ADAPT-IT

Adaptive Designs Accelerating Promising Trials into Treatments

University of Michigan Health System

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA

LABioMed Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center

Berry Consultants Statistical Innovation

Adaptive Design--Definition

- Terminology is variable
- In its simplest form:
  - **Adaptive design** refers to a clinical study design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial

FDA definition

- A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are performed at prospectively planned timepoints within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing

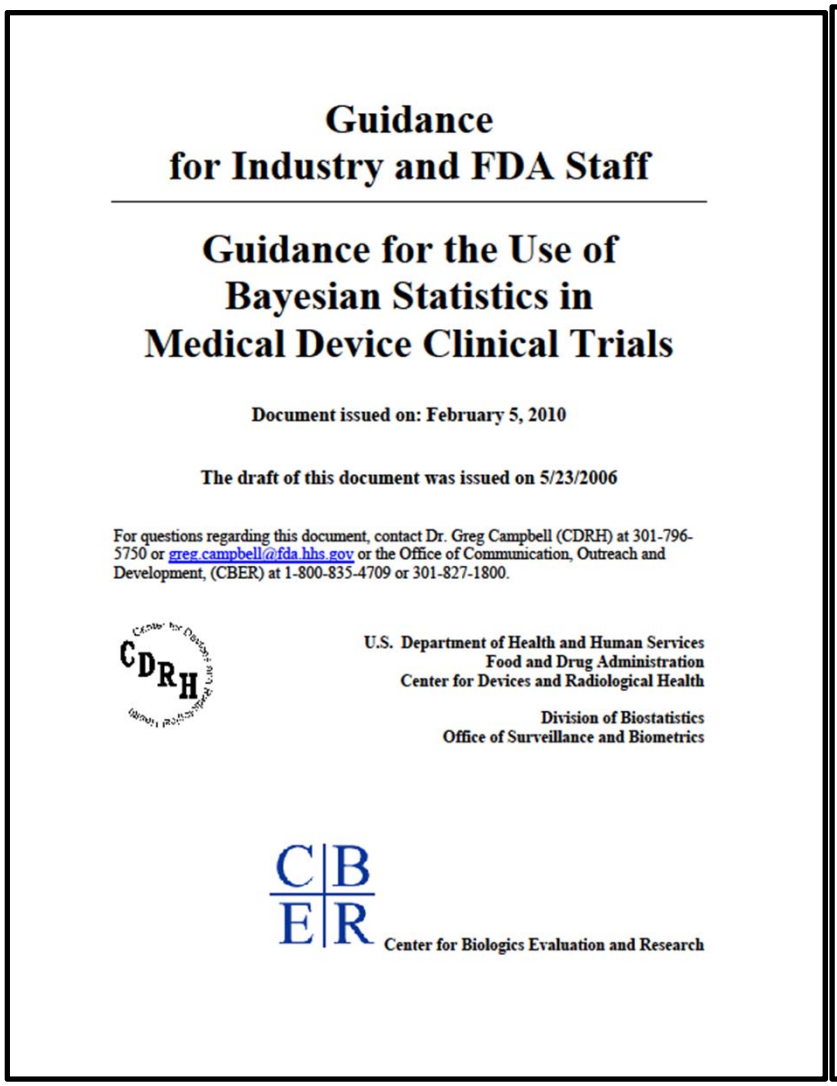
Motivation for Adaptive Trials

- When designing a trial there is substantial uncertainty regarding how best to treat subjects in the experimental arm (e.g., uncertainty in optimal dose, best duration, target population)
- This creates uncertainty in the optimal trial design
- Traditionally, all key trial parameters must be defined and held constant during execution
- This leads to increased risk of negative or failed trials, even if a treatment is inherently effective

Motivation for Adaptive Trials

- Once patients are enrolled and their outcomes known, information accumulates that reduces uncertainty regarding optimal treatment approaches
- Adaptive clinical trials are designed to take advantage of this accumulating information, by allowing modification to key trial parameters in response to accumulating information and according to predefined rules

