Chapter 12
Pragmatic Trials

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The Case for Pragmatic Trials

Reports from the Institute of Medicine, the Federal Coordinating Council for Comparative Effectiveness Research, and the Congressional Budget Office cite the lack of evidence to support a given course of treatment as a significant obstacle to improving the quality and lowering the cost of health care [1–4]. Also recognized is the inability of current models of evidence generation to meet this need fully. Widespread gaps in evidence-based knowledge result from a paucity of randomized clinical trials of comparative effectiveness [5]. Reliable evidence of this type is needed to improve health-care quality and to support the efficient use of limited resources [5].

Pragmatic Trials: One End of the Spectrum

Randomized controlled trials have traditionally been viewed as a dichotomy, either as effectiveness trials or as efficacy trials [6]. Current thinking places trials on a spectrum between "explanatory trials" which attempt to test causal hypotheses and "pragmatic trials" which attempt to help clinicians choose between treatment

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options [7]. Explanatory trials focus on the efficacy of an intervention under "ideal conditions." In contrast, pragmatic trials are designed to determine the effects of an intervention under the usual condition(s) in which it is delivered in a health-care setting [7]. Few trials are purely pragmatic or explanatory and, as a result, we are "left with a multi-dimensional continuum rather than a dichotomy where a particular trial may display varying levels of pragmatism across [many] dimensions" [7].

Explanatory trials are a necessary component of the research process as they are required for the introduction of novel therapeutics into clinical care. Most pre-approval trials of health-care interventions are on the explanatory end of the trials spectrum [8] and are intended to demonstrate benefit under ideal circumstances in an ideal patient population. Failure in this mode, where there is the greatest perceived chance of success, warrants future effectiveness trials unnecessary [8]. If, however, efficacy is demonstrated, an effectiveness trial may be helpful in determination of the utility of the intervention to a more generalized patient population being treated in everyday practice. Thus, demonstrated success in an efficacy trial is an important prerequisite for progression to an effectiveness trial [9].

Pragmatic trials assessing the effectiveness of an intervention in a setting that resembles usual care informs health-care practitioners and health-care planners on the best treatment options for their patients [10]. A key issue for pragmatic studies is the balance between internal validity (reliability and accuracy of the results) and external validity (generalizability of the results). Explanatory trials seek to create an environment that will maximize internal validity by rigorous and stringent control of factors that may obscure or diminish the ability to measure the utility of an intervention. (e.g., inclusion criteria, exclusion criteria, and protocol-defined treatments). Pragmatic trials seek instead to maximize external validity so that the trial results can be widely generalized and hence integrated into clinical care. Pragmatic trials must balance internal and external validity such that treatment effects are preserved, but are observed across a greater diversity of patients treated by processes extant in the more relaxed clinical environment [10].

Karanicolas et al. [11] point out that the usefulness and generalizability of results of pragmatic trials are dependent on the context (i.e., the distinctive features of the trial setting, population, and investigative staff) in which the trial was performed. Consider a clinical trial comparing web-based self-help for problem drinking where inclusion criteria required the participants to have internet access [8]. Treweek and Zwarenstein [8] point out that this is likely less an issue in the Netherlands where internet penetration was close to 88% in 2007, than in Poland where internet penetration was just under 30% in the same year. Thus, the context of a pragmatic trial will directly impact both interpretation of the effectiveness of the intervention and its external validity. Balance of internal and external validity and the context of the trial are inextricably linked design issues for pragmatic trials.

Key Design Features of Pragmatic Trials

Features of both explanatory and pragmatic trials are presented in Table 12.1. Gartlehner et al. [12] and Thorpe et al. [7] independently built tools to help investigators assess the degree to which their trial is pragmatic or explanatory to assure that the design is optimized for the intended purpose. These tools focus on the design features in Table 12.1 and help investigators understand the design features that contribute to the validity balance. Below, we focus on design decisions that enhance external validity or internal validity.

External validity, or generalizability, is maximized by limiting exclusion criteria and keeping inclusion criteria broad. Enrolled subjects will then more closely resemble the heterogeneity of the general patient population as reflected by their comorbidities and medications usage patterns. External validity is further improved when the treatment protocol allows for flexibility in the management of the subject by allowing the health-care provider the freedom to deviate from the study protocol

Table 12.1 Comparison of pragmatic and explanatory trial designs

	Pragmatic trials	Explanatory trials
Objective	To compare the effectiveness of health care and delivery	To assess the efficacy of the intervention
Setting	Routine clinical care	Research/experimental care
Patient population	Heterogeneous to mimic real world; little or no selection	Homogeneous to minimize bias; highly selected
Investigators; stakeholders	health-care providers; CEO and CFO of health-care institution	Scientists and clinical trialists; sponsor
Interventions	Complex intervention; applied flexibility with treatment regime; mimics routine care	Standardized intervention; protocol strictly enforced; regime often simpler than pragmatic trials
Outcomes	Direct impact on clinical care and practice guidelines (e.g., QOL; function)	Impact understanding of action; indirect (or no real) impact on clinical care (e.g., biomarker, range of motion)
Design issues	• High external validity • Low internal validity • Randomized • Large sample Size • Unblinded • Not placebo controlled • Long-term follow-up	• Low external validity • High internal validity • Randomized • Large sample Size • Blinded • Placebo controlled • Short-term follow-up
Sponsor	health-care systems; ACOs; NIH	Pharmaceutical industry; NIH; government
Funding	$$$	$$$
Example trial	Comparative effectiveness of two diuretics for the prevention of MACE outcomes (CSP 597)	Investigational new drug application for a third-generation oral hypoglycemic agent

