Data and Safety Monitoring in Pragmatic Trials

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Outline

- Distinguish specific questions
- For each question:
  - Describe goals and process of monitoring
  - Describe what's different about pragmatic trials

What are we monitoring?

GroupHealth

From 1998 NIH policy:

“Evaluate the progress of interventional trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.”

What are we monitoring?

- Viability – Are we recruiting enough of the right kind of people?
- Fidelity – Are treatments/programs being implemented or delivered adequately?
- Adverse Events – Are study treatments or procedures causing harm?
- Safe Practice – Are study staff providing safe and appropriate care in high-risk situations?
- Benefit – Do we already know which treatment is superior?

Viability

- Why– Will the sample be adequate to answer the question?
- What – Monitor overall rate of recruitment and characteristics of those recruited
- How – Compare recruitment rate and sample characteristics to assumptions used for power calculations
- When – Throughout recruitment period – but especially early in recruitment.
- Who – Can assess without knowing treatment assignment. Study team, funding agency, and DSMB can see same data.

Viability – What's different in pragmatic trials?

- If recruitment is more automated (i.e. less dependent on provider referral), rate may be more predictable.
- But – if recruitment is limited to specific practice settings, increasing recruitment may be more difficult.
- Generalizability may be more important.

Fidelity / Adherence

- Why– Will the “separation” between study arms allow a valid test of the study question?
- What – Summary measures of quality or fidelity of treatment delivery, focusing on key differences between study arms.
- How – Compare “separation” to assumptions used for power calculations; Examine contamination or cross-over.
- When – Throughout intervention period.
- Who – Depending on design specifics, DSMB and study team may or may not be able to see the same data.

Fidelity/Adherence – What's different in pragmatic trials?

- Need to be clear whether study question primarily concerns efficacy, effectiveness, or implementation.
- Tension between maximizing "separation" and generalizability.

Individual Adverse Events

- Why– Identify unanticipated harms of study procedures or treatments (signal detection).
- What – Case reports of adverse events, with enough detail to determine attribution.
- How – Determine if individual events could be attributable to study procedures or interventions.
- When – Throughout intervention period.
- Who – May require breaking of blind, usually limited to DSMB.

Individual Adverse Events – What's different in pragmatic trials?

- Treatments are established and risks often well known.
- Attribution of "relatedness" for individual events may be more difficult (if not impossible).
- Must often consider competing risks (especially for complex interventions and/or patients with co-occurring conditions).
- Should we just stop doing this?

Rates of Adverse Events

- Why– Compare rates of anticipated harms of study procedures or treatments (hypothesis testing).
- What – Rates of specific and/or overall adverse events.
- How – Compare rates (with appropriate caution for multiple comparisons and sequential testing).
- When – Throughout intervention period.
- Who – Requires breaking of blind, usually limited to DSMB.

Rates of Adverse Events – What's different in pragmatic trials?

- Treatments are established and risks often well known.
- Must often consider competing risks.
- Longer follow-up periods: Must consider differences in timing for benefits and adverse events by intervention condition.
- What if the "adverse event" is the study outcome?

Safe Practice

- Why– Study staff assume some level of clinical responsibility, creating the potential for conflicting interests.
- What – Reports regarding care provide in specific scenarios of concern.
- How – Evaluation of care provided against community standards or standards established by protocol.
- When – Throughout intervention period.
- Who – May require breaking of blind, usually limited to DSMB.

Safe practice – What's different in pragmatic trials?

- Study staff often less directly involved in care.
- Information regarding concerning situations may be delayed and limited in detail.

Benefit

- Why– Accelerate access to more effective treatments (and minimize exposure to less effective ones).
- What – Interim data regarding study outcome(s).
- How – Sequential testing in comparison to a boundary or stopping rule.
- When – Throughout follow-up period (but less important early on).
- Who – Requires breaking of blind, usually limited to DSMB.

