Regulatory Overview of Adequate and Well-Controlled Studies in TB Regimen Development

Karen Higgins, Sc.D.
Statistical Team Leader,
Division of Biometrics IV
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Outline

- Regulatory requirements
  - Substantial evidence
  - Accelerated approval
  - Added contribution of components of TB regimen
- Design of Clinical Trial
  - Patient population
  - Control
  - Endpoints
  - Statistical analysis

Substantial Evidence of Effectiveness

- Required by law since 1962
  - Section 314.126 of Title 21 of the Code of Federal Regulations (CFR)
  - Adequate and well-controlled trials (interpreted as 2+)
- Clinical Effectiveness Guidance (1998)
  - Gives situations were one adequate and well controlled trial sufficient, along with independent substantiation of findings
  - For TB, possibly one adequate and well controlled trial plus information from Early Bactericidal Activity (EBA) studies plus animal/in vitro studies
- Importance of adequate comparative safety data (at intended dose and duration)
  - Limited use indication (for patients without any options), safety database may be smaller

Accelerated Approval Program*

- Allows for earlier approval of drugs that treat serious conditions that provide meaning therapeutic benefit over existing therapies
  - Uses an accelerated approval endpoint that is reasonably likely to predict clinical benefit, but is not itself a measure of clinical benefit
  - Can considerably shorten the time required prior to receiving FDA approval
- Required to conduct post-marketing studies to confirm the anticipated clinical benefit
  - If the clinical benefit is shown, then the FDA grants traditional approval for the drug.
  - If the clinical benefit is not shown, drug can be removed from the market.

*21 CFR 314 Subpart H

Accelerated vs. Standard approval

- High impact of the regimen, more likely accelerated
  - MDR regimen – more effective, less toxic
  - XDR regimen – with great efficacy
- Need for more complete information, more likely standard approval
  - Drug sensitive regimen – may need information on final long-term outcome before switching from highly effective (HRZE) treatment
  - MDR - if test regimen has markedly shorter duration, likely will need an endpoint that is past the end of treatment to make sure patients not at risk for very high relapse rate

Accelerated approval of Bedaquiline*

- Approved in 2012 for the treatment of adults with MDR pulmonary tuberculosis
- Add-on trial: Randomized to B vs. placebo (24 weeks), all patients received best available therapy for 18-24 months
  - Accelerated approval was based on time to sputum culture conversion
  - Due to limited safety, "Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided"
- Confirmatory trial assessing patient survival, clinical resolution of tuberculosis, and rate of relapse at a later endpoint after patients have completed TB treatment

* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf

Combination Rule

- 21 CFR 300.50: Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects
  - Factorial design trial
    - 2 component regimen need at least a three arm trial of AB, A, B
      - AB > A, demonstrates contribution of B
      - AB > B, demonstrates contribution of A

Added contribution

- 2013 Guidance on Codevelopment of Two or More New Investigational Drugs for Use in Combination
  - Factorial designed clinical study is preferred
  - If not possible, then in vitro, in vivo animal models, phase 1, other early studies, with clinical study assessing the full regimen

Development of TB regimens

- Development of full TB regimen
  - Fixed-dose combinations
  - Co-packaged products
  - Individually packaged, but labeled to be used in combination
- Efficacy and safety requirements similar for the three situations above

Designing a TB efficacy clinical trial

- Issues to consider are:
  - TB regimen
  - patient population
  - control
  - endpoint
  - analysis

New regimen vs. New drug

- Totally New Regimen (high impact)
  - Examples:
    - 3-4 new drugs with new mech. of action to treat TB in 4-6 months
    - 2 new drugs with new mech. of action paired with an older drug
  - If contribution of effect of components from earlier phase of development, clinical trial may assess efficacy of regimen as a whole
- Single new TB drug being developed
  - Example:
    - A new drug to treat MDR given on top of a best available therapy
    - A new drug to replace one drug in the standard DS regimen
  - Development of single drug, efficacy of that single drug needed from clinical trial (Bedaquiline example)

Patient Population

- Drug Sensitive TB
- MDR-TB
- XDR-TB
- All combined

- Different patient populations might lead to different routes of approval
  - Accelerated vs. Standard

Control

- Expectation is for a randomized, controlled, blinded trial
  - If blinding is not feasible, trial should be conducted in a blinded manner however possible
- Control treatment depends on the patient population and regimen
  - For DS-TB that would be HRZE for 6 months
  - For MDR-TB, depends on the resistance patterns and location
- For XDR-TB, given poor outcome and long duration of treatment, may be possible for a drug with great effect to conduct a single arm trial with a historical control group

