My Experiences as an FDA Statistician

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FDA/CDER/OB/DB3

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Disclaimer

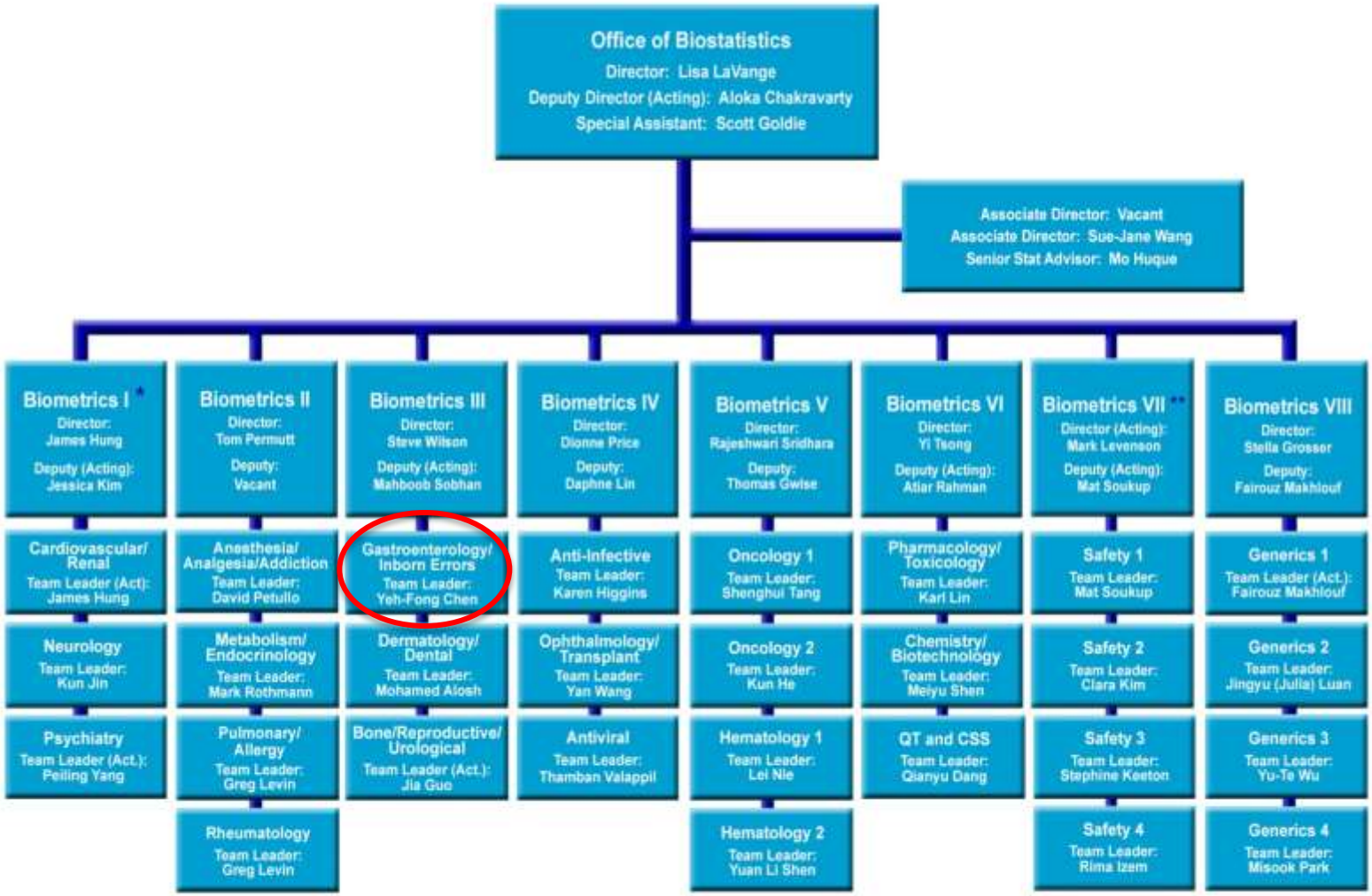
This presentation reflects the views of the author and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.

