National Institute of Diabetes and Digestive and Kidney Diseases

A Pragmatic Approach to Better Trials

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The Embedded Pragmatic Clinical Trial

- Goal: Provide generalizable effectiveness data about an intervention that is tested where patients receive usual clinical care
- Implementing Quality improvement in health systems
  - Education/training
  - Operations expertise
  - Hard EHR modification
  - Real time data reporting
  - Buy in from the healthcare ecosystem
  - May require modifications to supply chains and staffing schedules
  - Ongoing monitoring for unanticipated bottle necks and low performers; root cause analysis to identify solutions for process re-engineering
- PCT are at higher risk for failure when the goals of research and operations do not align

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Go, No Go Decision:
Indications for stopping a trial early

- Futility
  - Enrollment failure
  - Significantly lower event rate that impacts power
  - Intervention fidelity (uptake failure)
  - Intervention is ineffective
  - New information on intervention that discounts its benefit or suggests harm
- Safety/harm
- Efficacy/effectiveness
  - Overwhelming effectiveness
  - Unexpected inferiority (intervention causes harm instead of expected benefit)

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Data Monitoring in Pragmatic Trials

- Data quality of real world data
  - Non-adjudicated data from EHR, claims, and reports from treating clinicians leads to less data accuracy, more missing data
  - outcome/safety endpoints may not be uniformly ascertained across sites, delayed reporting (ie EHR extraction)
  - Missing data, data noise

1) Power
   - Enrollment, retention, cross-over
   - Separation (effect size):
     - Measure of real world adherence/fidelity
     - Failure to adhere will lead to no treatment effect
   - Event rate
   - Clusters
     - Lower or imbalanced ICC can decrease power
2) Preferential, non-random bias (unblinded study)
   - Compare intervention vs control: rate and reason
     - exclusion, approached, consent, withdrawal
   - Baseline characteristics
3) Safety
   - Delayed reporting of SAE events ascertained from EHR/claims

Ellenberg et al. Clin Trials 2015

Fidelity and Adherence in PCT

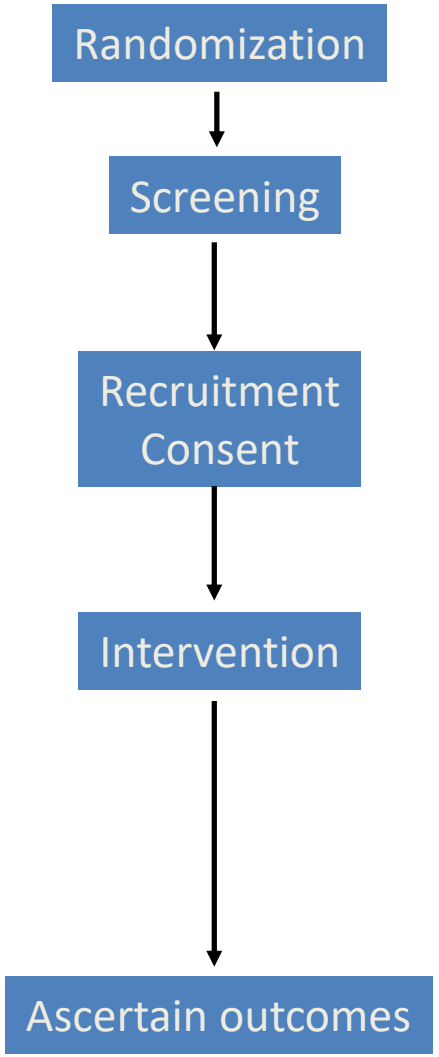
- Adherence to the intervention is less tightly controlled by the research team in PCT
- Will the study achieve adequate “separation” between the study arms to statistically detect a difference in outcomes?
- Design consideration: over power trials to protect against lower uptake of the intervention

The Power of the Blinded Study

- Double blinding
  - Mitigates performance and ascertainment bias
  - Cornerstone for preserving internal validity in traditional trials
- In pragmatic trials, blinding often is not possible
  - Intervention is embedded in usual practice
  - Intervention is delivered by healthcare providers without research training
  - Capacity to maintain standardization, fidelity, and careful control is diminished without site-level research infrastructure
- An unblinded trial assumes healthcare workers and patient are in equipoise about the two treatment groups

Eldrige et al. BMJ 2009

Potential bias when dieticians and patients are not blinded to treatment



- Differential application of inclusion/exclusion criteria

- Differential vigor and messaging during recruiting
- Different consent forms for each group
- Patient preference for one group: difference in enrollment rate and patients who enroll

- Performance bias by both patient and dietician
- Patient attrition or cross-over if not assigned to their preferred group
- Differential enthusiasm for providers to implement intervention
- What happens if a breaking study claims one group is superior?
- What happens if new payment incentives change management globally?

- Differential reporting of outcomes (especially if patient or healthcare provider reported)

Can We De-risk PCT's?

- Embedding trials in clinical practice increase the study's complexity
- New trials can uncover early and unanticipated "signals" that suggest problems
- AHRQ approach to the QI process
  - Engage and communicate with stakeholders
  - Small scale demonstration projects to test and refine
  - QI is an iterative process
- It is OK to fail: Should we see the first 10-20% enrolled as a pilot trial to learn from the data and re-engineer the protocol?

CAHPS Ambulatory Care Improvement Guide, AHRQ. May 2017

Pausing trials: Some Pragmatic Tips

- Have robust and persuasive data to support the decision
- Base the decision on the totality of data, over individual metrics
- “Burden of proof”: clear and convincing (highly and substantially more likely true than untrue)
- Prepare Investigators, DSMB, and sponsors for impending futility. Ideally, stopping a trial should not come as a surprise decision
- Investigators are not blinded to DSMB members. Stopping your Colleague’s trial can be seen as bad etiquette with possible professional repercussions. DSMB hesitancy.
- A bioethicist can frame key issues from a moral perspective to our patients:
  - Is it ethical for healthcare providers and patients to continue contributing effort to a trial that is unlikely to answer the question they were told the trial would provide?
- It’s not personal, but it sure feels that way to the Investigators

The End

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Strategies to mitigate bias in screening, recruitment, and consent

- Randomize after recruitment/consent

- Masked individual from outside site conducts the screening, consent, and enrollment
- Waiver of informed consent
- Same consent form must be given to all patients even if they know what group they have been assigned
- Promote scripted consent processes with neutral messaging
- Grassroot patient/dietician input to identify unrecognized language that could augment preferences

Eldrige et al. BMJ 2009

Strategies to mitigate contamination during trial

- Minimize information in consent while maintaining ethical transparency
  - Patients who are aware of alternative treatment are more prone to switch
  - More likely if both interventions occur in the same clinic:

    "patients talk to patients", "dieticians talk to dietician"
- Cluster randomize by clinic (preferred) or by healthcare provider
  - Physically cohort patients and providers to a single intervention
  - Minimize interaction of patient and providers between clusters
- Ongoing patient and dietician engagement
  - Emphasize importance of maintaining fidelity in the setting generating trial results that could improve their care in the end
- External blinded adjudication of outcomes

Other strategies

- Propensity score: Use post-hoc to biostatistically adjust for patient and provider preferences
- Pilot trial: Identify unexpected sources of bias to inform protocol amendments
- Practice and healthcare system ”buy in” is a must
- Ask the right research question: There are only a handful of interventions that can successfully tested in a pragmatic study design