director of Orthopaedic Surgery and Interventional Trials, University of Oxford
Professor Jane Blazeby	Professor of Surgery, University of Bristol Director, Bristol Surgical Trials Centre and MRC ConDuCT Hub
Miss Natalie Blencowe	NIHR Doctoral Research Fellow, Surgery, University of Bristol Co-director of the Severn and Peninsula Audit and Research Collaborative (SPARCS)
Professor Julia Brown	Professor of Clinical Trials Research Director, Clinical Trials Research Unit (CTRU), University of Leeds
Mr Richard Bulbulia	Consultant Vascular Surgeon, Cheltenham General Hospital Research Fellow, CTSU, University of Oxford
Professor Marion Campbell	Professor of Health Services Research Director, Health Services Research Unit, University of Aberdeen
Professor Andrew Carr	Nuffield Professor of Orthopaedics and Musculoskeletal Sciences, University of Oxford Director, Surgical Interventions Trials Unit, Oxford
Miss Beth Conroy	Research Assistant, University of Liverpool
Dr Jonathan Cook	MRC Senior Research Fellow, Health Services Research Unit, University of Aberdeen
Professor Matthew Costa	Professor of Trauma and Orthopaedics, Warwick Clinical Trials Unit RCSEng Surgical Specialty Lead (Orthopaedics)
Dr Peter Davidson	Director of HTA NIHR Evaluation, Trials and Studies Co-ordinating Centre
Professor Jenny Donovan	Professor of Social Medicine, School of Social and Community Medicine, University of Bristol
Dr Caroline Doré	Senior Statistician, MRC Clinical Trials Unit, London
Dr Trish Groves	Deputy Editor, British Medical Journal and Editor-in-chief, BMJ Open
Professor Iain Hutchison	Consultant Oral and Maxillofacial Surgeon, St Bartholomews and The Royal London Hospitals Director of the National Facial Oral and Oculoplastic Research Study Centre
Mr Abhilash Jain	Clinical Senior Lecturer and Consultant Plastic Surgeon,

Name	Title and affiliation
	University of Oxford and Imperial College NHS Trust London RCSEng Surgical Specialty Lead (Plastics and Hand surgery)
Professor David Jayne	Professor of Surgery, University of Leeds and Consultant Surgeon, Leeds Teaching Hospitals NHS Trust
Mr Angelos Kolias	NIHR Academic Clinical Fellow Lead of British Neurosurgical Trainee Research Collaborative
Professor Sallie Lamb	Professor of Trauma Rehabilitation, University of Oxford Director, Warwick Clinical Trials Unit
Mr James McCaul	Consultant Oral and Maxillofacial Surgeon, Bradford Teaching Hospitals NHS Foundation Trust RCSEng Surgical Specialty Lead (Maxillofacial surgery)
Professor Hisham Mehanna	Chair of Head and Neck Surgery, School of Cancer Sciences Director, Institute of Head and Neck Studies and Education, University of Birmingham
Dr Chris Metcalfe	Reader in Medical Statistics, University of Bristol
Professor Alan Montgomery	Professor of Medical Statistics and Clinical Trials, University of Nottingham
Professor Dion Morton	Professor of Surgery, School of Cancer Sciences, University of Birmingham Director of Clinical Research, Royal College of Surgeons of England
Professor Jon Nicholl	Professor of Health Services Research, University of Sheffield
Mr Thomas Pinkney	Senior Lecturer, University of Birmingham and Consultant Colorectal Surgeon, University Hospitals Birmingham NHS Foundation Trust
Miss Shelley Potter	NIHR Academic Clinical Lecturer in General Surgery, University of Bristol
Professor Amar Rangan	Clinical Professor, Trauma & Orthopaedic Surgery, School of Medicine & Health, Durham University and Consultant Orthopaedic Surgeon, The James Cook University Hospital RCSEng Surgical Specialty Lead (Orthopaedics)
Dr Chris Rogers	Reader in Medical Statistics Co-Director, Clinical Trials & Evaluation Unit, University of Bristol
Professor Peter Sasieni	Professor of Biostatistics & Cancer Epidemiology, Queen Mary University of London National Facial Oral and Oculoplastic Research Study Centre lead
Dr Linda Sharples	MRC Senior Statistician and Program Leader (statistics), MRC Biostatistics Unit, Cambridge
Professor Sally Stenning	Professor of Medical Statistics and Senior Statistician, MRC Clinical Trials Unit, London
Professor Shaun Treweek	Professor of Health Services Research, Health Services Research Unit, University of Aberdeen
Dr Catrin Tudur Smith	Senior Lecturer in Biostatistics, North West Hub for Trials Methodology Research, University of Liverpool