FDA Guidance Documents



Guidance
for Industry and FDA Staff

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

Document issued on: February 5, 2010

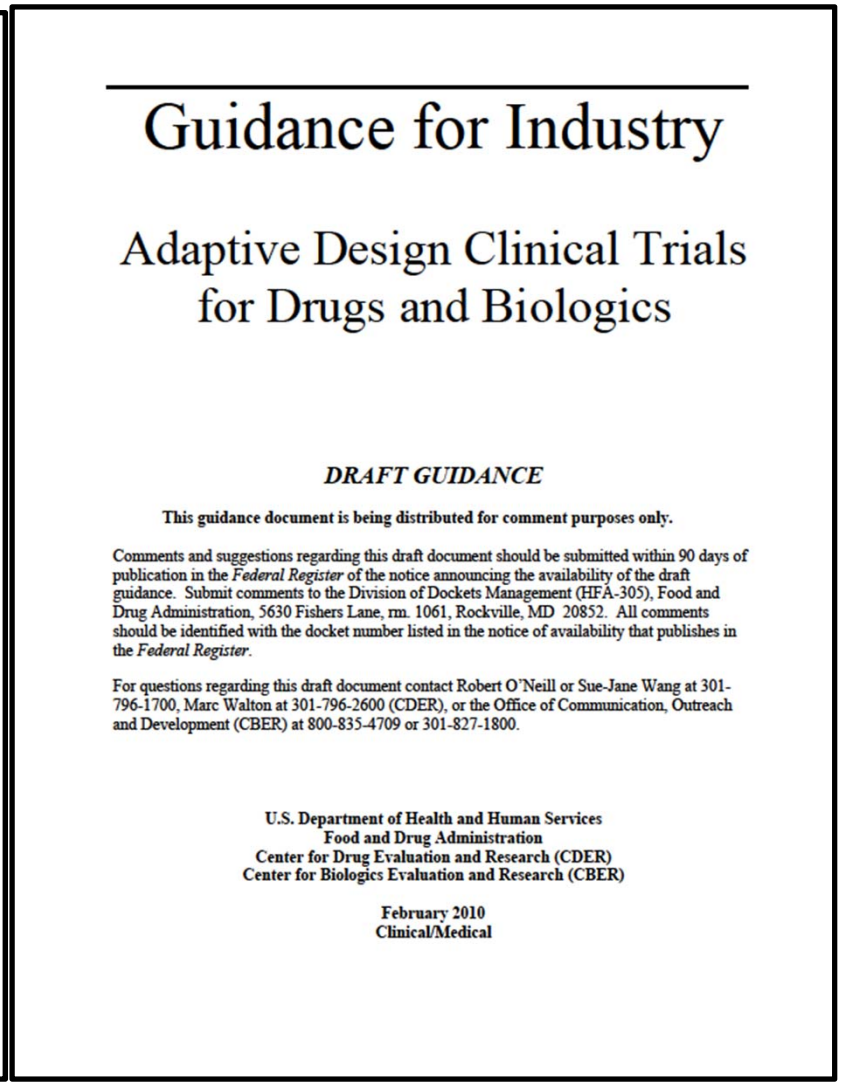
The draft of this document was issued on 5/23/2006

For questions regarding this document, contact Dr. Greg Campbell (CDRH) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Biostatistics
Office of Surveillance and Biometrics

Center for Biologics Evaluation and Research



Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Robert O'Neill or Sue-Jane Wang at 301-796-1700, Marc Walton at 301-796-2600 (CDER), or the Office of Communication, Outreach and Development (CBER) at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2010
Clinical/Medical

NIH - FDA

- Joint RFA for “Regulatory Science Innovation”
- 4 funded proposals
  - ADAPT-IT
  - Replacement Ocular “Battery”
  - Nanoparticle-complement interaction modeling
  - Heart-lung “Micromachine”

Source: NIH press release

ADAPT-IT Investigators

- Principal Investigators
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ADAPT-IT - Objective

- *"To illustrate and explore how best to use adaptive clinical trial designs to improve the evaluation of drugs and medical devices and to use mixed methods to characterize and understand the beliefs, opinions, and concerns of key stakeholders during and after the development process."*

Specific Tasks

- Design ~~four~~, five clinical trials
  - Status Epilepticus (Refractory)
  - Glycemic control in stroke
  - Spinal cord trauma
  - Post cardiac arrest hypothermia
  - Neuroprotection across ischemic and hemorrhagic stroke

- Learn about process
  - Surveys
  - Focus Groups
  - Observation
  - Key Stakeholder Interviews
  - Thematic analysis

- Educate
  - Clinicians
  - Statisticians

FDA – NIH – Academic Interface

- Unique, in that FDA expert biostatisticians are involved early and throughout the design process
- NIH program officials from NINDS – Clinical Trials are invited to all meetings

