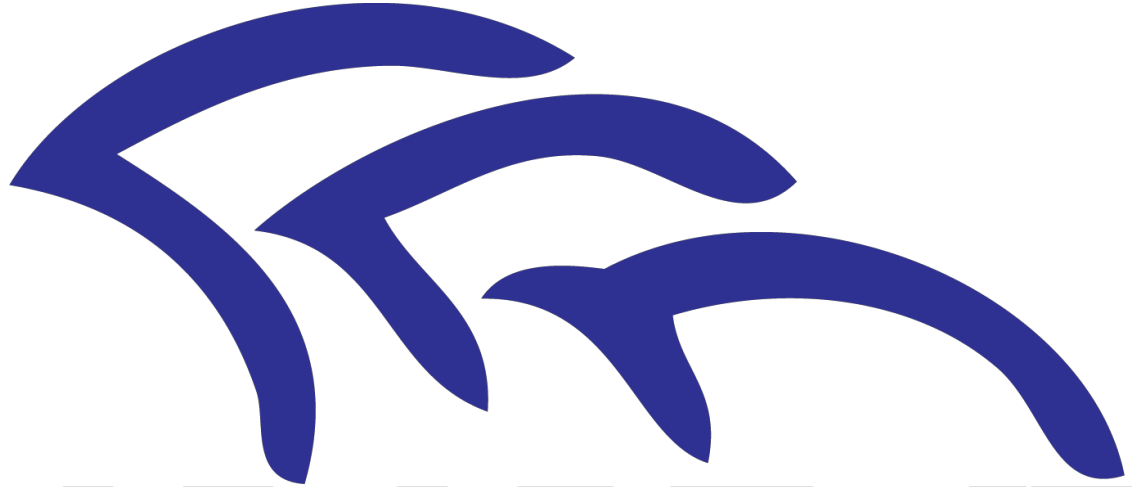

ADAPT-IT

Adaptive Designs Accelerating Promising Trials into Treatments

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(U01NS073476) **from the NIH Common Fund**

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- IRB approved UM
- Participants advised of data collection, analysis, and plans for publication

