

International Partnership for Microbicides



*Phase III Clinical Trial Design
Institute of Medicine
February 6, 2007*



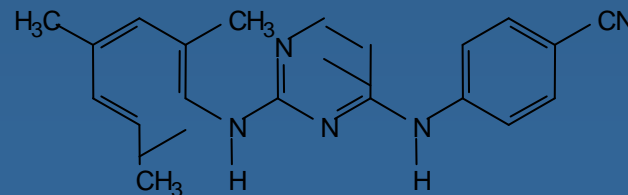
IPM Product Development Strategy

- **ARV-based gels, intravaginal rings, tablets, etc.**
 - Once daily or once monthly use
 - Allows for daily/monthly observed application (DOP)
- **Trials to be conducted in women at high risk of sexual transmission of HIV**
 - Currently working to establish 22 clinical sites
 - *12 sites in South Africa*
 - *11 sites in 8 other African countries (Kenya, Tanzania, Rwanda, Mozambique, Zimbabwe, Namibia, Nigeria, Uganda)*
- **Goal: Product licensure**



TMC120 (Dapivirine) Background

- NNRTI developed by Tibotec/J&J, licensed to IPM (2004)
- Developed originally as therapeutic, 11 clinical studies conducted via oral administration
- Highly potent ARV
- Low cytotoxicity, non-mutagenic, non-teratogenic
- Easily manufactured, cheap
- Stable drug substance
- IP clarity
- Multiple dosage forms



IPM Clinical Studies

Study	Study name	Location	Volunteers	Status
IPM001	Dapivirine vaginal ring safety trial	Belgium	12	Completed
IPM003	Dapivirine gel safety trial	South Africa, Rwanda, Tanzania	112	Completed
IPM004	Dapivirine gel pK trial	South Africa	18	Completed
IPM005B	Dapivirine gel expanded safety trial	Belgium	36	Completed
IPM007	Seroconverter protocol	Various sites	N/A	Planned, 2008
IPM008	Dapivirine vaginal ring safety trial	Belgium	13	Completed
IPM009	Dapivirine gel efficacy trial	Various sites	TBD	Planned, 2008
IPM010	Dapivirine gel male tolerance trial	Belgium	36	Planned
IPM011	Vaginal ring acceptability study	Kenya, South Africa, Tanzania	200	Q1, 2007
IPM012	Dapivirine gel pK trial	TBD	TBD	Q2, 2007
IPM013	Dapivirine vaginal ring pK trial	Belgium	60	Q2, 2007
IPM014	Dapivirine gel safety trial	South Africa, TBD	TBD	Q3, 2007
IPM015	Dapivirine vaginal ring safety trial	Kenya, South Africa, Tanzania	TBD	Q2, 2007
IPM016	Small volume applicator pK trial	TBD	TBD	Q3, 2007
IPM017	Dapivirine vaginal ring safety trial	Belgium	TBD	Q3, 2007
IPM018	Vaginal ring feasibility trial	Belgium	24	Q1, 2007



IPM Phase III Microbicide Efficacy Trial Design

- **Objectives**
 - Reduction of HIV-1 infection among HIV-negative, sexually active women
 - Safety
- **Directly-monitored application**
- **High levels of efficacy hypothesized (50-80%)**
- **Assumptions**
 - HIV incidence $\geq 2.5\%$ (on trial)
 - 20% of women lost to follow-up or pregnant
- **Randomized (1:1) NNRTI:placebo**
 - 90% power
 - $\alpha = 0.0025$ (one-sided)
 - 12 months follow-up



HIV Incidence

- **Accurate estimates crucial to successful trial**
- **Historically difficult to estimate**
- **Can vary from site to site even in close proximity**
- **Strategies**
 - **Extensive epidemiologic characterization of annual incidence in proposed sites**
 - *Cross-sectional - lab assays on prevalent specimens (BED, avidity index)*
 - *Prospective cohort studies*
 - **Conservative estimates of annual incidence**



Study Sample Sizes for Phase III Trial

True efficacy of DOP microbicide	Expected annual incidence on trial (placebo)	
	2.5%	4.0%
80%	3200	2000
70%	4500	2800
60%	6500	4000
50%	10000	6400

One year follow-up; 1:1 randomization; 90% power; 20% loss to followup; $\alpha = 0.0025$ (1-sided). All sample sizes are rounded.



