LEADING ARTICLE

The Randomised Controlled Trial at the Intersection of Research Ethics and Innovation

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Abstract

The randomised controlled trial (RCT) has been considered for a long time as the gold standard for evidence generation to support regulatory decision making for medicines. The randomisation procedure involves an ethical dilemma since it means leaving the treatment choice to chance. Although currently contested, the ethical justification for the RCT that has gained widespread acceptance is the notion of 'clinical equipoise'. This state exists when "there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested"; it is argued that this confers the ethical grounds for the conduct of an RCT. The prominent position of the RCT is being challenged by new therapeutic modalities for which this study design may be unsuitable. Moreover, alternative approaches to evidence generation represent another area where innovation may have implications for the relevance of the RCT. Against the backdrop of the debate around the equipoise principle and some recent therapeutic and data analytical innovations, the aim of this article is to explore the current standing of the RCT from a regulatory perspective.

Key Points

The relevance of the equipoise principle as an ethical justification for randomisation in clinical trials has been contested in recent years.

New therapeutic modalities and new approaches to evidence generation may promote the acceptability of non-randomised data in regulatory decision making.

1 Introduction

The randomised controlled trial (RCT) has been considered for a long time as the gold standard for evidence generation to support regulatory decision making for medicines [1–4]. However, randomisation involves an ethical dilemma that is centred around the conflicting roles of the physician as a

'healer' or 'investigator' [5, 6]. The physician as a 'healer' has an obligation to provide patients with care consistent with professional standards and this appears to conflict with an 'investigator' leaving the treatment choice to chance as required by a randomisation procedure. The ethical justification for the RCT that has gained widespread acceptance came with the notion of equipoise, or more specifically 'clinical equipoise' [7]. According to Freedman's formulation, clinical equipoise exists when "there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested." Proponents of this principle maintain that, if clinical equipoise exists, no participant in an RCT is knowingly given inferior treatment [8]. The relevance of equipoise as an ethical justification for randomisation has been criticised in recent years [6, 8].

The prominent place of the RCT in the evidence generation 'toolbox' is also being challenged by innovations in at least two areas [3]. First, the RCT may be unsuitable for evaluating new treatment modalities such as precision medicine or gene and cell therapies, the latter often referred to as Advanced Therapeutic Medicinal Products (ATMPs) [9–13]. Second, alternative approaches to evidence generation represent another area where innovation may have implications for the relevance of the RCT [14–18]. Against the backdrop of the criticism of the equipoise principle and some recent therapeutic and

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data analytical innovations, the aim of this article is to explore the current standing of the RCT from a regulatory perspective.

2 The Evolution of the Randomised Controlled Trial

Regulatory decision making for medicines has a public health perspective and for its proper functioning robust evidence is pivotal for evaluating causal relationships between medicinal products and health outcomes [19]. Although there is some flexibility, the preferred source of evidence for favourable outcomes is often the RCT [2]. The strength of randomisation is that it likely balances known and unknown confounding factors across experimental treatment groups thereby making them similar at the start of the trial [1, 3, 4]. Therefore, differences in outcomes can with high confidence be attributed to the assigned interventions.

The publication in 1948 of the British Medical Research Council's trial of streptomycin in patients with pulmonary tuberculosis is often cited as the first published RCT [20]. Although the uptake of this study design initially was slow, it successively established itself as the best means to assess the efficacy of an intervention [21]. Early on, RCTs primarily evaluated interventions in infectious disease and these trials assessed large treatment effects in patients at high risk of clinically important outcomes. Hence, the number of patients included in these trials could be kept low. Later, as RCTs evaluated interventions aiming to prevent rare events or having moderate but clinically important effects, the sample sizes of the RCTs grew considerably.

