STATISTICAN TO JOIN CLINICAL RESEARCH TEAM

by Larry Schwartz, December 2017

INTRODUCTION

The Adult Polyglucosan Body Disease Research Foundation (APBDRF) is gearing up for a clinical trial to test the safety and efficacy of Guaiacol in treating APBD patients in the United States. There is about 160 known APBD cases, and the Foundation's registry has somewhat less than 100 of them. A similar trial will first take place in Israel.

In the literature, a strong case is made for a statistician to be part of the research team not only to analyze the clinical trial results, but also to collaborate on its design and study protocol.[1] Accordingly, the Foundation should seek a qualified statistician to be a co-investigator of the Guaiacol clinical trial for APBD in the United States.

Below I summarize some clinical trial issues and the role of the statistician in addressing them.

ISSUES and ROLES

***Trial Design**: The Parallel Design does not seem appropriate for the Guaiacol trial; the Crossover Design does. But are there other designs?*

The FDA-NIH Workshop on Natural History Studies of Rare Diseases, May 2012, warns rare disease investigators not to use a patient registry to allocate some patients to a control group and others to a treatment group; the heterogenous nature of rare diseases is not sufficiently well understood to ensure that separate but equally afflicted patients are so allocated. APBD is no exception. As a result, the Parallel Design would not be a good choice for this APBD trial. We expect the statistician to work with the other investigators to select the appropriate Guaiacol clinical trial design for APBD; in the Triheptanoin clinical trials for APBD, 2007-2015, Phase 1 used the Single Group Assignment and Phase 2 the Crossover Design.

***Surrogate Primary Endpoint:** Measuring glycogen levels might be a good biomarker and serve as a surrogate primary endpoint. Are there others?*

Dr. Schiffman pointed out that glycogen levels might be a biomarker for the Guaiacol trial. Specifically, *"Glycogen content can be evaluated in skin, muscle and non-invasively using the method of a (13) C nuclear magnetic resonance (NMR) spectroscopy; there is a group in Minnesota that does that…"* If chosen as a surrogate primary endpoint, the statistician should work with the other research investigators to define the sample size necessary to power the detection of a specified mean difference of glycogen levels at a 0.05 error rate.

[1] See Beverley Adams-Huet and Chul Ahn, "Bridging Clinical Investigators and Statisticians: Writing the Statistical Methodology for a Research Proposal", Journal of Investigative Medicine, Volume 57, Number 8, December 2009.

Secondary Endpoint(s): **The Six-minute Walk does not have a good record for sensitivity; the ALS Functional Rating Scale does. But we still need a measure of bladder problems**.

Thus far, investigators have focused on four measures as endpoints (primary or secondary) for APBD trials:

(1) The Six-minute walk (6MW) ---an objective measure;
(2) The 13-item Spastic Paraplegia Rating Scale (SPRS)---subjective measure;
(3) The Rand 36-item Health Survey (36HS) ----subjective measure; and
(4) The 10-item Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS)--a subjective measure.

With a range of disease/condition trials documented online, I compiled the correlations for the validity, reliability, and sensitivity of the four potential primary endpoints against their clinical measures.[2] Then averaged the correlations for each of the three properties in each of the four potential primary endpoints (12 in total); summarizing their strengths as follows:

"Weak" for a correlation less than .70;
"Moderate" between 0.70 and 0.85; and
"Strong" greater than 0.85.

As shown in the Table 1 below, the ALS Functional Rating Scale had the best sensitivity record, along with good properties of validity and reliability.

Table 1. Strength of Measures for Meeting Desirable Properties

PROPERTY	***POTENTIAL PRIMARY ENDPOINT***			
	6MW	**SPRS**	**36HS**	**ALSFRS**
Validity	**Moderate**	**Strong**	**Moderate**	**Moderate**
Reliability	**Moderate**	**Strong**	**Moderate**	**Moderate**
Sensitivity	**Weak**	**Weak**	**Weak**	**Moderate**

We expect the statistician to work with the other investigators to ensure that the validity, reliability, and sensitivity of any secondary endpoint is thoroughly considered in the upcoming Guaiacol clinical trial for APBD in the United States.

[2] Schwartz, Larry, Evaluations of Potential APBD Primary Endpoints, February 2017. These evaluations were based upon the online material readily available at the time of the inquiry.

Statistical Tests: ***The clinical trial should limit the number of primary or secondary endpoints to avoid the problem of false positives***.

The FDA is very concerned about reaching false positive conclusions in clinical trials.[3] In statistical testing for the safety and efficacy of a drug, the FDA limits the risk of a false positive conclusion (Type I error probability) to 1 in 20 chances (probability of .05); or a 95 percent confidence level. The statistical test procedures are straightforward when working with a single primary or secondary endpoint, but much more difficult when working with multiple primary or secondary endpoints

When working with multiple endpoints, greater risks of false positives may arise. The following (joint probability) formula shows the relationship between the number of multiple endpoints and the risks of false positive conclusions: $[1-(0.95)^n]$; where n equals the number of endpoints and 0.95 the confidence level. With n=4 primary or secondary endpoints, for example, the Type 1 error probability deteriorates to 0.19 (almost 1 in 5 chances). Such a large risk is unacceptable to the FDA.

With such multiple endpoints, the FDA requires that a statistician employ the appropriate multiplicity adjustment methods to ensure adequate control for the Type I error. Several methods are outlined in the FDA Guidance and the statistician should work with the other investigators to select the appropriate adjustment method if that should become necessary.

Better yet the statistician should work with the other investigators to limit the number of secondary endpoints to two or three. Or when that is not possible, to develop composite endpoints or endpoint indexes that circumvent this statistical problem.

GENERAL REQUIREMENTS: The selected statistician will have a Ph.D. in statistics; have significant experience with rare disease clinical trials in the past five years; and have expert knowledge of the issues illustrated here.

[3] FDA, Multiple Endpoints in Clinical Trials: Draft Guidance for Industry, January 2017.