CLINICAL TRIAL DESIGN CONSIDERATIONS IN RARE DISEASE STUDIES

Frank Sasinowski, MS, MPH, JD

Director, Hyman, Phelps & McNamara, P.C.

Vice Chair, EveryLife Foundation for Rare Diseases

Adjunct Professor of Neurology, University of Rochester Medical School

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DESIGN CONSIDERATION #1: CONTINUOUS DEVELOPMENT

- Continuous Development – Seamless and Adaptive Design
  - Dr. Woodcock has been preaching this for years
  - Have to get beyond traditional "one off" trial system and move into *continuous development* where patient data is collected and housed centrally for all to draw on, and when patient completes trial, returns to pool to become available once more.
    - See, for example, Global Genes RareX registry.
  - For example, same patient may start with randomized 4:2 SAD trial and after washout, move into 6:2 MAD trial and then into an open-label extension or Phase 2/3 trial.

- Blow up our silos and embrace our community of investigators and caring for patients

DESIGN CONSIDERATION #2: FDA HAS BROADER FLEXIBILITY ON STUDY DESIGN THAN IS PUBLICLY ACKNOWLEDGED

- FDA's description of its responsibilities for assessing effectiveness of orphan drugs:
  - Traditional description (1980's thru late '90's): Orphan Drug Act (ODA) did not amend 1962 law's substantial evidence of effectiveness standard (full stop).
  - Current description: While ODA did not amend 1962 law, FDA recognizes two types of situations in which a single study may meet the standard: 1. a statistically highly persuasive (p value of at least less than 0.01) single study as per FDA's May 1998 guidance, or 2. a single study of conventional statistical significance (p value of less than 0.05) but with "confirmatory evidence".
- Frank's view: FDA's practice has been to apply even more "flexibility" than that presented in the 1997 FDAMA alternative standard and in the FDA's 1998 guidance
- FDA has long had the authority to exercise such "flexibility" and has historically applied such flexibility (see 21 CFR 314.105)

DESIGN CONSIDERATION #2: FDA HAS BROADER FLEXIBILITY ON STUDY DESIGN THAN IS PUBLICLY ACKNOWLEDGED

- To justify the 1/3rd of orphan drug approvals* that do not meet either the 1962 standard or either of the single study exceptions (under the 1997 FDAMA standard or 1998 Evidence Guidance), there needs to be a new way of describing and communicating FDA's authority to act on drugs for rare diseases. Consider the following as a proposed new EXECUTIVE SUMMARY OF SUCH A STATEMENT (& see next slide for fuller statement):
  - The 1962 law established a standard that FDA has interpreted as usually requiring 2 adequate and well-controlled (A+WC) positive trials.
  - In 1997 this was amended to allow, in the alternative, for a single A+WC study with confirmatory evidence. FDA's 1998 Evidence Guidance described another single study approval pathway.
  - Yet, FDA's practice has been to apply even more "flexibility" than that presented in the 1997 alternative standard or in the FDA's 1998 guidance.
  - FDA has long had the authority to exercise such "flexibility" (see 21 CFR 314.105).
  - FDA has historically applied such flexibility* on a "case-by-case" basis.

*See Sasinowski 2012 & 2015 papers on Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs

DESIGN CONSIDERATION #2: PROPOSED STATEMENT OF FDA'S AUTHORITY TO ACT ON THERAPIES FOR PATIENTS WITH RARE DISEASES

1. Current Statement:

Even though the ODA did not amend 1962 law, a single positive A+WC study may meet the statutory standard if it is EITHER:

a. Highly statistically persuasive (p value of at least less than 0.01) study with no other evidence of effectiveness as per May 1998 guidance, OR

b. Conventionally positive (p value less than 0.05) study with some form of confirmatory evidence (note: there is growing recognition of this alternative standard).

2. Proposed Addition to Current Statement:

In addition, the Agency has long-established authority that "demands flexibility in applying the [statutory (1962 and 1997) and administrative (1998)] standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information for a particular drug to meet the statutory [and administrative] standards." 21 CFR 314.104(c).

