Lessons From ADAPT-IT

William J. Meurer, MD, MS

University of Michigan

DESIGNIT 2015 : Society for Clinical Trials Workshop

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

ADAPT-IT

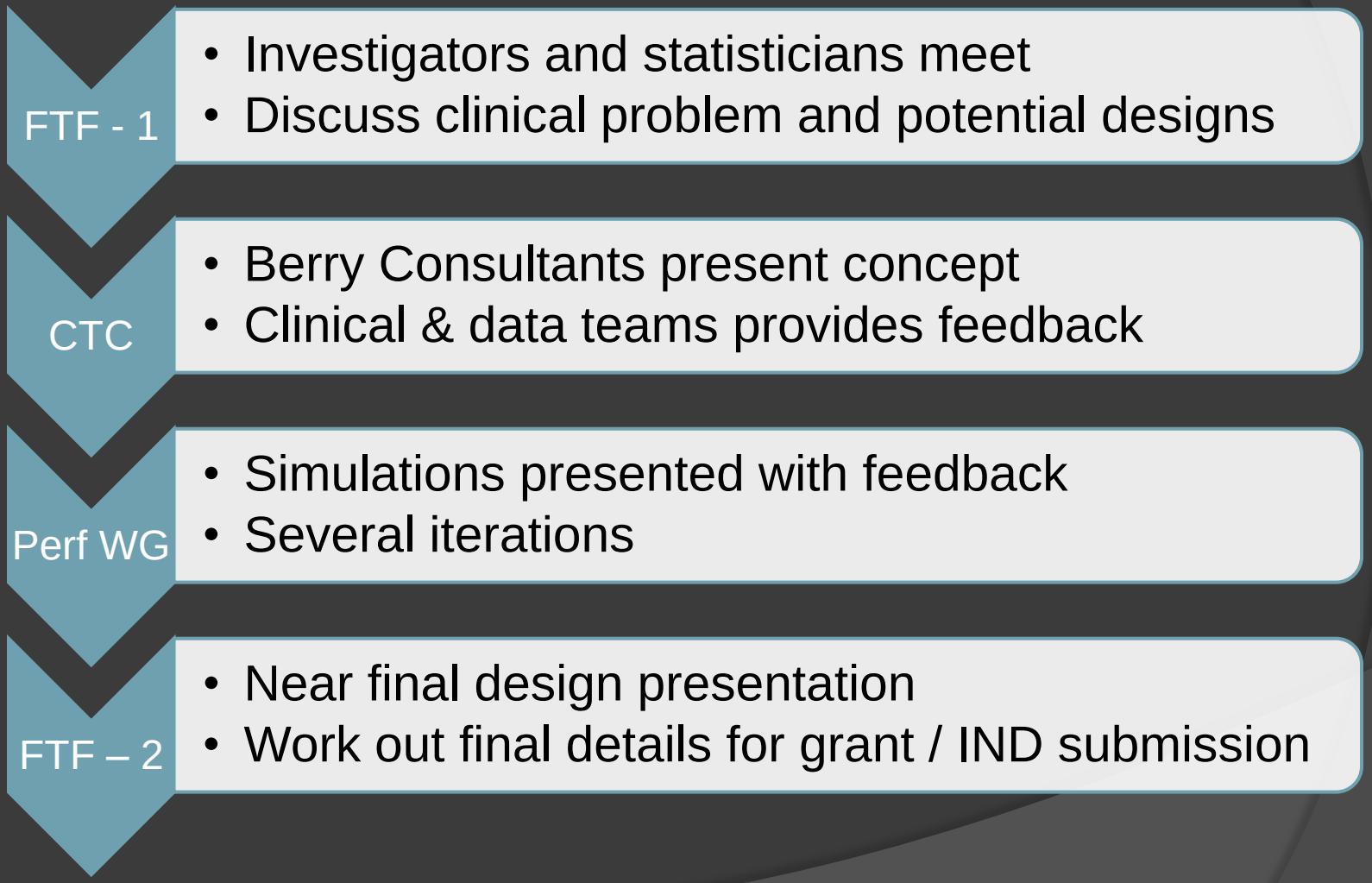
Methodology:

- 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



ADAPT-IT

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- Draft guidance document for assessing simulations of fixed vs adaptive designs

ADAPT-IT

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

ADAPT-IT

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

ADAPT-IT

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

ADAPT-IT

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

ADAPT-IT

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)

