Title - International orthopaedic trials: global reach for a global burden of disease

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Abstract

Musculoskeletal diseases are having a growing impact worldwide. It is therefore crucial to have an evidence-base to most effectively and efficiently implement future health services across different health care systems. International trials are an opportunity to address these challenges and have many potential benefits. They are, however, complex to set up and deliver, which may impact on the efficient and timely delivery of a project. There are a number of models of how international trials are currently being delivered across a range of orthopaedic patient populations which are discussed. The examples given highlight that the key to overcoming these challenges is the development of trusted and equal partnerships with collaborators in each country. International trials have the potential to address a global burden of disease, and in turn optimise the benefit to patients in the collaborating countries and those with similar health services and care systems.

Global burden of musculoskeletal disease

Musculoskeletal diseases are having a growing impact worldwide.(1) This can be in terms of treatment costs, disability, sick leave, and quality of life.(2-4) Disability-adjusted life years (DALY), which combines the years of life lost and the years lived with disability, from 183 countries worldwide, was found to increase significantly for musculoskeletal disease from 80,225,635 in 2000 to 107,885,833 in 2015 ($P<0.001$).(5) This increase in global burden of the disease means it is crucial to have an evidence-base that allows health professionals and policy makers across different health care systems to most effectively and efficiently implement future health services.

General considerations of international trials

Randomised controlled trials (RCTs) are the most rigorous study design to minimise bias, establish a cause-effect relationship between treatment and outcome, and to assess the cost-effectiveness of a treatment.(6) Potential benefits of undertaking international RCTs includes: enabling projects to proceed when there is a smaller patient population, the pooling of data to allow analyses of sub-groups of a patient population, improving the generalisability of study findings and enabling a greater understanding and learning of how to manage challenges in study design and delivery of a project. International RCTs, however, are more complex to organise in terms of, for example, funding arrangements, agreeing on protocols and data collection/sharing, and agreeing issues around publication and intellectual property. These complexities may impact on the efficient and timely delivery of a project and delay the potential for patient benefit.

There are a number of models of how international RCTs are currently being delivered across a range of orthopaedic patient populations, which we summarise below using examples from the United Kingdom (UK), along with some of the challenges in their set up and delivery.

UK-funded RCTs based in other countries

The UK National Institute for Health and Care Research (NIHR) was created with a remit to improve the health and wealth of the UK population and, for many years, it's focus was upon the UK exclusively. However, in 2016, the NIHR extended its remit to also fund 'high quality global health research that addresses the diverse health needs of people in low and middle income countries' (LMICs). Specifically, to fund research in developing countries that are eligible to receive Official Development Assistance (ODA) from the UK aid budget. This global health research is delivered through programmes that award funding to equitable partnerships between groups of researchers and institutions in LMICs and the UK. Many other countries have similar programmes addressing the healthcare needs of people in LMICs. This funding has allowed UK based researchers

to partner with researchers and clinicians in LMICs to use NIHR funding to address healthcare problems specific to these countries, as opposed to the UK itself.

The HIPCARE trial is an example of an NIHR trial within a LMIC setting.(7) In the high-income setting, research has shown that implementing a programme of multidisciplinary teamwork reduces mortality following hip fracture, improves patients' health-related quality of life and reduces economic costs.(8-10) This multidisciplinary care involves different groups of healthcare professionals working together to target specific aspects of care for patients with a hip fracture; for example, surgeons and anaesthetists working towards early surgery, and physiotherapists and nursing staff to facilitate early mobilisation. However, a multidisciplinary team approach to hip fracture is rare in LMIC settings. The HIPCARE trial aims to test a multidisciplinary team support package for improving the care provided to patients with hip fracture in LMIC in Asia. However, before testing a change to existing care pathways it was necessary to understand the current pathways of care in each country. This required clinicians in the UK and LMICs to develop trusted collaborations whereby there can be a free exchange of what can be, sensitive information, for example the proportion of patients being treated non-operatively. Through the Global Fragility Fracture Network(11) researchers were able to map service availability and readiness to deliver care for patients with hip fracture in Philippines, Vietnam, India, Thailand and Sri Lanka, laying the groundwork to develop a multidisciplinary care intervention that addressed the specific needs of each LMIC.(12) For example, the pathway mapping project found that orthogeriatricians – now working routinely alongside surgical teams to deliver comprehensive geriatric care in many counties – did not exist as a specialty group in many LMIC in Asia. Creating a multidisciplinary team containing orthogeratricians would therefore make no sense in those countries. However, the mapping project also highlighted that, for instance, rehabilitation physicians in Philippines and acute medicine specialists in India would likely be able to provide the same medical input as orthogeriatrician in those healthcare settings.

The HIPCARE trial highlights the importance of working with colleagues in other countries to define a research problem from their perspective, before embarking upon an RCT to address that problem.

UK-based RCTs which also recruit in other countries

The NIHR also sometimes permits UK trials recruiting overseas. This may be planned from the outset of the study (i.e. through a joint funding arrangement between the NIHR and Australian National Health and Medical Research Council (NHMRC)) or may evolve in response to events during the progress of the study.

