***The Cures Act: Novel Clinical Trial Designs***

 by Larry Schwartz

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***Introduction***

The Adult Polyglucosan Body Disease Research Foundation (APBDRF) is entering into a clinical trial phase. Currently, the Foundation is planning a clinical trial to test the safety/efficacy of Guaiacol for APBD patients in the United States; a similar trial will first take place in Israel. Also, the APBDRF has other research projects at various stages of development.[[1]](#footnote-1) At last count, the APBD registry has 100 people to draw upon for such clinical trials.

The FDA concurred with the Metabolic Institute of Dallas’s use of the Crossover design in its Triheptanoin Phase 2 clinical trial for APBD, completed in 2015. By definition, the Crossover design for a clinical trial assigns APBD participants to a control group at one time and to a treatment group at another time. As a result, the comparison of participants against themselves precludes *intra*-patient heterogeneity in the clinical trial. But the Crossover design does not solve the problem of *inter*-patient heterogeneity or extreme variability across patients.[[2]](#footnote-2)

Currently, a Crossover design for a clinical trial is “locked in” once it has begun. That is, once the endpoints, protocol and other trial features are defined they are held constant throughout the entire conduct of the clinical trial.

In 2010, the FDA considered adding an adaptive feature to the design of a clinical trial. That would allow prospectively planned modifications to one or more aspects of the clinical trial as long as they are tied to the participants’ data at the baseline or later interim points. The FDA put out a draft guidance on such adaptive clinical trials for comment, entitled “Adaptive Design Clinical Trials for Drugs and Biologics,” but it was never made final.

With the December 2016 passage of the Faster Cures 21st Century Cures Act----specifically Section 3021, Novel Clinical Trial Designs---the FDA has turned once again to the adaptive design for clinical trials**.** On 20 March 2018, the FDA convened an all-day public workshop, entitled “Promoting the Use of Complex Innovative Designs [CID] in Clinical Trials,” with statisticians, Pharma, academicians, clinicians, and care givers. As a result, in the next year or so, the FDA plans to do a pilot CID study that works with the latest analytical tools (more on these tools later).

In this paper, I cover the practical significance of adaptive clinical trials for the Foundation. My primary sources are the transcript of the 2018 CID workshop and the draft of the 2010 adaptive trial guidance. The two overlaps considerably.

***Single trial that incorporates phases 1 and 2 trials***

The 2018 workshop on adaptive clinical trials covers “rolling up” traditional phase 1 and 2 trials into a single trial (the 2010 guidance does not cover this). It requires a trial plan that spells out the intentions and detailed rules for combining the two phases into a single trial. The adaptive rule is straightforward: If Phase 1 successfully establishes safety, then Phase 2 “kicks in” seamlessly and with little if any delay; if not successful, the trial would end with Phase 1, as is the case now. By combining these two phases into a single trial, the study effort would take place more quickly and at reduced costs---a key goal of the Cures Act. Also, it would be relatively easy to implement and entail virtually no risk to the integrity of the clinical trial.

***Types of adaptive changes to a clinical trial***

Both the 2010 and 2018 initiatives break down adaptive changes into medical and statistical types. The medical type includes adaptively changing the primary endpoint, dosage level, or treatment arms. The statistical type includes adaptively changing the sample size, the power of the test, or analytical methods to evaluate endpoints. The intentions and detailed rules for making either type of change would have to be pre-specified in detail before a trial begins.

***An example of adaptive treatment arms for a clinical trial***

To change treatment arms with the baseline data, the author wrote: “The Case for APBD Trials with Two Arms,” January 15, 2018; see Design/protocol,

[**https://apbdrf.org/research/clinical-trial-considerations**](https://apbdrf.org/research/clinical-trial-considerations)

Using the baseline data from the Phase 2 Triheptanoin Clinical Trial for APBD, the author demonstrates how to break down its highly heterogenous APBD participants (*inter*-patient variability) into two relatively homogeneous sub-groups, “mild” and “severe.” This is accomplished by applying the statistical technique of cluster analysis to the baseline ages of the participants and to the primary endpoint, distances they cover in a six-minute walk. The two-armed trial would not only show the treatment effect for the aggregate, as the one-armed study does, but also the treatment effect for each of the two sub-groups. A statistician and principal medical person should be co-investigators to prespecify the intentions and detailed statistical and medical rules for making such a change with the baseline data of the trial.