Apart from balancing known and unknown confounders across treatment groups, the RCT study design has evolved over time to include other features that reduced biases and increased the confidence in the evidence [1, 4, 21, 22]. Important improvements of the RCT include allocation concealment, blinding of study participants and investigators in addition to prospective choices of endpoints and better articulation of design estimands. Furthermore, strategies such as stratified randomisation can help avoid unbalanced groups in small studies. RCTs have drawbacks and a common criticism is that multiple inclusion and exclusion criteria may result in selection bias, limiting the generalisability of the results [23, 24]. Moreover, they may be difficult to perform in the setting of rare diseases, and costs may be prohibitive. Interestingly, the RCT has also been found to be useful to research in development economics with the aim of reducing poverty. For their work relying on this methodology, Esther Duflo, Abhijit Banerjee and Michael Kremer were awarded the Nobel Prize in Economics in 2019 [25].

3 The Ethical Dilemma of Randomisation and the Equipoise Principle

The evolution of research ethics in the context of public health has been discussed elsewhere [26].

Although the concept of the RCT had been around for decades, it was in the 1980s that bioethics scholars first defined the core ethical dilemma of the conflicting roles of the physician as a 'healer' or as an 'investigator' [5, 6, 27]. Put in other words, because of the randomisation procedure, patients enrolled are used primarily to provide data that enhance medical knowledge and this is done at the expense of potentially not being assigned the best possible treatment [28]. Some have argued that given this tension between objectives, the interests of the patient must always prevail over the interests of science and society, making randomisation incompatible with the inviolable patient–physician relationship [5]. This stance is at odds with the claims by those who believe it would be unethical not to conduct RCTs to sort out ineffective or toxic interventions [29–31].

Attempts to provide an ethical justification for the randomisation procedure have often involved an examination of the nature of the uncertainty around treatment alternatives. The point of contention has been whether it is the individual physician's uncertainty ('the uncertainty principle') or the collective uncertainty of the medical community ('clinical equipoise') that matters [32–35]. In Freedman's interpretation of 'clinical equipoise', the preferences or beliefs of the individual investigator are irrelevant [7]. Hence, Freedman states the formal conditions under which a trial would be ethical as follows: "at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed. In other words, the results of a successful clinical trial should be convincing enough to resolve the dispute among physicians." Moreover, if a state of clinical equipoise is thought to imply that there is insufficient evidence to suggest that any intervention in an RCT is inferior to the others, a corollary of this would be that all treatment arms are broadly consistent with competent medical care [8]. This would also mean that patients can enrol without having to worry about being disadvantaged, and physicians can refer patients without violating the duty of care. Furthermore, lack of equipoise in situations where no uncertainty exists ensures that no human or material resources are wasted on low value trials. When there is no standard treatment for a condition or when there are doubts about the standard treatment, a placebo control group can be seen as consistent with equipoise.

Some criticism of the equipoise principle centres on the vagueness of the concept [8]. Apart from the problem of

defining who belongs to the 'expert clinical community', demonstrating 'lack of consensus' may also be difficult. If 55% of the experts favour intervention A and 45% intervention B, is this difference still within the limits acceptable for declaring a 'lack of consensus' or should smaller differences be required? Another related problem is that a 'research system' conducting RCTs and embracing the equipoise principle must have a success rate of trials close to 50% over time, indicating that trial outcomes cannot be predicted [36]. If success rates are higher, the system would not be sustainable as physicians and patients would be increasingly reluctant to accept randomised intervention assignments.

There seems to be no systematic investigation of actual success rates of RCTs and it is reasonable to expect that these rates vary across therapeutic areas and over time. In a small study with several limitations, Fries and Krishnan found that all 45 industry-sponsored RCTs in rheumatology had favourable outcomes, suggesting that equipoise was violated [37]. The authors hypothesised that 'design bias', in which extensive preliminary data are used to design studies with a high likelihood of being positive, was the major cause of the asymmetric results. Design bias occurs before the trial is begun and is, according to the authors, inconsistent with the equipoise principle. However, design bias is not inherently unfavourable since it increases scientific efficiency, decreases drug development costs, and limits the number of subjects required, thereby probably reducing aggregate risks to participants.