Stopping Rules

- **Safety and futility**
- **Safety remains top priority**
- **Allows early culling of “minimally” effective or ineffective products**
- **Endpoint for efficacy and safety: HIV**
 - **Lack of validated surrogate markers for efficacy**
 - **HIV infection is critical measure of safety**
- **Efficiently informs future product development**
- **Better utilizes scarce resources (clinical capacity; \$)**

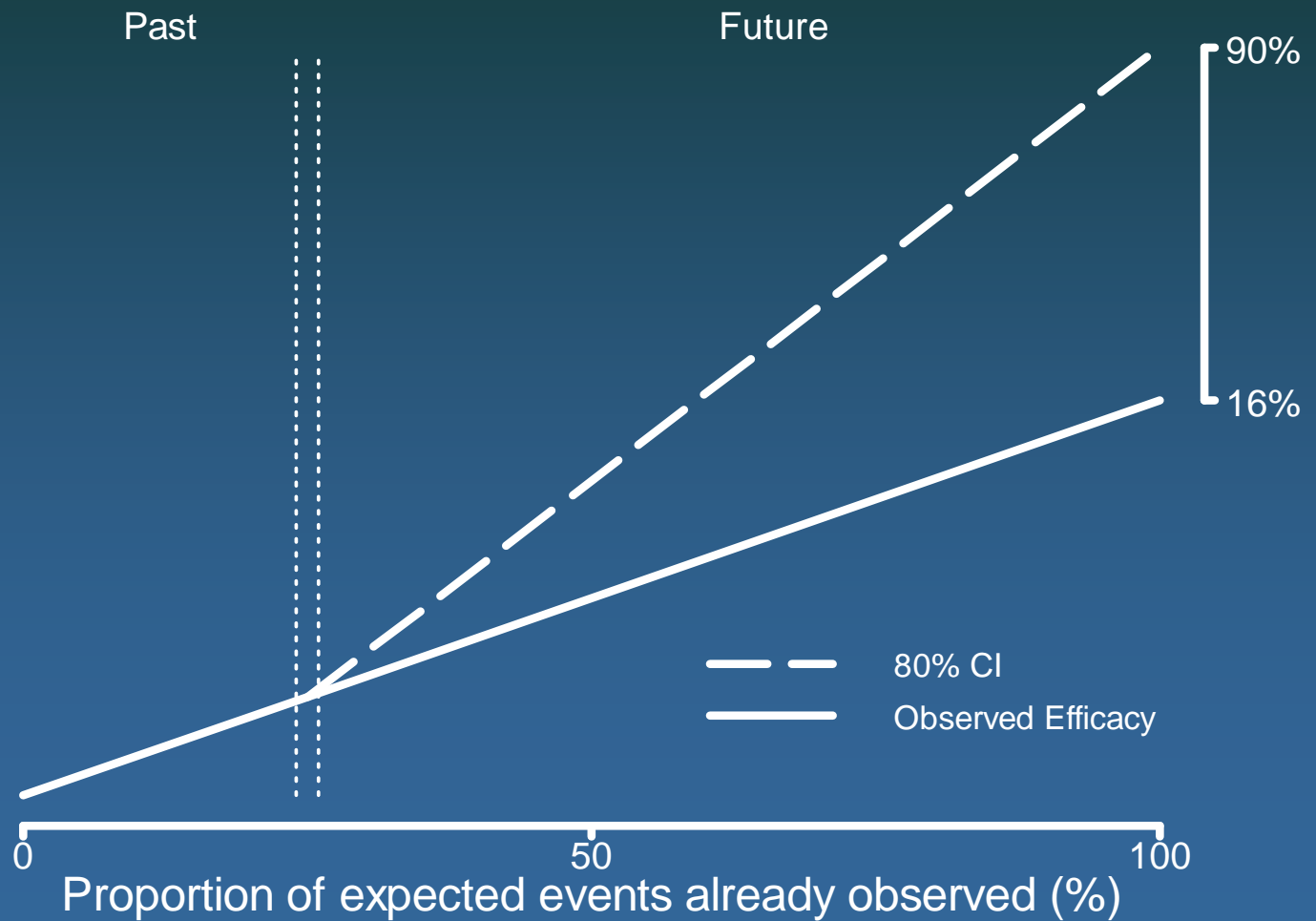


Stopping Rules for Futility

- Based on conditional power
- Probability of a statistically significant positive outcome at the end of the trial, *conditional* on data observed thus far
- Choices to make in planning stopping rules
 - What trend to use for projection of future events?
 - When (how often) to evaluate conditional power?
 - How low is too low a probability of success to continue?