“Detectable Difference” threshold (for power calcs and interim analyses)

- General principle: What is the difference we would not want to miss?
- For efficacy trials: Clinically meaningful difference at the patient level - What difference would be large enough to affect a clinical decision?
- For pragmatic trials: Actionable difference at the population level - What difference would be large enough to prompt implementation or change in policy?

Why stop? – Levels of ethical obligation

- Strong – How would stopping now affect people enrolled in this trial?
- Moderate – How would stopping now affect other people with this health conditions?
- Weak – How would stopping affect the broader community (e.g. in terms of other uses for limited resources)?

What to stop?

Distinguish between:

- Not enrolling new participants
- Stopping delivery of a study treatment
- Disclosing results and allowing choice

Always depends on the specifics of the situation

DATA AND SAFETY MONITORING IN PRAGMATIC TRIALS: PART 2

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WHAT PCTs NEED A DMC?

- An independent DMC is usually needed when
  - Treatments and/or disease are high risk
  - Safety assessment will require comparison of outcomes by treatment group
  - Credibility of results particularly important
- Most PCTs will probably need a DMC
  - Will address issues that affect large populations
  - May be intended to influence practice
  - Results may be subject to intense scrutiny
- But some may not
  - If no safety imperative to compare outcomes during trial, may not need a DMC

WHAT DATA NEED TO BE MONITORED?

- Should adherence to assigned treatment be monitored?
  - NO: pragmatic trials seek real world answers, so we want to see what happens in actual practice
  - YES: important to interpretation of findings; need to disentangle adherence issues from true treatment effects
- Should a DMC make recommendations for ways to improve adherence?
  - NO: again, need real world answer
  - YES: lack of adherence may be due to incomplete understanding of intent of study

WHAT DATA NEED TO BE MONITORED?

- In traditional trials, data quality is typically monitored by the DMC
- One aspect of data quality is care in entering only participants who meet inclusion criteria
- In some cases, when trial is not double-blind, "ineligible" could be euphemism for "participant doesn't want this treatment," or "I don't want this participant to get this treatment"
- Important to monitor ineligibility rates to see if treatment groups differ

WHAT DATA NEED TO BE MONITORED?

- 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
  - Interim estimates of ICC important to see whether study will have expected power

WHO SHOULD BE DOING THE MONITORING?

- Traditional DMC members: clinicians, biostatistician(s)
  - Sometimes bioethicists
  - Sometimes patient representatives
- Pragmatic trials may need special expertise
  - Patient reps may be more important
  - May need community-based in addition to academic clinicians
  - For trials deriving data from electronic health records, may need someone with expertise in medical informatics

PATIENT REPRESENTATIVES

- Included on many DMCs for NIH trials
- Would seem especially valuable for trials with patient-centered outcomes
- Unique insights
  - Evaluating participant burden
  - Balance of potential benefits and harms
- What type of patient representative?
  - Scientist who is also a patient?
  - Leader in patient advocacy organization?
- Need for all DMC members to have a basic understanding of clinical trials methods, and appreciate importance of confidentiality

MEDICAL INFORMATICS

- Pragmatic trials may increasingly derive data from electronic health records (EHRs)
- May involve more than one EHR system
- Different systems may have different schedules for updating files
- Other "new" types of data, such as biosensors and activity monitors
- Complexities in such data may require input of someone with more "high tech" expertise

CHALLENGES IN MONITORING INTERIM DATA

- Operational procedures may not be fully standardized across sites, to best reflect "real world" practice
- This could mean in some cases that data will be collected on nonuniform schedules
- Interim comparisons of study outcomes will need to take this complicating factor into account

MAKING DECISIONS ABOUT MONITORING

- The DMC and the study sponsor and investigators need to reach consensus about monitoring approaches prior to study start
- Consideration of the dimensions of "pragmatic-ness," as can be done from the PRECIS criteria, may facilitate these decisions