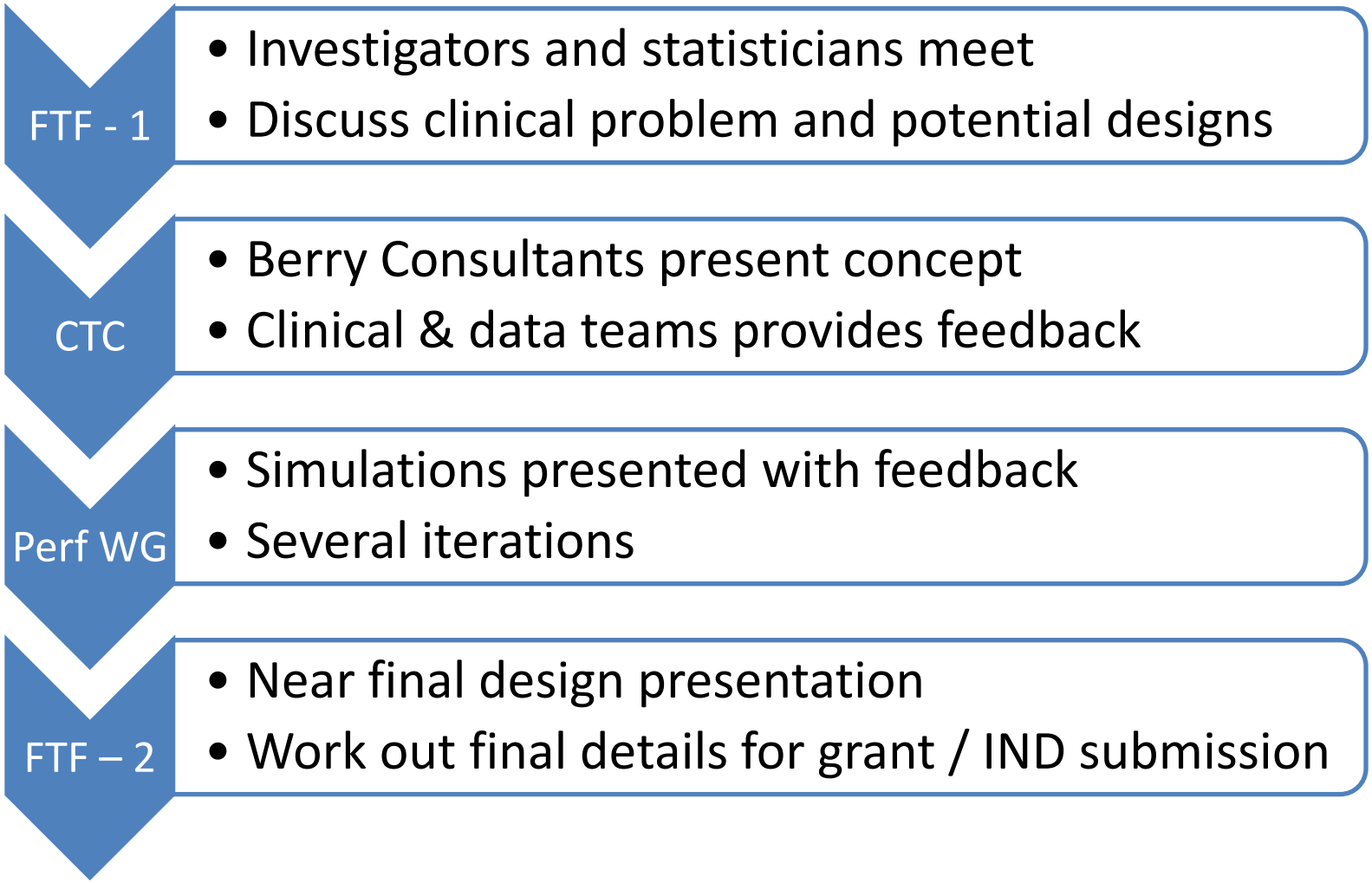
Objectives-Lessons learned

- What has worked in the our ACT development experience?
- What have been the challenges during this experience?
- How can clinical trial researchers and adaptive trial designers collaborate most effectively?