As such, FDA is compelled to exercise its scientific judgment on a case-by-case basis in reviewing each therapy being investigated for a rare disease. That exercise of judgment can be affected by many factors, including among others, the rarity and severity of the condition and the relative availability of other satisfactory therapies.

DESIGN CONSIDERATION #3: WHY RELY UPON JUST ONE CONTROL WHEN UP TO 3 CONTROLS ARE POSSIBLE?

- Natural History (NH) Studies & Patients as Own Control (PAOC)
  - In every rare disease, key biological understandings will remain beyond current scientific reach
  - Randomizing subjects in any small trial may result in Type 1 or Type 2 error simply because a key prognostic variable that would predict which persons will progress more rapidly and which more slowly is not yet recognized
- Therefore, apply "Frank's Rule"!

All rare disease research should always:

1) Secure as much clinical and biomarker information on each subject BEFORE BASELINE to use for analyzing patients as their own control and;
2) Have a Natural History control

✓For PAOC, look to see whether those randomized to placebo act as they did before randomization and look to see whether there is an inflection point (a divergence) that occurs in the pattern at the time of randomization for those randomized to the investigational arm.

✓For NH, compare both placebo and drug arms to their matched NH controls and see if there is a concordance between NH and those randomized to placebo and divergence between NH and those on drug.

ADDITIONAL FDA ACTIVITIES AFFECTING DESIGN CONSIDERATIONS: RARE DISEASE FORUM FOR COLLABORATIVE RESEARCH

Rare Disease Forum for Collaborative Research

- Inaugural Meeting, Oct. 17, 2018: Dr. Woodcock was opening speaker
  - Other opening remarks by Dragos Roman (FDA), John Crowley (Amicus), Marshall Summar (NORD), + Frank Sasinowski (EveryLife Foundation)
- Second Meeting, March 20, 2019: Chaired by Dragos Roman with 20 other CBER and CDER officials
- Exploring 5 topics:
  - Innovation in trial design
  - Best practices for natural history studies and registries
  - Biomarker and intermediate clinical endpoints (ICE)
  - Innovation in biostatistics
  - Totality of evidence – co-chairs: Jeff Sherman (Horizon) and Frank Sasinowski
    - Ex: Multi-Domain Responder Index (MDRI)

THANK YOU

Frank Sasinowski, MS, MPH, JD
FJS@hpm.com

BACKUP SLIDES FOR DESIGN CONSIDERATION #2

❖21 CFR 314.105(c)

- "FDA will approve an NDA after it determines that the drug meets the **statutory standards** for safety and **effectiveness**….
- While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs **demand flexibility in applying the standards.**
- Thus **FDA is required to exercise its scientific judgment** to **determine the kind and quantity** of data and information an applicant is required to provide for a **particular drug** to meet the **statutory standards."**

BACKUP SLIDES FOR DESIGN CONSIDERATION #2

- In response to the AIDS crisis in mid-1980's, FDA on its own initiative created a policy that recognized that patients with serious diseases and without satisfactory therapy should have access to therapies even though these may carry more risk and have less certainty of effectiveness. This was the Subpart E program under the IND regulations at 21 CFR 312.80.

- 21 CFR 312.80 starts off by referencing that earlier regulation at 314.105 and builds on it.
- Many, if not most, therapies for rare diseases fit into this IND Subpart E policy category.

BACKUP SLIDES FOR DESIGN CONSIDERATION #2

21 CFR 312.80:

"…to establish procedures to expedite the development, evaluation & marketing of new therapies intended to treat persons with [serious] illnesses, especially where no satisfactory alternative therapy exists.

As stated [in] section 314.105(c) .., while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, **demand flexibility in applying those standards**.

The FDA has determined that it is **appropriate to exercise the broadest flexibility in applying the statutory standards**, while preserving appropriate guarantees for safety and effectiveness.

These procedures reflect the recognition:

that … **patients are generally willing to accept greater risks …**than they would accept from products that treat less serious illnesses…

[and] that the benefits of the drug need to be evaluated in light of the severity of the disease being treated."