FDA Mission

- protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation
- advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable
- helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health
- regulating the manufacturing, marketing and distribution of tobacco products

Centers at FDA

- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- Office or Regulatory Affairs (ORA)
- National Center for Toxicological Research (NCTR)
- Center for Biologics Evaluation and Research (CBER)
- Center for Tobacco Products (CTP)
- **Center for Drug Evaluation and Research** (**CDER**)
- Center for Devices and Radiological Health (CDRH)



* Includes Support for Medical Imaging
** Includes Support for OTC

Clinical Trials

- Clinical trials: experiments done in clinical research to answer specific questions regarding biomedical or behavioral interventions, including new treatments
- Depending on development stages, trials may generate data on safety and/or efficacy.
- Drug Development Process:

Phase 0	Phase 1	Phase 2	Phase 3	Phase 4
P-K and P-D Studies in Humans	Screening for Drug's Safety	Establishing for Drug's Efficacy	Final Confirmation of Drug's Safety and Efficacy	Post-Marking Studies

- Investigational New Drug (IND) application: Before Phase 1
- New drug application (NDA): Completion of Phase 2 and 3

ICH E9: Statistical Principles for Clinical Trials

- Phase 2 Exploratory Trials: dose finding for efficacy
- Confirmatory trial: an adequately controlled trial in which the hypotheses are stated in advance and evaluated
- Primary vs. Secondary Endpoints
  - The primary endpoint should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial.
  - Secondary variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives.

FDA Guidance

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

- For drugs approved in US, the sponsors need to demonstrate the drugs are safety and effective with substantial evidence in at least two adequate and well controlled clinical trials.
- When only a single adequate and well-controlled study is conducted to demonstrate effectiveness of a new use, pertinent information from other adequate and well-controlled studies of a drug may be considered.