Mixed Methods AIM

To study the collaborative process itself using mixed methods

ADAPT-IT Process



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%

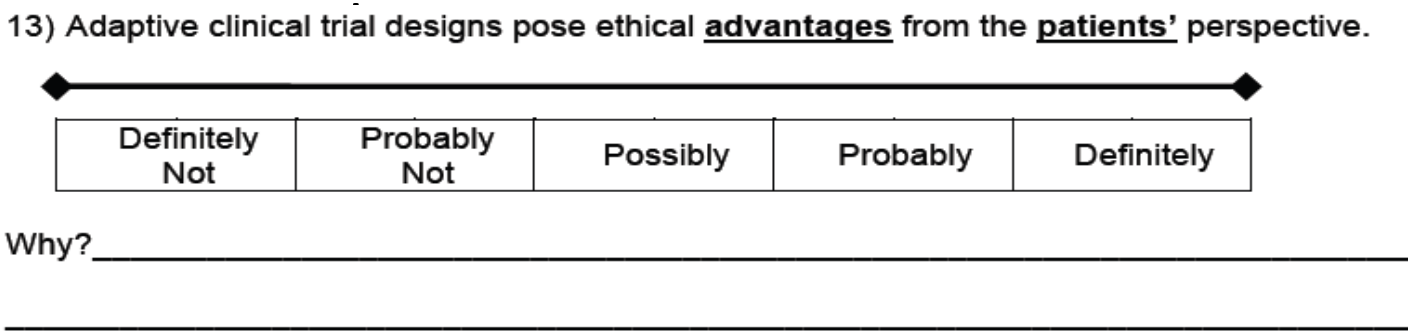


Table 4. Qualitative Assessment Procedures

Purpose	Approach	Data Collection	Expected Outcome
To understand the concerns and strategies of personnel participating in face-to-face (FTF) meetings, both prior to initiation of design activities (pre-FTF-1) and after completion of substantial design activities (pre-FTF-4)	• Visual Analog scale ratings of ACT features • Pre-meeting Mini-Focus Group Interviews (MFGIs) with 3 expert panels: (1) NETT clinical leadership (2) NETT statistical leadership (3) Statisticians experienced in ACT design	• 7 VAS ratings per person on general ACT features (14* persons for 2 FTF meetings • N=6 MFGIs (3 MFGIs prior to FTF-1 and 3 MFGIs prior to FTF-4)	• Quantitative assessments of 7 general ACT features to be examined pre/post FTF meetings • Identify variations in views of experts regarding potential value, barriers, risks, and advantages of ACTs • Establish baseline views on ACTs to delineate how those views change after participating in design processes
To understand interactions that occur during FTF meetings with respect to ACT development	• Unstructured observations and audio-recordings during 4 FTF meetings to assess participant non-verbal reactions	• 32 hrs direct observation (8 hours per 4 FTF meetings	• Process evaluation regarding constructive and unconstructive approaches to resolution of disagreements during the development of ACTs.
To determine participants' assessments of each proposed ACT's strengths, weaknesses, and probability of success using both quantitative and qualitative measures	• Administer Visual Analog Scale (VAS)-based assessments after the discussion of each proposed trial in all 4 FTF meetings • Written, short-answer, qualitative assessments at each FTF meeting by all participants	• 6 VAS ratings per person on each trial (14* persons and 2 trials per meeting for 4 meetings • N=72 (18* per FTF meeting) per 4 trials	• Quantitative assessments of 6 ACT features per trial that will be compared with funding success • Assessment by all participating members regarding the design and meeting processes • Examination of degree that qualitative assessments support or conflict with VAS results
To identify the views of stakeholders external to the project	• Stakeholder Interviews including NIH and FDA personnel, patient advocates, and peer reviewers	• N=12 semi-structured telephone interviews of key informants in Year 1 and 2	• Stakeholders' knowledge and views regarding potential value, barriers, risks, and advantages of ACTs
To elicit assessments of participants on the ACT design process	• Summative evaluations, using individual interviews at end of two years	• N=12 evaluations conducted in early Year 3	• Global assessments of the clinical trials design development process
To evaluate grant reviewer responses to submissions that include ACTs	• Summary statement ("pink sheets") document analysis of 4 trials submitted for funding	• N=4 documents of around 6 pages each in year 3	• Grant reviewers' knowledge and views regarding potential value, barriers, risks, and advantages of ACTs

* While 18 people will participate in each face-to-face (FTF) meeting during a day, only 14 are anticipated to participate in the discussion of each individual trial. Note: Abbreviations: FTF face-to-face; ACTs Adaptive Clinical Trials; VAS Visual Analog Scale; MFGI Mini-Focus Group Interviews

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Methods Analysis

- Qualitative data
  - Transcription and data cleaning
  - Immersion in data
  - Atlas TI used for coding and analytics
- Quantitative data
  - VAS portrayed using box plots
- Integration
  - Parallel presentation using figures

Participant Characteristics

- Four Constituent Groups (N=53)
  - network biostatisticians (n=5),
  - consultant biostatisticians (n=6),
  - clinicians (n=22), and
  - other stakeholders (n=20) including FDA, NIH and patient advocates.

Data Collection Procedures by Step

Clinicians, academic statisticians, consultant statisticians, other stakeholders (FDA, NIH, patient advocate

Steps	Data Collection Procedures				
	Mini FG	VAS	Short Answer	SWOT	Field Notes
FTF1	15 Qs, 5 MFGs N=22 participants	21 Qs X 25 participants	15 Qs X 25 participants	15-5/trial 24 participants	1-2/trial N=8
CTC	-	-	-	-	N=5
Perf WG	-	-	-	-	N=5
FTF2	-	21 Qs X 37 participants	N=37	N=11	1-2/trial N=8

Stakeholder Interviews

External – completed

	N=10
Who	2 NIH 2 FDA 3 Pt Advocates 2 Study Section 1 Clin Opin leader
Age range	40 to 60
Gender	4 F 6 M

Internal – projected

	N=10
Who	6 PIs Co-Is Acad Statisticians 3 Consult Statisticians
Age range	TBD
Gender	TBD

