NIH Collaboratory Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Data Monitoring in Pragmatic Clinical Trials: Points to Consider

Data monitoring is needed for pragmatic clinical trials (PCTs). However, the design, intent, and operational features of PCTs may influence how monitoring obligations should be met. Two articles have described considerations for data monitoring in PCTs,[1,2] and a template charter for PCT data monitoring committees (DMCs)[3] has been proposed. Additionally, the NIH Health Care Systems Research Collaboratory convened a workshop regarding deliberations about the possibility of early stopping of PCTs based on emerging trial data for futility, safety, or efficacy.[4] Collectively, these resources suggest several general points to consider for data monitoring in PCTs.

Points to Consider	
Composition of DMCs	PCTs raise a number of issues that are distinct from those in explanatory trials. Appropriate monitoring may therefore necessitate including individuals with particular expertise who can address certain characteristics of specific PCTs, such as the use of novel study designs, and the fact that these trials are embedded in clinical care systems. Relevant expertise may include those with PCT experience, experts in informatics, clinicians and/or healthcare operational leaders, and patients.
Health systems records data	If study outcomes are ascertained from health system records, the study is dependent on the quality and reliability of those systems and the accuracy and timeliness of the data entered into them. Any changes by the health system to the record system or to a specific patient record during the course of the study may affect the integrity of the study data.[2]
Study design and statistical analysis	• If study outcomes are ascertained from health system records, delays in access to health system data (such as would occur when data are accessed only at prespecified intervals) may impede the feasibility of interim analyses.[2] • Sites for PCTs may be more heterogeneous than in an explanatory trial with respect to both patient characteristics and practitioner or institutional behavior. Consequently, DMCs may need to pay closer attention to site-specific data when considering the generalizability of emerging results.[1]

Prepared by: Stephanie Morain, PhD, MPH, and Pearl O'Rourke, MD, for the Ethics and Regulatory Core
Version: June 28, 2021

Points to Consider	
	• As statistical power is influenced by within-cluster correlation of outcomes, monitoring enrollment may need to include monitoring of cluster size and within-cluster correlation.[2]
Monitoring adherence	• Unlike in explanatory trials, in which monitoring participants' adherence to their prescribed intervention is standard, in a PCT, monitoring for adherence may reduce the pragmatic nature of the trial. Nevertheless, information on adherence is sometimes needed to interpret trial results (See Futility below). • There is arguably special importance for monitoring for differences in adherence across control and intervention arms, particularly for cluster-randomized trials, given the potential for differential changes in healthcare delivery across sites, which will impact the interpretation of results.[5]
Futility	• The failure of a PCT to find a difference in treatment effects may result from a failure of intervention adherence/fidelity, rather than true equivalence of treatments or inadequate sample size. Therefore, in deliberating about futility determinations, DMCs might need to consider not only the primary outcome of effectiveness but also adherence.[1] • While futility determinations are typically based on the primary outcome of an explanatory trial, in PCTs there may be value to learning not only about intervention effectiveness but also about challenges and successes with the implementation of the intervention. Consequently, DMCs s might need to consider whether secondary outcomes that may be related to implementation should also be considered—even if emerging data from a PCT indicate that it may be futile in terms of the primary outcome measure. Accordingly, DMCs should be prepared to evaluate secondary aims.[4]
Safety	• PCT data are often extracted from health system records at prescribed intervals or simply at the end of the trial. Therefore, the data needed to ascertain a safety signal may be both limited and not available in real time. Further, the frequency or intensity of data collection may differ between study arms. DMCs should consider both the availability of data and its balance across study arms when evaluating potential decisions about early stopping for safety. In some cases, this may require sites to modify their standard clinical follow-up practices to standardize data collection across sites.[1,2,4] • The nature of the treatments being compared may influence obligations related to early stopping for safety. For some PCTs,

Points to Consider	
	the study arms being compared both reflect treatments in wide use (e.g., A versus B trials). Consequently, DMCs should weigh any apparent signal of an unknown adverse event against prior evidence.[2] However, other PCTs compare a standard treatment to a standard plus enhancement approach (e.g., A versus A+ trials). For these trials, DMCs should consider monitoring for potential adverse consequences related to the "plus," for which there may be less data on safety compared with standard treatments.[4]
Efficacy	Trial leadership, sponsors, and DMCs should agree at the outset of a trial on the extent and type of evidence that would serve as grounds for early termination. Issues to consider include both the relevance of secondary aims in making this determination and whether the threshold for concluding that one treatment is superior to another should be greater for a PCT compared to an explanatory trial.[4]
Describing DMC experiences	While there are substantial descriptions of DMC deliberations regarding explanatory trials, this is not the case for PCTs. Accordingly, finding ways to describe and disseminate experiences with PCT DMCs should be encouraged in an effort to improve practices and policies.

References

1. Ellenberg SS, Culbertson R, Gillen DL, et al. Data monitoring committees for pragmatic clinical trials. *Clin Trials*. 2015;12(5):530-6.
2. Simon GE, Shortreed SM, Rossom RC, et al. Principles and procedures for data and safety monitoring in pragmatic clinical trials. *Trials*. 2019;20(1):690.
3. Ethics and Regulatory Core. Data Monitoring Committee Charter for Pragmatic Clinical Trials: Template. August 22, 2017. Available at: https://dcricollab.dcri.duke.edu/sites/NIHKR/KR/Data%20Monitoring%20Committee%20Charter%20Template.pdf. Accessed June 28, 2021.
4. Ethics and Regulatory Core. Early Stopping in Pragmatic Clinical Trials: Workshop Summary. March 29, 2021. Available at: https://dcricollab.dcri.duke.edu/sites/NIHKR/KR/Early%20Stopping%20in%20Pragmatic%20Clinical%20Trials%20-%20Workshop%20Summary.pdf. Accessed June 28, 2021.
5. Ellenberg S, Sugarman J, Zatzick D. Data and Safety Monitoring: Introduction. In: Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials. Bethesda, MD: NIH Health Care Systems Research Collaboratory. Available at: https://rethinkingclinicaltrials.org/chapters/design/planning-data-safety-monitoring/planning-data-safety-monitoring-introduction/. Updated October 30, 2020. DOI: 10.28929/039.