



## ■ INSTRUCTIONAL REVIEW

# Designing clinical trials in trauma surgery

## OVERCOMING RESEARCH BARRIERS

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The surgical community is plagued with a reputation for both failing to engage and to deliver on clinical research. This is in part due to the absence of a strong research culture, however it is also due to a multitude of barriers encountered in clinical research; particularly those involving surgical interventions. ‘Trauma’ amplifies these barriers, owing to the unplanned nature of care, unpredictable work patterns, the emergent nature of treatment and complexities in the consent process. This review discusses the barriers to clinical research in surgery, with a particular emphasis on trauma. It considers how barriers may be overcome, with the aim to facilitate future successful clinical research.

**Cite this article:** *Bone Joint Res* 2014;3:123–9.

**Keywords:** Clinical Trial, Trauma, Orthopaedics, Research, Randomised Controlled Trials

### Introduction

There is a worldwide epidemic of trauma, which now accounts for 5.8 million global deaths each year.<sup>1</sup> This is only marginally less than the 7.6 million deaths attributable to cancer,<sup>2</sup> but there is a large disparity in research activity. The National Library of Medicine indexes 2.9 million results for the search term ‘cancer’, but only 890 000 for ‘trauma’.<sup>3</sup> Likewise, the US National Institute of Health clinical trial registrations reveal 41 000 results for ‘cancer’, but just 7000 for ‘trauma’.<sup>4</sup>

The surgical community has a poor reputation for delivering high quality trials, as outlined by the editor of *The Lancet* in a commentary entitled ‘Surgical research or comic opera: questions, but few answers’.<sup>5</sup> Trials in trauma are particularly challenging, as its unpredictable nature adds to the difficulties that prevent the successful delivery of trials.

Surgical research, particularly in the form of controlled trials, is essential to advance understanding, and particularly to avoid a state of subconscious maleficence which may occur when techniques are performed without due scrutiny. It is uncomfortable to consider that harm through ignorant practice may exist in ‘modern-day’ surgery. However there is little doubt that it is widespread. An example where this practice occurred in elective surgery is the knee arthroscopy. Throughout the 1990s,

650 000 arthroscopies per year were performed in the United States (USA), mostly for osteoarthritis. However, in 2002 a trial demonstrated no difference between sham surgery and intervention.<sup>6</sup> Such studies challenge conventional care by rigorous investigation and prevent unnecessary surgery, with inherent morbidity and complications. These studies also highlight the current dichotomy that exists between medicine and surgery – with medicinal products highly regulated and tested before widespread use, but surgical products and techniques often widely introduced with little prior experimental investigation.

The need for surgical trials in trauma is undisputed, but in order to deliver them, there is a need to overcome the barriers that prevent widespread trial development and patient recruitment. Large research-orientated organisations, such as the National Institute for Health Research (NIHR) in the United Kingdom (UK), provide an extensive infrastructure to enable high quality research. However, recognition of the practical ‘barriers’ by clinicians and methodologists, is crucial to increase the quantity and quality of research outputs. These barriers may exist in a number of guises and at various stages throughout the research process. They may manifest as difficulties in establishing new research studies, or as difficulties in recruiting to established studies, therefore potentially reducing both power and generalisability.

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10.1302/2046-3758.34.2000283 \$2.00

*Bone Joint Res* 2014;3:123–9.  
Received 22 January 2014;  
Accepted after revision 28 January 2014

## Search strategy

We searched the Cochrane Library, MEDLINE, and GoogleScholar (from inception to January 2013). We used the search terms ‘trial’ or ‘clinical research’, along with the terms ‘barrier’ or ‘obstacle’. We gave priority to recent publications, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy, and selected those we judged relevant. Several review articles were included because they provide comprehensive overviews that are beyond the scope of this review. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers

## Surgeon barriers

‘Equipose’ is almost certainly the primary barrier to surgical trial recruitment. It is used to describe a case of genuine uncertainty related to a particular clinical problem, and was first described by Freedman.<sup>7</sup> If two treatments are believed to have similar efficacy, then equipose is said to exist. Surgeons, perhaps through nature or nurture (i.e. surgical training), are widely perceived to be a decisive group of individuals, amongst whom uncertainty may have negative connotations towards success and performance. When a problem has two different, yet valid, treatment approaches, individual surgeons often have a very strong preference for one approach, even though this may be based only on anecdote or ‘gut feeling’ – the surgeon is said to lack personal equipose. This situation creates an ethical dilemma for surgeons considering recruiting patients to clinical trials. There is a widespread belief that if a surgeon ‘knows’, or has good reason to believe, that therapy A is better than therapy B, then they cannot ethically participate in a trial of the therapies. Historically, this philosophy has been upheld by trial methodologists, who have suggested that clinicians who ‘know what is best’ should not partake in a trial, owing to the absence of personal equipose.<sup>8</sup>

There is now increasing recognition amongst trial methodologists, ethicists and the medical profession that equipose is less concerned with the opinions of an individual clinician, and more focused on those of the medical community – termed ‘clinical’ or ‘corporate’ equipose.<sup>7</sup> Enrollment to a clinical trial is therefore considered ethical, if clinical equipose exists; i.e. there is genuine disagreement amongst the expert medical community about the preferred treatment, not merely the views of an individual surgeon. Surgeons may therefore ethically engage in a trial, even if they have a personal belief that one treatment approach is more successful than another. The first major step to overcome in the facilitation of trials in trauma surgery is to encourage and enable surgeons to divorce themselves of their personal beliefs, and instead employ the principle of clinical equipose, and focus on the wider ‘public health’ agenda.

Whilst an acceptance of clinical equipose may enable surgeons to engage in clinical trials ethically, other concerns also exist. Randomisation is at the heart of high quality clinical trials, and is used to balance the distribution of unknown confounders. Surgeons may fear the process of randomisation,<sup>9</sup> believing that this process instills doubt and uncertainty in their patient. Some surgeons may perceive this uncertainty as a challenge to their competence and undermine their clinical decision-making ability.<sup>9,10</sup>

The challenge faced by clinical trialists is therefore to encourage surgeons to openly acknowledge the doubt that exists within the surgical community about any given surgical approach, and to identify shortfalls in knowledge. An evidence-based treatment strategy may then be formulated. In situations whereby no evidence exists, the most appropriate response is to generate evidence, thus ensuring a net-gain in wellbeing for patients, and importantly to ensure non-maleficence. This ‘thirst’ for evidence would change the ethos of surgery, with clinical trial involvement changing from a rare occurrence, to normal practice.

After a surgeon agrees to recruit patients into a trial, and overcomes the ‘fear’ of randomisation, the trial must be presented to the patient. This presentation must be balanced, withholding personal beliefs that may inadvertently influence recruitment. This is particularly challenging, as subconscious preferences may be subtly revealed, or the inevitable question may arise – *what would you do doctor?* – which for some may be difficult to resolve. These problems may be overcome with use of independent research practitioners who are employed specifically to recruit participants and offer an unbiased, impassionate view of the treatments within trial.<sup>11</sup> Commonly, a nurse or physiotherapist who has been through a training program related to the trial, adopts this role. The employment of research practitioners is well established and appears similarly efficacious in terms of recruitment uptake, as senior investigators with individual equipose.<sup>12</sup> Research practitioners also reduce the time-burden of the trial on the recruiting clinicians, which is an additional commonly cited barrier to trial involvement.<sup>13</sup>

Once a surgeon is engaged with a trial and recruitment begins, their role is to act as a ‘gatekeeper’<sup>14</sup>; the gatekeeper is the individual who highlights potential trial candidates to the research practitioners, advocates trial engagement as the optimal treatment strategy to patients, and facilitates adherence to the trial protocol. The gatekeeper must have influence over the team of clinicians with whom they have charge, as erroneous or misleading information in the form of treatment proposals, even by the most inexperienced staff, may have an influence on patient preferences and trial recruitment. A strong alliance between research team members, the chief investigator, surgeon ‘gatekeepers’ and research practitioners, is essential to maximise recruitment.<sup>14</sup> The chief

investigator is key to this alliance, and must have “charm with brains”<sup>14</sup>; the ability to act as the intermediary between surgeons and methodologists, and to understand the wants and needs of both groups of individuals.