Fries and Krishnan identified a number of conceptual and ethical issues with the equipoise principle and subsequently proposed two different principles that they believed more appropriately underlie the ethics of enrolment of patients into an RCT: 'positive expected value' and 'exercise of personal autonomy' [37, 38]. For the 'positive expected value', the standard becomes the expected value of outcomes after declining the RCT (usual care) as compared with the average reasonable expected value of outcomes after accepting the trial (i.e. pooling of all the RCT arms). If the latter expected value is larger than the former, the RCT is ethically sound. The second principle, related to personal autonomy, emphasises patients' right to accept or decline being included in an RCT for whatever reason they believe is relevant (e.g. wanting to participate for altruistic reasons despite a negative average expected value).

In addition to sharing some of the aforementioned arguments, Miller and Joffe have criticised the equipoise solution to the ethical dilemma of the RCT because it narrowly places the concern within the doctor–patient relationship and the need for knowledge to inform individual patient care [6]. This focus can be seen as disregarding wider societal interests such as evidence generation for regulatory decision making, in which a public health perspective must be salient.

The authors explicitly argue that "trials of new treatments for life-threatening diseases that violate equipoise are both ethical and necessary for the development of evidence to support health policy decisions made on behalf of populations of patients."

A similar strand of critique maintains that the equipoise principle is a misguided attempt to align clinical research with the norms of clinical practice [8]. Conducting RCTs is ethically different from providing clinical care and these two activities should be kept apart. Clinicians must have the interests of their patients at the centre whereas clinical investigators may perform procedures that provides data but do not necessarily benefit the patients (e.g. biopsies to assess treatment effects), and trials may also involve some level of 'net risk'. Other potential negative implications of the equipoise requirement are that it may discourage the conduct of valuable placebo-controlled trials (in conditions with high placebo response rates) or the too early stopping of trials before obtaining definitive results [39, 40]. Hence, it has been argued that alternative and more relevant frameworks should be applied when assessing the ethical aspects of a traditional RCT and other emerging trial designs [41].

In addition to the principles of 'positive expected value' and 'exercise of personal autonomy', an alternative to the equipoise requirement is the 'net risk framework' [42]. This framework demands that researchers ensure the given trial's social value; reasonably reduce risk to participants; ensure that the risks to participants are justified by potential clinical benefits for them or by the social value of the research; and respect absolute upper risk limits to participants. Moreover, the 'non-exploitation framework' has also been suggested as an ethical justification for randomisation [40]. This latter framework acknowledges the need for balancing the dual ethical obligations of clinical research: the protection of human subjects and the generation of new medical knowledge.

4 New Treatment Modalities

For some time, the pharmaceutical industry has been moving away from its previous 'blockbuster philosophy' aiming to develop products intended for large groups of patients and in this way generate sales [43]. As payers turned increasingly unwilling to reimburse new drugs with only limited advantages over existing therapies, in addition to the increased use of generic drugs, the need for a new business strategy became obvious. Instead, the pharmaceutical industry has focussed on developing products for smaller groups of patients who are likely to respond to a treatment, and so making payers more inclined to reimburse the therapy. While the RCT had a central role in evaluating the small to moderate benefits of small

molecule 'blockbuster drugs', its role in assessing new therapeutic modalities may not be as evident [11].

One example is the concept of precision medicine that has evolved in recent years and typically relates to the use of predictive tools such as biomarkers to select treatments, tailor dosing, or monitor response [10, 13]. In oncology, an improved understanding of relations between various biomarkers and treatment responses has now led to approvals of co-developed treatments and in-vitro diagnostic tests for some malignancies. Cancer is now routinely thought of in a molecular context, and biomarker-centric (i.e., tissue agnostic) rather than histology-centric drug development approaches have been successfully pursued. It is expected that by tailoring treatments to patients' biomarker profiles, larger indications will be split into smaller ones making randomisation impractical.