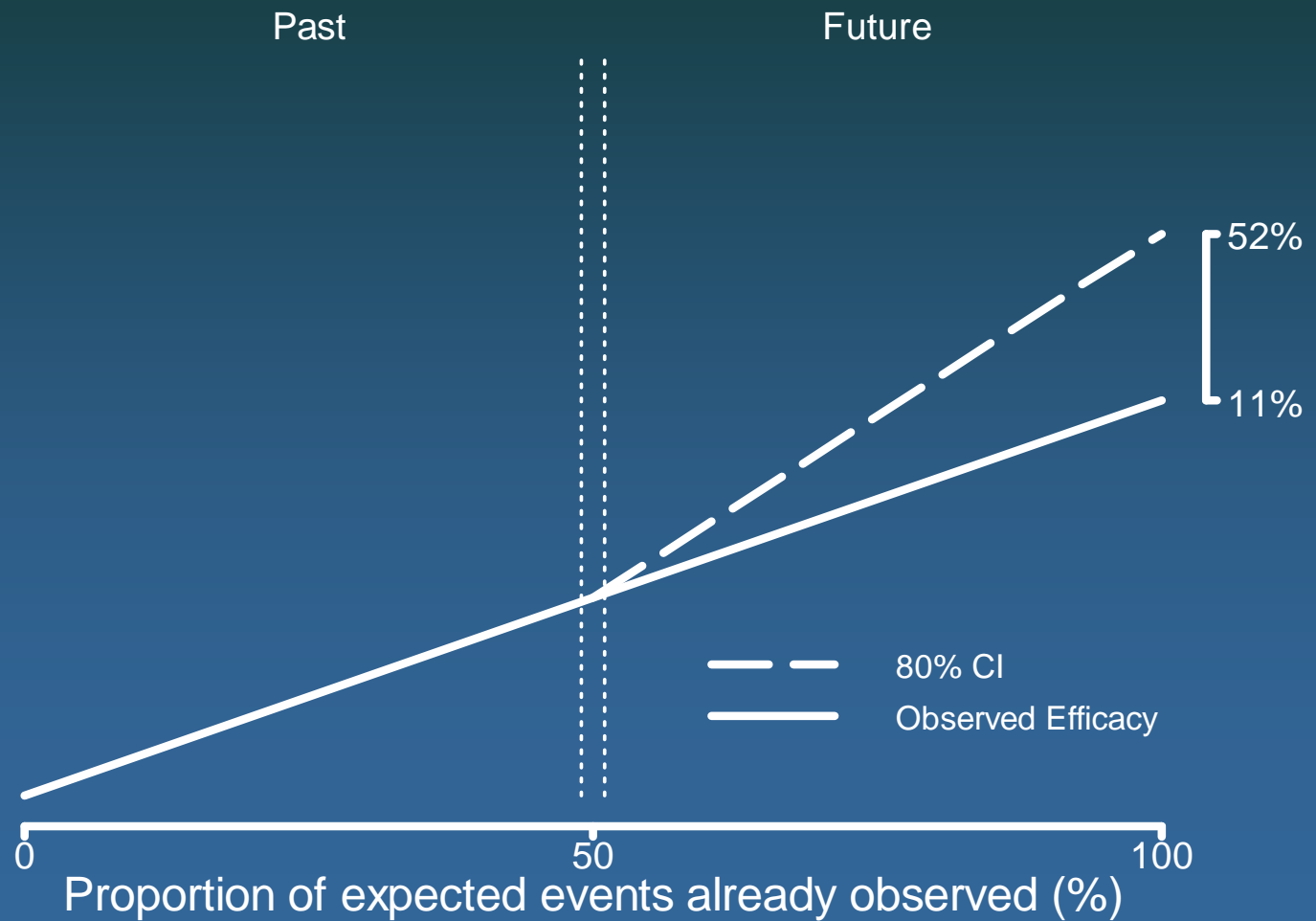


Conditional Power: 25% look



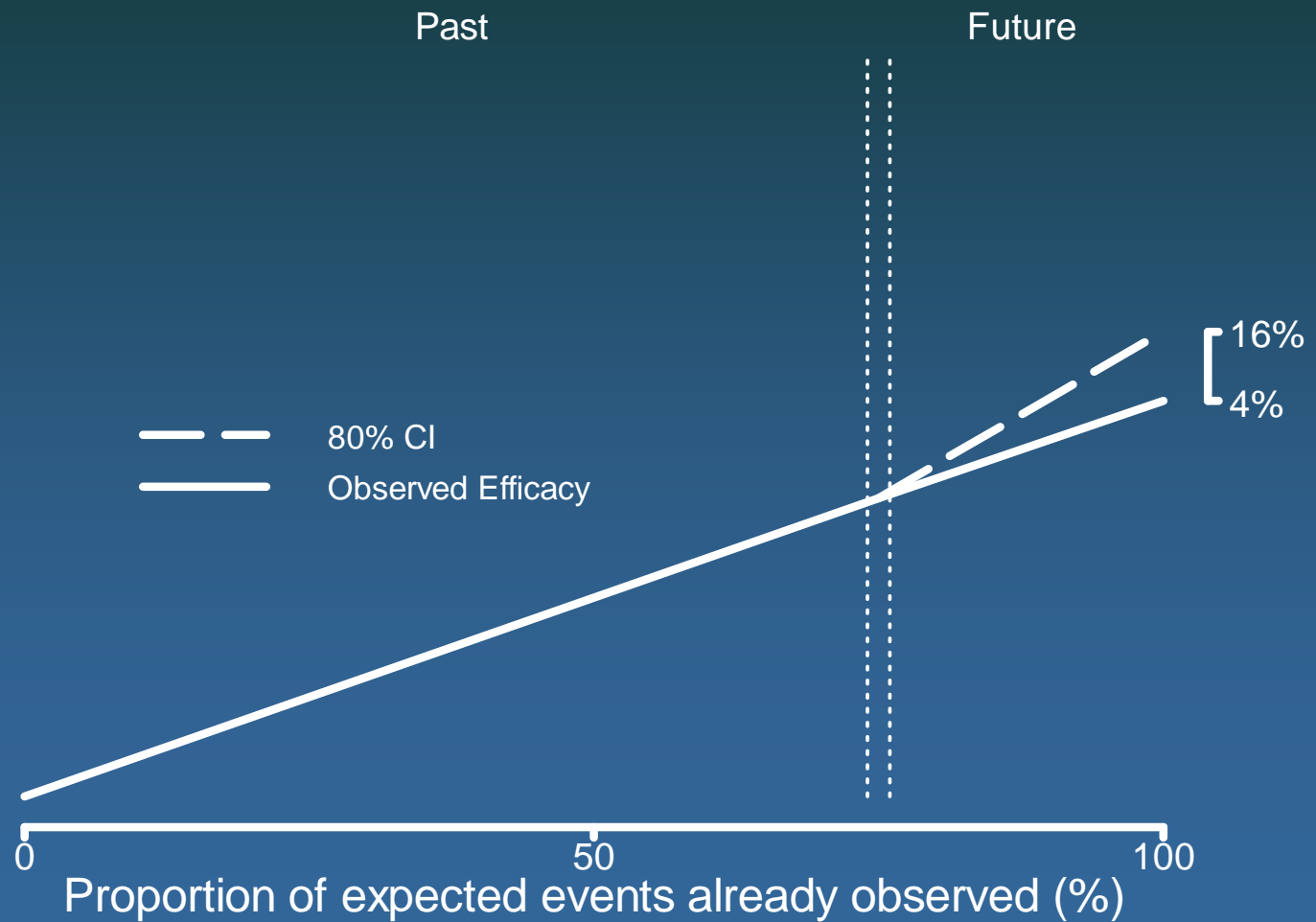


Conditional Power: 50% look



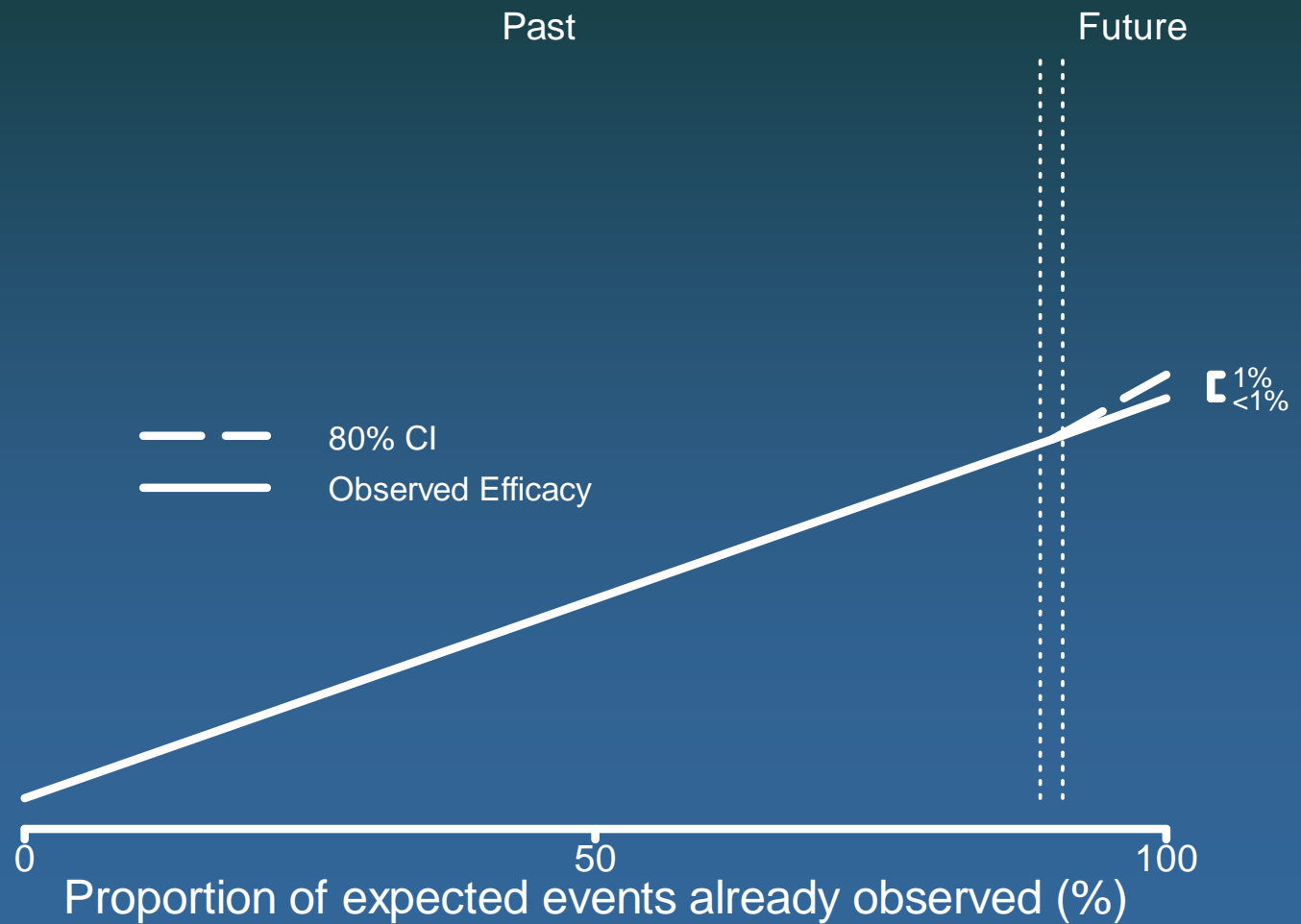


Conditional Power: 75% look





Conditional Power: 90% look