Surgeon barriers cannot always be overcome, and outlier surgeons may exist for whom trial engagement is not possible. The ability for such surgeons to ‘opt out’ is likely to be the optimal strategy, as they are unlikely to convey equipoise, are therefore unlikely to successfully recruit, or may introduce bias. However, ‘opt-out’ should be reserved as a last resort tactic, as this may introduce bias, and limit the generalisability of the findings. Provision should be made for patients to be offered trial involvement, even if their treating surgeon is an ‘outlier surgeon’, as this would ensure that an evidence-based approach is universally offered, and would help to ensure the generalisability of the results. Such provision may be made via a local colleague, or through a trial network established by the chief investigator to spread equipoise.

### Patient barriers

Amongst the patient barriers to trial recruitment, treatment preference is arguably the most important. Patients may have preconceived ideas of the optimal treatment strategy, which may be based on non-expert experiences or information from the media, and some may have sought the particular expertise of a specific surgeon with a desire to pursue a predetermined treatment. Strong prior patient preferences limits the generalisability and validity of trials, owing to a reduction in recruitment and a tendency to switch intervention groups post-randomisation.<sup>15,16</sup> Additionally, patients with a strong preference who are randomised to receive their desired intervention, have better outcomes than those with no preference randomised to the same intervention.<sup>17</sup> Patient preference therefore should be acknowledged, discussed and documented at an early stage, in order to adequately address the concerns of patients, and later to analyse the results of a trial adequately. Preference is perhaps less of a challenge in trauma surgery compared with elective surgery, as time frames to surgery are reduced, and the access by individuals to resources are restricted owing to illness, confinement to hospital and the unplanned nature of care. Nevertheless, patients are likely to formulate an early opinion of what they consider the optimal treatment strategy, which should be considered when planning trials.

Researchers must ensure that patients can actively engage in the research, and plainly see the clinical problem, with equivalent risks and benefits evident; trial balance is important whereby the risk-benefit profile of each intervention seems equivalent to the patient. A stream of qualitative research during the trial preparation and development is important to ensure that a trial is balanced. Qualitative research seeks to explore the understanding of patients with regards to the disease, and the proposed research study. The outcome of the qualitative

work is to determine what more could be done to inform and engage patients, with the aim to maximise recruitment.

An example demonstrating successfully the importance of balance was a urology study of interventions for prostate cancer (surgery vs radiotherapy vs observation).<sup>18</sup> Patient-centred qualitative research increased recruitment in this study from 40% to 70% in less than one year. Key aspects of balance were to ensure that all aspects of a trial are presented in similar detail, and with similar enthusiasm. Balance is particularly problematic when a study involves both a radical (i.e. surgery) and non-radical (i.e. observation or physiotherapy) treatment option. Researchers within the prostate cancer study identified that clinicians tended to present ‘watchful waiting’ to patients with a palpable reluctance, and as the final treatment regime offered. Patients subsequently interpreted ‘watchful waiting’ as a ‘neglectful’ or a ‘watch them die’ approach, and were subsequently reluctant to engage with the study. One of the key changes driving increased recruitment was simply to change the ethos from ‘watchful waiting’, to ‘active monitoring’. Clinicians were encouraged to discuss the merits of ‘active monitoring’ with detailed information of the monitoring process, and to introduce this as the first treatment option discussed. A similar approach may be translated into trauma surgery, with interventions such as surgery *versus* conservative treatment, better presented as surgery *versus* individualised exercise therapy or similar.