Control

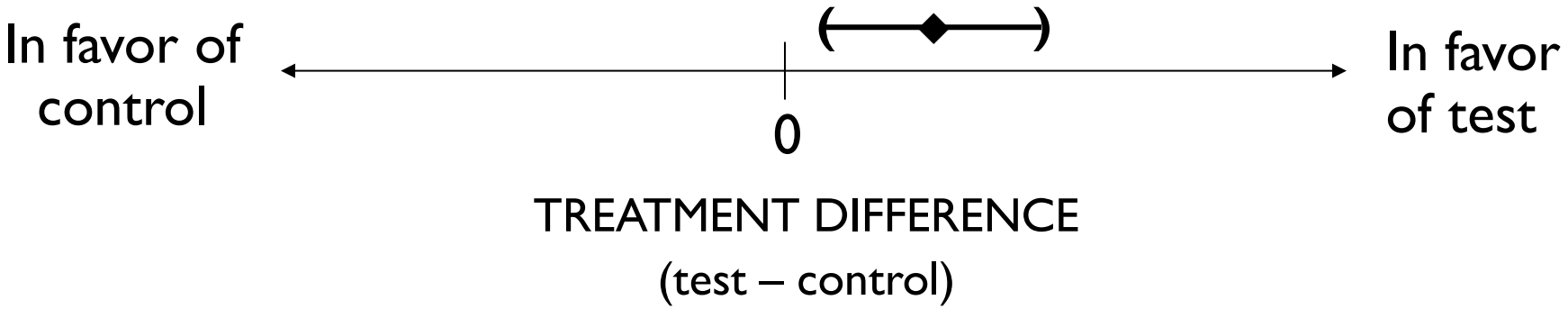
- New single drug for MDR or XDR, might use an add-on design
  - Optimized background regimen (OBR) + new drug vs. OBR + placebo (this is a placebo controlled trial)

Endpoints

- Early endpoints
  - Sputum culture conversion at 2 or 6 months,
  - Time to sputum culture conversion
  - Note that these early endpoints do not test whether the planned duration of the regimen will be adequate
- Late endpoint
  - Sustained culture conversion to 6 – 12 months after treatment ends
  - Timing of endpoint based on time from randomization and is the same for the two treatment arms
  - Capture reason for failure: treatment failure, relapse, re-infection, lost

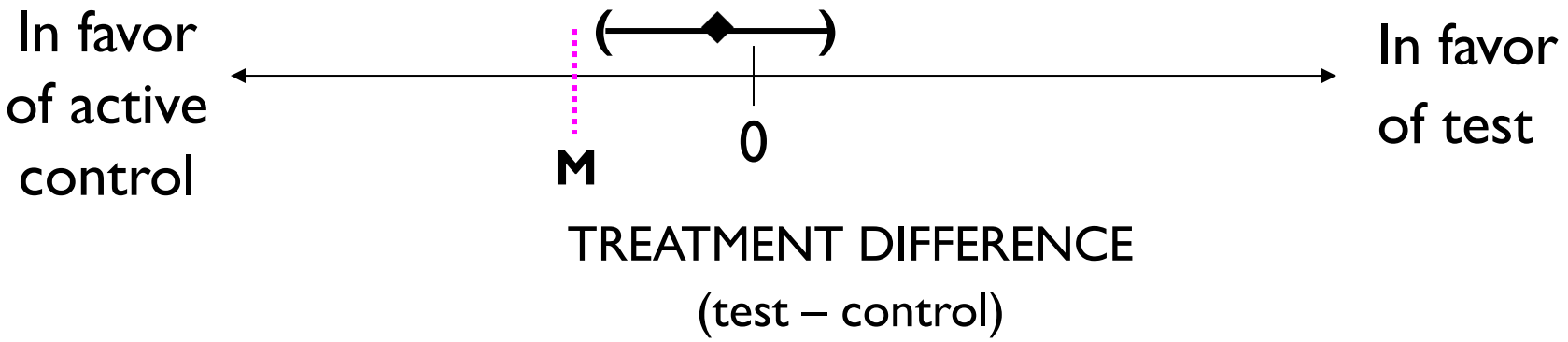
Analysis

- Superiority
  - Efficacy is determined by showing test arm is better than control
  - Needed for Add-on designs



Analysis

- Non-inferiority
  - Efficacy is determined by showing efficacy of test arm is "close to" a known effective control
  - How "close" it needs to be is the non-inferiority margin (M)
    - Depends on how effective the control is (based on data from previous trials) (**M1**)
    - How much efficacy willing to lose (clinical judgment) (**M2**)



Non-inferiority margin for TB

- Depends on specific trial design, including the patient population, timing and definition of endpoint.
- Assessing non-inferiority of a test regimen to the control regimen
  - Should be high impact regimen, NI assessment make sure not losing anything on long-term endpoint
  - Control regimen as a whole has a large treatment effect compared to no treatment (M1 large)
    - In DS-TB, HRZE vs. no treatment,
    - In MDR-TB, best available therapy vs. no treatment
  - In this case, NI margin will be based largely on clinical judgment (M2).

Non-inferiority margin for TB

- Assessing non-inferiority of a test drug to a control drug
  - Control is a single drug in a multi-drug regimen
    - Its effect likely modest (M1 small)
    - Data likely limited to justify a margin
  - Examples:
    - New drug replaces ethambutol in the DS-TB regimen, HRZ**X** vs. HRZ**E**. The effect of **E** would need to be estimated (M1), to be sure that **X** has efficacy.
    - New drug added to DS-TB regimen and regimen is shortened by 2 months, 4HRZE**X** vs 6HRZE. The effect of the final two month of treatment would need to be estimated.

Conclusion

- Adequate and well controlled trial required to determine the efficacy of TB regimens or drugs
  - Need to put together evidence on contribution of each drug in a regimen
- Pathway of approval depends on the impact of the regimen
  - Accelerated approval is possible, might lead to limited indication, especially if safety data limited
- Development of a single drug will lead to different study design than development of a full regimen with high impact
- Important to discuss development program with FDA early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