



Design issues in microbicide trials

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Outline

- Role of biomarkers
- For and against Phase IIb
- Short v long follow-up
- Assessing long term effectiveness
- The Super DMC – pooling for safety
- Pooling for efficacy
- Whose trial is it? Engaging the south

Biomarkers – how can they help?

- Biomarkers may provide valuable information on:
 - Safety
 - Efficacy
- Results from a Phase III trial (positive or negative) together with data from lab experiments and early phase clinical studies offer the possibility of predictors which can inform the selection of new products.
- Biomarkers are likely to be most useful in helping to eliminate potentially unsafe microbicides; biological markers of activity (such as those used in treatment of active disease) are unlikely.
- Biomarkers may not necessarily be helpful when assessing new classes of microbicides.

A word of caution

(M2004 slide)

- We could select candidates for Phase III solely on the basis of activity *in vitro* and in the macaque, **BUT**
- The most effective products in these models may not be the safest, **AND**
- Activity in these models may not translate into effectiveness because of biological differences, coital effects, the presence of semen, etc
- Acceptability and adherence will be critical determinants of effectiveness in women.

Phase IIb: the case in favour

- The opportunity to eliminate ineffective products
- A way to rank multiple products
- A fast answer for a highly effective product
- A substantial cost reduction – but only if no further trials are indicated
- Insights on trial design and site preparedness

Phase IIb: the case against

- A longer more costly process – for moderately effective microbicides a subsequent Phase III trial will be required.
- A risk of eliminating a potentially effective microbicide.
- A positive finding (whether statistically significant or not) may seriously inhibit the conduct of a Phase III trial – participants and possibly ethics committees may regard it as unethical to conduct another placebo controlled trial.

Short versus long follow-up

- Advantages
 - Loss to follow-up (and pregnancy) likely to increase with time
 - Adherence may fall with time, especially in high risk groups.
 - Increase the likelihood of demonstrating proof of concept
- Disadvantages
 - Need to screen and recruit larger numbers
 - Increased costs
 - Only short term data on AEs – may not be suitable for licensing
 - No data on long term acceptability or effectiveness
 - Adherence *could* improve with time

Super DSMB/DMC

- Why?
 - provides earlier detection of an adverse outcome (increased infections) necessitating termination of trials
 - reduced chance of stopping early for false positive AE finding based on one trial
 - important to maintain public confidence
 - can be done without threat to the integrity of the study

Super DSMB/DMC

- In what circumstances?
 - Could be for parallel trials of the same product, or
 - Trials of different products in the same class

Super DSMB/DMC

- How might it work?
 - a system of continuous monitoring (say 4-monthly) is set up.
 - HIV seroconversion data from each of the trials are sent to an independent centre.
 - a program is run to detect whether the combined results from the two or more studies suggest there is evidence of an excess of sero-conversions on the treated arms at a predetermined level.
 - in the event of the threshold being crossed the Super DSMB convenes to assess the strength of the evidence.
 - if considered appropriate the Super DSMB informs trial DMCs
 - DMCs decision could include a joint meeting of DMCs, with or without the Super DSMB.

Pooling data to monitor efficacy

- Advantages
 - early detection of benefit
 - could reduce chance of stopping early for a false positive finding in one trial
- Disadvantages (Dixon & Lagakos 2000)
 - reduced independence
 - shared data will be incomplete
 - confidentiality is put at risk
 - may create conflicts of interest
- Might be possible if trials were designed in parallel with the intention of combining data

Improving trial efficiency

Selection of population

- stable, i.e. non-mobile
 - high incidence area
 - ensure participants are aware of the commitment involved in joining the trial
 - limit age range to those most sexually active
- Minimise loss to follow-up
 - shorten follow-up duration
 - Involve male partners at time of enrollment
 - establish means of contacting participants who fail to attend for scheduled visits.

Whose trial is it?

- Traditional model
 - trials designed in the north
 - proposals sent south for comments
- Need
 - engage African researchers at an early stage of new proposals.
 - more south based workshops at the time of trial outline discussion.
 - African expertise based in centres of excellence