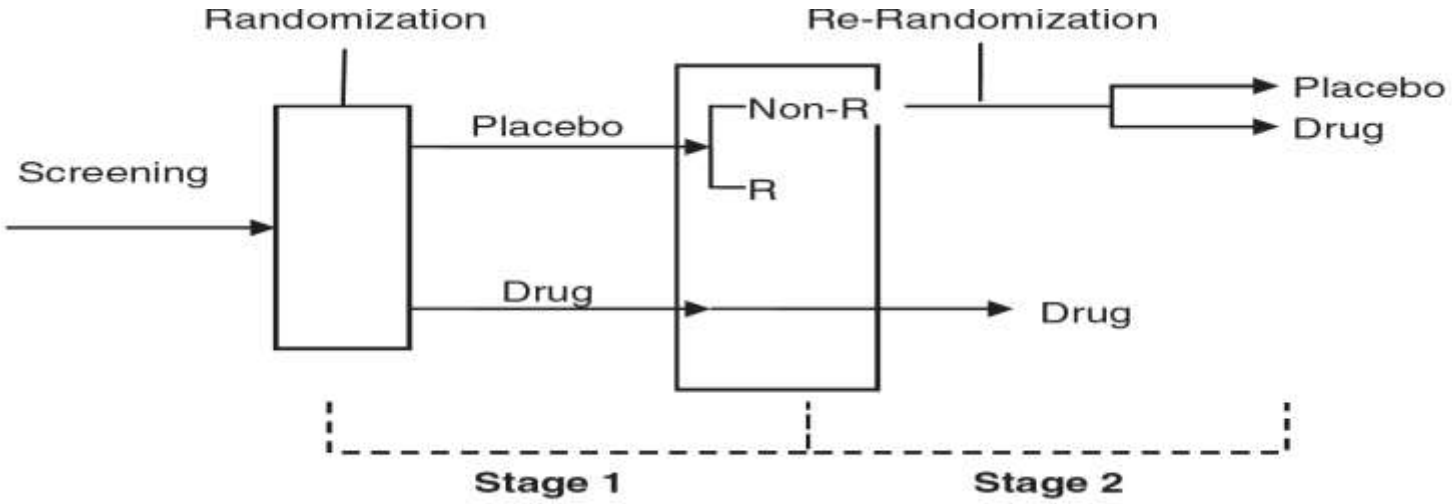
Statistical Hot Topics

- Study Designs

  Enrichment designs and Adaptive Designs
- Determination of Efficacy Endpoint
  - Continuous vs. Binary Endpoints
  - Clinical Outcomes vs. **Patient Reported Outcomes**
  - Co-Primary Endpoints vs. Composite Endpoints
  - Key Secondary Endpoints
- **Multi-Regional Clinical Trials**
- Missing Data Control and Analysis: LOCF, BOCF, MI, MMRM,…,etc.
- Study-wise Type I Error Control in terms of Multiplicity
- Subgroup Analysis
- **Accelerated Approval through Surrogate Endpoint**

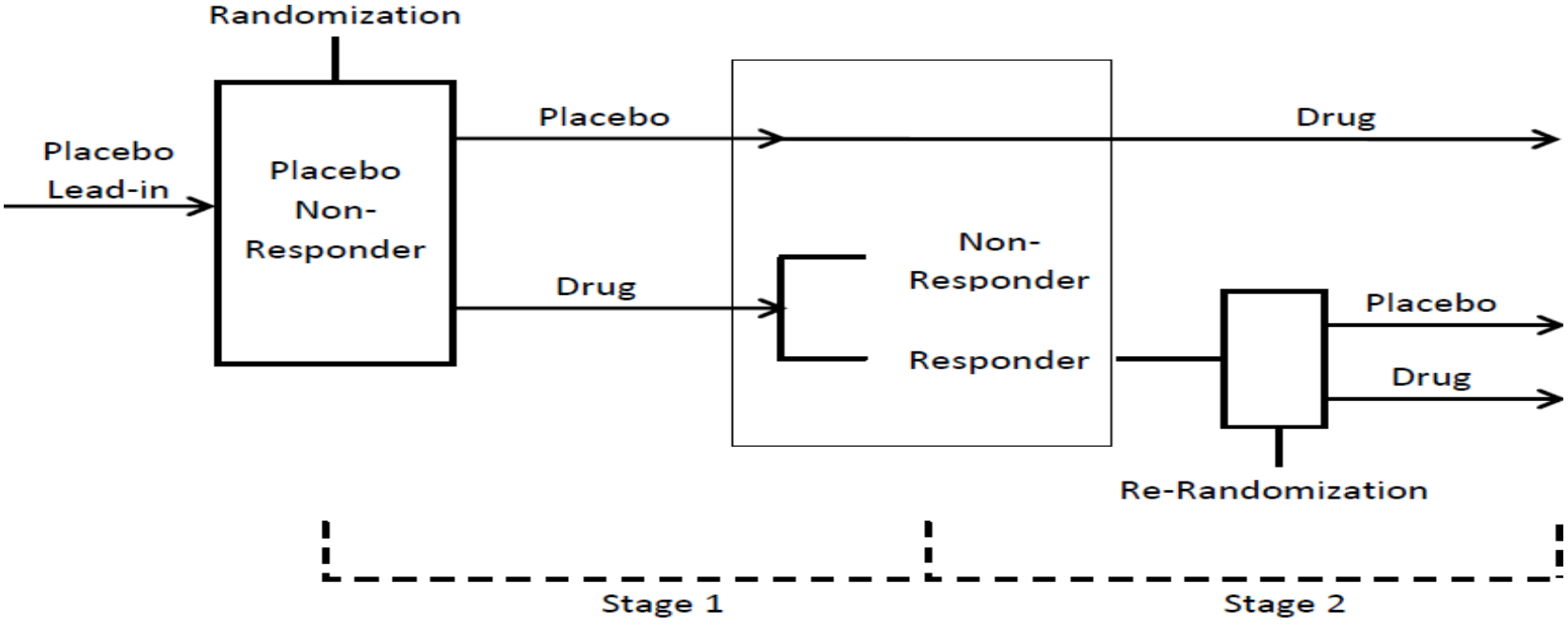
Enrichment Design

- Sequential Parallel Design (SPD) for dealing with high placebo response
  - proposed by Fava et al. (2003) & SPD with re-randomization by Chen et al. (2011)



Enrichment Design

- Sequential Enriched Design (SED) for Dealing with High Placebo Response & Studying Target Patient Population
  - Proposed by Chen et al. (2014)



Rationale of SED

- The target patient population is those who would respond to a drug but not to a placebo.
- A placebo lead-in phase is implemented before randomization to screen out those patients who would respond to placebo at the beginning of the trial.
- At the 2nd stage, only patients who are drug responders will be further re-randomized and studied.

