Lessons From ADAPT-IT

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Disclosures

- Grant Funding (current)
  - NIH-NINDS
  - AHRQ
- No financial conflict of interest as I have no ownership in or compensation from any companies or commercial interests
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Methodology:
- Public/Private partnership: Neurological Emergencies Treatment Trials Network/Berry Consultants

Goals:
- Design innovative, adaptive clinical trials for the evaluation of drugs and devices used in the emergency care of patients with acute neurological illness or injury
ADAPT-IT Process

**FTF - 1**
- Investigators and statisticians meet
- Discuss clinical problem and potential designs

**CTC**
- Berry Consultants present concept
- Clinical & data teams provides feedback

**Perf WG**
- Simulations presented with feedback
- Several iterations

**FTF – 2**
- Near final design presentation
- Work out final details for grant / IND submission
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Goals:
- Identify and qualitatively characterize key steps and barriers
- Define gains of adopting the adaptive design process versus traditional clinical trial design
- Develop best practices in designing adaptive trials
- Draft guidance document for assessing simulations of fixed vs adaptive designs
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Challenges:

- Harder to understand characteristics of trials
  - Customized software
- Few statisticians understand the more complex designs; clinicians defer to them
- Logistics: rapid data turnaround, central randomization, drug supply-line
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Challenges:

- Acceptance of designs by stakeholder groups varies
- Expertise of reviewers varies
- Time and lack of funding before applications are submitted
- Incorporating designs based on genetic markers of small subgroups is complex
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Challenges:

- Operational gap in expertise between clinicians and statisticians
- Availability and understanding of software simulation (particularly to reviews trying to assess proposed designs)
- Relevance and acceptance in early exploratory versus confirmatory trials
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Challenges:

- Terminology and use of term “adaptive trial”
- Designed trial projects will not be underway when 5 year project ends
- Need for biomarker/outcomes to iterate upon; issues with long outcome times
- NIH page-limits restrict descriptions of simulation results
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Adaptive Design Process

- Multi-step, iterative
- Extensive interactions with FDA statisticians and NIH staff
- Extensive, up-front planning for more frequent, preplanned interim analyses
- Face to face meetings with various stakeholders (statisticians, clinicians, NIH/FDA, patient advocates)
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Adaptive Design Process

- Early discussions of potential designs
- Concept teleconferences to get feedback from clinicians
- Development of simulations
- Near-final design presentation for incorporation in grant or IND submission
## ADAPT-IT

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Target Illness</th>
<th>Proposed Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARCTIC</strong> – Acute Rapid Cooling of Traumatic Injuries of the Cord</td>
<td>Traumatic spinal cord injury</td>
<td>Modest intravascular hypothermia (33.5° +/- 0.2°C)</td>
</tr>
<tr>
<td><strong>ESETT</strong> – Established Status Epilepticus Treatment Trial</td>
<td>Status epilepticus refractory to benzodiazepines</td>
<td>Rapid IV infusions of fosphenytoin vs. valproate vs. levetiracetam</td>
</tr>
<tr>
<td><strong>ICECAP</strong> – Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients</td>
<td>Comatose survivors of cardiac arrest</td>
<td>Duration of induced hypothermia vs. normothermia</td>
</tr>
<tr>
<td><strong>ProSPECT</strong> – Progesterone in Acute Stroke</td>
<td>Acute stroke</td>
<td>IV progesterone infusion</td>
</tr>
<tr>
<td><strong>SHINE</strong> – Stroke Hyperglycemia Insulin Network Effort</td>
<td>Ischemic stroke and hyperglycemia</td>
<td>Insulin infusion therapy</td>
</tr>
</tbody>
</table>
Methods

- Prospective, mixed methods data collection
- Qualitative
  - Mini Focus Groups (3-6 people)
  - SWOT (Strengths, Weaknesses, Opportunities, Threats)
  - Field observations-FTF1, CTC, PWG, FTF2, emails
  - Key Stakeholder Interviews
- Quantitative
  - Visual analog scales with ranges from 0-100%

13) Adaptive clinical trial designs pose ethical advantages from the patients’ perspective.

