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

*FDA Workshop on Innovative Trials*

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Sampling of Innovation in Drug Development

Topic #3: Examples of Innovation in Clinical 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)

IGA: Focus on Patient

IGA collaboration with Institutions and Regulators (EMA, FDA etc)

IGA collaboration with researches and industry

117 total studies
48 open studies

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
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!*
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