Multi-Regional Clinical Trials (MRCT)

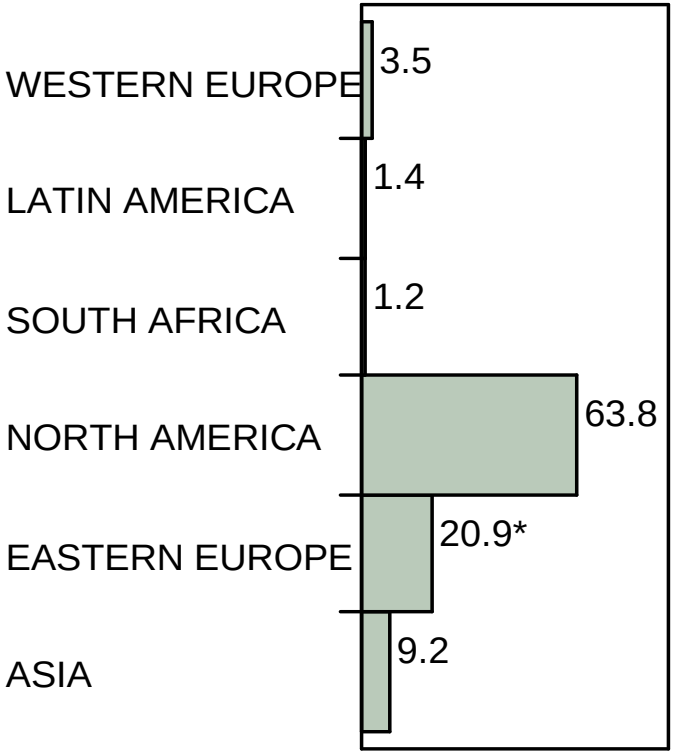
from Khin et al. 2013

- PLATO (Platelet Inhibition And Patient Outcomes) trial

Region	Total N	Ticagrelor N(%)	Clopidogrel N(%)	HR (95% C.I.)	P-Value
Overall	18,624	9,333 (9.8%)	9,291 (11.7%)	0.84 (0.77, 0.93)	<0.0003
Non-US	17,211	8,626 (9.6)	8,585 (11.8)	0.81 (0.74, 0.90)	<0.00001
US	1,413	707 (12.6)	706 (10.1)	1.27 (0.92, 1,75)	0.146