The NIHR funded ACTIVE RCT compares an external frame with internal locking plate for intra-articular pilon fracture fixation in adults.(13) Pilon fractures are relatively uncommon and account for 5% to 7% of tibial fractures. Early in the study, it was proving to be a challenge to recruit participants (due to surgeon and patient preferences and the relative rarity of the fracture). Having successfully set up all interested Major Trauma Centres in the UK, it was agreed with NIHR to open international sites within the existing budget.

Setting up the international sites within an existing budget had to be carefully balanced with ensuring the UK sites continued to have the necessary support with recruitment and data collection. Furthermore, although the international sites with whom we identified to collaborate was largely with colleagues we knew, careful attention was given to exploring their feasibility to deliver the study. Interested sites completed an Expression of Interest Form that established the expected volume of patients, experience of the clinical staff and hospital department in delivering

(international) research, as well as support available through R&D. This also informed another important consideration, with regard to the cost-effectiveness evaluation embedded within the trial, which was that there should be a sufficient number of study participants enrolled from the UK to allow for a health economic analysis to be done from a UK perspective. Other healthcare systems having different approaches to the economic evaluation of healthcare interventions.

A main consideration in the set-up of the international sites was about who would take overall responsibility and oversight for the study. This role is done by a 'Sponsor', which in the UK was an NHS Trust. However, a key consideration was whether the NHS trust would sponsor the international hospitals (South Africa and Australia) and provide the necessary insurance arrangements. Having a single Sponsor had the potential advantage of efficiency, rather than finding alternative Sponsors for each country and the associated individual agreements required on contractual, financial and insurance arrangements. Ultimately, it was agreed to have separate Sponsors in South Africa and Australia (both were Universities). Having a country-specific Sponsor was valuable in helping to navigate the various local regulatory and ethical environments and to have access to expertise in research delivery in the local setting. It took around two years (from early 2020) from starting to discuss the study in earnest with our international collaborators to opening sites to recruitment. A substantial amount of the work was around agreeing sponsorship arrangements and contracts between collaborating parties, which was compounded by the global pandemic. Given the stage of the study, protocol changes were not feasible but delivery was adapted to local circumstances including modification of the Case Record Forms to reflect the nuances of wording in different countries. All of this set up was in close collaboration with our partners at the international sites and could not have been achieved without their enthusiastic engagement and support and subsequently with recruitment and data collection.

Similar challenges have been overcome in the UK NIHR SCIENCE (surgery or casts for injuries of the epicondyle in children's elbow) study. The SCIENCE study recruits in New Zealand and Australia. A particular consideration of recruitment in New Zealand was the need to ensure that Māori communities were consulted and agreed to the study conduct, to ensure that it honoured Māori health aspirations in the ethical review of health research.

The support of our international colleagues, and effective relationship with our international Sponsors, has helped to ensure that the opening of sites in South Africa, New Zealand and Australia should ensure our study-wide recruitment targets are met.

RCTs which use the same protocol but are funded separately in each country

The are some instances where there may be challenges in involving overseas sites in UK studies. For example, in the United States (US) and Canada, the cost of study setup and sponsorship can be particularly restrictive to overseas funding. Furthermore, it's possible that an international study may not be generalisable to a particular country owing to a particular set of patient or disease factors, or simply the desire amongst clinicians to repeat a study externally. In these instances, separately funding a trial may be the most appropriate action.

The UK SCIENCE and CRAFFT (Childrens Radius Acute Fracture Fixation) study are both now recruiting in the US and Canada. Whilst the UK studies are ongoing, the US studies are completely independent in terms of the sample size needed to complete the study. In the US, the studies are funded by the National Institute for Health (NIH), using the names of COMET (Cast or Operation for Medial Epicondyle Fracture) and DRIFT (Distal Radius Interventions for Fracture Treatment) study. There are even differences in the timing of the primary outcome, with US surgeons believing that 3-

months should be the primary outcome for medial epicondyle fractures – whereas this is a year in the NIHR trial. However, the trials are also closely aligned, with shared recruitment experiences, shared collaborators, shared outcomes and outcome timepoints with the plan to perform an individual patient data meta-analysis when reporting the outcomes of the last of the trials to report. Therefore, even though there are minor differences between the studies, there is sufficient similarity to draw the studies together to provide an overarching result which will have more statistical power and generalisability than each of the studies in isolation.

Conclusions

International RCTs have the potential to answer research questions that could never be answered in a single country, for example, for rare conditions. They also facilitate the pooling of data to allow more precise and reliable analyses of sub-groups of a patient population, and improving the generalisability of research findings. Perhaps most importantly, they allow researchers and clinicians in different countries to exchange ideas and knowledge, breaking down introspective practices and traditions which limit progress. However, there are many challenges in delivering international trials. While some of these challenges are specific to a particular research project, many are generic. The examples above highlight that the key to overcoming these challenges is the development of trusted and equal partnerships with collaborators in each country. This international collaboration, to address a global burden of disease, will in turn optimise the benefit to patients in all of those countries and beyond.

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Take home message

- Musculoskeletal diseases are having a growing impact worldwide. It is crucial to have an evidence-base to most effectively and efficiently implement future health services across different health care systems.
- International RCTs can help answer research questions that could never be answered in a single country, and allow the pooling of data to analyse sub-groups of a patient population, improving the generalisability of research findings.
- While there are challenges to their delivery, these can be overcome with the development of trusted and equal partnerships with each country.

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