[Based on data from Ref. 8 & 14]

if it is in the best interest of the patient. This freedom is "fundamentally pragmatic and has to be permitted if the results are to be accepted as generalizable" [10].

Internal validity is instead maximized by features such as restriction of enrollment and randomization and blinding. Restriction as operationalized in inclusion and exclusion criteria assures a tightly controlled and highly selected homogeneous study population that reduces bias and confounding by comorbid conditions, treatment indication, etc. Randomization further ensures that the remaining diversity of the patient population is equally distributed between treatment allocations by balancing known and unknown baseline confounders. The assumption of equal distribution is not absolute, and further control may be required in the secondary analyses of the trial. Finally, blinding of participants and/or the providers helps ensure that opportunities for information bias are reduced.

Analysis of Pragmatic Trials

Analysis of pragmatic trials follows the "intent-to-treat" principle (i.e., once randomized always analyzed) where study groups are analyzed according to the treatment group to which they were *originally* assigned. Intention to treat analysis becomes problematic for pragmatic studies when subjects' treatments are changed in the course of usual care to that of the non-assigned study arm. The downstream result of this is an observed dilution of the treatment effect. Although dilution effect is often viewed as a weakness of pragmatic trials, as it is for explanatory trials, it does reflect the expected results when the treatment is used in the "real-world setting" and, as such, is informative for clinical care. Explanatory trials, on the other hand, impose protocol-defined restrictions on patient care that more successfully maintain treatment fidelity and reduce the dilution effect, at the expense of perhaps misrepresenting the benefit when the treatment is applied to a non-study setting.

Strengths and Limitations of Pragmatic Trials

Strengths

The greatest strength of pragmatic trials is the evidence of effectiveness in everyday clinical contexts [13]. Explanatory trials are often restricted in their patient populations under study and in the treatment regimens followed. For this reason, the results are often poorly translated into clinical care. The broad inclusion criteria and the flexible treatment guidelines of pragmatic trials ensure greater generalizability of the results to real-world settings. Economic impact and quality of life are also better studied in a pragmatic trial [14]. The results will contribute to a better understanding of the acceptability of interventions to patients, providers, and health-care systems.

Limitations

Pragmatic trials focus on the clinical and comparative effectiveness of interventions in routine care settings where considerable variability in patient care can result in obscuring the effect attributed to the treatment under study [14]. Another important consideration is that for practical reasons pragmatic studies often lack blinding as a design feature, thus increasing the risk of bias and decreasing internal study validity. Importantly, the reduced interval validity of pragmatic studies is balanced by increased external validity that allows study results to generalize better to normal clinical settings [14]. Pragmatic trials conducted in the clinical care ecosystem have design limitations based on what trial related activities can and cannot be carried out in this setting given time commitment and cost considerations. Kent and Kitsios [9] argue that extrapolating the results of broadly inclusive pragmatic trials to the care of real patients may often be as problematic as extrapolating the results of narrowly focused explanatory or efficacy trials. For example, a null explanatory trial will provide definitive evidence that a therapy is not of value while a null pragmatic trial will not provide similar definitive evidence. As discussed above, dilution of the effect may reduce the observed difference in effect such that a treatment proven successful in an explanatory trial has no demonstrated utility in a pragmatically designed study. Moreover, the relaxed inclusion and exclusion criteria of pragmatic trials result in greater heterogeneity of baseline risks of enrolled subjects and difficulty in interpreting the trial result for a "typical" patient [9]. Instead, a negative effectiveness trial will underscore the caution that physicians must use when generalizing the results of a positive efficacy trial. Kent and Kitsios emphasize: "that while both types of trials yield useful information, pragmatic trials do not provide a more accurate measure of the "true" treatment effect, since the concept of a true effect is fundamentally illusory. While extrapolating the results of efficacy trials to the care of individual patients in the real world can be problematic, and requires careful physician judgment and decision-making, the same is unfortunately true for the results of effectiveness trials. Unless more attention is paid to these underappreciated limitations, pragmatic trials run the risk of driving harmful policies" [9].

Conclusion

Pragmatic studies are designed to address an evidence gap in health-care delivery. Such trials often have a mixture of efficacy and effectiveness outcomes and should carefully balance issues related to internal and external validity. Care should be taken in interpretation of pragmatic trials. Pragmatically designed trials have a host of limitations that are often underappreciated, and extrapolating results from such limited studies can lead to the implementation of "harmful" policies.

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