Schizophrenia MRCT DATA

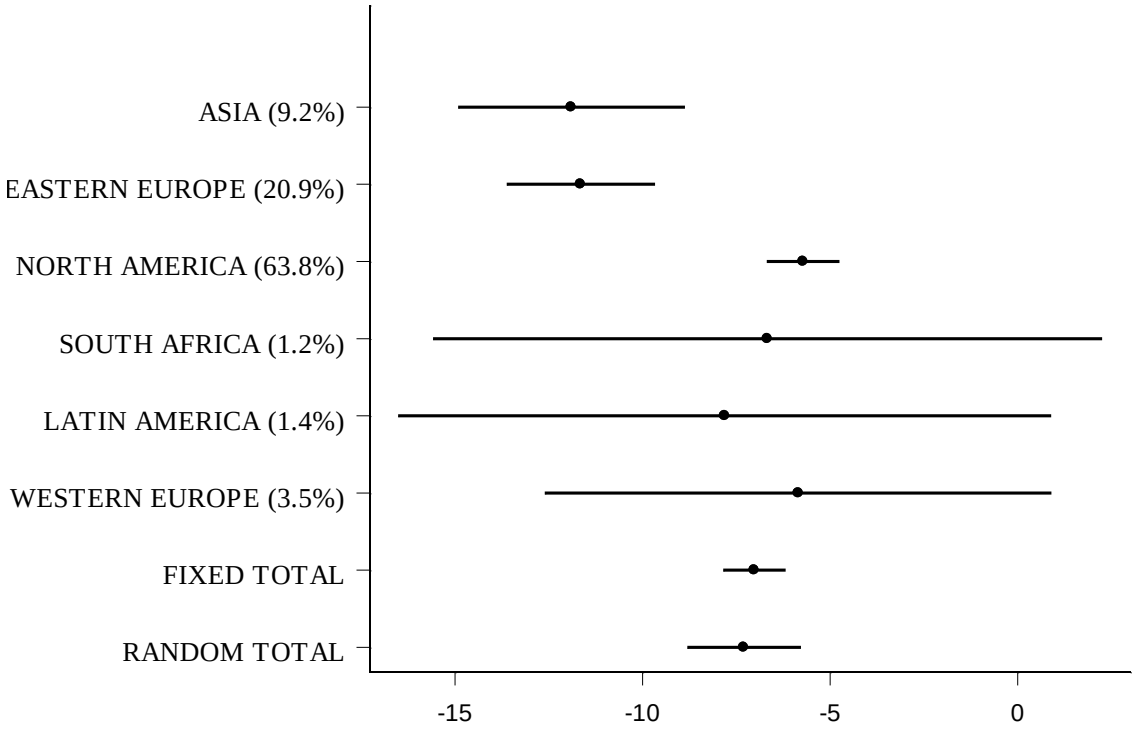
33 Trials with 12,585 patientsfrom Chen et al., 2010



