The Impact of Attrition: The Dilemma of Dropout

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The Premise

Design and analysis of clinical trials should be driven by the scientific and clinical questions of interest.

What Does FDA Want to Know?

Question posed to the PDAC on Nov 4 2002 concerning clozapine:

Do the data from the InterSePT study, along with other data provided in this NDA supplement, provide a sufficient basis for a new claim involving suicidality in schizophrenia and schizoaffective disorder?

What Does FDA Want to Know?

Questions to the PDAC on Feb 14 2001 concerning olanzapine and ziprasidone:

- Has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that (olanzapine/ziprasidone) is effective for the treatment of agitation?
- Has the sponsor provided evidence that (olanzapine/ziprasidone) is safe when used in the treatment of agitation?

What Are the Relevant Questions?

- Are we interested in the causal inference concerning the drug's efficacy and safety?
- Implication: Information will come primarily from within the trial in a well-controlled environment.

- Are we interested in how a drug contributes to patient care or management in a naturalistic setting?
- Implication: Information outside of the trial could contribute, especially with event endpoints.

Questions Relevant to Clinicians?

- If I prescribe this medication for my patient for 3 months, what will her symptoms (disorder) be like after 3 months of treatment with this medication? Will she be helped by taking this medication for 3 months? But, what is the chance that she won't tolerate the medication?

- Will my patient be better off at the end of 3 months if I start him on this medication today? If he can't tolerate the med, what will I do next? If my patient received any benefit, will the benefit sustain or disappear when I remove the med? If the latter, how fast?

What About Safety Evaluation?

- With dropout, the crude rates for AE are likely to under-estimate the true rates. Even incidence rate estimates could be biased unless we can assume constant risk for the events.
- Deliberately withdrawing patients early because of mild abnormality in lab values means we will not know how severe a reaction can be until the drug gets on the market when clinicians do not have regular lab reports to guide the decision.
- Is it ethical to study the progression of some adverse reactions in a carefully monitored environment?

We Feel It Is Important That

- We articulate the scientific questions that are important to the healthcare providers in the context of the specific disorder.
- Discuss the role of these questions in support of product approval with the regulators.
- Look for the appropriate ways to design and analyze the data that are best to address individual well-defined questions.