Getting placebo controls of surgery to work (in orthopaedics) - the CSAW experience

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Many of the readers here will be familiar with the Oxford University led CSAW (Can Shoulder Arthroscopy Work) RCT. For those who are not, or need a refresher, the trial was designed to explore the efficacy of arthroscopic subacromial decompression for patients with subacromial pain, who had previously completed a programme of conservative management[1] with a recruitment target of 300 randomised patients.

This venture into surgical placebo trials was not taken lightly. There was much consideration of not only the ethical aspects and challenges of this type of research as Charles Weijer discusses in his article but also the practical uncertainties associated with such a study: Would the proposal of a surgical placebo RCT be accepted by stakeholders and their communities? Would there be buy in and willingness to be actively involved? Would surgeons be willing to enter their patients into the trial? Would patients accept the uncertainty and consent to receive a treatment allocated through randomisation?

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Clinical research is often a long time in the development stage and the 'work-up' of CSAW was no exception. Various methods (formal and informal) were used to establish stakeholder views on the proposed trial. Patient views were sought via a workshop meeting where the proposed study was discussed, with a questionnaire distributed to those attending shoulder clinics, to match the cohort of the proposed RCT, and anecdotally via informal discussions with patients by the lead investigators. In all cases, there was a consensus from these patients that they would, theoretically, be willing to participate in such an RCT.

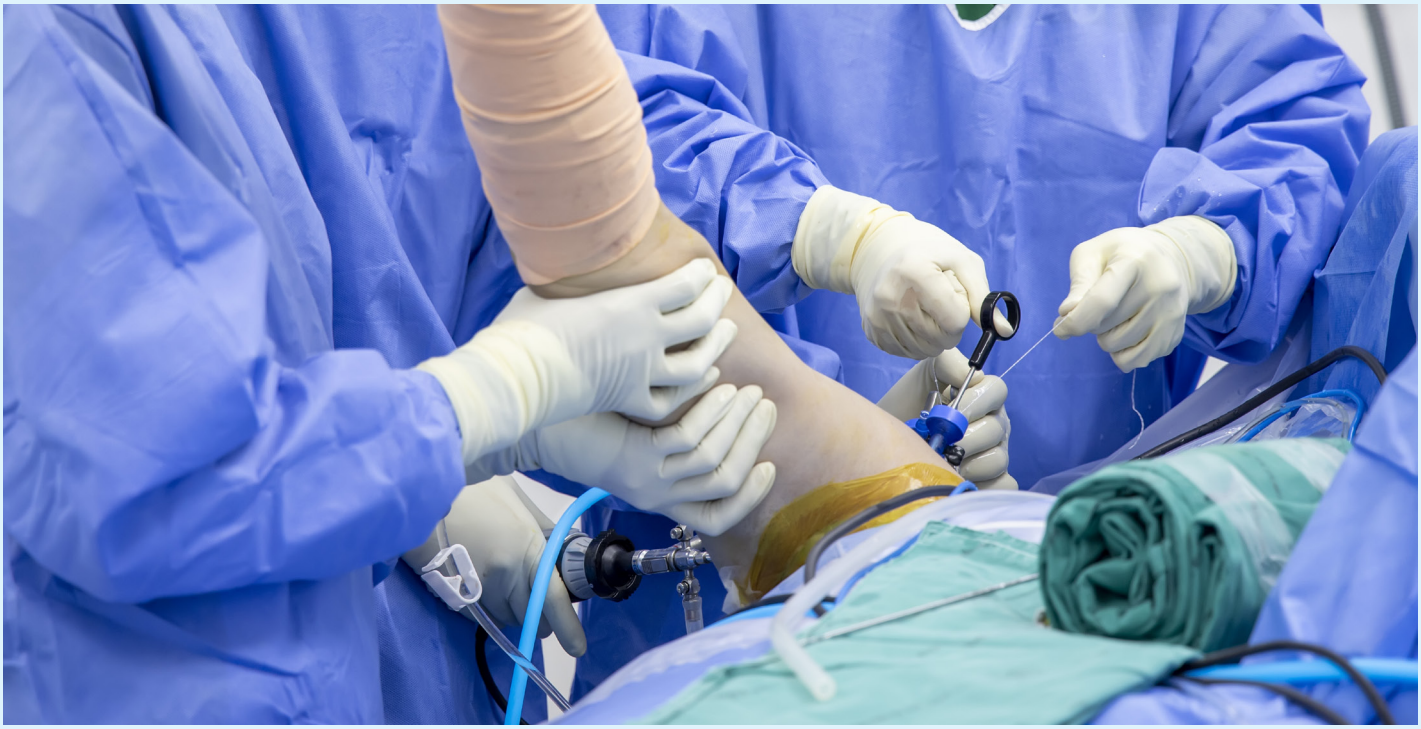
Alongside informal discussions within the orthopaedic surgical community, meetings were organised with representation from funding bodies, orthopaedic surgeons, physiotherapists, neurologists, ethicists, trial methodologists and statisticians. The proposed trial design was presented and 'hot topics' such as ethical considerations and the placebo intervention were debated. The outcome of this pre-work was positive with consensus across stakeholder groups being in favour of the trial. Importantly, debate around the placebo surgery arm of the trial

found stakeholders unable to justify the use of skin nicks only, leading to a procedure whereby the aspects considered to be the critical surgical element would be omitted (as discussed earlier by DB and MC). Hence, there was a need to ensure that the comparator was more than 'just a sham'. The (ambitious) study design ultimately aimed to assess surgery vs no surgery; the need for a specific component of surgery; and a quantification of the placebo effect.