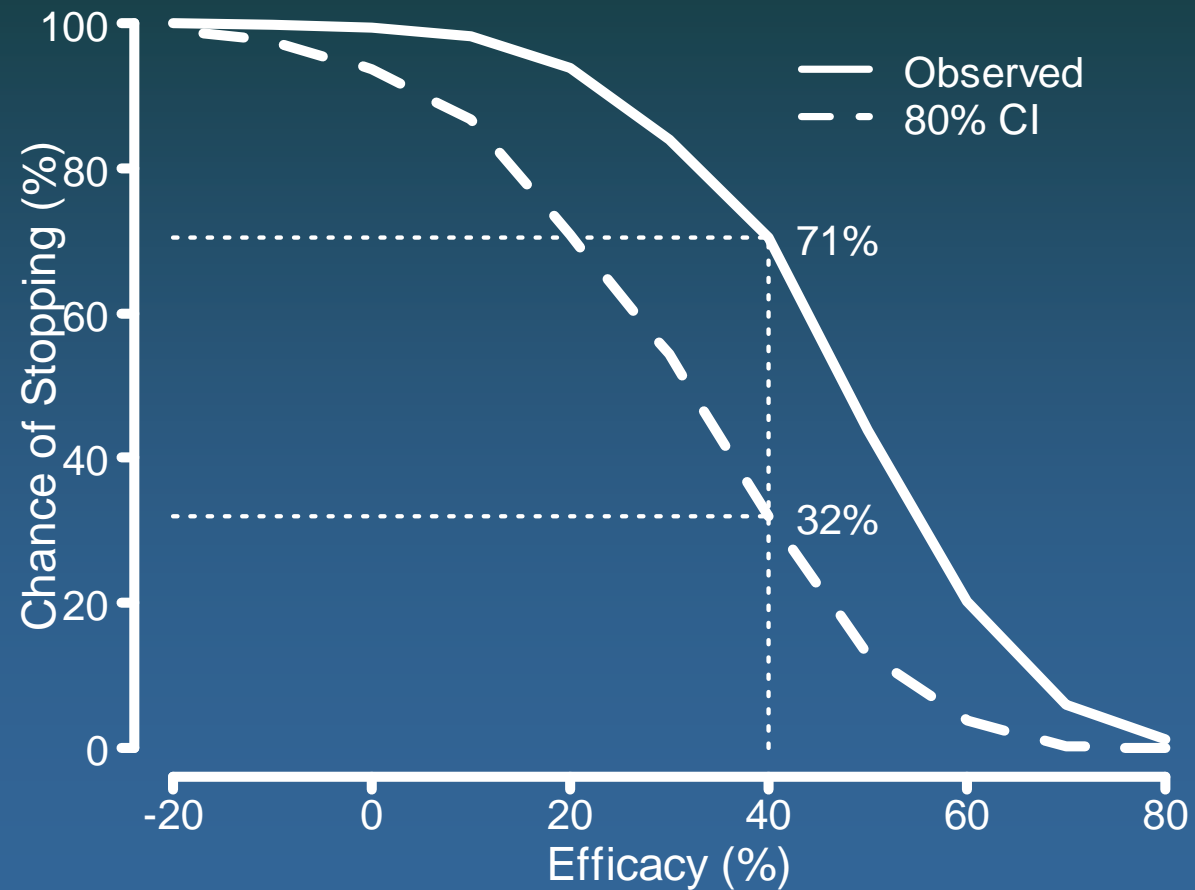


Futility Stopping Rules Based on Conditional Power

- **Select a rule with good properties**
 - Stop early for low/negative efficacy (harm)
 - Continue for moderate/high efficacy (benefit)
 - No alpha penalty for futility looks
- **Evaluate potential rules through simulation**
 - Fix sample size, true placebo incidence, true efficacy
 - Generate many simulated trials (# of infections/group)
 - Evaluate conditional power at intermediate timepoints
 - Summary: % of trials that would stop (CP below 30%)