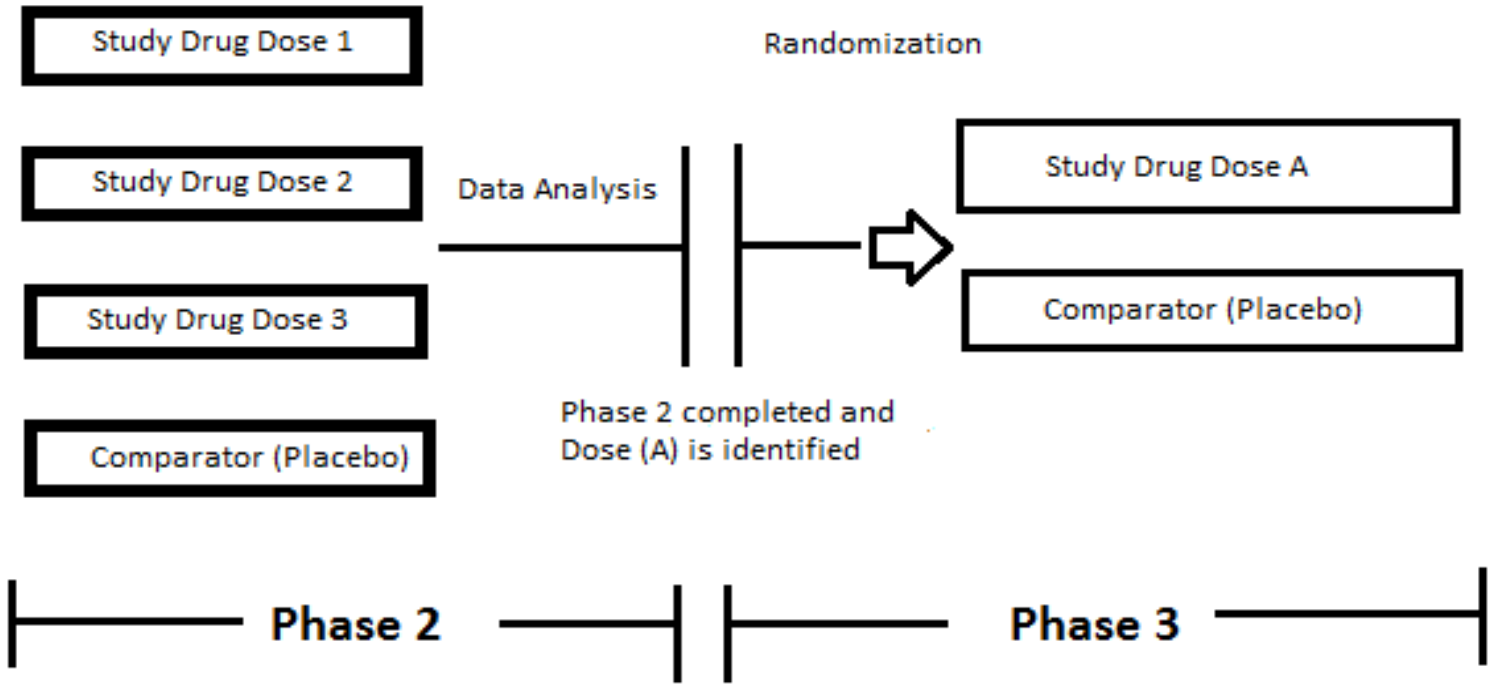
* Russia 7%

Treatment Effect by Region & Average

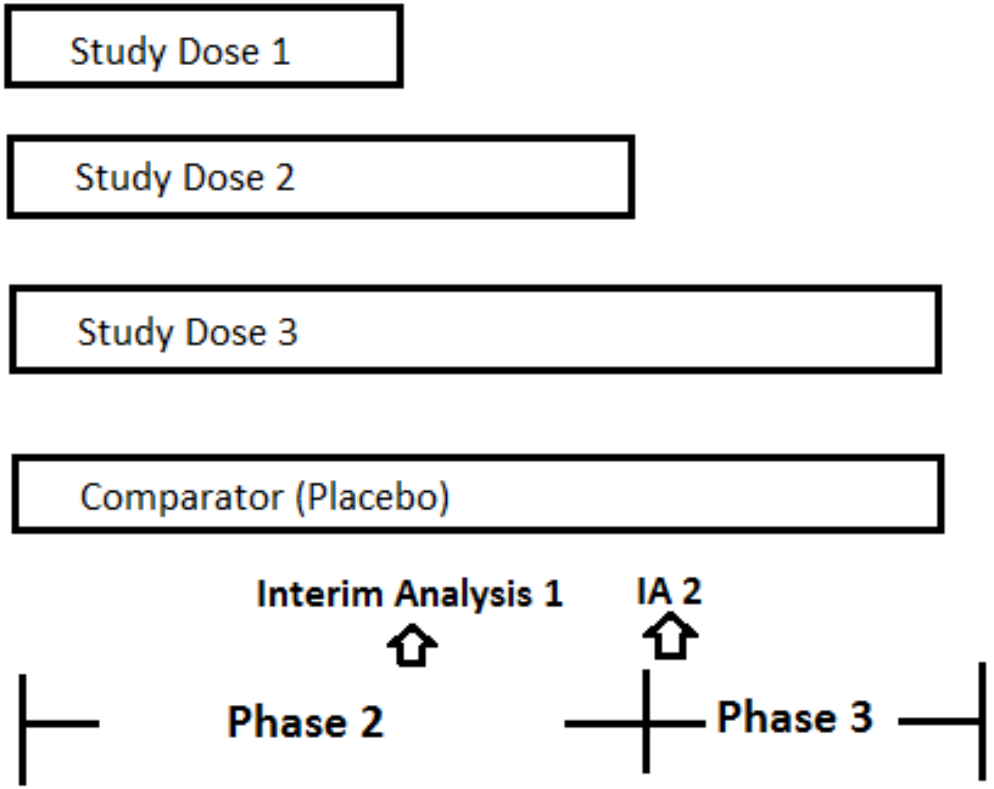
from Chen et al. 2010



Conventional Design for Phase 2 & 3



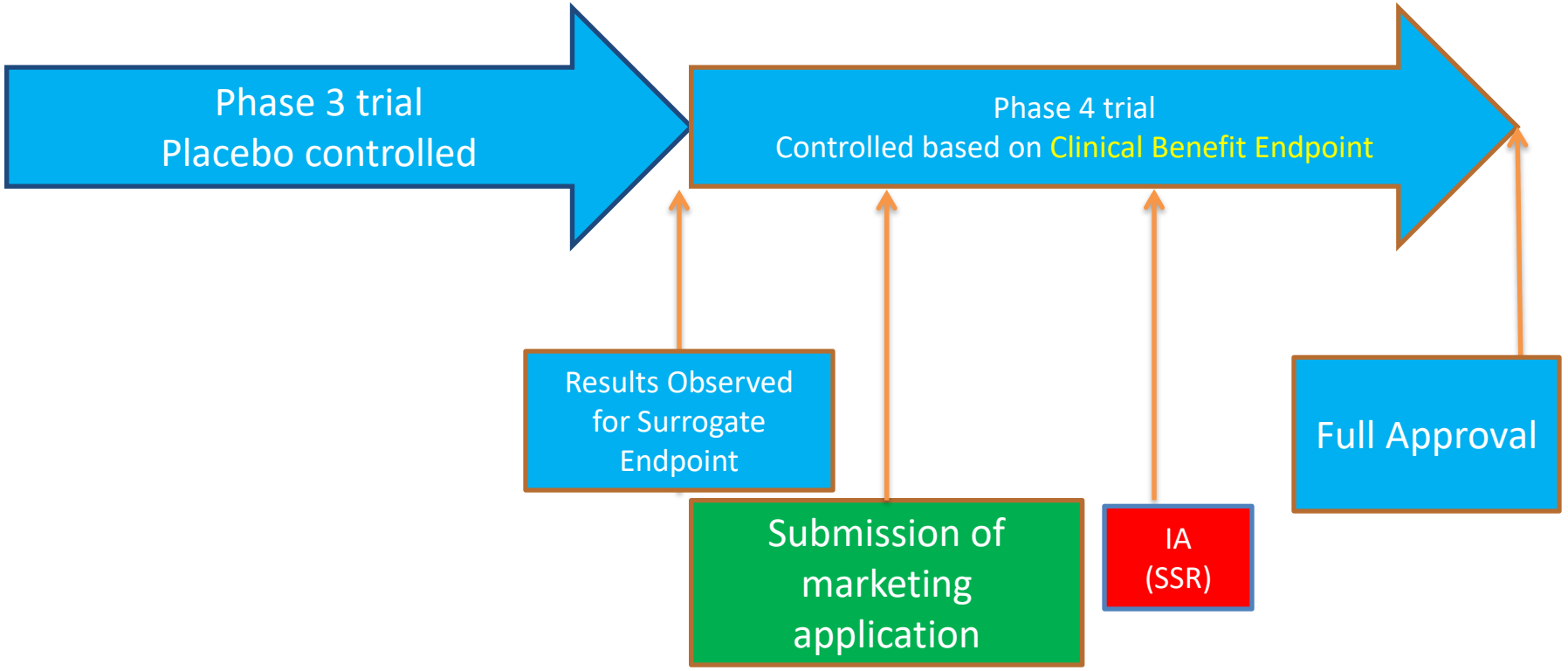
Two-Stage Adaptive Phase 2/3 Seamless Design



Clinical Trials in Pre-cirrhotic Non-alcoholic Steatohepatitis (NASH)

- NASH has been recognized as one of the leading causes of cirrhosis in adults and NASH related cirrhosis is currently the second indication for liver transplants in the United States [Younossi ZM et al., 2015]
- In a recently published study of 108 Non-alcoholic fatty liver disease (NAFLD) patients who had serial biopsies, 47% of patients with NASH had a progression of fibrosis, and 18%, had spontaneous regression of fibrosis over a median follow-up period of 6.6 years [McPherson S et al. , 2015]
- Question: Can any clinical trials for treating NASH be conducted less than 6.6 years? With innovative design?