Name	Title and affiliation
Dr Ian White	Senior Statistician, MRC Biostatistics Unit, Cambridge
Professor Brian Williams	Professor of Behavioural and Health Sciences Director, Nursing, Midwifery and Allied Health Professions Research Unit, University of Stirling
Professor Paula Williamson	Professor of Medical Statistics, University of Liverpool Director, North West Hub for Trials Methodology Research

Appendix 2: Conference agenda

Day 1		
0930	*Tea and Coffee*	
1000	Introductions and welcome	Professor Jane Blazeby
1010	Surgical interventions: simple, complex or chaos?	Professor Marion Campbell
1050	Pragmatic and explanatory RCTs: differences & similarities	Professor Shaun Treweek
1130	*Tea and Coffee*	

Day 2		
0900	*Tea and Coffee*	
0930	Intervention development, standardisation and delivery within the IDEAL framework for evaluation of innovations in surgery	Professor Jane Blazeby
1000	Designing interventions that incorporate issues of acceptability, delivery and fidelity: the role of integrated qualitative research	Professor Jenny Donovan
1030	Descriptions of surgical interventions in practice: vignettes from past and present RCTs in surgery	Surgical CIs/trialists
1100	*Tea and Coffee*	
1115	Descriptions of surgical interventions in practice: vignettes from past and present RCTs in surgery	Surgical CIs/trialists
1150	Methods to analyse pragmatic trials with surgeons of differing expertise	Dr Linda Sharples
1230	*Lunch*	
1310	Minimising protocol deviations and their impact: implications for study design and analysis	Dr Ian White
1350	The next steps: working groups (tea and coffee will be served)	Professor Jane Blazeby
1545	Summary and close of meeting	

Appendix 3: Vignettes of RCTs in surgery

Trial name	Description
TARVA	Total ankle replacement versus ankle arthrodesis: A pragmatic RCT.
LIHNCS	A multi-centre, randomised controlled trial assessing the effectiveness of Lugol's Iodine to assist excision of moderate dysplasia, severe dysplasia and carcinoma in-situ at mucosal resection margin of oral and oropharyngeal squamous cell carcinoma.
ROSSINI	Reduction Of Surgical Site Infection using a Novel Intervention. A multicentre, prospective randomised controlled trial of a wound-edge protection device to reduce surgical site infection.
ProFHER	Conservative versus surgical treatment of displaced proximal humeral fractures.
TREC	Radical surgery and organ preservation with radiotherapy and TEMS for rectal cancer.
SEND	The Role of Selective Neck Dissection Used Electively in Patients With Early Oral Squamous Cell Carcinoma (1-3cm Primary Size) and No Clinical Evidence of Lymph Node Metastases in the Neck.
TOPKAT	Total Or Partial Knee Replacement Arthroplasty Trial: a multi-centre randomised controlled trial designed to examine the clinical- and cost-effectiveness of total and partial knee replacements for medial compartmental osteoarthritis.
CSAW	Is Arthroscopic Sub-Acromial Decompression (ASAD) More Effective Than Arthroscopy Only (AO) for Shoulder Pain?
PET neck	Surgery versus PET-guided CT (computed tomography) surveillance post chemoradiotherapy and surgery if positive.
ACST-2	A randomised trial comparing surgery (carotid endarterectomy) versus stenting in patients with asymptomatic carotid stenosis.
UK-BeST	A multi-centred randomised controlled trial of a primary-care based cognitive behavioural program for low back pain.
ROCSS	A randomised controlled trial of Reinforcement Of Closure of Stoma Site using a biological mesh.
CRISP	Coronary artery grafting in high RISk patients randomised to off pump or on pump surgery.