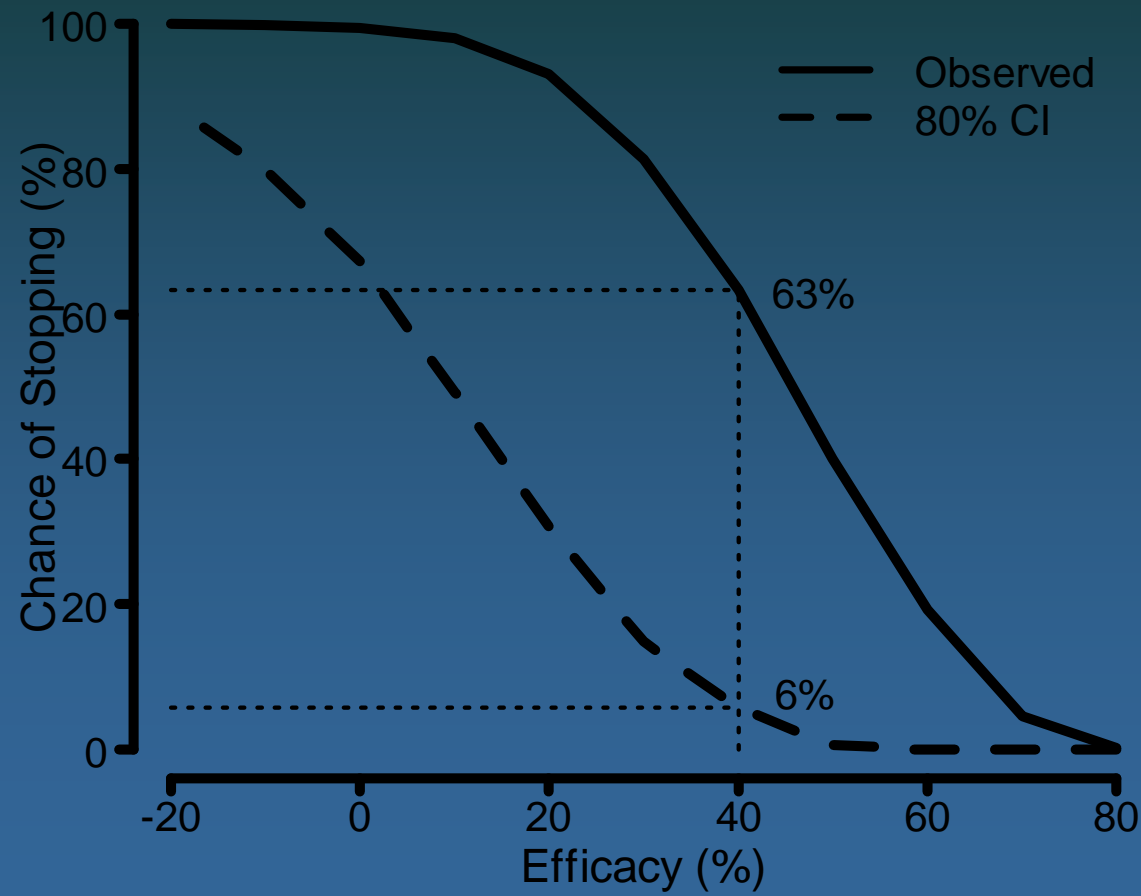
Conditional Power (1) – 50% look



3200 women, 2.5% annual incidence (placebo), 50% way through the trial (~24 infections)



