DSMB Roles in Pragmatic Trials: NIMH Progress & Challenges

Galia Siegel, Ph.D., NIMH/Office of Clinical Research
Anna E. Ordóñez, MD, M.A.S., NIMH/Office of Clinical Research
Scott Kim, MD, Ph.D., NIH/Department of Bioethics
Kate Comtois, Ph.D., MPH, University of Washington/ Department of Psychiatry and Behavioral Sciences

July 28, 2017
Acknowledgements

• Drs. Kate Comtois & Scott Kim

• Pam Shell & Gene Kane (NIMH Human Research Protections Branch Chief and Deputy Branch Chief)

• Dr. Jane Pearson (NIMH Program Officer)

• Drs. Greg Simon & Doug Zatzick (Collaboratory PIs of NIMH-funded studies)
Overview

• Introductions, Background & Overarching Considerations
  ■ Galia Siegel & Anna Ordóñez

• Post-randomization Consent and Pragmatic Trials
  ■ Scott Kim

• Safety & Adverse Event Reporting
  ■ Kate Comtois

• Going Forward/Lessons Learned
  ■ Galia Siegel & Anna Ordóñez
NIMH Extramural DSMBs

• NIMH
  - 5 Standing Boards
  - Independent oversight bodies
  - NIMH Staffing
    - NIMH DSMB Administrator
    - NIMH Study Team Liaison to the DSMB

• Reviewing 3 Pragmatic Trials in Health Care Systems
  - SPOT/PI Greg Simon
  - TSOS/PI Doug Zatzick
  - SUAY/PI Rob Penfold
NIMH DSMB Pragmatic Trial Experiences

- Study Designs
  - Modified Zelen Design (SPOT)
  - Stepped Wedge Cluster Randomized Design (TSOS)
  - Large & Complex Trials
Implications of Designs for Consideration of:

- Human Subjects
  - Risk/Benefit Assessment
  - Waivers/Alterations of Consent
  - Privacy/Confidentiality
  - Standard of Care & Practice within Health Systems
  - Safety Monitoring & Reporting

- Data Integrity
  - Sources of Variability
  - Recruitment & Enrollment
  - Statistical Plans
Post-randomization Consent and Pragmatic Trials:

Implications for Investigators, IRBs, and DSMBs

Scott Kim
Department of Bioethics
NIH Clinical Center
Outline

• Waivers of informed consent in pragmatic RCTs

• NIMH example: SPOT trial

• Varieties of post-randomization consent designs explained

• How to understand the asymmetry between two arms of RCT
  • IRBs and DSMBs may need a broad new framework for reviewing these studies?
Increasing use of waivers of informed consent in large pragmatic RCTs

• Research IC and pragmatic imperative: in the ‘real world’ of clinics, no lengthy IC is used
  • Increasing frequency of waivers in large comparative effectiveness RCTs (e.g., HEAT PPCI, HeadPoST)

• FDA will now allow waiver of IC for qualifying RCTs (21st Century Cures Act)

• Post-Randomization Consent design is one example within this trend
NIMH example: **SPOT**  
(Suicide Prevention Outreach Trial; PI: G. Simon)

- Comparison of 2 low risk interventions with usual care for suicide prevention
- Patients who have SI on a **clinical** measure
- Randomization first; contact and IC with intervention arms only
- Outcome source: medical and public records. No other study measurement.
- N about 20K

- Extra 9-10 months of IRB review time; prolonged discussions with DSMB about design, and about how to monitor study
- Suggests a need to better understand and to better communicate the implications of post-R consent designs
Post-Randomization Consent Variations

Common Theme
• Randomization of eligible subjects precedes informed consent from the intervention arm participants

Variations
• Amount of communication and interaction prior to randomization

• Could be part of a cohort observational study (see Trials within Cohorts, or Cohort Multiple RCT designs), but not necessarily (Relton et al)
Rationales for Post-R consent

• **Subject perspective:**
  • less burden and less unnecessary info;
  • lower likelihood of disappointment in some trials
  • More realistic consent sequence—mimics real life (one does not get consent for two possible outcomes of a test ahead of time in usual practice of medicine)