An RCT may also be inappropriate for ATMPs, which often are administered at one point in time but may have very late effects. Recent regulatory marketing authorisations of some 'single-treatment cures' for life-threatening and previously incurable diseases suggest that with these new treatment modalities a new era of modern medicine has been entered [9, 44, 45]. Development of techniques involving ex vivo gene modification of haematopoietic stem cells (HSC) for autologous transplantation have led to the development and approval in Europe of Strimvelis® (autologous CD34+ cells transfected with retroviral vector containing adenosine deaminase gene) for a rare primary immune deficiency and Zynteglo® (betibeglogene autotemcel) for beta-thalassaemia. A related marketing authorisation was that of Luxturna® (voretigene neparvovec) as a gene therapy for an inherited form of vision loss [46]. The regulatory challenges associated with treatments for very rare genetic disorders have recently been discussed [47].

Other ex vivo gene-modified cell therapies include two chimeric antigen receptor (CAR)-T cell therapies Yescarta® (axicabtagene ciloleucel) and Kymriah® (tisagenlecleucel) against B cell malignancies [12, 48]. For the relapsed or refractory diffuse large B-cell lymphoma (DLBCL) indication, both approvals were based on single-arm phase II trials showing significantly favourable outcomes when compared with historical outcomes. The properties of CAR-T cell-based therapies significantly differ from traditional small-molecule or antibody-based anticancer drugs [49–51]. Differences include aspects such as toxicity profile and dose-exposure relationships, all of which may have implications for clinical trial design. However, it appears as if traditional approaches to characterising the pharmacokinetic and pharmacodynamic properties of a therapy sometimes can be adapted to describe these gene-modified cells with a capability to proliferate in vivo [52–55].

5 Novel Methods of Evidence Generation

Despite obvious similarities, it has been suggested that the 'brand of science' and the approaches to evidence generation are somewhat different in academic versus regulatory settings [56, 57]. In the latter setting, the quest for decision-relevant evidence is at the centre and new data sources and study designs that could replace or complement the traditional RCT have been put forward as being worthy of further evaluation [16, 22].

Among new approaches to evidence generation are those prompted by the continued growth of predictive biomarkers in oncology. Alternative study designs that have received growing interest in recent years are trials governed by a master protocol, defined as one overarching protocol designed to answer multiple questions and establishing certain common aspects of the substudies [58, 59]. Included under this broad definition of a master protocol are three distinct entities, which may in some cases involve randomisation: umbrella, basket, and platform trials. The objective of the umbrella trial is to study multiple targeted therapies in the context of a single disease, whereas the objective of the basket trial is to study a single targeted therapy in the context of multiple diseases or disease subtypes. To study multiple targeted therapies in the context of a single disease in a perpetual manner, a platform trial allows therapies to enter or leave the platform based on a decision algorithm [58]. The flip side of the efficiency of trials governed by a master protocol is that these complex study designs have raised challenging regulatory and statistical questions, especially the control of multiplicity in confirmatory trials [59].

There are now some signs that investigators are willing to consider the use of external controls such as historical placebo controls or real-world data (RWD) [14, 17, 60, 61]. The approach is generally accepted in rare disease indications to reduce the burden to the limited number of patients concerned and to accelerate clinical development. A wider use of historical placebo controls in trial design and analysis is still in its infancy but could potentially minimise risks, cost and inconvenience by reducing enrolment time, decreasing participant number and accelerating trial completion. From a research ethics perspective, a major advantage would be a reduction of the number of patients exposed to inactive placebo. However, the considerable heterogeneity in trial design and patient characteristics pose major challenges to placebo arm data reuse.

