Designing, Conducting, Monitoring, and Analyzing Data from Pragmatic Randomized Clinical Trials: Proceedings from a Multi-stakeholder Think Tank Meeting

Trevor Lentz, PhD, PT, MPH
Lesley Curtis, PhD
Frank Rockhold, PhD

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

U.S. FOOD & DRUG ADMINISTRATION

FRAMEWORK FOR FDA'S

REAL-WORLD EVIDENCE PROGRAM

December 2018

www.fda.gov

Pragmatic Clinical Trials

Randomized trials designed to inform clinical or policy decisions by determining the real-world effectiveness of an intervention

- Compared to other study designs that generate RWE
  - Use of randomization

- Compared to RCTs
  - Generalizable (i.e., clinical and policy/regulatory decision-making versus efficacy)
  - Clinical endpoints of interest to patients and clinicians versus surrogate RCT outcomes
  - Compare the intervention of interest to other active therapies in use

Acceptability of RWD/RWE in the scientific community

Quality and completeness of clinical data repurposed for research application to meet regulatory standards

Availability of data to capture primary/secondary endpoints

Consistency of measurement/ heterogeneity of data across systems

Misalignment between traditional culture of conservatism and monitoring capabilities in pragmatic trials

Adequacy of risk-based monitoring

Timeliness of adverse event reporting

Fidelity to study interventions

Effective collaboration with and among health systems

Limited examples of PCT "success" in informing regulatory decisions

Study Design and Methodological Considerations

"A properly designed PCT begins with a research question that is precise and clearly stated"

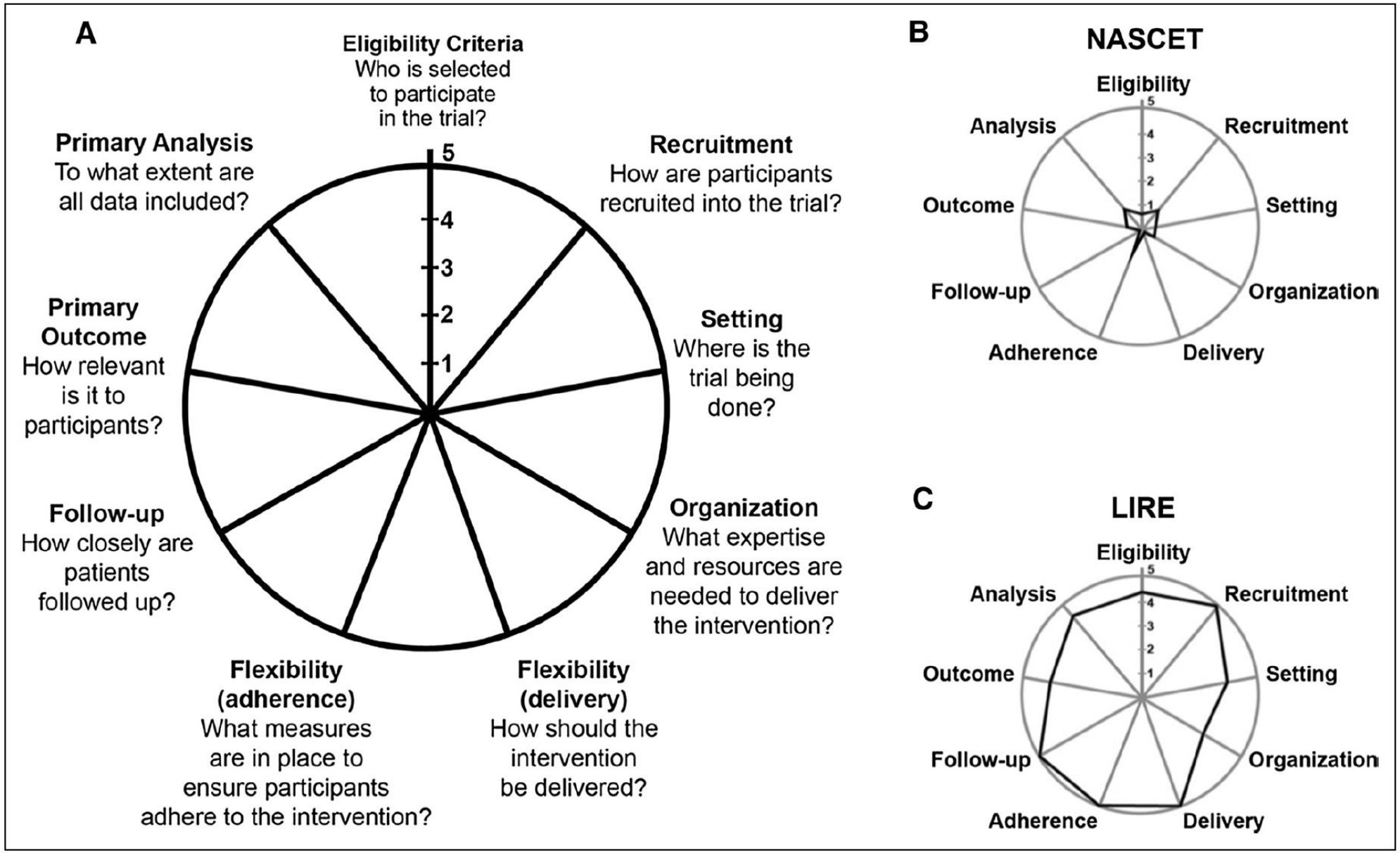
"Study protocol adherence is necessary for any rigorous trial, and is consistent with the goals of a PCT"

Study Design and Methodological Considerations

- Pragmatism in study design is not a binary concept

Purely explanatory elements (created to establish efficacy in idealized settings)