An aversion to randomisation is another barrier among patients. Researchers within the prostate cancer study identified that whilst patient aversion to randomisation was a concern, this was more often a subtle effect of a lack of clinician equipoise.<sup>18</sup> Therefore, if the research team was not completely committed to the study, even if they were outwardly in favour of the trial, this would often subconsciously be detected by the patients and expressed as uncertainty in the randomisation process. Whilst there may be some patients who genuinely have reservations concerning the process of randomisation, the suggestion is that this barrier is frequently a symptom of other barriers (i.e. surgeon equipoise, study balance, patient understanding), and not a true aversion to the process.

Intervention concealment, or blinding, and the use of placebos, or sham surgery, may also pose particular difficulties and concerns for patients in surgical trials. Sham procedures are sometimes used, and these may have elaborate designs, such as in the case of the large 2008 knee arthroscopy trial.<sup>6</sup> In this trial, individuals in the non-intervention group had standard arthroscopy incisions made, the knee manipulated, and all equipment asked for by the surgeon as if the procedure were being performed, no instruments were placed inside the knee. However, patient concern was reflected in the low recruitment of only 40% of eligible participants, which may limit the generalisability. Ethical difficulties and patient concerns,

remain a key issue for trials using blinding or placebo interventions in surgery.<sup>19,20</sup> These barriers are difficult to overcome, though sham surgery is the gold-standard means by which to test surgical procedures, in the form of randomised double-blind placebo controlled trials.

Some of the barriers experienced by patients may be overcome by providing adequate materials to enhance their understanding. These must be used carefully to provide factual and well-balanced information. The provision of information is known to be an intervention which may maximise recruitment, with evidence suggesting that increasing the awareness of the disease under investigation (i.e. via an interactive computerised information sheet, a disease orientated video, or attendance at an education session) has a positive effect on recruitment.<sup>12</sup> However, increasing the awareness of the research process rather than the disease, does not appear to improve recruitment, and instead provides unnecessary detail.<sup>12</sup>

Terminology may be a barrier amongst patients. In the most basic form even the words 'randomisation' and 'trial' are used in research somewhat out of context to the usual use in society. 'Randomisation' is generally perceived to mean 'haphazard' or 'disordered', whilst 'trial' is often interpreted by patients as a flippant 'try and see' approach, often in the context of a 'free trial'. This may therefore not convey the methodological rigour, scientific support and ethical review that have undoubtedly occurred in order to enable the trial to proceed. This may easily confuse patients, but simple substitutes, such as 'study', are generally clearer and more acceptable. This barrier may appear trivial, yet is nevertheless real, and researchers may be so engrossed within their study that they miss such subtle barriers.

Other generic patient barriers must also be considered, including the time required for participation and the financial cost to patients, through repeated hospital attendances. The trial therefore needs to be efficient, such that the maximum information is extracted during the minimum number of clinical contacts; ideally part of 'routine clinical care'. Alternative forms of contact may be considered, such as mail or electronic communications, although the effect that these may have on patient follow-up and retention must be considered.

### Disease barriers

Diseases, or specific patterns of trauma, may generate their own specific barriers. Disease frequency is perhaps the most obvious barrier, as studies of rare conditions are undoubtedly more difficult to undertake, yet nevertheless the societal burden from such diseases may be great. Ensuring the optimal number of patients within studies may require the involvement of multiple centres, or longer trial recruitment periods, in order to ensure that adequate statistical power is achieved. An alternative is to accept a reduced statistical power (i.e. the ability to detect only a very large effect size), yet this approach may

be less acceptable to major funding bodies. Feasibility studies are therefore an integral part of clinical research, in order to determine the likely numbers of patients available for recruitment, and to ensure that recruitment rates are maximised amongst eligible patients. Feasibility studies can be completely independent from a full trial, or in-built with progression to the full trial after a defined period if specific 'stop-go' criteria are met.