RWD turned into real-world evidence (RWE) could have a larger role to play in regulatory decision making [50, 62, 63]. Proponents of RWD analyses argue that the applied analytic methods now have matured and that major biases often can be ruled out [15]. Examples of

methodological advances include cohort studies of new users, active comparators when possible, propensity-score adjustment based on pre-treatment confounders, biologically informed exposure effect windows and induction periods informed by biology in addition to a range of pre-definable sensitivity analyses. Promotion of non-randomised analyses of databases as a rapid source of RWE about the effects of treatments has been criticised as a false solution to the problems caused by the perceived bureaucratic burdens imposed on randomised trials [64]. Finally, if non-randomised data constitute a substantial part of the evidence in a marketing authorisation application, enhanced post-authorisation evidence generation based on RWD may be necessary [65].

6 Discussion

When an RCT is conducted for evidence generation to support regulatory decision making, a central ethical tension is that between the welfare and safety of the trial population and regulators' need for data relevant for regulating therapies to be used by a large future target population. While there certainly are opportunities to alleviate this tension, it may not be possible to entirely eradicate it. By explicitly acknowledging the tension [66], it becomes possible to reason around positions on a continuum where at one end the interests of science and society never can prevail over those of patients, as contrasted with those who believe it can in certain situations [5, 6].

Apart from the criticism of the relevance of the equipoise requirement discussed above, there are reasons to believe that true equipoise will be an increasingly rare situation, thereby further undermining its importance. Given the high costs of conducting RCTs, there are strong incentives for the pharmaceutical industry to try to improve the predictive values of pre-RCT data analyses, thereby increasing the overall success rate of initiated RCTs (i.e. introducing 'design bias'). Over time, scientific progress in various areas will likely aid in this pursuit.

A factor that could impact the feasibility of conducting RCTs would be if patients are becoming increasingly reluctant to participate. Participation in a clinical trial requires to some extent that patients are willing to be exposed to some risk and discomfort in exchange for some satisfaction from having contributed to medical science with potential wider health benefits. If such altruistic attitudes become rarer and replaced by more individualistic 'zeitgeist', recruitment to RCTs could be hampered. One could contemplate whether current movements advocating patients' access to medicinal products outside clinical trials ('Right-to-Try') is reflecting a more general unwillingness of patients to participate in RCTs [67, 68]. Expanding access outside trials may delay the generation of data needed to make evidence-based decisions about product approval and use of new drugs in a larger population.

The difficulties of getting patients and physicians to participate in RCTs during the recent COVID-19 pandemic could also be seen as reflecting an increased reluctance to participate in RCTs [68–70]. The rapid spread of this serious disease accompanied by dire economic consequences initially spawned a deluge of clinical trials. Even when equipoise prevailed, a sense of urgency in this unprecedented public health crisis gave rise to concerns that the conduct of traditional RCTs was not feasible or could not be morally justified. Hence, in the pursuit of potential treatments or vaccines, basic scientific principles were often disregarded and numerous substandard trials (e.g. small, open-label, non-randomised trials) investigating similar hypotheses risked duplication of efforts and inconclusive results. London and Kimmelman therefore admonished that "the exigencies of crisis situations like global pandemics require exceptional steps to combine efforts, divide labour, and triage out low-value and duplicative research" [70]. The difficulties of interpreting the equipoise principle in the context of COVID-19 vaccine trials have been noted by some researchers [71].

7 Conclusions

For the foreseeable future, the strength of the RCT appears unquestionable when measuring small to moderate treatment effects in large populations. It remains to be seen to what extent the standing of the RCT will be affected by the debate around the equipoise principle or a changing willingness of patients to participate in randomised research. Although alternative kinds of evidence in some situations already are accepted by regulators, new therapeutic modalities in combination with new approaches to evidence generation may promote the acceptability of non-randomised data [11].

Declarations

Conflict of interest The author is an external medical advisor to the Malta Medicines Authority and has no conflicts of interest that are directly relevant to the content of this article. The views expressed are the personal views of the author.

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Consent to participate Not applicable.

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