Equipoise and the technology curve

RELEVANCE IN THE DESIGN OF SURGICAL TRIALS

Keywords: Clinical trials, Equipoise, Technology curve, Methodology

A. H. R. W. Simpson, I. R. Murray, A. D. Duckworth
Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Elimination of bias is a core element of high quality clinical trials. In addition to selection, detection, attrition, reporting and spectrum bias, a further type of bias has been reported, known as ‘design bias’. This occurs before the trial is begun and is inconsistent with the principle of ‘equipoise’ and has relevance for surgical trials in a different manner to the bias described in drug trials. Equipoise is defined as the ‘even balance of weight or other forces’, or alternatively as an ‘equilibrium’. Equipoise is an important concept in clinical trials, not only from an ethical standpoint but also with regards to feasibility and recruitment on the part of both the clinicians involved and the patients who may be recruited. ‘Clinical equipoise’ exists if there is genuine uncertainty within the expert medical community – not necessarily on the part of the individual investigator – about the preferred treatment.

A clinician or researcher enrolling and/or consenting patients into a prospective randomised clinical trial must believe that the available evidence does not indicate that the new treatment or intervention being studied is either superior or inferior to the existing standard treatment. However, an individual’s equipoise can be altered by personal experience, anecdotal evidence or even by single case studies. Thus the term clinical equipoise is used to reflect the views of the wider medical community, rather than the individual clinician. In order for patients to agree to participate in a clinical trial, they need to be well informed and understand there is equipoise, otherwise this will inevitably result in inadequate recruitment.

The technology curve

When a new treatment is introduced whether it is a new drug or implant, the point of uncertainty within the medical community is not constant and fluctuates with time from the point of introduction. This can be compared with the introduction to other new technologies, such as 3D printing. For these innovations, the uptake of these new devices has been described as the technology life cycle or ‘hype’ curve, which has five phases (Fig. 1).

The technology curve can be adapted to the uptake of medical interventions and follows the levels of evidence of research available, as well as the evolution of data for a given subject area. The first phase is the ‘technology trigger’ when a new intervention appears on the market and there is initial proof of concept data, commonly from the medical company or innovators bringing the product to market. The initial sharp rise in uptake of an intervention is caused by early adopters, followed by a growing number of clinicians using the technology based on positive data from tightly controlled case series, and explanatory/efficacy randomised trials that use strict indications for the intervention, and which are often carried out by experts in the given area. This represents the second phase known as the ‘peak of inflated expectations’.

There is an inevitable decline in use due to a combination of the expansion of indications for employing the intervention in both case series and trials, leading to an inevitable rise in associated complications and poorer outcomes reported in the literature. This results in phase 3 - the ‘trough of disillusionment’. These data are eventually drawn together in the form of systematic reviews and meta-analyses, and lead to the ‘slope of enlightenment’ (phase 4), where the indications and limitations of the intervention become clear. Phase 5 represents the ‘plateau of productivity’ when a ‘steady state’ is reached, the indications for the intervention...
are clear, and the techniques and technology involved has been evolved and adapted as necessary. At this stage, clinical equipoise is less likely to change during the recruitment phase, and is therefore less likely to confound the results of trials comparing the new intervention with the current benchmark. A diverse spectrum of products, ranging from bone morphogenetic proteins and pulsed electromagnetic fields to meniscal transplantation are thought to be following this pattern.

Emerging and established technologies and treatments in orthopaedic surgery can be considered to exist at different points along this curve. For example, emerging animal and exploratory clinical studies have raised expectations that mesenchymal stem cell-based therapies may be used to regenerate bone and cartilage, although such therapies are not yet part of mainstream treatment. An increasing number of clinical trials evaluating the use of platelet rich plasma (PRP) across a wide range of applications have not supported promising initial in vitro and early clinical data. While a number of clinicians have become disillusioned with PRP, it is possible that further analysis of emerging and published literature may reveal particular indications in which such therapies are effective. These new therapies are likely to follow the ‘technology/hype’ curve, whereas others have followed a more damped pattern such as metal-on-metal hip arthroplasties, which has been cited as an example of Scott’s parabola. In some cases, such as the introduction on vitamin C for preventing scurvy, the curve is even more damped (Fig. 2).

**Implications for clinical trials**

The technology curve for a novel product reflects the change in perceived benefit of the clinical community concerning that new treatment, i.e., it reflects the clinical equipoise of the community. During the recruitment phase of a clinical trial it is desirable that clinical equipoise remains constant. Strict inclusion and exclusion criteria are used to achieve this in ‘explanatory trials’, which aim to determine the efficacy of an intervention in ‘ideal
conditions21 and are, by definition, tightly controlled clinical trials. In contrast, pragmatic trials aim to test the effectiveness between an established intervention (the current benchmark) against the new intervention in a setting most representative of day-to-day clinical practice.21 This often results in broader inclusion/exclusion criteria, making the trial more prone to changes in clinical equipoise.

However, even in explanatory trials, a change in equipoise may occur, for example when new interventions are being initially tested and an unexpected adverse event rate becomes apparent on interim monitoring and data analysis.22 If a ‘steady state’ has been reached prior to carrying out a large multi-centre pragmatic trial,23 this will not only give equipoise, but will also inform the investigators which groups of patients should be included, thus establishing robust inclusion and exclusion criteria. If an established plateau ‘steady state’ has not been reached at the time of commencing a pragmatic trial, there is a risk that the intervention being assessed will not be evaluated in the clinical circumstances most relevant to routine contemporary practice.