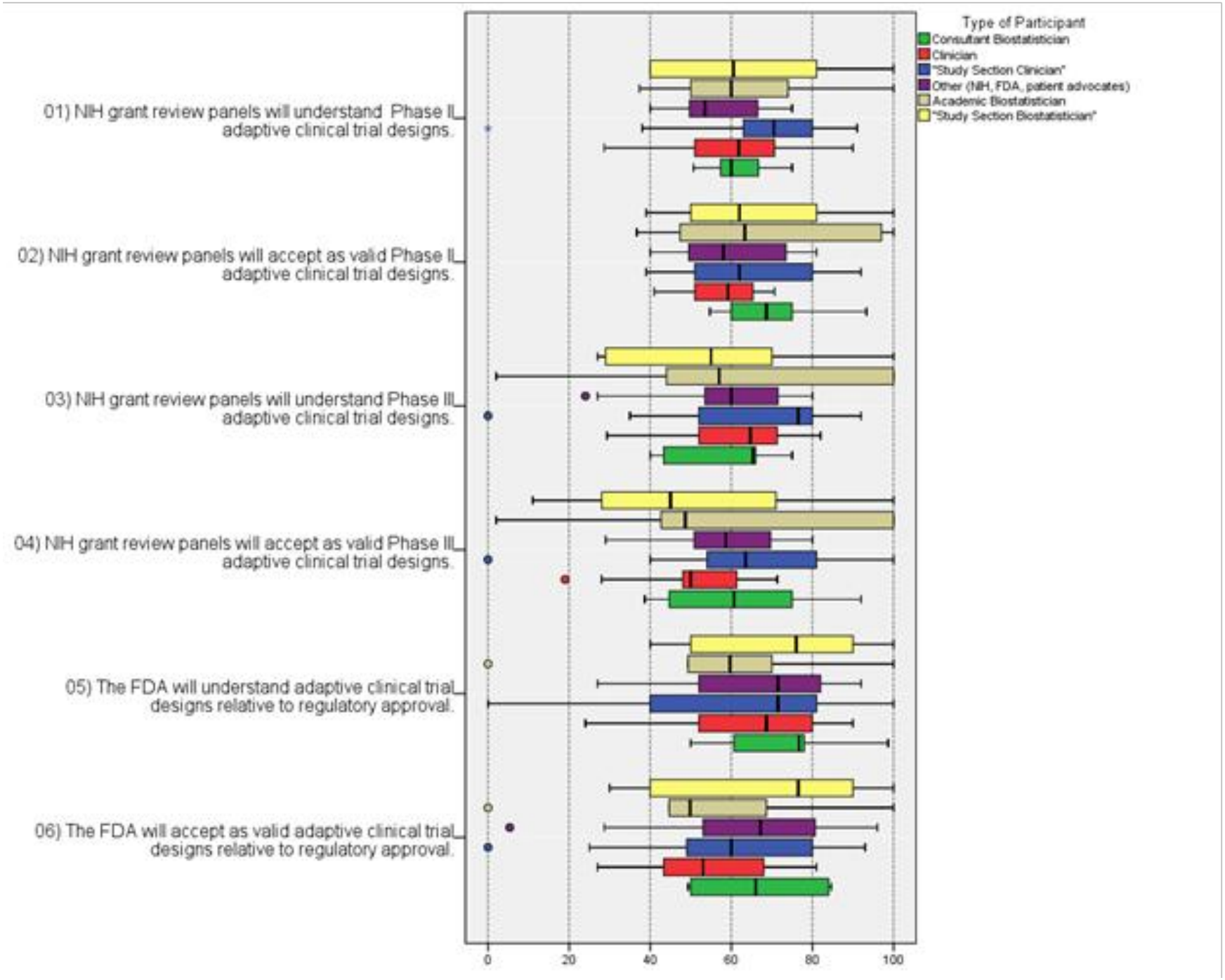
Forthcoming: Qualitative analysis of Pink Sheets

Questions

- **General impressions** ACTs
- **Experience** with ACTs
- **NIH grant review panels response** to ACT designs for **Phase II, Phase III** trials (experiences/views)
- **Ethical dimensions** of ACT designs (experiences/views)
- **Journal peer review of ACTs** (experiences/views)
- **ACTs change clinical practice** (experiences/views)

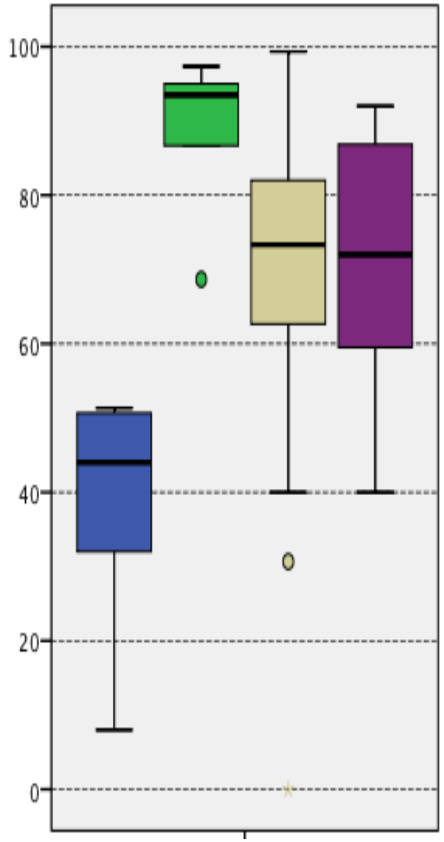
Stakeholder General Impressions/Experience