<table>
<thead>
<tr>
<th>Definitely Not</th>
<th>Probably Not</th>
<th>Possibly</th>
<th>Probably</th>
<th>Definitely</th>
</tr>
</thead>
</table>

Why? __________________________________________
Qualitative Analyses

STRENGTHS

- Open communication, thorough discussions
- Collaborative approach; interaction between clinical and statistical experts
- Exploration of design options
- Feedback on design from external viewpoints, allowing for improvement of a grant
- Support and input from regulatory groups during the design process
Qualitative Analyses

WEAKNESSES

- Insufficient time to fully discuss scenarios of adaptation
- Resistance to different approaches
- Decision-making not clear
- Varied level of engagement from clinical teams
- More specific examples of simulations were needed to foster greater understanding
Qualitative Analyses

OPPORTUNITIES

- Focus on specific plans more quickly
- Provide more specific examples of simulations
- Send information ahead of time to allow for preparation before meetings
- Allow more time for review of statistical assumptions during meetings
- Encourage the use of more standardized terminology
Qualitative Analyses

THREATS

- Lack of understanding of concepts by different stakeholders
- Economic and logistical constraints
- Time constraints
- Lack of acceptance of design/resistance to new design
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Qualitative observations:

- Development of trust in the methodology is key
- Issues identified – unclear use of terminology; validity; un-blinding; attribution
- Maturity of design is important (SHINE, too late; ARCTIC accepted changes)
  - Communicate upfront cost for simulation work
  - Team development and interaction critical
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• Provide arena for education and debate within statistical and clinical community
• Address “fear” of reviewer reaction (at NIH and FDA, DSMBs, IRBs, journals)
• Address logistics of infrastructure development
Adaptive clinical trial designs pose ethical advantages from the patients’ perspective.

- It depends on the design, but it may be more advantageous to have a higher probability of being randomized to the active arm. (academic Stat VAS)
- When done well they [ACTs] treat patients in and out of the trial better (Consult Stat VAS)
- I think it only makes sense that if you are going to avoid exposing subjects to ineffective therapies that that’s the ethically obligatory thing to do. (Clin MFG)
- There is no problem explaining to patient that if we find one are to be clearly inferior we drop it, and one to be clearly superior we’ll stop [the trial] early. (Clin MFG)
- Patients [in an ACT] are shunted to the more promising area as a difference develops [between two arms]; for the first time, patients may actualize benefit from being a subject (Other VAS)
Summary Insights

From the clinician perspective
Phenotype

Clinician – Scientist Question Asker

Clinician – Practitioner Answer Needer

Clinician – Methodologist ?Oracle
Outline - insights

Speaking for the genus: “Clinician”

- We should think of clinical trials as diagnostic tests.
- We inadequately acknowledge our own uncertainty.
- We often aren’t collaborative enough with biostatisticians.
Clinicians should think of **CLINICAL TRIALS AS DIAGNOSTIC TESTS**
Therapeutic Response Surface

Best Regimen

Benefit

Maximum Benefit

Your Patient

Regimen

Prognostic Factors

Clin Pharmacol Ther 1997;61:275-91
Preclinical Experiments

- Mechanism
- Targets
- Translational Dose Ranging

Clinical Trials

- Efficacy
- Safety / Feasibility*
- Dose Ranging
Clinical Trials are Models with Tons of Guesses Assumptions

- Dose from animal models is close
- No heterogeneity of effect
- Subgroups respond equally
- Some subgroups excluded
- Effect size to create “reasonable” sample size
- “Noise” in outcomes can be understood and overcome

Duration of treatment practical

LESSON: Make many compromises to reduce number of parameters to make model “solvable”
Clinicians and biostatisticians should

**SPEND MORE TIME WITH EACH OTHER**
Areas to spend more time

- What is the question
- Pre-mortem (anticipated regret)
- Simulate trials
- Attempt to balance and “cost” flexibility versus complexity
In preparing for battle I have always found that plans are useless, but planning is indispensable.
Summary - insights

ADAPT-IT has taught me that clinicians of all species should...

- Think of clinical trials as diagnostic tests.
- Acknowledge our own uncertainty.
- Spend more time with biostatisticians.

Biostatisticians considering adaptive designs

- Consider how to present simulations
- Actively engage clinician partners on what simulations should be done