• **Researcher perspective:**
  • At least for control arm, perfectly mimics ‘real world’ & 100% participation rate
  • Resources needed for usual IC procedures reduced by 50%
  • potential for higher recruitment in intervention arm (depends...);
  • ‘If IC for intervention can mimic usual ‘clinical consent,’ more ‘pragmatic’ and also able to assess ‘naturalistic’ uptake of intervention arm
Zelen consent

• No prior broad consent of any kind

• Must rely on waivers for all research aspects involving patients
Simple Broad Consent

• Some form of broad consent for research use of data collected for health care purposes.
  • VERY Broad: Could be part of entering a clinic or a health system
  • Less Broad: more focused, e.g., disease domain or types of research specified

• Based on idea that randomization *per se* does not need consent, as long as it does not involve actually changing course of events.

• Q: what are the reasonable expectations of patients re ‘broadness’ of permission?
’Just in Time’ Consent (Vickers et al)

• Two stage consent
  • First stage:
    • Discuss that fact that there may be RCTs
    • Permission for: randomization, contact for intervention group, use of data only for usual care group
  • Second stage:
    • Approach randomized to intervention and traditional IC for RCT

• Most patient-centered of the post-R designs, in that main focus is on reducing burdens and disappointment.
• Best suited when usual care options are poor
Which is the correct way to picture the design?

All Patients Randomized

VS

Experimental intervention

Usual intervention

All Patients

Selected Randomly

Usual clinical decision pathway

Experimental intervention
Post-R consent not appropriate in some situations

• Identifying eligible patients should not create an ethical obligation on the researcher.
  • E.g., in QI studies, identifying first patients receiving substandard care; cannot simply leave the control to ‘usual care’

• Randomization itself cannot be packaged with alteration in course of patient management, EVEN IF everyone is randomized to a ‘standard of care’ treatment (as in so called “standard of care” RCTs)
Questions that need more attention

• Why not apply TWO review pathways for post-R consent studies?
  • One for the intervention arm
    • Can be greater than minimal risk, since IC obtained.
  
  • One for the observational usual care pathway arm
    • Waiver or
    • Broad consent of some type
    • Just in time consent

• Rationale: unlike pre-randomization consent, waiver would ONLY ever apply to those known to face minimal risk or less. No in principle reason against applying different procedures for the two arms.
Questions that need more attention

• When is waiver permissible when there is an opportunity to obtain consent? (Especially for Zelen design—i.e., no prior permission at all)

• Important question because:
  • Comes close to active withholding of information
  • Unclear what the patients’ expectations are re such a practice
  • Impracticability of research cannot rest on the fact that the intrinsic function of IC would make the research impracticable (e.g., if subjects knew, they would not want to participate)
Bibliography

• Kim S, Flory J, Relton C. Ethics and Practice of Trials within Cohorts (TwiCs): An Emerging Pragmatic Trial Design. Forthcoming in Clinical Trials.


Safety & Adverse Event Reporting

Kate Comtois, Ph.D., MPH, University of Washington/
Department of Psychiatry and Behavioral Sciences
Concerns as 14 year NIMH DSMB Member with Focus on Suicide Prevention Trials and Suicide SAEs

- Treatment outcomes in suicide prevention trials examined in course of DSMB review of adverse event review – inadvertent interim analysis?
Concerns as 14 year NIMH DSMB Member with Focus on Suicide Prevention Trials and Suicide SAEs

- Treatment outcomes in suicide prevention trials examined in course of DSMB review of adverse event review – inadvertent interim analysis?

- How to determine if adverse events are study related?
  - Participant attempted suicide later the same day they participated in a study activity... is this related? What about a day later? A week later?
  - Individual suicide events cannot be predicted – so how are we deciding?
Concerns as 14 year NIMH DSMB Member with Focus on Suicide Prevention Trials and Suicide SAEs

- Treatment outcomes in suicide prevention trials examined in course of DSMB review of adverse event review – inadvertent interim analysis?

- How to determine if adverse events are study related?
  - Participant attempted suicide later the same day they participated in a study activity... is this related? What about a day later? A week later?
  - Individual suicide events cannot be predicted – so how are we deciding?

