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Extension of novel trial designs: addressing the needs, utilizing models and data, and overcoming resistance

FDA Workshop on Innovative Trials

Russell Reeve, PhD
IQVIA, Inc.

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Topic #3: Examples of Innovation in Clinical Development

Sampling of Innovation in Drug Development

Evidence of Efficacy and Safety
- External comparators
- Real-world data

Trial Designs (Protocol)
- Master protocols
- Adaptive designs
- Modeling and simulation
- Precision dosing/medicine

Trial Designs (Operational)
- Virtual trials
- Connected devices
- PROs

Topic #3: Obstacles to Using More Innovative Designs

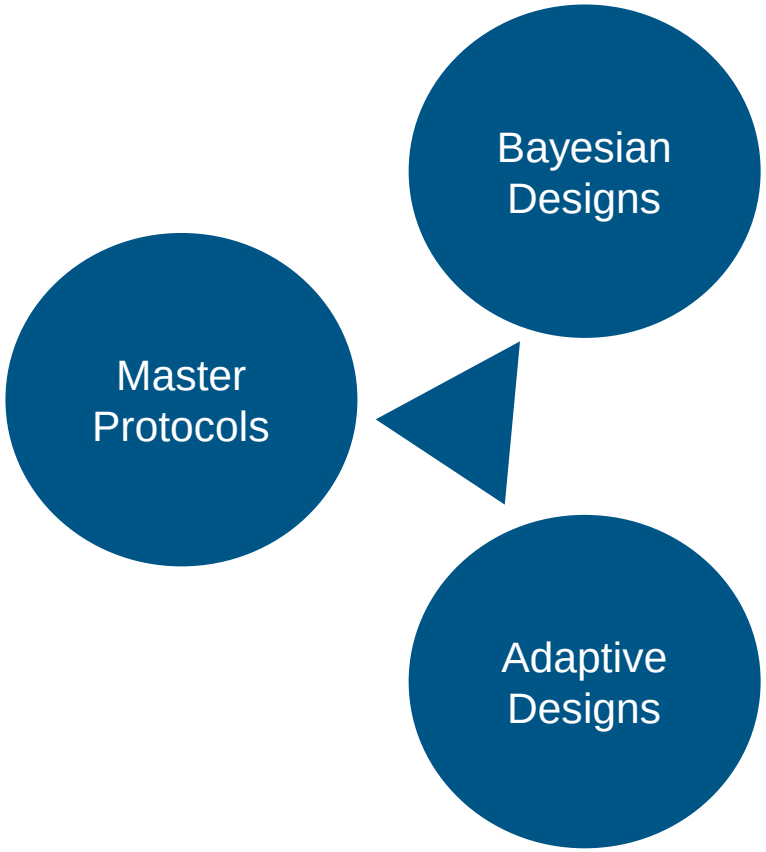
Based on our observations, with different obstacles in different organizations

- Not always appropriate, or useful
  - Example: Endpoint at 1 year is needed, with recruitment finished in 1.5 years
- Timing
  - Typically take longer to design than traditional trials, but reduce overall development timelines
- Lack of expertise
  - Would include statistical, regulatory, and medical expertise in novel trial designs
  - Fear of lack of interpretability
- Conservatism of sponsors and regulators
- Uncertainty of acceptance by regulatory agencies
  - Has been somewhat alleviated by recent guidances

- More experience, case studies, when appropriate and not
- Encourage holistic view of development process, including risk and time-to-market
- Conferences, short courses, and workshops would be helpful
- Hackathons on trial design: Multidisciplinary
- Simulation games

Master Protocols, Bayesian, Adaptive

Allow borrowing among subprotocols, and adding, stopping, or expanding arms



Subprotocols may have similar characteristics

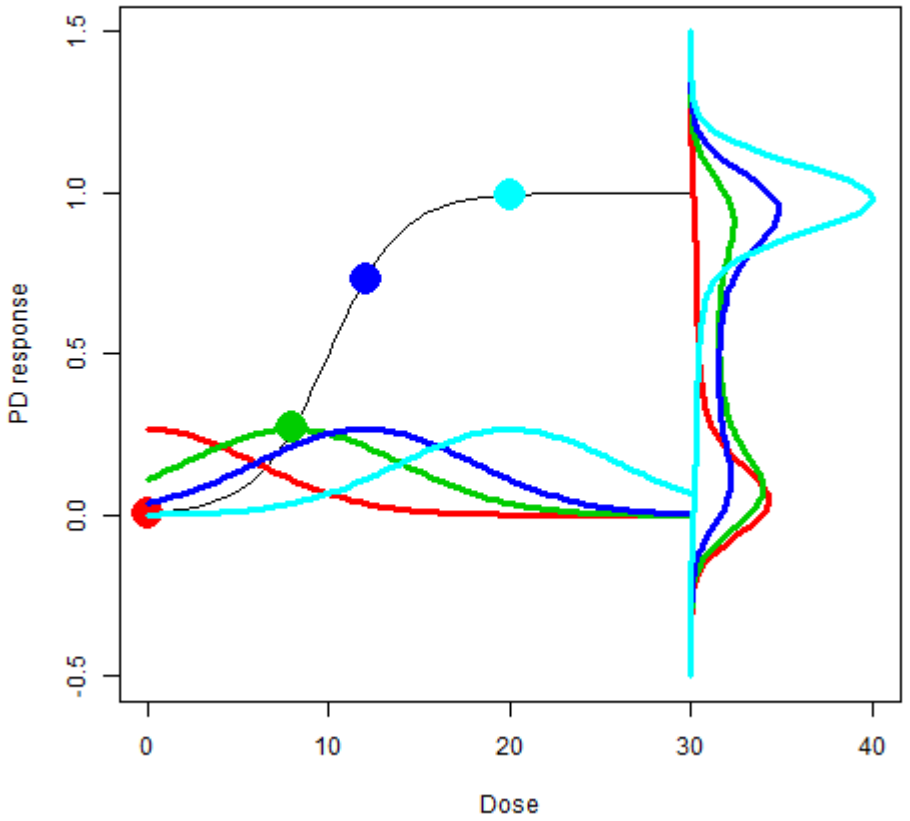
- Response relative to control may be similar among arms
- Response of different compounds with similar mechanism of action may be similar
- May have some arms that vary
- Cluster hierarchical model would be appropriate