ADAPT-IT

Adaptive Design Process

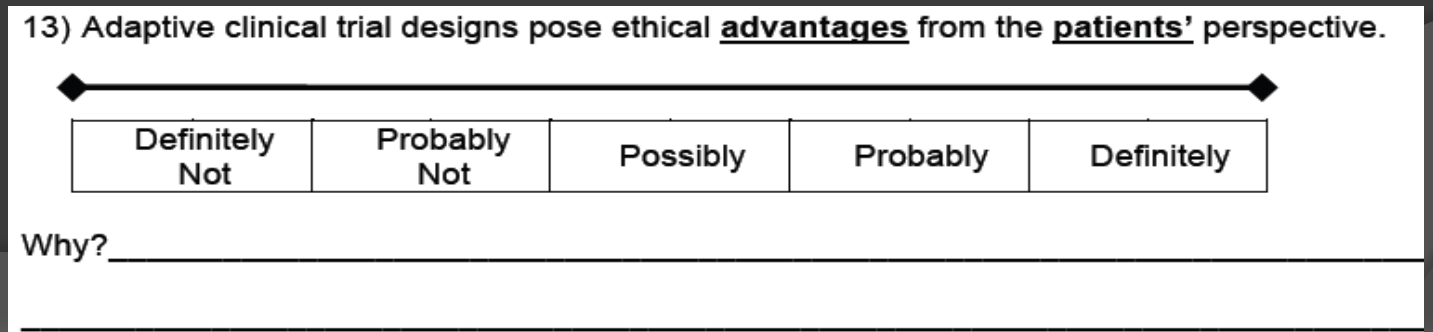
- Early discussions of potential designs
- Concept teleconferences to get feedback from clinicians
- Development of simulations
- Near-final design presentation for incorporation in grant or IND submission

ADAPT-IT

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

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%



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

ADAPT-IT

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)

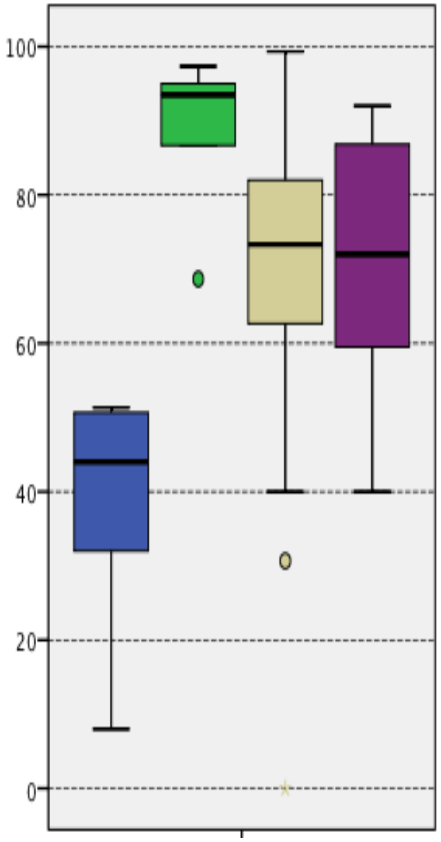
- Communicate upfront cost for simulation work
- Team development and interaction critical

ADAPT-IT

- 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

Diverging Stakeholder Anchors on Ethical Aspects of Trials

Adaptive clinical trial designs pose ethical <u>advantages</u> from the patients' perspective.