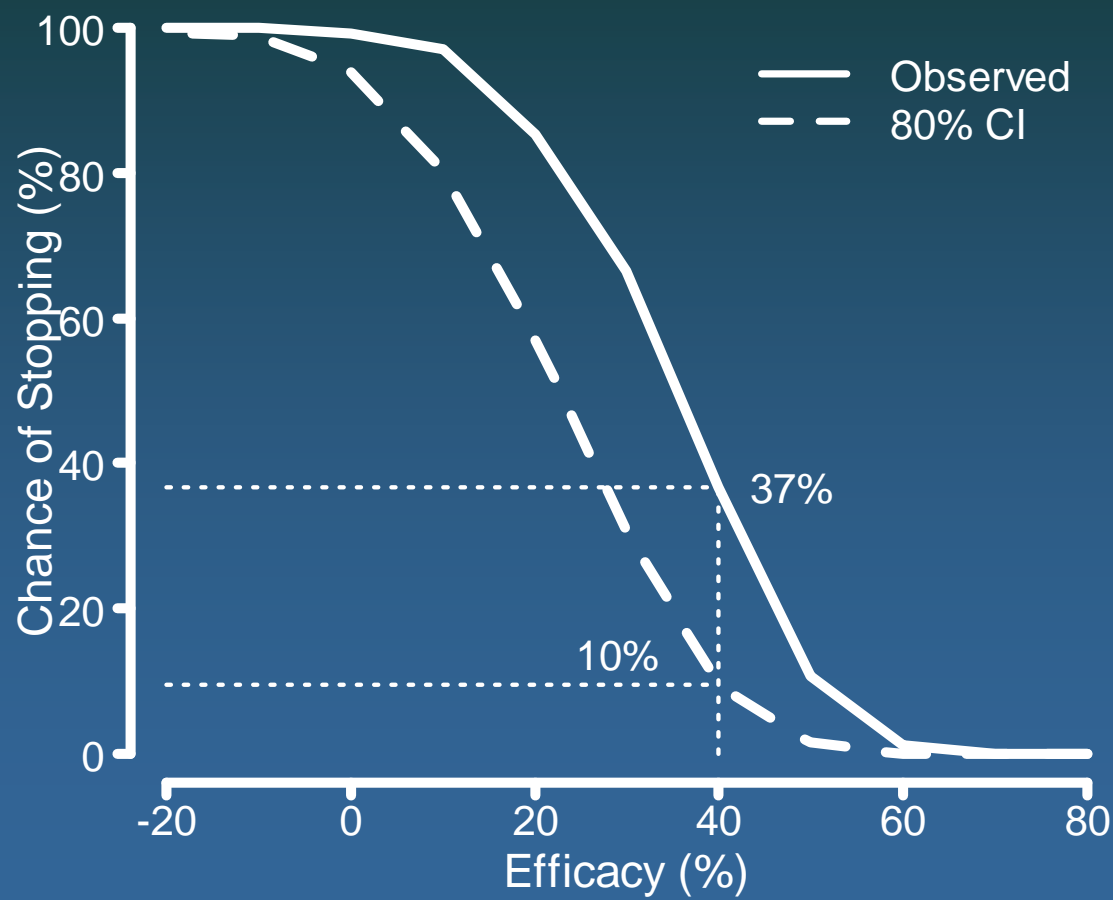
Conditional Power (1) – 25% look



3200 women, 2.5% annual incidence (placebo), 25% way through the trial (~12 infections)