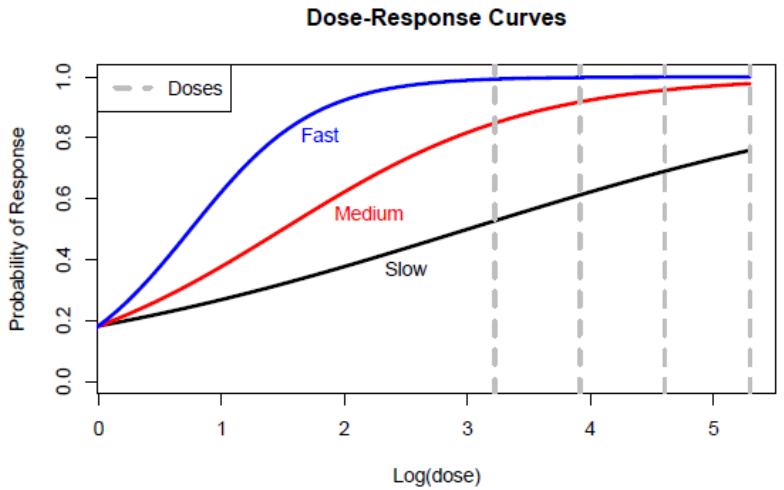
Adaptive nature allows for more efficient trial and decision making

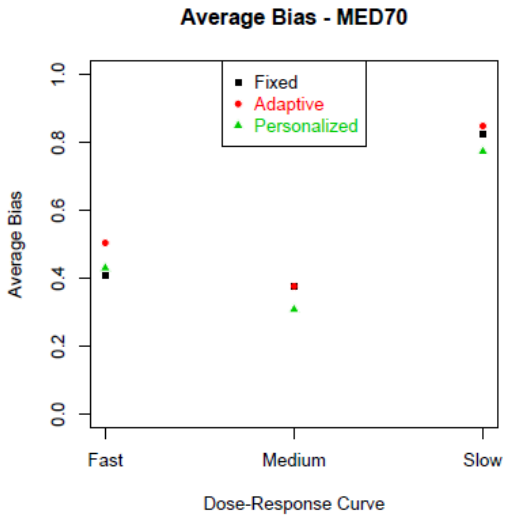
Hesitancy to combine product with other companies. Need patient advocacy or disinterested third-parties to support, while maintaining confidentiality.