Purely practical elements (created to establish effectiveness in the real world)


A
Eligibility Criteria
Who is selected to participate in the trial?
Recruitment
How are participants recruited into the trial?
Setting
Where is the trial being done?
Organization
What expertise and resources are needed to deliver the intervention?
Flexibility (delivery)
How should the intervention be delivered?
Flexibility (adherence)
What measures are in place to ensure participants adhere to the intervention?
Follow-up
How closely are patients followed up?
Primary Outcome
How relevant is it to participants?
Primary Analysis
To what extent are all data included?
5
4
3
2
1
B
NASCET
Eligibility
Recruitment
Setting
Organization
Delivery
Adherence
Follow-up
Outcome
Analysis
C
LIRE
Eligibility
Recruitment
Setting
Organization
Delivery
Adherence
Follow-up
Outcome
Analysis

Reducing Bias

- Randomization, blinding, standardized outcome assessment, adjudication criteria, audits

  Example: Provider blinding may be infeasible or discouraged altogether in PCT designs

  - Could hinder ability to make therapeutic decisions and manage patients
  - Dearth of guidance in the literature on how to mask treatment allocation and whether it is even necessary in PCTs

Group (i.e., Cluster) Randomization

Important considerations for group randomized trials:

- Balance of baseline covariates and group sample size through stratification or constraints in allocation

- Account for variance inflation due to correlations in outcomes within clusters – may require larger sample size

Informed Consent

- Waiver of consent

- Electronic consent
  - ADAPTABLE study

Best Practices for Data Quality and Completeness

Data Provenance - Understand where data originate, as well as why and how data were collected

- Provides insights on their reliability and meaningful use for research and regulatory applications.

Best Practices for Data Quality and Completeness

- Embed streamlined **Electronic Data Capture (EDC)** modules with succinct eCRFs into the EHR so trial data are automatically collected

  - Potential to improve the cost and efficiency of PCTs
  - Requires early strategic agreements
  - Should begin with a minimal set of core data elements

Selecting Data Sources

- Select based on suitability to address specific questions
- A single data source may not be sufficient, hybrid data solutions may be necessary, which can involve linking EHR data, medical claims, PGHD, or other sources.
- Using hybrid data sources requires longer planning phases and more complex cost distributions than single-source collection.

Event verification

- Investigators may encounter situations in which they cannot confidently verify individual events, or two sources give different outcomes.
  - *Example*: EHR and administrative claims data

- Develop decision rules, or a hierarchy of what is considered closest to the truth, for resolving discrepancies by considering what is most accurate for individual data elements.

Best Practices for Data Quality and Completeness

STUDY DESIGN

Designs close to standard of care can reduce the missing data

Limit number of assessments to what is needed for capturing primary endpoint

DATA COLLECTION/ MONITORING

Minimize patient burden for data collection

Identify response device (e.g., computer, mobile device, hardcopy) likely to be most desirable to participants, and consider multiple response device options as necessary and as the budget allows.

SITE-LEVEL SELECTION & TRAINING

Evolve the role of clinical operations staff to focus on data science and informatics

Provide training to sites and patients so they clearly understand why they should continue in a study

Evolution in Study Monitoring

- Variability in data quality, gaps, and availability delays can hamper timely ascertainment of adverse events (AEs).

- Important implications for studies where safety is a primary endpoint (e.g. cardiovascular outcomes trial for a diabetes drug)

Risk-Based Monitoring

- The FDA encourages the development of centralized study monitoring plans that take advantage of modern clinical trial technologies and innovations.

  - **Risk-based monitoring (RBM)** - responding to predefined indicators of risk to patient safety, data integrity, or trial conduct and evaluating data trends that should trigger in-depth evaluation of trial activities

Risk-Based Monitoring

- Uncertainty surrounding the appropriate level of rigor for RBM and a poor collective sense of safety risks in PCTs → limited the uptake of RBM and contribute to cautious monitoring and reporting.

- Collaborate with technology and data partners to develop and share adaptive learning strategies utilizing RWD sources.

- Human oversight of monitoring systems will remain a key component of PCT excellence.

Data Monitoring Committees and PCTs

- Will data be adequate and timely to allow the DMC to accept responsibility for safety monitoring?

- Oversee test runs of data extractions and/or linkages from all complex data streams involved to determine if these systems are adequate.

Data Monitoring Committees and PCTs

- Unique randomization schemes in PCTs also present challenges.

Example: Cluster-randomized trials

1. How to manage inter-site differences in harms or benefits?
2. Does the estimate of intra-cluster correlation used in the trial design remains accurate to appropriately power the study?
3. How to manage site differences in reporting approaches?

Data Monitoring Committees and PCTs

- Experts in informatics, data science, and measurement
- Informatics scientist with expertise in devices that collect PGHD (i.e., wearables or mobile applications) (as applicable)
- Experts with knowledge in deriving novel biomarkers from continuous real-time monitoring devices (as applicable)
- Patient representatives

Ask precise questions
and select the appropriate level of pragmatism in study design to answer the question

Optimize data quality
by design of the trial

Data capture should focus on primary endpoints
to maximize probability of trial success and minimize operational costs.

Innovate on data capture mechanisms
to improve quality, completeness and patient centeredness

Promote adherence to study protocol,
which is not inconsistent with the goals of a pragmatic trial

Evolve clinical trial operations staff
to focus on data science and informatics

Investigators, sponsors, regulators, and health care systems should not only collaborate, but share learning experiences openly and widely,
especially if those experiences can inform better study development in earlier stages.

Duke Clinical Research Institute

FROM **THOUGHT LEADERSHIP**
TO **CLINICAL PRACTICE**