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EDITORIAL

Equipoise and the technology curve

RELEVANCE IN THE DESIGN OF SURGICAL TRIALS

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A. H. R. W. Simpson, I. R. Murray, A. D. Duckworth

Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

■ A. H. R. W. Simpson, MA(Cantab), DM (Oxon), FRCS(England & Edinburgh), George Harrison Law Professor of Orthopaedic Surgery, Royal Infirmary of Edinburgh, Editor-in-Chief, Bone & Joint Research, 22 Buckingham Street, London WC2N 6ET, UK.

■ I. R. Murray, BSc(Hons), MBChB, MSc, FRCSEd(Tr&Orth), PhD, ECAT Clinical Lecturer and Honorary Specialty Registrar (StR) Trauma and Orthopaedics, Department of Orthopaedics and Trauma

■ A. D. Duckworth, BSc(Hons), MBChB, MSc, FRCSEd(Tr&Orth), PhD, Professor of Orthopaedics and Trauma, Department of Orthopaedics and Trauma, University of Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SU, UK.

Correspondence should be sent to A. H. R. W. Simpson; email: e.vodden@boneandjoint.org.uk

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Elimination of bias is a core element of high quality clinical trials.[1] In addition to selection, detection, attrition, reporting and spectrum bias,[2] a further type of bias has been reported, known as 'design bias'.[3] 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".[4,5]

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.[6] 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

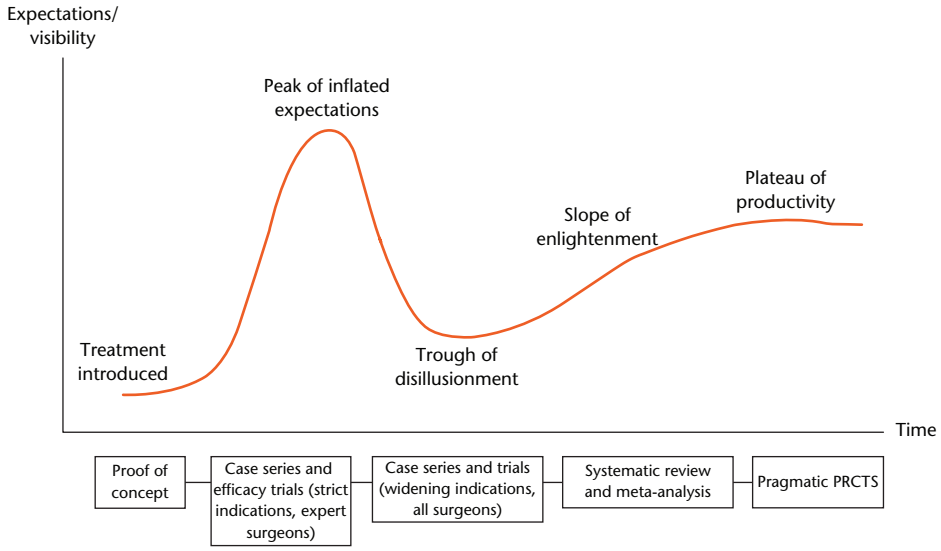

Fig. 1

Technology curve applied to the expectations of emerging treatments in orthopaedic surgery. The levels of evidence of research often available at each phase are outlined.

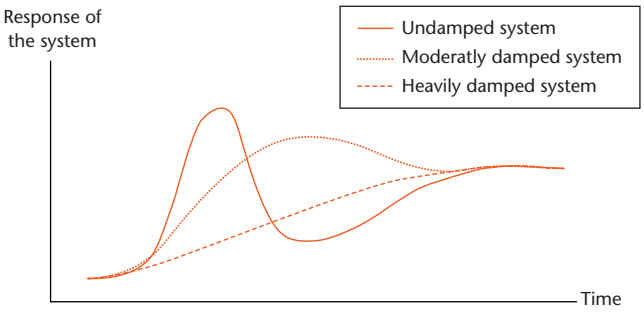

Fig. 2

Graph showing the response of differently damped systems to 'response of the system'. The solid line represents an undamped system, the dotted line a moderately damped system and the dashed line, a heavily damped system. In clinical practice, it has been suggested that the uptake of agents such as platelet rich plasma follow the solid line, whereas others such as metal-on-metal hip arthroplasties follow the dotted line, and vitamin C uptake the dashed line.

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[7] and pulsed electromagnetic fields[8] to meniscal transplantation[9] are thought to be following this pattern.

When a system is perturbed by some agent (or data) it will either return to the established 'steady state' or settle at a new steady state. The path this dynamic system follows depends on how heavily 'damped' the system is (Fig. 2). In relation to medical interventions, the damping of the system (and thus the path the system follows) will depend on a variety of factors including how 'conservative' any group of clinicians and patients are, the marketing of the product to both clinicians and patients, the simplicity of implementing the treatment, and the perceived and reported complications with which it is associated.

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.[10-13] 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.[14-16] 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 joint arthroplasties,[17,18] which has been cited as an example of Scott's parabola.[19] In some cases, such as the introduction on vitamin C for preventing scurvy,[20] 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

conditions'[21] 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.

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ICMJE conflict of interest

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