The predilection of diseases for certain social groups is also a barrier to clinical research. Population data suggests that major trauma occurs in men, in socioeconomically deprived groups, and in minority ethnic groups.<sup>21</sup> However, trial data suggests that the highest trial attrition rates occur amongst men, the socioeconomically deprived, and those from minority ethnic groups.<sup>22-24</sup> This discrepancy must therefore be addressed early in the study design of such disease states. Higher drop-out rates of participants must be anticipated by accounting for these in power calculations, and ensuring maximal recruitment and follow-up in the feasibility stages of trial design. Specific modalities of follow-up may have different successes, amongst individuals with different diseases - it appears unlikely that those with major trauma would respond well to web-based follow-up, and similarly, attempting to measure outcomes at distant time-points appears unlikely to yield research success.

### Process barriers

The culture of research within different medical specialties is very different, and a strong research culture undoubtedly drives research success. The comments by the editor of *The Lancet* on poor surgical trial outputs, undoubtedly reflects the absence of a research culture within surgery.<sup>5</sup> Currently, patient recruitment to trials is the exception rather than the norm. Other specialties, such as paediatric oncology, have a strong research culture with over 70% of patients enrolled into trials, and most of the remainder treated according to protocols established through trials.<sup>25</sup> This ethos has driven collaboration and success such that rare malignancies, with annual UK case numbers in single figures, may be recruited into international collaborative trials, with survival increasing from 10% to over 80%.<sup>25,26</sup> In cancer treatment, both patients and clinicians consider trial recruitment 'normal', and perceive that research will deliver optimal clinical outcomes. Indeed this may be true, as there is some suggestion that trial participation may convey an 'inclusion benefit', such that patients within the trial have improved outcomes compared with those treated outside it. This is thought to be a consequence of closer monitoring of disease amongst participants.<sup>27,28</sup> The 'inclusion benefit' is a compelling argument against the 'fear' of randomisation, further supporting patient involvement in trials. A Cochrane review was unable to authenticate this 'inclusion benefit', however it did offer reassurance to patients that there is no additional 'risk' through clinical trial involvement,

compared with standard care.<sup>29</sup> The culture in orthopaedic surgery may be changing in the UK, with several large multicentre studies underway,<sup>30,31</sup> and organised methods of data-collection becoming routine at a national level.<sup>32,33</sup> Long-term outcome collection is increasingly becoming part of this routine data. This provides a new opportunity to deliver cheap, efficient and large-scale clinical trials by allowing randomisation of interventions within established national cohorts or audits,<sup>32,33</sup> with follow-up made using routinely collected outcome data.

Consent is considered by many as a barrier to clinical research, especially for prospective studies of trauma care. However, consent in research is considered essential, and has been since outrage erupted after a long-term study of the natural history of syphilis failed to treat participants after the discovery of antibiotics; the aim was to understand the natural history of untreated disease.<sup>34</sup> This outrage was formalised through the Helsinki Declaration following the Nuremberg trials, which has been continually updated ever since.<sup>35</sup> However, the now-established process of 'opt-in consent' creates challenges. Randomised trials of 'opt-in' versus 'opt-out' consent strategies have demonstrated higher rates of recruitment and similar rates of retention, with an overall gain in participants for opt-out consent strategies.<sup>36</sup> Likewise, an opt-in approach limits the 'generalisability' of the research, with opt-in less likely amongst those groups with higher rates of study attrition (i.e. males, socioeconomically deprived and ethnic groups). There is a strong argument to suggest that low-risk studies, particularly those comparing interventions already in common use, should adopt an opt-out approach,<sup>36</sup> though debate continues.