Having gained in-principle buy-in from the main protagonists, the next step in the process was actualising the planned RCT. The three study arms were: the 'standard' surgical arm of arthroscopic subacromial decompression (ASAD), to overcome the ethical and practical concerns of avoiding a purely sham procedure, the surgical 'placebo' comparator involved an investigative shoulder arthroscopy only (AO), and, thirdly, to compare surgery with a non-surgical intervention, a conservative management arm, initially named 'active monitoring'. Study sites were identified and set up, typically with one 'keen' surgeon fulfilling the role of local collaborator and heading up their local team with support from a research nurse.

Recruitment to RCTs can be challenging at the best of times, and given the very different comparators at play here, those challenges were amplified in CSAW. In the early stages of the study, patient recruitment was slow. In an attempt to mitigate for this, a QuinteT recruitment Intervention (QRI)[2] was incorporated into the study. Briefly, the QRI is a two-stage complex intervention, using standard and innovative qualitative research methods to 1) identify and understand recruitment challenges and 2) work with the study team to resolve those challenges. For CSAW this involved interviews with study management and staff involved in recruiting patients, along with audio-recording consultations with patients where the CSAW study was presented to them. Rapid analysis of these data pointed to some of the common challenges in patient recruitment, previously seen in RCTs in other contexts. For example, in interviews, whilst local collaborators were often willing to demonstrate their apparent support for the study, they 'gave away' that they were not considering (and thus, not approaching) all potentially eligible patients. They also described their lack of equipoise towards the active monitoring arm, typically describing an expectation that the *"surgical options are more likely to be of benefit"*.

The audio recorded data of what actually happened in clinic discussions provided even more valuable insights into how the study was presented and discussed with patients. For example, it became apparent that 'active monitoring' was not being presented thus, rather as variations on a theme of *"carry on with what you've been doing"*, which proved to be less than appealing for the many patients with several months of physio behind them, typically referred by their GP to 'go and see a surgeon' who they expected to tell them that they would have surgery. Perhaps more interestingly given the 'placebo' theme of this collection of articles, neither surgeons nor patients experienced difficulty with the presentation, or acceptance of the arthroscopic only arm. Most recruiters used a turn of phrase that described first arthroscopy only, closely followed by ASAD. For example: *"(in the RCT) there are two surgical options: one is done arthroscopically where we just go in and wash it out... the other, as well as putting the camera in, we shave a bit of bone off too"*. We reflect therefore that maybe a consequence of having surgeons 'on-board' with the concept of a placebo arm made it more comfortable for them to describe to their patients. >>



Where recruitment encounters broke down, analysis pointed to previously identified 'hidden challenges'[3] associated with RCT activities. For example, the way the randomisation process was described was off-putting for some: *"your treatment will be chosen literally by the flip of a coin"*[4], apparent (misguided) patient preferences[5] were not always explored: *"My neighbour had an operation and did well"* (despite the neighbour having a different diagnosis).

Having identified recruitment challenges and recruitment successes, we sought to ensure these were shared with all of those engaged in recruiting to CSAW. All staff from recruiting centres were invited to attend a CSAW training day. This was an opportunity for staff involved in the recruitment of patients to share their experiences and the challenges and barriers they faced. Staff were encouraged to practice and develop their recruitment skills. A mix of teaching sessions and workshops covered topics such as, working through a recruitment conversation, conveying uncertainty, providing a balanced view (study arms), explaining randomisation, working with patient preferences (exploring and understanding these preferences), informed decision making (non-coercive), and guidance on how to make space for patient views.

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We provided ongoing support to study sites to help with recruitment, by amending training materials to reflect the emerging data from the QRI. A suite of training/support materials were created and shared with existing recruiting centres, and follow-up visits were organised at sites where recruitment was slower than expected, and included training based on the qualitative evidence.

It is interesting and worthy of reflection, that the 'placebo' element of the CSAW study was not in any way the main hindrance to recruitment of patients. Rather the bigger melting pot of 'clear obstacles' to RCT recruitment (such as lack of on-site support for the study, finding time to explain the RCT to patients in busy, over-subscribed clinics, fewer than expected eligible patients coming through the door), combined with some CSAW specific 'hidden challenges' (less than appealing presentation of non-surgical procedures, willingness to accept unexplored patient preferences) were the headline causes of difficulties.

What, then is our message here? We believe that the success of surgical trials is dependent on the attitudes and commitment to the research question of participating clinicians, and ensuring that they are able to demonstrate that commitment to their (eligible) patients by presenting study information with equipoise[6]. Orthopaedic surgical trainee Shiraz Sabah gives us a good insight in the surgeon's psyche in the next article and helps to explain why, in order to get a trial to work, there must be equipoise, interest, and willingness within the surgical community. Our experience on the CSAW study shows that in-depth pre-trial work can help to pre-empt and assess issues which may hinder the integrity of surgical trials. Monitoring recruitment activity and how the study is presented to patients helped us to identify those recruitment difficulties. Supporting and training recruiters based on strategies to address those challenges helped to keep recruitment on track, and formal and anecdotal feedback indicated that CSAW training interventions led to site staff feeling more confident when presenting the study to potential recruits. Ultimately, the experience of the management group, and participating collaborators on CSAW demonstrates that patients may be willing to accept a 'placebo' allocation in a surgical trial[7]. ■

References

References can be found online at www.boa.ac.uk/publications/JTO.