

Table 1: Hypothetical Outcomes, Relative Risks and Likely Regulatory Response to a Randomized Control Trial Comparing Microbicidal Product with Placebo and to “Condom Only” Arm*§

	vs placebo	vs Condom Only	Two-arm Placebo Only ¹	Two-arm Condom Only ²	Three arm Both controls FDA Action? ³	Possible Interpretation
A	RR < 1	RR < 1	Approve	Approve	Approve	Microb is effective
B	RR > 1	RR > 1	Disapprove	Disapprove	Disapprove	Microb increases risk
C	RR = 1	RR = 1	Disapprove	Disapprove	Disapprove	Microb has no impact on risk; no worse than condom only
D	RR < 1	RR = 1	Approve	Disapprove	??	Microb better than placebo, but no better than condom only
E	RR < 1	RR > 1	Approve	Disapprove	??	Microb better than placebo, but less effective than condom only
F	RR > 1	RR = 1	Disapprove	Disapprove	Disapprove	Microb worse than placebo; equals condom only; Placebo protective?
G	RR > 1	RR < 1	Disapprove	Approve	??	Microb worse than placebo; both better than “condom only”
H	RR = 1	RR < 1	Disapprove	Approve	??	Microb equivalent to placebo; both better than condom only
I	RR = 1	RR > 1	Disapprove	Disapprove	Disapprove	Microb equivalent to placebo; both worse than condom only

* HIV incidence compared in experimental microbicide arm vs control arm: “RR<1.0 denotes increased risk in the control arm as compared with the experimental arm; “RR> 1.0” denotes decreased risk in the control arm compared with the experimental arm; and “RR = 1.0” denotes approximately equal risks of infection in the experimental arm

§ These interpretations assume a) that true levels of condom use do not vary across trial arms, and (b) that self-reports of condom use reflect reality. With a necessarily unblinded “condom-only” arm, both true levels and self-reports of their use might well vary systematically across trial arms, rendering these comparisons uninteruptible.

¹ Likely response of regulators to the scenario presented, if they were reviewing a two-armed trial of experimental product and a placebo control

² Likely response of regulators to the scenario presented, if they were reviewing a two-armed trial of experimental product and a “condom-only” control

³ Likely response of regulators to the scenario presented, if they were reviewing a three-armed trial with both a placebo and “condom only” control arm

Source: Adapted from Stein Z, Myer L, and Susser M. 2003. The design of prophylactic trials for HIV: The case of microbicides. *Epidemiology*.14(1):80-84.