The last word on placebo-controlled surgical trials

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We've heard lots already about placebo-controlled trials in surgery, but it is fitting that the last word should go to the surgeon. After all, isn't this where the buck stops? It is the surgeon who agrees to do an operation with a potentially key ingredient missing, and to follow-up the patient. With this in mind, this article asks you to consider whether *you* would enrol your patients into a placebo-controlled surgical trial? And, how would *you* feel about carrying out a placebo operation?

The place to start is perhaps with an even more fundamental concept in surgical evaluation. Let's ignore the placebo aspect for now and consider the question: How do you feel about the idea of a trial in surgery more generally? Or, asked in a more confrontational way: How willing are you to put your surgical decision-making to the test? What happens if some of the decisions you've been making (potentially for years) are suggested to be arbitrary or, even worse, *wrong*? As surgeons, we've been trained to be decision-makers. We've even trained those around us to recognise this as sacrosanct - "clinical correlation is advised" remains very welcome in any report of an investigation offered up to us. The decision to operate or not is binary and absolute, though you can choose when and how. If you do decide to operate, the effects of surgery typically are not reversible. It is not a tablet that can be discontinued and the status quo returned. And so, surgical decision-making requires confidence. Indeed, some of us spend large parts of our careers developing, cultivating and perfecting this confidence. It's the *art* of surgery, isn't it? We've listened to the surgical mantras: "In my hands, it works." It is about "putting things back as you found them," "knowing how to pick winners," or something else that is difficult to measure: attention to detail; theatre principles; a look in the eye that you give the patient at the end of the day to say the operation could not have gone any better. But is this really the best we can give our patients?

When Christiaan Barnard did the first human-to-human heart transplant, he told his patient, Louis Washkansky, that he had "an 80% chance of success"[1]. It is difficult to know where this estimate came from, but it seems unlikely that there was much in the way of evidence to support it. We do know that Mr Washkansky died 18 days later. More than fifty years has passed since then, and most would now agree that confidence is best backed up by objective evidence. Indeed, one may find that for many of our current interventions the final beatitude is *surgical equipoise*. This is a state where we recognise that whilst we could do this operation or that operation (and indeed some do), when we look at the body of evidence, it is not clear which of these options is best for the population >>

as a whole. However, similar to how "absence of evidence is not evidence for absence"[2], remember that this does not necessarily mean that *nobody* knows which of these options is best, that the measurement of clinical outcome is perfect or that there are not some patients where we do know the best option. The clinical challenge is to marry these viewpoints for individual patients – appraisal of the current evidence, recognition of "confluences of interest"[3], and acknowledging the tacit knowledge of experts. Surgical trials are a tool to help us do this more consistently and fairly and to remove as many sources of bias as we can from the mix.

Sometimes it is a fundamental question that needs to be answered. Is the patient really better off with an operation at all compared to doing nothing? Take knee replacement, for example, millions have been performed to date, so you would expect a trial to have been undertaken to answer this question, *right*? Indeed, it has. But, you would be forgiven for thinking this was ancient history. This trial was, in fact, published in 2015[4] and showed a benefit to total knee replacement versus non-operative treatment. What it did not tell us was *why* the operation was beneficial. Which bits of the intervention made the all-important clinical difference? The skin incision? Resurfacing the bones? Balancing the ligaments? *Blessing* the joint with a betadine lavage at the end of the case? Or, just doing something that the patient wanted you to do in the first place? It also does not tell us just how important it is to know which bit worked. Why does it matter? If the operation works, it works, doesn't it? Except science is a search for 'the truth' and this is where we find ourselves with placebo-controlled surgery: a series of experiments where parts of an operation are deliberately left out to help us to understand the bits that really do matter.

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So, what kinds of placebo surgery have we seen? It will be no surprise to learn that the majority of trials have investigated arthroscopic procedures[5]. These procedures generally have low complication profiles and, whilst small incisions can sometimes hide a multitude of sins, the scars left behind are often difficult to see and more easily forgotten. The theory behind informed consent for placebo-controlled trials is very well discussed by Charles Weijer. However, the process of explaining to an individual patient that they are not expected to benefit from surgery and yet them wanting an operation anyway is perhaps also familiar. It probably is important what the placebo is in any surgical trial or, if the patient chooses not to enrol, what options are they then presented with? Would their surgeon do the (non-evidenced based) operation anyway? Or, is the trial the only chance of getting surgery? In particular, where diagnostic arthroscopy is used as the placebo-control, it is likely that many patients (and surgeons?) will envisage a benefit to the procedure (to *understand more about the condition*), no matter how well

it is explained or sign-posted that no benefit is expected. For all of these reasons, the process of informed consent for placebo-controlled trials is challenging. The careful use of language (including avoiding emotive words like 'sham' or 'fake') and using tools to help with consent (such as decision aids) has been highlighted by recent guidelines[6]. However, for many surgeons, this may be a significant departure from their normal consenting practices. Patients often look to the surgeon for reassurance before their procedure (*Am I doing the right thing, doctor*?) and it is worth thinking about how you would respond to that question in the setting of a placebo-controlled trial.

Indeed, we all understand that surgery can and does sometimes go wrong and the responsibility of performing a placebo operation on an individual patient is an important *cross to bear* for the surgeon. It is worth considering: How would this responsibility weigh on *me*? You can even think of this on a more practical basis. What would I tell the patient on the ward before they go home? We are used to telling patients that we worked hard, did our best and left things looking neat and tidy at the end of the case. With placebo-controlled surgery, you may have intentionally not done that. Whilst the trial is likely to have been designed to prevent unblinding before an agreed timepoint, and patients will probably understand if you choose not to disclose, it may still sit uncomfortably. On the other hand, it is important to reflect that concerns around unnecessary surgery appear to weigh a lot less for operations that are already established, but with limited evidence for their efficacy. This is despite often far greater numbers of patients at-risk. Indeed, we sometimes seem to have things the wrong way round in surgery: when we decide to do a new operation, or to continue with an existing one, we have an understanding that it is effective, or that it makes sense that it should be effective, just because it is biologically plausible. Perhaps instead we should start from the opposite viewpoint: ineffective until proven effective?

Finally, do randomised trials really send a jolt through the system? Surely, that must be one of the key considerations when deciding whether to enrol in any surgical trial, but particularly one with a placebo control? Take knee arthroscopy for osteoarthritis. It was as long ago as 2002 that the first evidence was published to suggest surgery had limited efficacy over placebo[7]. Whilst the rates of surgery do now appear to be decreasing[8,9], implementation science perhaps still does not work quite as quickly as many would like it to[10]. Nevertheless, such trials have galvanised the orthopaedic community to address these important clinical questions more directly resulting in positive outputs such as the development of national and international clinical guidelines[11,12]. Particularly in the UK, we have seen surgical trialists focus more on pragmatic study designs over the past decade. These are intended to better reflect real-life practices than explanatory trials with very strict inclusion and exclusion criteria. The net result is that they are harder to bat away. More and better surgical evaluation is needed. This needs to be in conjunction with expert surgeons, who nearly all want the best for their patients. Placebo-controlled trials are likely to play an important part in this; however, we should remain hopeful that the day when these designs are no longer needed is not too far away. ■

References

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