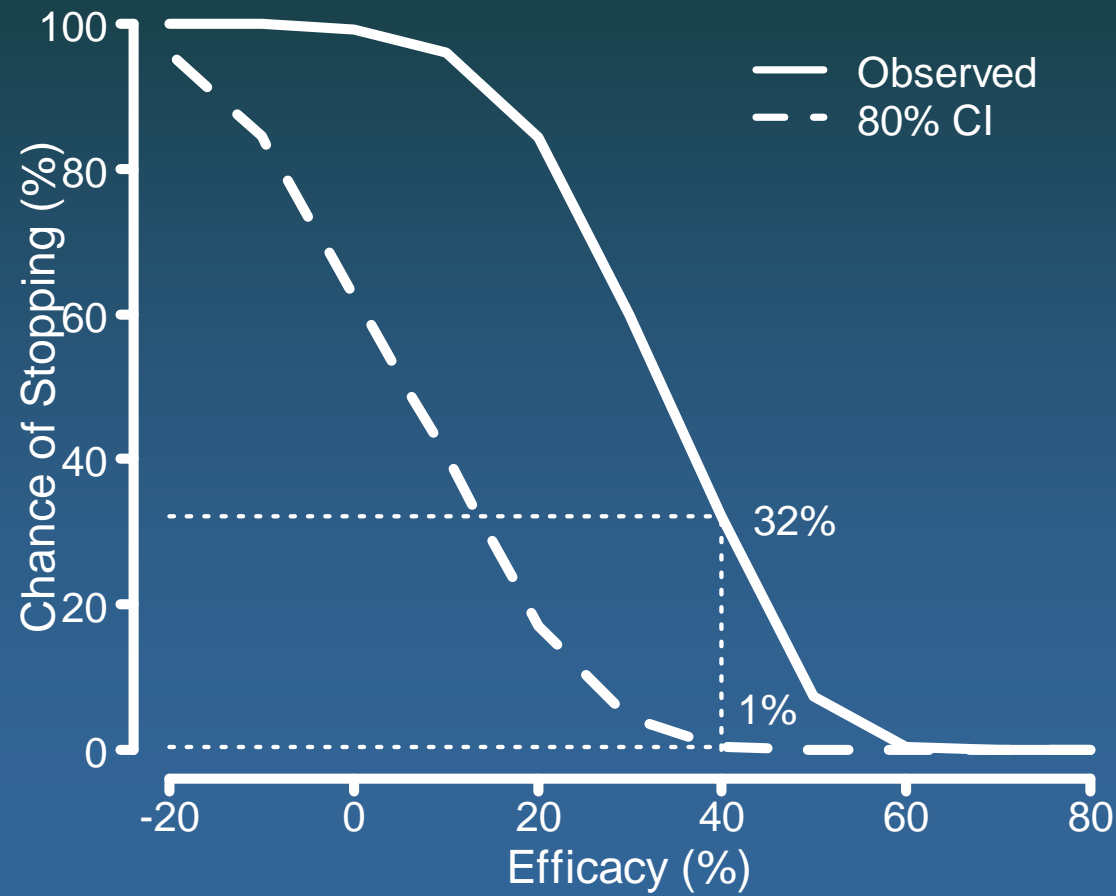
Conditional Power (2) – 50% look



6500 women, 2.5% annual incidence (placebo), 50% way through the trial (~65 infections)



Conditional Power (2) – 25% look



6500 women, 2.5% annual incidence (placebo), 25% way through the trial (~32 infections)



Challenges in Microbicide Trials

- **Trial integrity**
 - HIV incidence
 - Enrollment/retention
 - Adherence
 - High pregnancy rates
 - Follow-up for seroconverters
- **Follow-up for seroconverters**
- **Community/political support**



Conclusions

- **Lack of preclinical markers and clinical surrogates is a reality**
 - Resources need to be dedicated to addressing these issues
 - Answering these questions will take years to decades
 - Rigorously designed safety and efficacy trials of promising products should continue in parallel to this effort
- **Responsible trials speed development, minimize harm, and maximize resource utilization**
- **Plans are nothing; planning is everything.**
Dwight D. Eisenhower



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