Regulatory Considerations in Addressing Nonadherence in Clinical Trials

ISCTM

Mitigating the Effects of Nonadherence in Clinical Trials

February, 2015

Washington, DC

Thomas Laughren, M.D.

Laughren Psychopharm Consulting, LLC

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- 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

Nonadherence as a potentially useful outcome measure

- Rather than being a problem, an alternative view is that nonadherence is a potentially useful outcome
  - E.g, CATIE (dropout is the ultimate in nonadherence, and may tell us something important about the usefulness of a drug)
- Nonadherence does not of course tell us if, under ideal circumstances (adherent patients) a drug works
- Two types of studies
  - Explanatory (typical registrational trial strives for high adherence, in order to fairly test efficacy of drug)
  - Pragmatic trial tests real world utility
  - Both types of trials are need (but here our focus is on explanatory trials)

What you have heard so far

- Definition of artifactual nonadherence (distinct from real-world nonadherence)
- Detrimental impact of nonadherence on outcome of registration trials
- Various approaches to addressing artifactual nonadherence
- When to intervene to try to address artifactual nonadherence

Artifactual nonadherence is a problem

- Good case has been made that it is a very substantial problem in registration trials
- Increases type 2 error, and decreases efficiency of RCTs
- Drugs may be stopped at POC, even if effective
- Indirect methods to detect (e.g., pill counting) are clearly not effective
- A variety of promising approaches have been developed

What do FDA and other regulatory agencies think about innovative approaches to addressing this problem?

- General regulatory acceptance of need to address the problem of artifactual nonadherence
- Part of FDA mission statement: "The FDA is responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer…"
  - Improving precision of registrational trials is one approach to achieve this goal, and this would include interventions to improve adherence and detect nonadherence
- Other regulatory agencies likely also support such efforts

When are Interventions Likely to be Acceptable from a Regulatory Perspective?

- Screening, e.g., patient registries
- Run-in phase before randomization, e.g., detecting nonadherent patients using adherence technologies during this phase
- Post hoc analyses of subsets of adherent patients in a failed study to inform “go/no go” decisions or subsequent studies, i.e., something other than attempting to salvage a failed study

Excluding data from patients detected to be nonadherent post-randomization is generally going to be a problem

- Primary basis for regulatory objection: potential for bias
  - Nonadherence may not be random, e.g., could be related to treatment assignment (intolerability or lack of efficacy)
  - Excluding data from patients based on nonadherence post-randomization would compromise randomization and threaten validity of analysis
- Possible exception: Patients who are discovered to have never taken even a single dose of assigned treatment
  - Modified Intent to Treat (mITT) sample: randomized patients who had baseline and at least one post-baseline efficacy assessment and who took at least one dose of assigned treatment
  - Documenting no doses of assigned treatment is a challenge, however

Recent example of study in which nonadherent patients were excluded from ITT analysis
(Chey, et al; NEJM; 2014)

- Study of noloxegel for opiod induced constipation
- 15 patients excluded from ITT sample due to post-randomization determination that they were participating in more than one study site
- Apparently review division at FDA also excluded them
- No information on actual adherence with assigned treatment, but clearly nonadherent with overall study requirements
- Example raises interesting question, however, not clear what right answer is, nor how FDA or other regulatory agencies would, in general, handle these patients in analysis
  - Could have sought out other sites if assigned to placebo

How to handle a patient discovered to be nonadherent post-randomization

- Note: Different question than whether or not to exclude data on that patient up to point of discovery
- Should the patient be dropped at that point?
  - Could introduce bias (depends on reason for nonadherence)
  - Of course, patients drop all the time for intolerability or lack of efficacy
- Should the patient be counseled, or have adherence technology added, or both?
  - Would that introduce bias, since would apply only to those patients?
- These discussions need to occur with regulators to establish clear policies on what is acceptable course of action
  - Answer not easy or straight-forward

Do these nonadherence technologies have a real impact on trial efficiency?

- Do they improve the ability of a trial to discriminate drug from placebo
- Difference between showing that a technology works in a carefully controlled artificial setting and showing that it works in the real world of clinical trials
- Are there data for any of these approaches to establish real world value
- Do pharmaceutical companies even ask this question?

Abilify (aripiprazole) Tablet with Embedded Proteus Sensor

- Recently announced filing of this application with CDRH at FDA
- Handling in CDRH essentially means that this will likely be a technical assessment of whether or not this “device” functions as claimed in an artificial test situation
- If approved, will this innovation actually improve adherence and patient outcome in clinical practice?
  - How will this be established?
- Would this innovation improve efficiency of registration trials?

Approach to Testing Impact of Adherence Technology on Efficiency of Registration Trials

- Could be sub-study of typical registration trial
- 2 X 2 factorial design:
  - Basic design is drug vs placebo for overall sample
  - Adherence is a second factor:
    - Randomize sites on adherence technology (half get it, half don't)
    - Stratified randomization drug vs placebo within sites getting technology and those not
  - Primary analysis would still be drug vs placebo overall
  - Secondary (exploratory) analysis would be for efficacy of adherence technology
- Separate issue than whether or not has to be tested for regulatory approval

Who would pay for this added exploration?

- Not likely adherence technology companies
  - Too costly and maybe too risky
- Pharmaceutical sponsor of a registration trial
  - Added cost relative to overall cost of trial may not be excessive, but also not trivial
  - May object that this added exploration benefits competitors more than them
- Big Pharma might consider funding
  - Might view as benefit to entire Pharma community
- Maybe costs could be shared among multiple players

Discussion (10 min)

Next up:

Earle Bain, M.D.,

Senior Medical Director, Oncology Clinical Development, AbbVie, N. Chicago, IL