***Expectations of an adaptive clinical trial***

According to the FDA, drug developers believe that adaptive changes to a clinical trial could be more efficient (e.g., revealing shorter durations and fewer trial participants) and increase the likelihood of success (e.g., freedom to make mid-stream changes to dosage levels and treatment groupings). The FDA agrees with the drug developers on these potential advantages but is also concerned with the “possible introduction of bias and the increased possibility of an incorrect conclusion.” To minimize these risks, the FDA says it is imperative to blind treatment group assignments and interim analyses; various statistical procedures are mentioned to correct for remaining errors.

***The complexity of multiple adaptive changes to a clinical trial***

Adaptive designs can be quite complex when introducing multiple changes to a clinical trial. “Multiple” is used in two senses: Changing more than one trial feature at a given interim trial point or changing trial features at different interim points.

Multiple adaptive changes introduce added complexity to the planning for clinical trials. To deal effectively with that complexity, the FDA believes that the study team should use more advanced planning tools than simply paper and pencil. The advanced tools include computer simulation to numerically integrate the multiple adaptive changes under consideration [[3]](#footnote-3) and Bayesian statistics to evaluate their likely merits. [[4]](#footnote-4) (The classical statistics normally used to draw conclusions on the overall effects of a drug remain the same.) These advanced tools will be demonstrated in the CID pilot.

Multiple adaptive changes for a clinical trial carry with it three heavier burdens. First, special arrangements have to be made to maintain the confidentiality of any and all interim results for avoiding bias. Second, increased documentation goes hand in hand with the additional interim analyses. And third, more frequent meetings between the FDA and the medical-statistical investigators are inevitable.

***Author’s summary of trial designs for APBD***

According to the FDA, the basic design for APBD clinical trials should be the **Crossover design**. Also, the **two-armed** Crossover design with separate mild and severe groups would reduce APBD heterogeneity. Finally, an **adaptive** two-armed Crossover design could provide further insights for or speed-up an APBD treatment or cure.

***References***

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1. **See the following link for a complete set of APBD research projects in the pipeline:** [**https://apbdrf.org/research/what-were-working-on**](https://apbdrf.org/research/what-were-working-on) [↑](#footnote-ref-1)
2. **The author has measured the heterogeneity of APBD patients in six-minute walking and found that it was four times as great as what an assay laboratory would accept for its work. See “*Heterogeneity in the APBD Condition: The Case of the Triheptanoin Trial*,” January 2018; see Heterogeneity of the APBD Condition,** [**https://apbdrf.org/research/clinical-trial-considerations**](https://apbdrf.org/research/clinical-trial-considerations) [↑](#footnote-ref-2)
3. ##  Jadhav, S. “In Modeling and Simulation in Clinical Trials: Real Potential or Hype?” Applied Clinical Trials, February 2017:

**….” Recently, many of the** [**major pharmaceutical companies**](http://pharma.bayer.com/en/innovation-partnering/technologies-and-trends/research-technologies/virtual-drug-tests/) **have begun to explore computer-based bio-simulation strategies to help generate the information necessary to make better decisions… These strategies go by many different names – clinical trial simulation (CTS), modeling and simulation (M&S), computer-assisted trial design (CATD), ... The** [**FDA**](https://www.federalregister.gov/documents/2016/03/07/2016-04965/mechanistic-oral-absorption-modeling-and-simulation-for-formulation-development-and-bioequivalence) **and** [**EMA**](https://www.ncbi.nlm.nih.gov/pubmed/23835942) **regulatory agencies have also taken notice of M&S strategies in an effort to support improved drug development efficiencies…”** [↑](#footnote-ref-3)
4. **Alvarez, J. “Introduction to Bayesian Adaptive Study Designs.” Biostatistics Department, Vanderbilt University of Medicine, November, 2011: “Challenges of adaptive designs: Require specialized statistical expertise and large time investment...”** [↑](#footnote-ref-4)