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Realistic approach trials in clinical research

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ABSTRACT

Pragmatism in clinical trials arose from concerns that many trials did not adequately inform practice because they were optimized to determine efficacy. [1] Because such trials were performed with relatively small samples at sites with experienced investigators and highly selected participants, they could be overestimating benefits and underestimating harm. This led to the belief that more Realistic trials, designed to show the real-world effectiveness of the intervention in broad patient groups, were required. Medical researchers, both academic and commercial, must deliver health care innovations (drugs, devices, or other interventions) that are safe, beneficial, and cost-effective, and they must identify the subgroups for whom the innovation will provide the greatest benefit relative to risk. A broad view of an intervention, including approaches to improve its effectiveness, is critical. An ideal trial includes a population that is relevant for the intervention, a control group treated with an acceptable standard of care, and outcomes that are meaningful, and it must be conducted and analyzed at a high standard of quality. Realistic trials frequently include complex interventions, sometimes consisting of several interacting components [2] and often involving the skills and experience of one or more health care professionals to deliver the intervention for example, surgeons, physiotherapists, or cognitive behavioral therapists.

In this article, a definitive exposition of the methods used for Realistic trials is not described. Rather, we explore the contexts in which a Realistic design is most and least attractive and identify the strengths and limitations of and challenges in implementing realistic approach based trials.

WHAT IS A REALISTIC APPROACH TRIAL?

Schwartz and Lellouch1 proposed a distinction between explanatory trials, which confirm a physiological or clinical hypothesis, and realistic trials, which inform a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice. The original PRECIS (Realistic–Explanatory Continuum Indicator Summary) tool [3] attempted to clarify the concept of pragmatism and provided a guide, scoring system, and graphical representation of the Realistic features of a trial. Features included the recruitment of investigators and participants, the intervention and its

delivery, follow-up, and the determination and analysis of outcomes.

CHALLENGES TO PRAGMATISM AND POTENTIAL SOLUTIONS

Recruitment of Study Participants

Realistic trials require that participants be similar to patients who would receive the intervention if it became usual care, which may be unknown for new interventions. Participation in trials has fallen over time; for example, among persons without established disease, a lower than 10% rate of response to a screening invitation is common. The fact that volunteers participating in certain types of trials are often healthier than persons in the general population (the "healthy-volunteer effect") and competing recruitment from other trials, particularly in academic centers, undermine attempts to achieve uniformity. Financial incentives associated with recruitment to industry trials can substantially affect recruitment to less-well-funded academic trials. Minimization of inclusion and exclusion criteria and reduction in the number and complexity of study visits, study procedures, and questionnaire burden are important but are likely to be only partial measures to increase participation in trials.

Informed consent is a barrier to unselected participant recruitment. To guarantee that everyone who is eligible is included, this requirement would need to be waived. In some contexts, it is possible — subject to ethics approval — to conduct trials without consent or with modified consent.

A trial involving 6394 participants was conducted to assess the effect of emergency short-term use of antiseptic-coated versus antibiotic-impregnated versus plain latex catheters with regard to the primary outcome of the incidence of symptomatic urinary tract infection for which an antibiotic was prescribed within 6 weeks. [28] After the initial admission, prospective consent was obtained according to usual practice from participants who were undergoing elective procedures, and retrospective consent was obtained in cases of emergency admissions, thus maximizing the uniformity of the findings. Routine use of antibiotic-impregnated or antiseptic-coated catheters was not supported by the results of this trial.

Such trials assessing a policy that is going to be implemented in any event arguably offer the greatest potential for Realistic trials, since they require no individual consent while allowing for some degree of control of ecologic changes in care that may be happening simultaneously.

Recruitment of Investigators

Trials need investigators to take responsibility for recruitment, treatment, and follow-up of participants. Many health care professionals outside of academic centers do not participate in clinical trials, in part because of the time pressures associated with their clinical duties or because they do not consider research to be a key component of their job. Hence, the investigators involved in a trial will often not encompass the heterogeneity of practice that is present in usual care. In contrast, investigators across Sweden who were contributing to a national quality registry were included in the TASTE trial. [26]

Good trials include a variety of investigators with a representative mix of experience appropriate to the intervention under study. Likewise, if an intervention involves substantial technical expertise, then that intervention should be delivered by practitioners with an adequate throughput of patients to enable them to maintain their levels of expertise. This is particularly true in surgical trials, in which complex surgery is increasingly delivered in high-volume centers. This creates a conflict in the design of Realistic trials.

Establishing a critical mass for efficient trial conduct is crucial. Providing incentives to investigators is important in the face of increasing demand to deliver clinical services more efficiently, since research takes additional time beyond standard clinical care. The development of clinical networks and establishment of disease-specific research communities is one way forward. Another would be to give credit to health professionals for research as a key component of professional work plans. In the United Kingdom, these approaches, along with the creation of a national network of clinical-trial units that have been registered as fit-for-purpose, has improved the recruitment and retention of clinical investigators and methodologists working together to deliver trials by avoiding the common approach of setting up a network to deliver a single trial that is then not reused for future trials. [35]

The Intervention and Its Delivery within the Trial

A trial with blinded interventions is not fully Realistic. In Realistic trials, the randomly assigned group is commonly not masked. Efforts that are made to minimize biases in open trials include focusing outcomes on major events, such as death and emergency hospital admissions. The CRASH trial involved a placebo control and blinding; nonetheless, it had many Realistic elements. In many situations, the need to avoid reporting bias will override purist Realistic considerations, making blinding the optimal approach. In complex intervention trials, in which blinding the intervention is often impossible, it is usually possible to blind the assessment of outcomes. [36] In any trial, the advantages and disadvantages of blinding must be considered; blinding is particularly important when the reporting of key end points or safety events could be biased in an open trial.

