U.S. FOOD & DRUG ADMINISTRATION

Welcome to ADEPT 7: Advancing Complex Innovative Trial Designs to Accelerate Drug Development in Pediatric Patients

Session 2: Bayesian techniques in Pediatric Studies

Bayesian Techniques (1/2)

- Bayesian techniques are a statistical inference framework that allows incorporation of prior information in the data analysis.
- We can use relevant prior information to reduce the number of patients needed in pediatric trials.
- The focus of the discussions today will be on how to use these methods in support of pediatric extrapolation.

Bayesian Techniques (2/2)

- Important factors when using these methods:
  - How to weight the prior information and discount the information.
  - Understanding the operating characteristics which require complex simulations.
- Need more back and forth discussion and work to reach agreement on the trial design.

Other Data Borrowing Methods

- While the session is focused on Bayesian methods, there are also non-Bayesian methods that can borrow information.
- These methods pose similar issues and require comparable discussion to implement.

Complex Innovative Trial Design (CID) Program

- Officially launched in August 2018, the CID Meeting Program is an FDA-led meeting program which supports the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs.
- The program provides two additional meetings to discuss specific CIDs proposals.
- This program will continue under PDUFA VII.

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-pilot-meeting-program

Progress to Date

- 5 accepted submissions span several therapeutic areas
  - Neurology
  - Analgesia
  - Rheumatology
  - Oncology
- Designs incorporated
  - Bayesian hierarchical modeling
  - Use of formal priors
  - Formulation of a master protocol

CID Case Example 1

- Summary:
  - Randomized, double-blind, placebo-controlled, phase 2/3 trial
  - Population: Duchenne muscular dystrophy
  - Bayesian adaptive design with the following potential adaptations:
    - Stop the trial for efficacy or safety
    - Modify the sample size
    - Drop an arm
    - Pool doses
    - Change randomization ratio
  - Also proposed to explore placebo augmentation with historical controls

https://doi.org/10.1002/sim.9021

CID Case Example 2

- Summary:
  - Randomized, double-blind, group sequential, non-inferiority trial
  - Population: pediatric multiple sclerosis
  - Bayesian framework utilizing meta-analytic predictive priors to leverage information from external adult and pediatric studies

Agenda: Day 2

- **10:10-11:05 am: Regulatory perspective**
  - 10:10-10:30: FDA Perspective (Mark Rothmann, FDA)
  - 10:30-10:45: EMA Perspective (Andrew Thomson, EMA)
  - 10:45-11:05: Industry Perspective (Meg Gamalo, Pfizer)
- **11:05-12:15 pm: Case examples**
  - 11:05-11:20: Belimumab approval for pediatric systemic lupus erythematosus (Nicky Best; Anne Hammer, GSK)
  - 11:20-11:50: Assessing disease similarity: multiple sclerosis in adult and pediatric patients (Paul Lee, FDA)
  - 11:50-12:15: Bayesian approach to support pediatric extrapolation in multiple sclerosis (Marius Thomas and Dieter Häring, Novartis)
- **12:15-1:00 Break**
- **1:00-2:50 pm: Q&A and Panel discussion**
  - **Q&A: All speakers**
  - **Panel discussion:** Nikolay Nikolov (FDA), Mark Rothmann (FDA), John Lawrence (FDA), Paul Lee (FDA), Robert Nelson (J&J), Forest Williamson (Lilly), Anna Shmagel (Abbvie), Mathangi Gopalakrishnan (Univ. of Maryland), Andrew Thomson (EMA)
- **2:50-3:00: Closing remarks (Lynne Yao)**


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