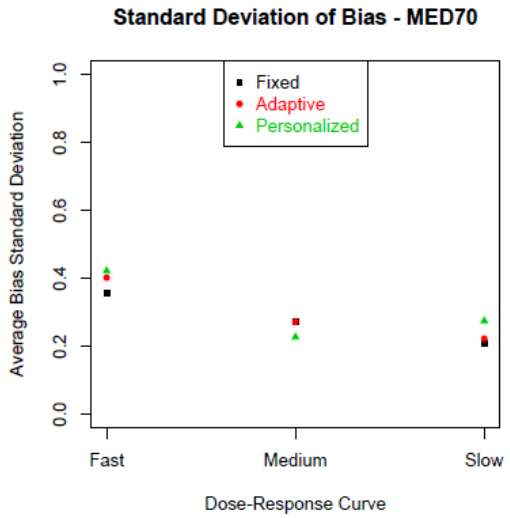
Precision Dosing

Improve efficiency via reduction in PK variability



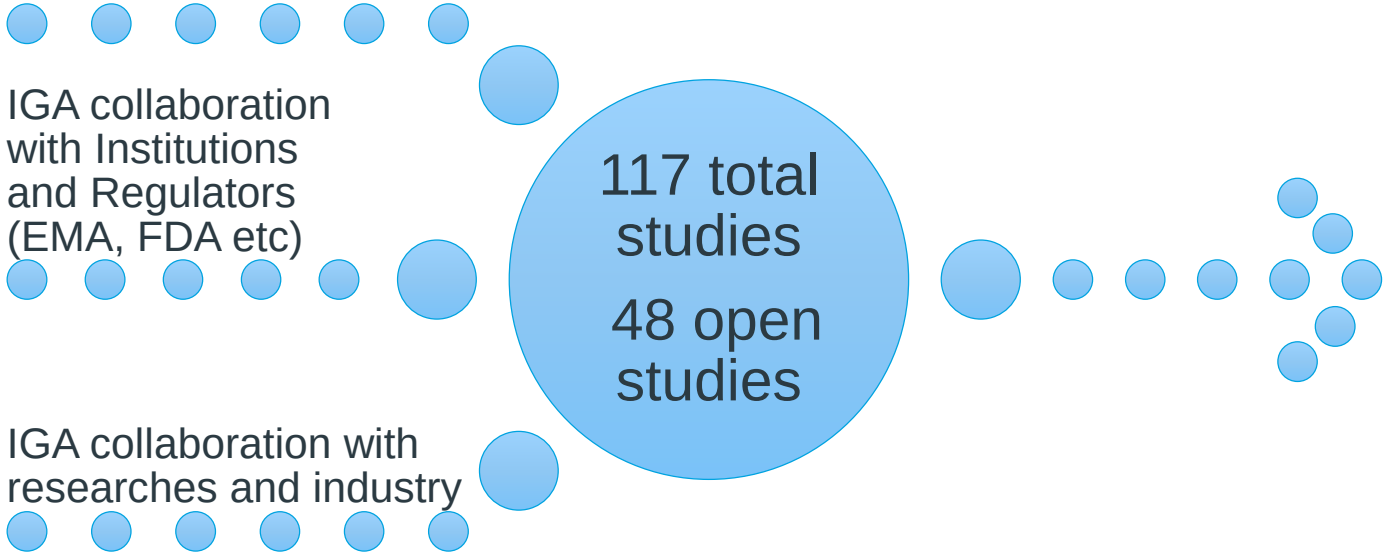






Gaucher Disease as an example of orphan drug development: demonstrating benefits of innovative approaches

1994 - meeting of European Working Group on Gaucher Disease
2018 - formation of International Gaucher Alliance (IGA)



International Collaborative Gaucher Group Registry (ICGG) established in 1991: • >60 countries • Anonymized data on >6000 patients representing some 54,000 patient-years of follow-up experience	
17	Natural history/observational studies
14	Follow up studies with approved therapies (mostly single arm with M/S)
4	Single arm studies for new therapies
3	Stem Cell therapy studies with a basket trial design
2	Screening studies of undiagnosed patients studies
1	Study to analyze molecular and clinical mechanisms of relationship between GBA mutations and Parkinson's disease
6	Other studies: device/biomarker assessment

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Reference: International Gaucher Alliance (IGA): https://gaucheralliance.org/gb/home
ClinicalTrials.gov (NCT00358943)

Lessons Learned

- Patient registries and natural history studies are critical for clinical development
- Statistical Modeling should be incorporated in clinical program
- Innovation in Clinical Trial Design is essential: adaptive design, master protocols, multi-arm, platform, basket studies as well as decentralized/virtual studies
- Patient engagement in study design is important
- Distraction and Deviation from traditional approaches is **GOOD:** May you live in interesting times…
- ***Think Rare – Think Innovative!***

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Providing Evidence of Benefits

Benefits are derived from mathematics, so are generalizable

- Disease areas affect characteristics, such as
  - Timing and type of endpoints
  - Recruitment rate
  - Treatment effect
  - Placebo effect
  - Options available in treatments
- Given this, the mathematics will describe the operating characteristics of the designs

- Difficult to show mathematically benefits, but generally Monte Carlo simulation methods will demonstrate it
  - Precision dosing has mathematical proof
- Need to simulate over wide range of possible states of nature

- How have we shown benefits of innovative methods
  - For platform trials, have developed costing and operational models for both traditional approach and platform approach
    - › Allows trialists to see benefits, and breakeven points in their specific application
  - Trial simulations
    - › In adaptive design, simulate both adaptive designs and more traditional fixed designs
      - » Simulations can include both statistical properties, and trial operating properties (time to complete, costs, distribution of sample size, etc.)
      - » Effect of better design on value of asset (financial aspect for sponsors need to be considered as well)

Topic #5: Suggestions to Encourage More Widespread Use of Innovative Designs

FDA can lead the way

- Forum for discussing innovative designs among regulatory, industry, and academic stakeholders
  - Example: ISCTM held adaptive design workshop, where we discussed nitty-gritty, and this was very helpful
  - Hackathons on developing designs

- Conference sessions
  - Discuss case studies on innovative design
  - More details than customary
  - Decision making processes
  - Comparison of different type of designs

- Guidances
  - Keep up the guidances
    - › These are very helpful
  - Word in such a way as to not be limiting
    - › E.g., adaptive design guidance with “well-understood” terminology

- Master Protocols
  - Work with patient advocacy groups, clinical trial nonprofits
  - Bayesian decision making
  - Pre-fabricated platforms for areas of high unmet need