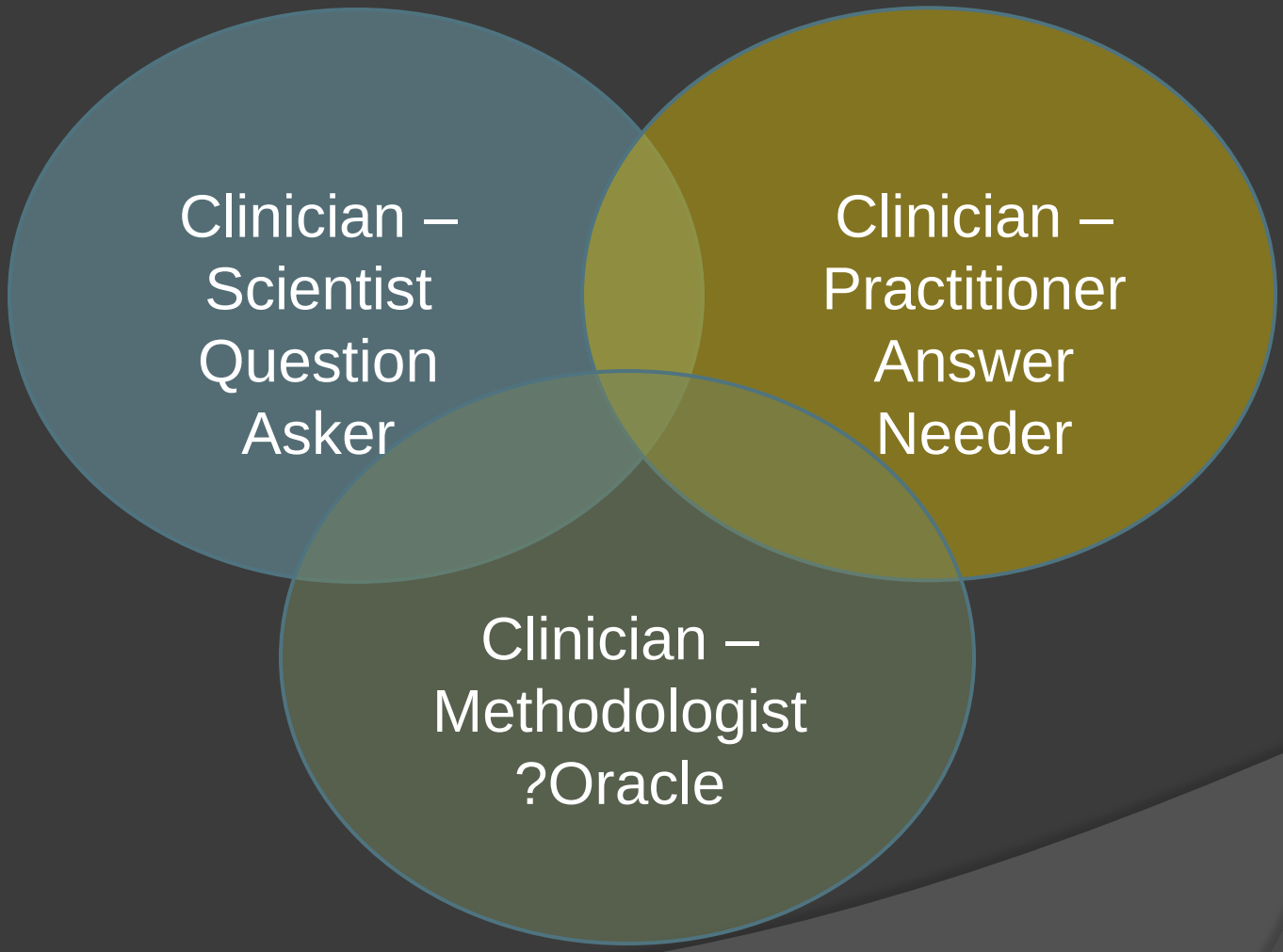


- It depends on the design, but it may be more advantageous to have a higher probability of being randomized to the active arm. (academic Stat VAS)
- When done well they [ACTs] treat patients in and out of the trial better (Consult Stat VAS)
- I think it only makes sense that if you are going to avoid 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)

Summary Insights

From the clinician perspective

Phenotype


Clinician – Scientist Question Asker
Clinician – Practitioner Answer Needer
Clinician – Methodologist ?Oracle

