DATA MONITORING COMMITTEES FOR PRAGMATIC CLINICAL TRIALS

Susan S. Ellenberg, Ph.D.
University of Pennsylvania
October 16, 2015

Penn Medicine

DATA MONITORING COMMITTEE

A data monitoring committee (DMC) is a group of experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial

PRAGMATIC CLINICAL TRIALS

- A type of clinical trial characterized by
  - Broad eligibility criteria
  - Flexibility in applying interventions
  - Primary outcome of clear clinical significance
  - Participation of "non-specialist" investigators
  - Reduced intensity of participant follow-up
  - Reduced attention to adherence to protocol
  - Strict intention-to-treat analysis of primary outcome

SOME BACKGROUND

- DMCs have been established for some clinical trials since the late 1960s
- DMCs became more frequently used in the late 1990s
  - Increased awareness in early AIDS era
  - NIH policy documents and FDA guidance
- DMC operations can be quite varied, depending on type of trial and preferences of trial sponsor and investigators
- Increasing interest in pragmatic trials has led to discussion of special issues in the conduct of such trials

DMCs FOR PRAGMATIC TRIALS

- What are the special issues for DMCs for pragmatic clinical trials?
- (ARE there any special issues for DMCs for pragmatic trials?)

COMMITTEE CONVENED TO ADDRESS THESE QUESTIONS

- Effort of the Bioethics/Regulatory component of the NIH Collaboratory and PCORnet projects
- Committee members
  - Richard Culbertson
  - Dan Gillen
  - Steve Goodman
  - Suzanne Schrandt
  - Maryan Zirkle
  - Susan Ellenberg
- Gina Uhlenbrauck served as facilitator

PROCESS

- Committee members discussed issues via teleconference
- Each member agreed to draft section
- Further discussion via telecons and emails
- In-person meeting in January 2015 to refine drafts and put everything together
- All committee members contributed to addressing comments and questions of reviewers
- Final publication: October 2015, *Clinical Trials*

ISSUE 1: DO PCTs NEED DMCs?

- All clinical trials require some monitoring of interim data
- General guidelines for requiring a DMC apply to pragmatic trials
  - Trials in which participant safety requires regular review of comparative safety and efficacy data
  - Trials intended to have substantial public health impact
- Since pragmatic trials will typically be addressing questions intended to impact health practices, an expert oversight group will be important for most PCTs

ISSUE 2: WHAT GETS MONITORED?

- Traditional trials: monitor data on safety, efficacy, and quality of study conduct
- These are important in pragmatic trials also
- Possible special issues in pragmatic trials
  - Study outcomes
  - Protocol adherence
  - Eligibility
  - Design factor in cluster randomized trials

ISSUE 2: WHAT GETS MONITORED?

- Study outcomes
  - PCTs may be more likely to include subjective outcomes as primary or key secondary endpoints
  - PCTs may be less likely to incorporate central adjudication of outcomes
  - DMCs will have to recognize that data may be more variable than in more restrictively designed trials

WHAT GETS MONITORED?

- Protocol adherence
  - A basic tenet of PCTs is to evaluate treatments as they would be given in practice
  - This means no great effort to promote, or even monitor, adherence to protocol
  - DMCs typically consider monitoring study quality as one of its mandates; may be uncomfortable making recommendations based on observed treatment effects without any sense of how effectively interventions are being administered
  - If adherence is very poor and there is no apparent treatment difference, 2 possibilities:
    - Treatment will be ineffective in general practice
    - Protocol not sufficiently clear to investigators and participants

DMCs AND PROTOCOL ADHERENCE

- Should a DMC ignore data on protocol adherence in a PCT? Should these data not even be reported?
- Poor adherence could lead to safety issues in some studies
- Important to distinguish between
  - Lack of adherence as reflecting how a treatment would be used in practice
  - Lack of adherence as reflecting insufficient understanding of trial on part of investigators and/or participants
- DMCs need to pay some attention to this issue
- May be particularly important to review adherence data by site, to assess need for re-training

