Regulatory Perspective on Complete Data for Registration Trials: Transparency, Access, Interpretation

ISCTM

Improving Transparency of Clinical Trial Data

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Active Consulting Relationships with Pharmaceutical Companies and NIMH, and Employment Relationship with MGH CTNI

- Part time employee of MGH CTNI
- Consultant to NIMH
- Consultant to Acadia, AgeneBio, Alcobra, Alzheon, Axovant, Axsome, Biohaven, Braeburn, Camurus, Cerecor, Corcept, CoMentis, DAvia NS, Durect, Edgemont, Fabre Kramer, Forum, Janssen, Lilly, Lumos, MAPS, Marinus, Medgenics, Neurolifesciences, Noven, Omeros, Pfizer, Reviva, Sunovion, Taisho, Teva, Tonix, Transition

Issues for My Talk

- Transparency regarding what is done in a drug development program
- Access to data from a drug development program
- Interpretation of the aggregate data from a drug development program
- Focus mostly on efficacy

FDA and NIH Roles in ClinicalTrials.gov

- FDAMA 1997: required public registration of information about registration trials involving “serious and life-threatening illnesses”
- NIH launched clinicaltrials.gov in 2000
- FDAAA 2007: expanded types of registration trials for which public registration is required
- Gradual expansion of the types of trials and types of information that are required for public registration

What else has FDA done to increase transparency?

- Once a new drug is approved, FDA now posts on website reviews, memos, letters, etc that supported the approval action
  - Drugs @ FDA
  - Extends back to about 2005
- DPP has on 2 occasions published manuscripts summarizing key issues in the review of a recently approved NDA
  - Viibryd (vilazodone)
  - Fetzima (Levomilnaciprin)

Other Efforts by FDA to Provide Useful Information to Patients and Consumers

- Medication Guides
- Wealth of information for patients and consumers on FDA's website (www.fda.gov)

What FDA Cannot Release to Public

- Federal law prohibits release of proprietary information
- What generally is included under proprietary information?
  - Raw data from development program
  - Any information on a program for a drug that is not yet approved
    - Exception: if NDA goes to PDAC the background material for meeting is public, even if drug not ultimately approved

Is there value in having more complete information on the multiple studies comprising development programs?

- Helpful in understanding the context for a successful program
- Helpful in understanding trends over time in placebo response, success rates for trials in different indications, effect size, etc
  - FDA and others have done such analyses (e.g., FDA papers on MDD and schizophrenia studies over 25 year period)
  - Academics would like to have access to same raw data that FDA has, but no legal mechanism for providing such access

How important is the context from which the 2 positive studies that support an approval arise?

- FD&C Act: “substantial evidence of effectiveness from adequate and well-controlled investigations…
  - No guidance on how to weigh the overall evidence
  - Usually interpreted to mean that 2 positive studies are sufficient
- For Major Depressive disorder programs, only about half of studies are successful (i.e., new drug beats placebo)
- Generally higher success rate in schizophrenia trials, but some decline in recent years
- DPP has generally not consider failed or negative studies to undercut 2 positive studies
  - Recent exception with antidepressant gepirone (see PDAC)

Negative vs. Failed Studies

- Negative: Only new drug and placebo, and new drug does not beat placebo
- Failed: Has active control and both new drug and active control fail to beat placebo
- DPP has generally discounted failed studies since considered to not have “assay sensitivity”
  - A negative study could also lack assay sensitivity, but no way of knowing

Approaches to aggregating data from multiple trials in a development program

- Binomial formula (calculating probability of getting 2 at 0.05 out of n total studies)
  - Overly simplistic; does not use the quantitative information available (simple yes or no)
- Fisher's method: RA Fisher developed an approach for aggregating p-values more than 70 years ago
  - Uses more of information, but still inefficient
- Meta-analysis using effect sizes for each trial
  - More efficient, but like both other approaches, does not take into account relevance and quality of individual trials

Why do trials not succeed (whether negative for failed)?

- Drug does not work
- Wrong dose
- Wrong population
- Stopped for business reasons
- Poor quality
  - Incompetent recruitment, incompetent ratings, nonadherence, incompetent data management, fraudulent patients, etc
- Key Message: study relevance and quality should be considered before using aggregation approaches to decide drug on effectiveness or effect size