Phase 3/4 Seamless Design for Accelerated Approval

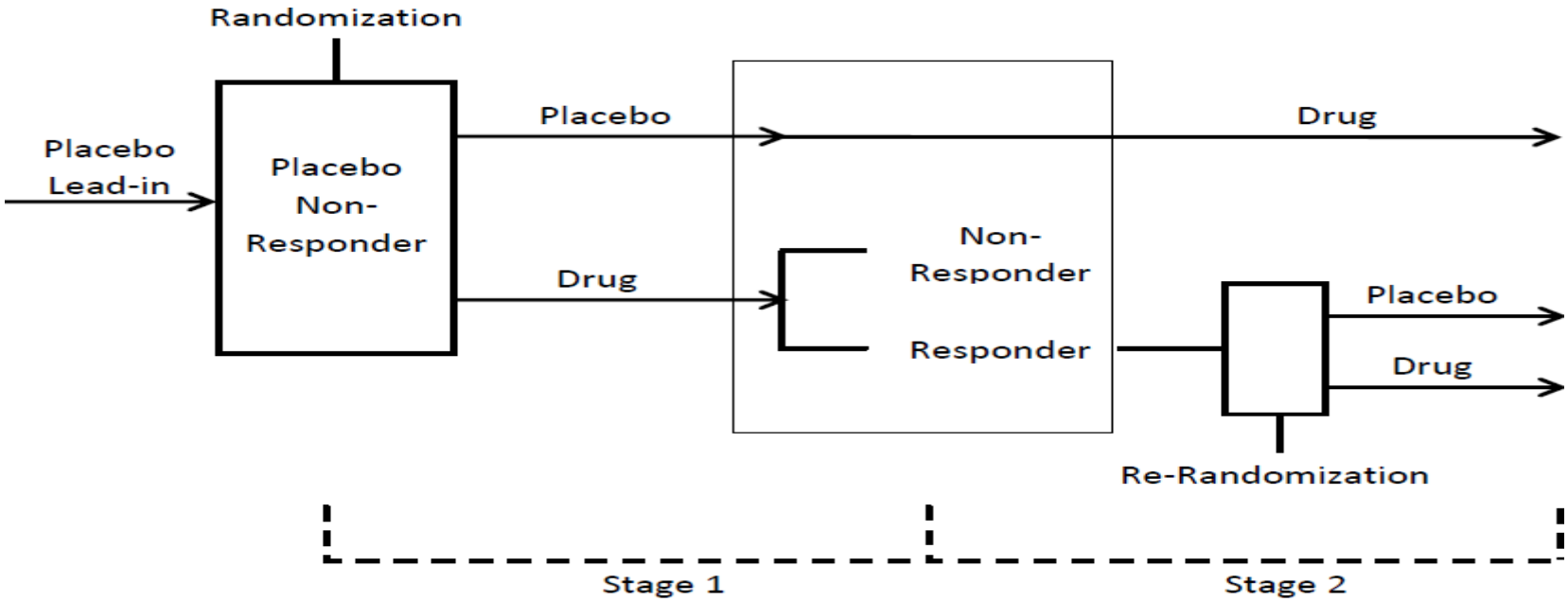


Challenges with Accelerated Approval Trials

- Need to plan far in advance for the entire phase 3/4 trial with the Statistical Analysis Plan submitted prior to trial initiation
  - Major issue: **The overall type I error control**
- Retention of patients in a placebo-controlled trial after marketing approval
  - Placebo control is best
  - Potential for use of historical control, however may lack of data for the sought indication at this time.

  Question: **Can we consider other types of design?**
- FDA Guidance for Industry—*E10 Choice of Control Group and Related Issues in Clinical Trials* (FDA, 2001)

SED to be Considered for dealing with Placebo dropouts at Phase 4



- For NASH trials, the placebo lead-in could be replaced by Vitamin E non-responders.

Concluding Remark

- Working at FDA as a statistician is rewarding
  - Making contributions for protecting public health
  - Personal and professional growth, in particular, have the opportunities to see the overall picture
- Many hot topics that Statisticians can help
  - Ensure the study drugs are safe and effective when marketing in US
  - Come up with innovative study designs, such as different enrichment designs and adaptive designs to shorten the drug development process