The opt-in consent process may pose a particular problem for trauma patients, as the ability of an individual to understand and consider the interventions posed may be impaired through head injury, pain, shock, medication or numerous other causes. Similarly, the timescale between presentation and intervention may be short, such that an individual is unable to consider the interventions proposed reasonably. The World Medical Association Declaration of Helsinki offered pragmatic guidelines for this purpose.<sup>37</sup> The declaration outlines that research may be carried out on such individuals, whereby the physical/mental barrier to consent is an integral component of the research population. The research protocol must state that consent to remain in the research should be obtained from the individual, or a legally authorised surrogate, as soon as possible. However, a subsequent European Union (EU) directive (Clinical Trials Directive 2001/20/EC), requires prior discussion with the individual, or a legal representative, before involvement in a trial. This directive is widely seen as a barrier to emergency care research within Europe,<sup>38</sup> and led to a group of interested parties (clinicians, lawyers and ethicists) forming the 'Vienna Initiative to Save European Research' (VISEAR).<sup>39</sup> This group sought to determine how the

European directive had been implemented throughout Europe, therefore exposing the interpretive variation of this directive. Germany has acted upon this directive most vehemently, requiring a judge to act as the legal representative authorising research.<sup>39</sup> Other countries, such as the United Kingdom, have allowed the clinician responsible for the care of the patient to act as their legal representative, as long as they are not connected to the conduct of the trial and that there is no person with a closer relationship to the individual willing or available to act. The EU has recognised the shortcomings of their directive, recently announcing plans to revise it in order to better accommodate emergency situations,<sup>40</sup> though some concern remains about whether the changes will be far-reaching enough.<sup>41</sup> The legislation remains in the consultation phase at present (January 2014).

There are a number of trauma studies, including those in orthopaedics, that have successfully used the emergency trauma consent guidelines to good effect. The clinical randomisation of an antifibrinolytic in significant haemorrhage (CRASH-II) trial was the largest trauma trial to date, with over 20 000 participants enrolled internationally, investigating the emergency use of tranexamic acid in major trauma.<sup>42</sup> Consent was initially sought from an individual close to the patient (the personal legal representative), or if immediately unavailable, a nominated professional legal representative within each hospital; if both were immediately unavailable, the individual was randomised, with later consent from a representative as soon as possible. When an individual regained competence, formal informed consent was sought for study participation. An example of this model of consent in orthopaedic trauma is in the Warwick Hip Trauma Evaluation (WHiTE) Study, which investigates different interventions in fragility hip fractures.<sup>43,44</sup>

### Delivering changes in clinical practice

Even if research barriers are overcome and the highest quality research is performed, results do not necessarily translate into clinical practice. An ethnography by Katz<sup>45</sup> identified that "surgeons have been resistant to accepting new scientific findings and applying them to their practice". Surgeons frequently suggest that randomised controlled trials (RCTs) lack generalisability to individual patients, with this cited as a common reason for the reluctance to accept RCT evidence.<sup>46</sup> Surgeons may intimate that irrespective of how well the RCT is conducted, outcomes of a study are only useful at group-level, and may not necessarily apply to the individual. Many expand this argument by suggesting that RCTs are too simple to adequately assess the complex nature of surgical interventions, and that there may be many factors or complexities about the intervention as a whole that influence outcomes.<sup>47</sup> These include individual surgeon nuances, or peri-operative care regimes, i.e. the care that occurs outside the environment of the specific

operative intervention.<sup>47</sup> Overcoming these attitudes involves a culture change, which may be possible by educating and inspiring the surgical community that research can successfully improve outcomes, and empower them to challenge their pre-conceived ideas through high-quality research.

## Conclusion

Despite the obvious need for trials in trauma surgery, there is a clear paucity of well-conducted research that has been undertaken. There are many factors that may act to prohibit high quality trials, which may relate to the surgeon, the patient, or the disease under investigation. Equipoise is the key concern amongst treating surgeons, and appears to be the most substantial barrier to research. A united surgical community, who openly acknowledge uncertainty, would be a powerful force to drive research. It is likely that such a group could erode many of the barriers that currently exist, which may lead to the development of robust programs of clinical research. However, while RCT evidence in trauma is either scarce or of poor quality, the impact of evidence from clinical trials is likely to be limited.