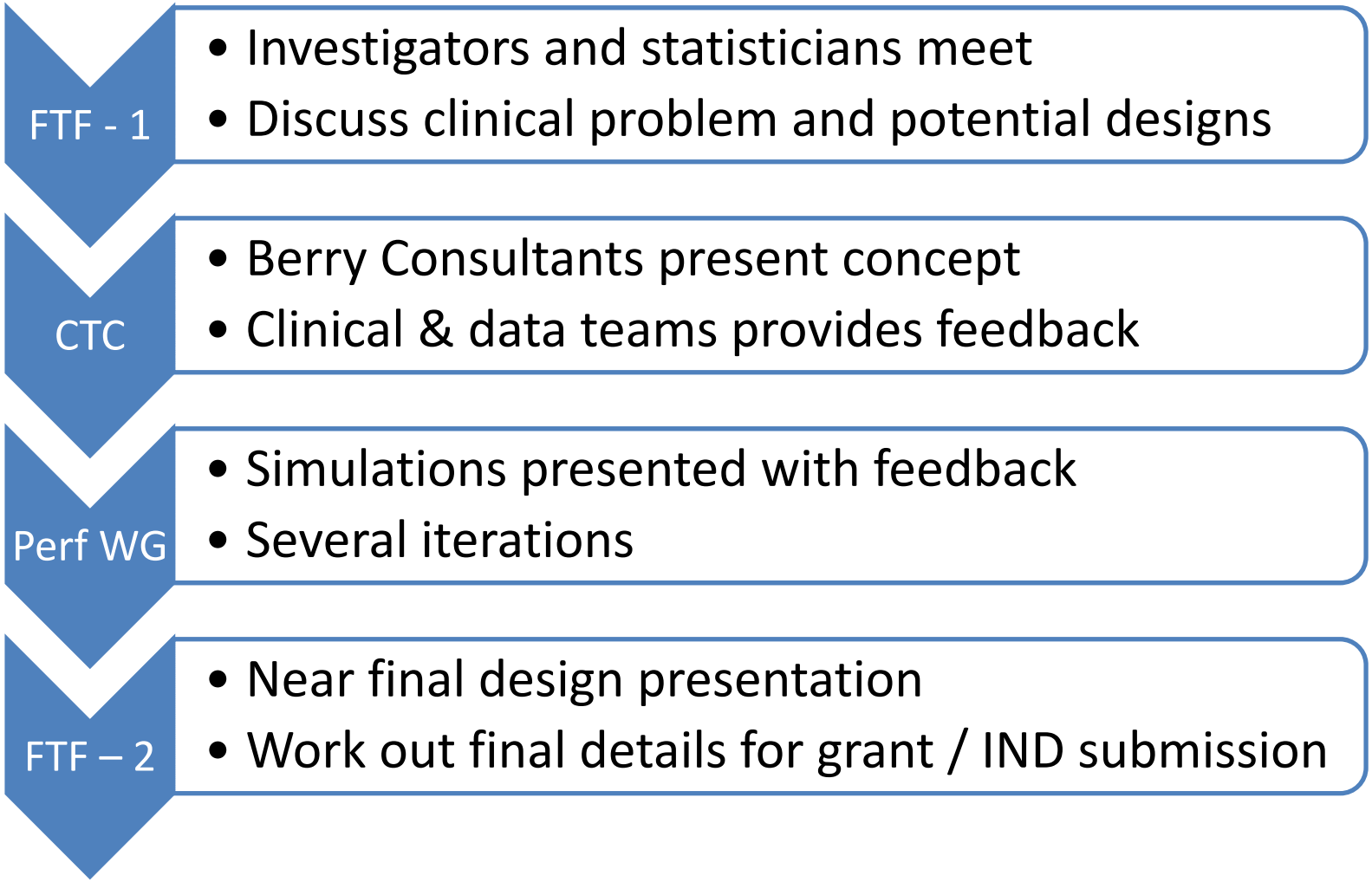
FDA Participants (partial)

- CDER
  - Sue Jane Wang, PhD
  - Robert O'Neill, PhD
- CDRH
  - Gregory Campbell, PhD
- CBER
  - Estelle Russek-Cohen, PhD

NIH Participants

- NINDS
  - Scott Janis, PhD
  - Robin Conwit, MD
  - Danilo Tagle, PhD

ADAPT-IT Process



ADAPTIVE TRIALS for the NETT

- ARCTIC
  - Hypothermia in SCI
- ICECAP
  - Duration of hypothermia after cardiac arrest
- ESETT
  - What is the best second line agent for Status Epilepticus?

Educational Supplement to Adapt-IT

- Funded in 2011
- To develop educational outreach in adaptive designs to the academic community

Objectives of Design-It

1. Introduce adaptive techniques that may enhance the efficiency and the potential value of clinical trials
2. Present examples of the evolution of an adaptive trial design based on scientific, statistical, and operational concerns
3. Participate in the interactive process of moving from trial idea to adaptive design concepts in real time
4. Illustrate the purpose and value of clinical trial simulation