Therefore, to take into account the effect of changing equipoise during a clinical study, it would be beneficial to monitor the uptake of the technology in a control group that is not in the trial.

This will allow changes that result from the trial to be distinguished from changes that result from the technology life cycle. In addition, appreciation of this curve allows us to introduce treatments in a manner that more rapidly reaches ‘plateau’. This may be by ensuring that treatments are optimised in a pre-clinical phase, or through a more concerted effort to avoid ‘widening’ applications of treatments without robust rationale or preliminary data.

References
1. Mundi R, Chaudhry H, Mundi S, Godin K, Bhandari M. Design and execution of clinical trials in orthopaedic surgery. Bone Joint J 2014;3:161-168.
2. Kleinlugtenbelt YV, Hoekstra M, Ham SJ, et al. Spectrum bias, a common unrecognised issue in orthopaedic agreement studies: do CT scans really influence the agreement on treatment plans in fractures of the distal radius? Bone Joint J 2015;4:190-194.
3. Fries JF, Krishnan E. Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. Arthritis Res Ther 2004;6:R250-R255.
4. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-145.
5. Perry DC, Griffin XL, Parsons N, Costa ML. Designing clinical trials in trauma surgery: overcoming research barriers. Bone Joint J 2014;3:123-128.
6. Katz JN, Losina E, Lohmander LS. DARS Clinical Trials Recommendations: design and conduct of clinical trials of surgical interventions for osteoarthritis. Osteoarthritis Cartilage 2015;23:798-802.
7. Bodalia PN, Balaji V, Kaila R, Wilson L. Effectiveness and safety of recombinant human bone morphogenetic protein-2 for adults with lumbar spine pseudarthrosis following spinal fusion surgery: a systematic review. Bone Joint J 2018;10:4:152-156.
8. van der Jagt OP, van der Linden JC, Waarsing JH, Verhaar JA, Weinans H. Electromagnetic fields do not affect bone micro-architecture in osteoporotic rats. Bone Joint J 2014;3:230-235.
9. Smith NA, Achten J, Parsons N, et al. Meniscal Transplantation and its Effect on Osteoarthritis Risk: an abridged protocol for the MeTEOR study: a comprehensive cohort study incorporating a pilot randomised controlled trial. Bone Joint J 2015;4:93-98.
10. Murray IR, Cresswell M, Petriglian FA, Sos C, Peault B. Recent insights into the identity of mesenchymal stem cells: implications for orthopaedic applications. Bone Joint J 2016;8:96-9:291-298.
11. Singh A, Goel SC, Gupta KK, et al. The role of stem cells in osteoarthritis: an experimental study in rabbits. Bone Joint J 2014;3:32-37.
12. Hogendoorn S, Duijnisveld BJ, van Duinen SG, et al. Local injection of autologous bone marrow cells to regenerate muscle in patients with traumatic brachial plexus injury: a pilot study. Bone Joint J 2014;3:38-47.
13. Ismail HD, Phedy P, Kholinne E, et al. Mesenchymal stem cell implantation in atrophic nonunion of the long bones: A translational study. Bone Joint J 2016;8:287-293.
14. Murray IR, LaPrade RF. Platelet-rich plasma: renewed scientific understanding must guide appropriate use. Bone Joint J 2016;8:9-2-94.
15. Murray IR, LaPrade RF, Musahl V, et al. Biologic Treatments for Sports Injuries II Think Tank—Current Concepts, Future Research, and Barriers to Advancement, Part 2: rotator cuff. Orthop J Sports Med 2016;4:eCollection 2016.
16. LaPrade RF, Geeslin AG, Murray IR, et al. Biologic Treatments for Sports Injuries II Think Tank—Current Concepts, Future Research, and Barriers to Advancement, Part 1: Biologics Overview, Ligament Injury, Tendinopathy. Am J Sports Med 2016 March 29. (Epub ahead of print).
17. Takamura KM, Maher P, Nath T, Su EP. Survivorship of standard versus modified posterior surgical approaches in metal-on-metal hip resurfacing. Bone Joint J 2014;3:150-154.
18. Barber R, Skinner J, Board T, et al; ISCCoMH. International metal-on-metal multidisciplinary teams: do we manage patients with metal-on-metal hip arthroplasty in the same way? An analysis from the International Specialist Centre Collaboration on MOPS Hips (ISCCoMH). Bone Joint J 2016;8:8-B:179-186.
19. Hamilton DF, Howie C, Gaston P, Simpson AH. Scott’s parabola and the rise and fall of metal-on-metal hip replacements. BMJ 2012;345:e3006.
20. Levine M. New concepts in the biology and biochemistry of ascorbic acid. N Engl J Med 1986;314:892-902.
21. Sedgwick P. Explanatory trials versus pragmatic trials. BMJ 2014;349:g6694.
22. Hamid N, Ashraf N, Bosse MJ, et al. Radiation therapy for heterotopic ossification prophylaxis acutely after elbow trauma: a prospective randomized study. J Bone Joint Surg [Am] 2010;1:92-A:2032-2038.
23. Carr AJ, Rees JL, Ramsay CR, et al. Protocol for the United Kingdom Rotator Cuff Study (UKUFF): a randomised controlled trial of open and arthroscopic rotator cuff repair. Bone Joint J 2014;3:155-160.

Funding Statement
None declared

ICMJE conflict of interest
None declared

©2016 Simpson, Murray and Duckworth. This is an open-access article distributed under the terms of the Creative Commons Attribution licence (CC-BY-NC), which permits unrestricted use, distribution, and reproduction in any medium, but not for commercial gain, provided the original author and source are credited.