## References

- No authors listed.** World Health Organisation: Injuries and violence: the facts, 2010. [http://www.who.int/violence\\_injury\\_prevention/key\\_facts/en/](http://www.who.int/violence_injury_prevention/key_facts/en/) (date last accessed 27 February 2014).
- No authors listed.** World Health Organisation: Cancer. Fact sheet no. 297, 2013. <http://www.who.int/mediacentre/factsheets/fs297/en/> (date last accessed 27 February 2014).
- No authors listed.** US National Library of Medicine. <http://www.nlm.nih.gov> (date last accessed 14 March 2014).
- No authors listed.** ClinicalTrials.gov, 2014. <http://clinicaltrials.gov/ct2/home> (date last accessed 27 February 2014).
- Horton R.** Surgical research or comic opera: questions, but few answers. *Lancet* 1996;347:984–985.
- Moseley JB, O'Malley K, Petersen NJ, et al.** A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81–88.
- Freedman B.** Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141–145.
- Shaw LW, Chalmers TC.** Ethics in cooperative clinical trials. *Ann N Y Acad Sci* 1970;169:487–495.
- No authors listed.** *From Theory to Theatre: Overcoming barriers to innovation in surgery.* London, UK: RCESENG, 2011.
- Ashton CM, Wray NP, Jarman AF, et al.** Ethics and methods in surgical trials. *J Med Ethics* 2009;35:579–583.
- Pocock SJ, Henderson RA, Seed P, Treasure T, Hampton JR.** Quality of life, employment status, and anginal symptoms after coronary angioplasty or bypass surgery. 3-year follow-up in the Randomized Intervention Treatment of Angina (RITA) Trial. *Circulation* 1996;94:135–142.
- Caldwell PH, Hamilton S, Tan A, Craig JC.** Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med* 2010;7:1000368.
- Lovato LC, Hill K, Hertert S, Hunninghake DB, Probstfield JL.** Recruitment for controlled clinical trials: literature summary and annotated bibliography. *Control Clin Trials* 1997;18:328–352.
- Patterson S, Mairs H, Borschmann R.** Successful recruitment to trials: a phased approach to opening gates and building bridges. *BMC Med Res Methodol* 2011;11:73.
- Brewin CR, Bradley C.** Patient preferences and randomised clinical trials. *BMJ* 1989;299:313–315.
- Howard L, Thornicroft G.** Patient preference randomised controlled trials in mental health research. *Br J Psychiatry* 2006;188:303–304.
- No authors listed.** Preference Collaborative Review Group: Patients' preferences within randomised trials: systematic review and patient level meta-analysis. *BMJ* 2008;337:1864.
- Donovan J, Mills N, Smith M, et al.** Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002;325:766–770.
- McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D.** Randomised trials in surgery: problems and possible solutions. *BMJ* 2002;324:1448–1451.
- McLeod RS, Wright JG, Solomon MJ, et al.** Randomized controlled trials in surgery: Issues and problems. *Surgery* 1996;119:483–486.
- Bruns J Jr, Hauser WA.** The epidemiology of traumatic brain injury: a review. *Epilepsia* 2003;44Suppl10:2–10.
- Arnow BA, Blasey C, Manber R, et al.** Dropouts versus completers among chronically depressed outpatients. *J Affect Disord* 2007;97:197–202.
- Snow WM, Connett JE, Sharma S, Murray RP.** Predictors of attendance and dropout at the Lung Health Study 11-year follow-up. *Contemp Clin Trials* 2007;28:25–32.
- Villacorta V, Kegeles S, Galea J, et al.** Innovative approaches to cohort retention in a community-based HIV/STI prevention trial for socially marginalized Peruvian young adults. *Clin Trials* 2007;4:32–41.
- Unguru Y.** The successful integration of research and care: how pediatric oncology became the subspecialty in which research defines the standard of care. *Pediatr Blood Cancer* 2011;56:1019–1025.
- Le Deley MC, Rosolen A, Williams DM, et al.** Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *J Clin Oncol* 2010;28:3987–3993.
- Schmidt B, Gillie P, Caco C, Roberts J, Roberts R.** Do sick newborn infants benefit from participation in a randomized clinical trial? *J Pediatr* 1999;134:151–155.
- Lantos JD.** The "inclusion benefit" in clinical trials. *J Pediatr* 1999;134:130–131.
- Vist GE, Hagen KB, Devereaux PJ, et al.** Outcomes of patients who participate in randomised controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database Syst Rev* 2007;(2):MR000009.
- Handoll H, Brealey S, Rangan A, et al.** Protocol for the ProFHER (PROximal Fracture of the Humerus: Evaluation by Randomisation) trial: a pragmatic multi-centre randomised controlled trial of surgical versus non-surgical treatment for proximal fracture of the humerus in adults. *BMC Musculoskelet Disord* 2009;10:140.
- Costa ML, Achten J, Parsons NR, et al.** UK DRAFFT - a randomised controlled trial of percutaneous fixation with kirschner wires versus volar locking-plate fixation in the treatment of adult patients with a dorsally displaced fracture of the distal radius. *BMC Musculoskelet Disord* 2011;12:201.
- No authors listed.** The Trauma Audit and Research Network. <https://www.tarn.ac.uk/> (date last accessed 14 March 2014).
- No authors listed.** The National Hip Fracture Database. <http://www.nhfd.co.uk/> (date last accessed 14 March 2014).
- Beauchamp T.** The Belmont Report. In: Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*, New York: Oxford University Press, 2008:149–55.
- No authors listed.** World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–2194.
- Junghans C, Feder G, Hemingway H, Timmis A, Jones M.** Recruiting patients to medical research: double blind randomised trial of "opt-in" versus "opt-out" strategies. *BMJ* 2005;331:940.
- No authors listed.** Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. <http://www.wma.net/en/30publications/10policies/b3/> (date last accessed 14 March 2014).
- Sterz F, A Singer E, Böttiger B, et al.** A serious threat to evidence based resuscitation within the European Union. *Resuscitation* 2002;53:237–238.
- Liddell K, Chamberlain D, Menon DK, et al.** The European Clinical Trials Directive revisited: the VISEAR recommendations. *Resuscitation* 2006;69:9–14.
- No authors listed.** European Commission: Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 2012. <http://ec.europa.eu/health/human-use/clinical-trials/#rlctd> (date last accessed 27 February 2014).
- Perkins GD, Bossaert L, Nolan J, et al.** Proposed revisions to the EU clinical trials directive—comments from the European Resuscitation Council. *Resuscitation* 2013;84:263–264.
- CRASH-2 trial collaborators<sup>1</sup>, Shakur H, Roberts I, et al.** Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376:23–32.