Outline - insights

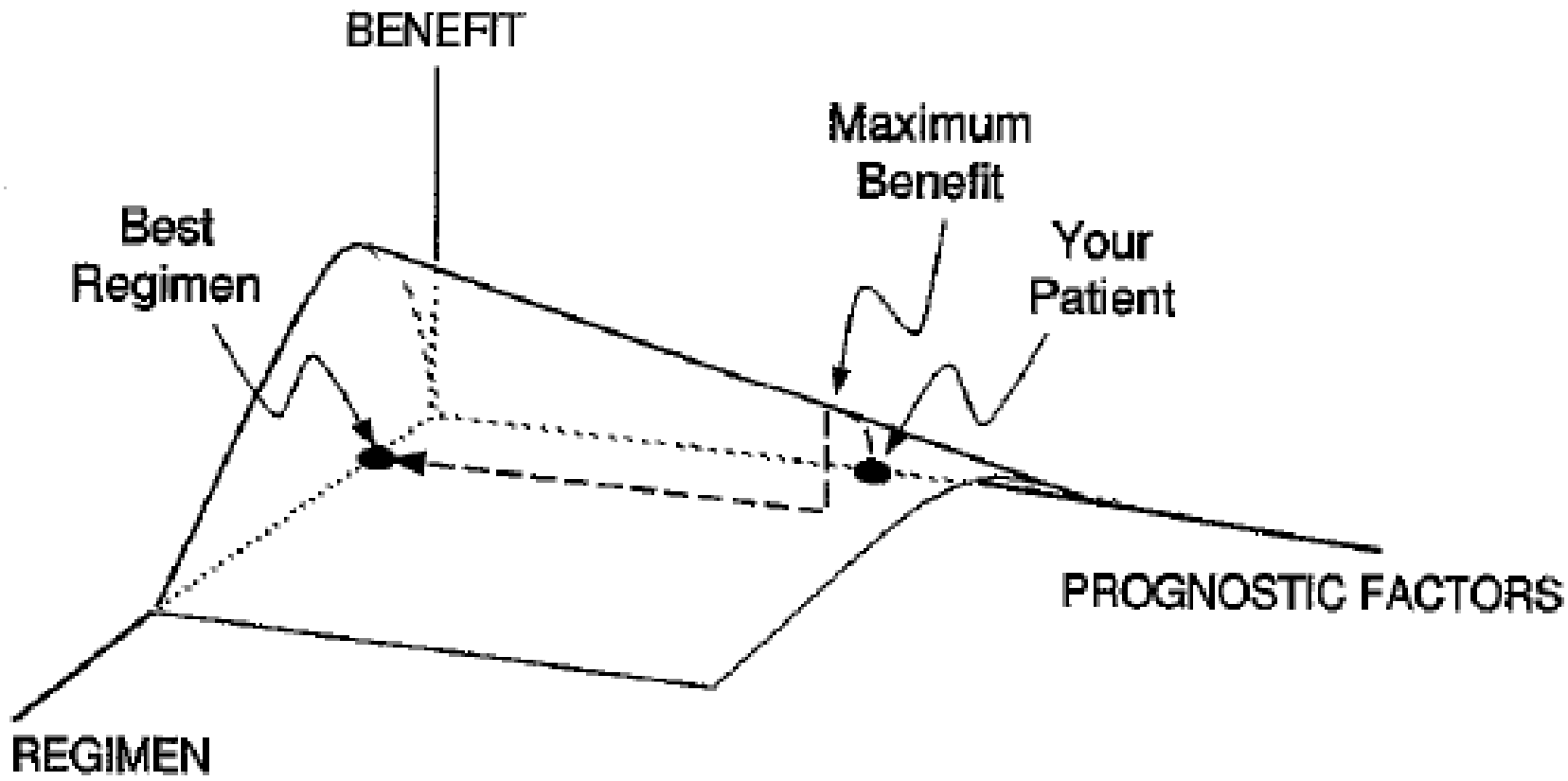
Speaking for the genus: “Clinician”

- 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



Clin Pharmacol Ther 1997;61:275-91

Preclinical Experiments

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

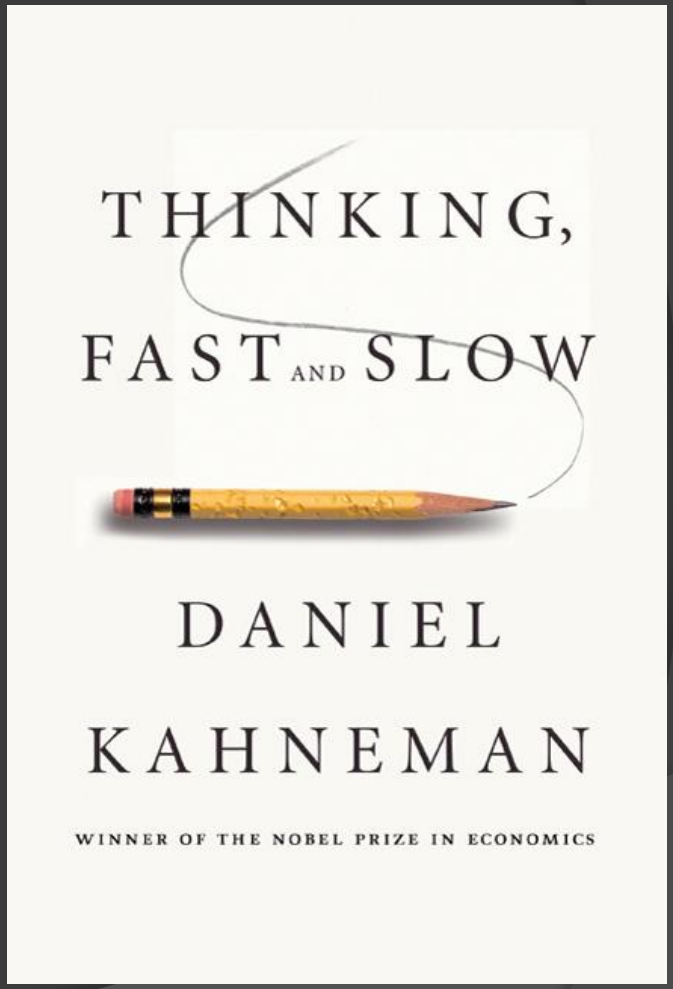
LESSON: Make many compromises to reduce number of parameters to make model “solvable”