- Vast majority of experience in adaptations among consultant statisticians and ADAPT-IT project investigators
- Among trialists, highly limited experience in actual research/peer-review, but high interest
- Variety of understandings regarding what adaptations encompass


01) NIH grant review panels will understand Phase II adaptive clinical trial designs.
02) NIH grant review panels will accept as valid Phase II adaptive clinical trial designs.
03) NIH grant review panels will understand Phase III adaptive clinical trial designs.
04) NIH grant review panels will accept as valid Phase III adaptive clinical trial designs.
05) The FDA will understand adaptive clinical trial designs relative to regulatory approval.
06) The FDA will accept as valid adaptive clinical trial designs relative to regulatory approval.
0
20
40
60
80
100
Type of Participant
Consultant Biostatistician
Clinician
"Study Section Clinician"
Other (NIH, FDA, patient advocates)
Academic Biostatistician
"Study Section Biostatistician"

Diverging Stakeholder Anchors on Ethical Aspects of Trials

Adaptive clinical trial designs pose ethical <u>advantages</u> 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)

Lessons Learned: What worked?

Developing a team and developing trust

- Unique roles: Clinicians, academic statisticians, academic statisticians, project officers
- Trust building critical

Lessons Learned: What worked?

Face-to-Face time

- Statisticians and consulting ACT designers need direct (face-to-face) time to work out detailed modeling issues
- Would not necessarily benefit from real-time involvement of clinician researchers

Lessons Learned: What Worked?

Starting early

- How much is candidate trial already developed?
- Change an existing trial — SHINE
- Redesign a project — ARCTIC
- Design from scratch—ESETT, ICECAP, PROSPECT

Challenges

- Inventory all the assumptions and compromises about your vision of the trial design
  - Only going to test one dose
  - Exclude elderly patients because…

Challenges: What is an ACT?

- The definitions, nomenclature and taxonomy are incompletely understood in the broader medical and statistical communities

Challenges

- Understanding the rationale for clinical trial simulations
- Presenting, interpreting, and grasping the results of clinical trial simulations

Challenge

- Funding the planning and simulations necessary to develop a rigorous design

Challenge

- What pros/cons for using a more complex design compared to a traditional design?
- I.e., are you getting adequate bang for your buck as the design becomes more and more complex

Challenge

- Lack of direct evidence of ACTs – Flexible adaptive designs and traditional trial designs have not been compared directly

Challenge

- How to communicate the trial design and its validity to external audiences, eg, Study sections, IRBs
  - Page limitations, how to put it in 12 pages?

Advice to clinician researchers

- Reassess all assumptions that have gone into your preliminary ideas for a design
  - Take off your blinders “Don’t know to ask how to do the things that you can do.”
- Bone up on adaptive designs
- Look for funding for planning/simulations
- Educate your IRBs
- Read methodological papers on ACT designs
- Identify statisticians comfortable with adaptive designs
- Assume you will need to educate your audience about adaptive designs

Advice to academic statisticians

- Get out of your comfort zone
- Familiarize yourself Adaptive Designs
- Spend time with adaptive design experts to develop an understanding of the assumptions and procedures
- Know your limits
- Share your designs

Conclusions

- Beware of professional lenses
- Paradigm shift
- Techniques are not for the feint of heart
- Need collaborators who, ideally, are knowledgeable in the emerged field of adaptive designs
- Best served by statistician knowledgeable of adaptive designs or at least willing to invest in understanding and gaining experience

Conclusion

- Educate yourself more about adaptive designs
- Look for creative ways to fund the modeling
- Simulations alone have proven to be publishable papers
- Scientific paradigm shifts never occur easily
- Have thick skin
- Tight rope walk between the cutting edge and bleeding edge