43. **Griffin XL, McArthur J, Achten J, Parsons N, Costa ML.** The Warwick Hip Trauma Evaluation One -an abridged protocol for the WHiTE One Study: An embedded randomised trial comparing the X-bolt with sliding hip screw fixation in extracapsular hip fractures. *Bone Joint Res* 2013;2:206–209.
44. **Griffin XL, McArthur J, Achten J, Parsons N, Costa ML.** The Warwick Hip Trauma Evaluation Two -an abridged protocol for the WHiTE Two Study: An embedded randomised trial comparing the Dual-Mobility with polyethylene cups in hip arthroplasty for fracture. *Bone Joint Res* 2013;2:210–213.
45. **Katz P.** *The Scalpel's Edge: The Culture of Surgeons.* Boston: Allyn and Bacon, 1999.
46. **Stirrat GM.** Ethics and evidence based surgery. *J Med Ethics* 2004;30:160–165.
47. **Avery KN, Barham CP, Berrisford R, et al.** Understanding surgical interventions in RCTs: the need for better methodology. *Lancet* 2013;381:27–28.

**Funding statement:**

- D. C. Perry and X. L. Griffin are funded through the NIHR clinical lecturer award scheme.

**Author contributions:**

- D. C. Perry: Initial author of manuscript.
- X. L. Griffin: Additions to and amendment of manuscript
- N. Parsons: Additions to and amendment of manuscript
- M. L. Costa: Additions to and amendment of manuscript

**ICMJE Conflict of Interest:**

- None declared

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