



Statistical Issues in Microbicide Trials

Greg Soon, Ph.D.

Thomas Hammerstrom, Ph.D.

Division of Biometrics IV
Office of Biostatistics/OTS/CDER/FDA

WHO Symposium
Regulatory considerations for the review of microbicide clinical trials
and product registration

Satellite meeting in conjunction with
Microbicides 2010 International Conference
Pittsburgh, PA, USA

Saturday, 22 May 2010 9:00 am – 5:00 pm

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Microbicides: Trial Design

Topics for Discussion:

- Evidence Level
- Adherence
- Adaptive Design Issues
- Is a Condom-only Arm Necessary?

1. Evidence Level

- Standards for drug approval include two adequate and well-controlled trials each with two-sided significance level 0.05 = one-sided 0.025.
 - Somewhat different populations enrolled in each trial is preferred.
- One large trial should have a one-sided level of $0.000625=0.025*0.025$ with consistency across sub-groups.

1. Evidence Level

- The absence of Phase II trials demonstrating proof of concept increases the risk that Phase III trials will be unsuccessful
 - If we have 10 trials with ineffective drugs, one could beat placebo at a level of 0.1
 - There is a 50% chance that one ineffective drug will win at a p-value of 0.05
 - Chance of replicating a trial with a p-value of 0.05 is not great unless the gel is truly effective

1. Evidence Level

- With the first approved gel, it may be difficult to conduct placebo controlled trials
 - All future trials will be non-inferiority trials against the approved gel
- If the first approved gel is in fact ineffective because of a lower statistical standard, then future development programs may be negatively impacted.

1. Evidence Level

- FDA's mission is to protect the public health
 - Setting reasonable criteria for the conduct and interpretation of clinical trials that support safety and efficacy of products to prevent HIV acquisition
 - Setting strong enough standards to terminate drug development programs of ineffective products

Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>

2. Adherence

- For public health and regulatory purposes, we recognize non-adherence will occur once a drug is approved.
- As regulators, we are interested in the effect of prescribing a drug which may be different from effect of using the drug in a clinical trial.
- Therefore, adjustment for non-adherence is not permitted in the primary analysis.

2. Adherence

- No reward for adherence should be offered in the trial if the same reward will not be available once the drug is on market.
- Condom and gel adherence information should be diligently collected to help understand how the drug works or why the drug fails.

3. Adaptive Design

- The lack of Phase II clinical trial information makes it necessary to have early reviews of large phase III trials to ensure the drug is safe before further enrollment
- Some changes based on this early look are permissible

Refer to FDA Draft Guidance “Adaptive Design Clinical Trials for Drug and Biologics,” February 2010.

3. Adaptive Design

- Planned number of patients enrolled may be increased if the total infection rate is much lower than expected.
- This increase is permitted because the sample size is actually based on the number of sero-conversions.

3. Adaptive Design

- Multiple doses of a test gel can be reduced by discontinuing the less effective doses.
- The initial design must include appropriate multiple comparison adjustments for the original number of arms. No further adjustment is needed for stopping some arms early.
- Other less stringent multiple comparison adjustments are possible if it can be shown to control Type I error

3. Adaptive Design

- Multiple arms with different drugs, possibly from different sponsors can be used.
- There is no multiple comparison adjustment here because the Type I error control is for each drug. Each drug vs. placebo is thought of as a separate trial.
- Permits smaller total enrollment because of shared placebo
- Could make the trial more acceptable by using fewer placebo subjects

3. Adaptive Design

- Enrollment criteria can be changed to recruit from higher risk subpopulations if such is identified by the early look

4. Is a condom-only arm necessary?

- HPTN035 found almost the same infection rates in the condom-only and placebo-gel arms, despite significantly different condom usage (81% vs. 70%)
 - HIV Infection more likely occurs during sexual acts when condoms are not used.
 - 19% of the time condoms were not used in the condom-only arm vs. 30% in the placebo arm, a half-fold increase
 - Similar sero-conversion rates in the condom-only vs. the placebo arm could be due to:
 - Small number of HIV infections making such even distribution possible despite underlying difference in overall infection rates
 - Placebo gel was protective, which compensated for the lack of condom use
- We prefer condom-only arm in new trials to confirm placebo non-inferiority to condom-only, if possible

4. Is a condom-only arm necessary?

- HPTN035 still leaves some uncertainty about the true difference in sero-conversion rates between placebo and condom-only.
- The new gel should beat placebo by a wide enough margin to provide confidence that the sero-conversion rate of a new gel will be better than condom-only.
- Sample size calculations need to account for the new gel vs. condom-only comparison
- Cumulative non-clinical and clinical safety data of placebo gel also need to be considered

Acknowledgements

Microbicide Guidance Working Group
Division of Antiviral Products
Center for Drug Evaluation and Research (CDER)
U.S. FDA

Debra Birnkrant, Director
Jeff Murray, Deputy Director
Kim Struble, Medical team leader
Linda Lewis, Medical team leader
Greg Soon, Statistics team leader
Damon Deming, Microbiologist
Jules O'Rear, Microbiology team leader
Ita Yuen, Toxicologist-Pharmacologist
Hanan Ghanous, Pharm/tox team leader
Sarah Connelly, Medical Officer
Charu Mullick, Medical Officer
Sarah Robertson, Clinical Pharmacology team leader
Tom Hammerstrom, Statistics
Dorota Matecka, CMC
Dan Davis (Division of Reproductive Products)
Colin Pollard (Center of Devices and Radiologic Health)