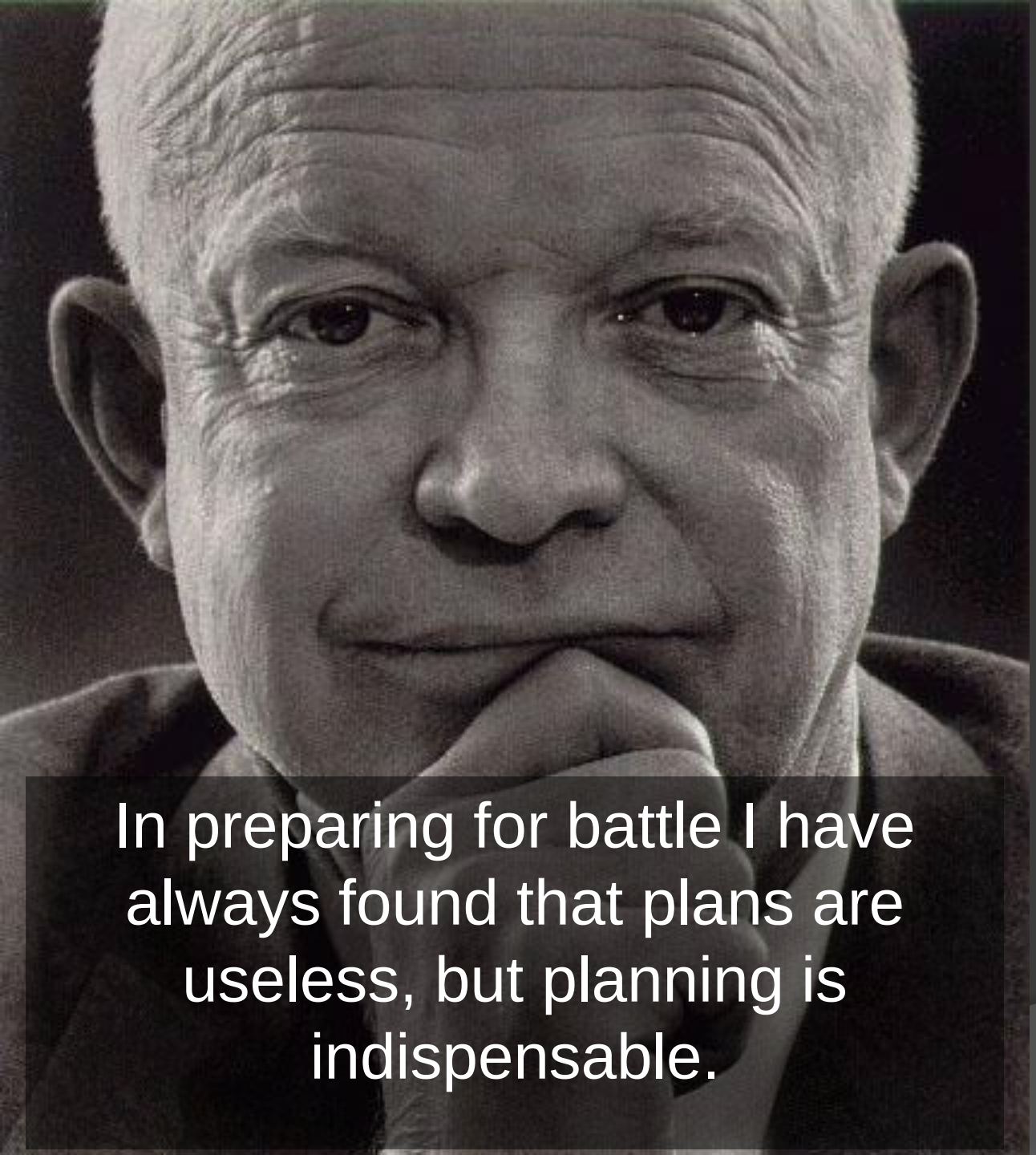
Clinicians and biostatisticians should

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