- How to determine if adverse events are study treatment related?
  - What if adverse events are expected... you might even want to see them... and they break the blind...
  - Such as standard side effects from an effective medication
Concerns as 14 year NIMH DSMB Member with Focus on Suicide Prevention Trials and Suicide SAEs

• Treatment outcomes in suicide prevention trials examined in course of DSMB review of adverse event review – inadvertent interim analysis?

• How to determine if adverse events are study related?
  • Participant attempted suicide later the same day they participated in a study activity... is this related? What about a day later? A week later?
  • Individual suicide events cannot be predicted – so how are we deciding?

• How to determine if adverse events are study treatment related?
  • What if adverse events are expected... you might even want to see them... and they break the blind...
  • Such as standard side effects from an effective medication

• Ultimately... if we believe in science and power analysis – how many decisions can we make by anecdotal review?
Questions to Consider

1. Recruitment Progress:
   Will the trial randomize and collect outcome data from an adequate number of participants answer the primary study question?

These questions were developed by Greg Simon, MD, MPH
Kaiser Permanente Washington Health Research Institute
Questions to Consider

1. Recruitment Progress:
   Will the trial randomize and collect outcome data from an adequate number of participants answer the primary study question?

2. Intervention Quality/Fidelity:
   Are the study treatment(s) or intervention(s) being delivered with adequate quality or fidelity to answer the primary study question?

These questions were developed by Greg Simon, MD, MPH
Kaiser Permanente Washington Health Research Institute
Questions to Consider

3. Adverse Events

Are participants receiving study interventions experiencing an unexpected number or type of adverse events, suggesting some previously unrecognized risk or harm?
Questions to Consider

3. Adverse Events

Are participants receiving study interventions experiencing an unexpected number or type of adverse events, suggesting some previously unrecognized risk or harm?

Will review of individual events allow us to determine if an event was causally related to study participant or receipt of study intervention?
Questions to Consider

3. Adverse Events

Are participants receiving study interventions experiencing an unexpected number or type of adverse events, suggesting some previously unrecognized risk or harm?

Will review of individual events allow us to determine if an event was causally related to study participant or receipt of study intervention?

To Consider:
• Is study treatment well-characterized?
• What are chances of unknown risk?
• What unexpected events to track?
• Is risk event the outcome of the study?
• What can be achieved by review of individual events? What could be lost?
Questions to Consider

4. Safe Practice:
   Are study staff responding appropriately to any urgent clinical needs that arise during delivery of the intervention (whether or not related to study procedures or intervention services)?
Questions to Consider

4. Safe Practice:
   Are study staff responding appropriately to any urgent clinical needs that arise during delivery of the intervention (whether or not related to study procedures or intervention services)?

5. Evidence of Net Benefit or Harm:
   Has the study intervention(s) already been proven beneficial or harmful so that recruitment or intervention delivery should be terminated ahead of schedule?

These questions were developed by Greg Simon, MD, MPH
Kaiser Permanente Washington Health Research Institute
Example: Trial of Brief Psychotherapy (CAMS) vs. TAU Where Suicidal Ideation and Behavior is Outcome

1. Recruitment Progress:
   Detailed consort chart and target/enrollment graph

2. Intervention Quality/Fidelity:
   Evidence study intervention received and measure treatment fidelity

3. Adverse Events:
   Unclear what unexpected events to track or how to determine if causally related to the study. Well-characterized psychotherapy. Review of individual events will not allow us to determine if an event is related to study participation nor intervention. Suicide events are primary outcome.

4. Safe Practice:
   Approve study protocols. Provide list of adverse events and the study’s response (not by condition). Tables confirm study protocols followed.

5. Evidence of Net Benefit or Harm:
   For each condition: Rate = Ss withdrawn from treatment/Ss randomized
Going Forward/Lessons Learned

- Early communication between DSMB and study team on study design and implications for data & safety

- Active NIMH staff collaboration with study team

- Consider knowledge exchange visits between NIMH & study team

- Include stakeholders in discussions of thresholds for study participation & plans for safety monitoring

- Increasing pragmatic trial expertise on standing DSMBs
  - NIMH DSMB training
Thank you.
Time for Discussion...