In Realistic designs, the intervention should be delivered as in normal practice, by staff with typical experience and with the use of routinely available equipment. The MI FREEE trial [27] tested a treatment policy by assessing drugs within a class, but decisions with regard to the specific drug and dose within that class were left to the investigators. A Realistic trial often investigates a general approach to treatment rather than dictating the specific details of that approach.

The Nature of Trial Follow-up

The unobtrusive collection of trial outcomes is attractive; it reduces the burden on the participants and investigators without introducing artificial aspects to follow-up. Such a strategy is most feasible in health care systems with reliable and accessible electronic health records that capture the events of interest. This might be achievable where there is a unified electronic health care record, but it is at present challenging in many countries. The High-STEACS trial, [31] which has no trial-specific data-collection visits at all, illustrates the potential of this approach. Likewise, MI FREEE [27] followed participants through a health care database, with outcomes determined algorithmically. An attractive alternative to trials in which electronic health records are used can be found in trials of alternative interventions involving patients who are already enrolled in disease-specific or intervention-specific registries that incorporate detailed patient phenotypes and long-term follow-up data. This framework provides an efficient and low-cost opportunity for conducting Realistic trials (e.g., the TASTE trial [26]).

The Nature, Determination, and Analysis of Trial Outcomes

Realistic end points should be important to patients — for example, major life events (e.g., death or emergency hospital admission). Realistic trials are also often large, identify limited treatment effects, and assess the safety of under investigated interventions in unselected populations. They are also often simple and minimize trial procedures and data-collection requirements.

Symptoms, disability, and quality of life are commonly key outcomes in Realistic trials. Unlike major life events, signs and symptoms and quality-of-life measures are seldom recorded consistently in routine practice and require patient visits or completion of questionnaires. Realistic trials often use mailed questionnaires or Web-based forms to avoid the need for study visits. Such methods reduce costs but can lead to substantial amounts of missing data, which creates challenges for analysis and interpretation. Offering participants alternative methods of providing responses, including mobile phones and other handheld devices, might increase response rates. Realistic trials can provide long-term safety data for unselected populations. However, there are challenges in interpreting safety data, which are often self-reported or subject to delays in availability, incompleteness, and coding variability associated with national registries. Explanatory trials can also present interpretational challenges with respect to adverse events, because data on events are sometimes not collected after discontinuation of the randomly assigned treatment, which introduces bias into statistical analyses.

It has been argued that Realistic outcomes should not need adjudication. We believe this is a quality issue rather than a Realistic issue. If the quality and consistency of outcome ascertainment can be improved by adjudication without affecting normal patient care, then surely that is desirable.

INDIAN CONTEXT OF REALISTIC TRIALS

India being the developing country, many of the patients involved in the trials are not aware of what they are taking and do not have medical knowledge in assessing the investigational drug they are taking through. There are a very few Indian patients who willingly and by thoroughly knowing participate in the clinical trials and 80 % of the individuals participating in clinical trials are not literate about the study they are part of and they would follow the investigator which they generally does [23]. Also there is need for the Indian set up of clinical trials to be happened with evidence based trial conduction with fair practices, making understand every patient about the trials, its implications on them with respective adverse events and also the benefits and risks associated with them. It is of great importance and emergency for Indian realistic clinical trials to be made understood by every citizen for the betterment of the society and also for the betterment of the India medically.

DISCUSSION

Drug development involves the cautious introduction of a new substance into human participants, with gradual evaluation in patients who have the relevant disease, in order to evaluate safety, early evidence of efficacy, and appropriate doses for future evaluation. The developments of nondrug interventions should, but often do not, involve proof-of-concept or pilot studies to tailor the intervention and evaluate its acceptability. Many such interventions also require selection of a dose, such as duration and intensity of physiotherapy or physical training.

Some trials, by virtue of their context and the intervention studied, are more Realistic than others. Trials that test a low-cost intervention, pose few risks to participants, or are applied at a cluster level will almost automatically be more Realistic in nature or easier to organize in a Realistic fashion than will trials with high-cost, complex interventions. Health care systems with comprehensive electronic records or condition-specific registries offer excellent environments for Realistic, low-cost trials.

A natural environment for clinical research might involve the integration of research and clinical practice through the development of "learning health care systems," as advocated by the Institute of Medicine, [36] with relevant clinical and patient-reported outcome data collected by default. However, some have questioned whether this is feasible, given the clinical delivery pressures within today's health care systems.

Pragmatism should not be synonymous with a laissez-faire approach to trial conduct. The aim is to inform clinical practice, and that can be achieved only with high-quality trials. A better approach is to assess how a trial design adequately addresses the main objectives of the trial, including its ability to inform clinical practice.

CONCLUSIONS

Some trials need not be forced to be Realistic, and others will naturally have realistic features because of the nature of the intervention and the health care context in which the trials are conducted. Very few trials can be fully Realistic. Trials of truly novel interventions can be game changers without being particularly Realistic. No single trial, Realistic or otherwise, is likely to answer all potential questions about the value of any health care technology. A Realistic approach to pragmatism would be to adopt the features of Realistic trials whenever feasible and sensible and when such features do not compromise trial quality and the ability to answer the clinical question of interest.

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