ELIGIBILITY

- PCTs may more frequently conducted in unblinded manner to generate "real-world" answers
- This could lead to increased early dropout due to dissatisfaction with treatment assignment
- Imbalance in ineligibility rates by treatment arm could suggest some dropouts are being miscategorized as ineligible
- Would be important to avoid excluding "ineligible" patients from analysis if this is the case; DMC should monitor these rates

ISSUE IN CLUSTER TRIALS

- For cluster-randomized trials, design often used in pragmatic trials, also important to monitor the "design factor"
  - Intra-cluster correlation coefficient (ICC)—the extent to which results within a cluster will be more similar than results across clusters—is a component of sample size calculation
  - Typically, hard to estimate ICC from prior data—estimates used to design trial may be way off
  - Interim estimates of ICC important to see whether study will have expected power

ISSUE 3: PARTICIPANT FOLLOW-UP

- Pragmatic approaches to follow-up may create challenges for DMCs
- Follow-up information will likely be derived from electronic health records (EHRs) in some trials which may be updated on different schedules if different systems are used
- Follow-up frequency may vary by institution according to local policies
- Interim comparisons will be more difficult without standardized follow-up schedules

ISSUE 4: DATA ANALYSIS

- Analytical issues
  - Precision of estimation
  - Cluster randomization
  - Decentralized analysis
- Philosophical issues
  - Early termination criteria

INTERIM MONITORING STRATEGY

- Early termination for efficacy
  - Since PCTs will be designed to influence practice, could be argued that early termination criteria should be extremely stringent
  - Will be important to ensure that DMC and trial leadership are in agreement on criteria
- Early termination for futility
  - When studies compare two "standard-of-care" regimens, questionable whether early stopping for futility should be considered at all
  - As with efficacy, DMCs and trial leadership must have common understanding of criteria for early termination

DATA ANALYSIS

- Precision of estimation
  - PCTs will typically study heterogeneous populations
    - Patient characteristics
    - Background supportive care
    - Approaches to delivering study interventions
  - Stratification/adjustment for prognostic factors may be especially important to help control variability of effect estimates

DATA ANALYSIS

- Use of cluster designs
  - Many PCTs currently underway with NIH collaboratory or PCORI funding randomize clusters rather than units
  - Analysis of such trials requires accounting for intra-cluster correlation
  - Differing practices among clusters will have to be accounted for in interim analyses
    - Example: minimally restricting usual practice may mean patients in different clusters are followed on different schedules

DATA ANALYSIS

- De-centralized analysis
  - Privacy concerns may preclude merging data from multiple EHR systems at a central site
  - In such cases, interim analyses may need to be done separately for each site, with summary data only delivered to central statistical group
  - Such arrangements will raise challenges in terms of timeliness of data, quality control and assurance that all analyses have been conducted in identical manner

ISSUE 5: DMC COMPOSITION

- DMCs typically require both clinical and statistical expertise
- Other areas of knowledge and experience are often valuable (eg, bioethics)
- Sometimes (more so in government-sponsored trials) representative of affected community
- Will DMCs for pragmatic trials require different types of expertise?

DMC COMPOSITION

- Clinical and statistical expertise needed
- Will probably be more common to include patient representative
  - PCORI-funded studies require patient partners as members of research teams
  - Studies aimed at questions intended to influence clinical practice may particularly benefit from patient insights
- Expertise in medical informatics may be desirable for some PCTs
  - Use of electronic health data
  - Complex database linkages
  - Natural language processing

SUMMARY

- Most aspects of DMC operations in PCTs will be similar to DMC review more generally
- Most PCTs will probably benefit from an independent DMC
- A few areas may warrant special attention by DMCs for PCTs
  - Accounting for increased heterogeneity of study populations
  - Ensuring that design factor for cluster designs has been reasonably well estimated
  - Accounting for potential site differences in data extracted from EHRs
  - Criteria for early termination
  - Need for patient perspective in most trials
  - Need for medical informatics expertise in some trials