

# WHEN RCTs MAY NOT BE THE BEST DESIGN

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An ineffective health intervention is

- at best a waste of money
- at worst detrimental to health

Randomised controlled trials **are the best design** to assess whether a microbicide protects against the acquisition of HIV infection.

## EXCLUSIONS / INCLUSIONS IN RCT's

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The trial population should be as much as possible representative for the population of interest

→ keep the eligibility criteria to a minimum

## EXCLUSIONS / INCLUSIONS IN RCT's OF MICROBICIDES

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Population of interest = women and men who are unable to successfully negotiate safe sex.



For ethical reasons study participants have to be encouraged to use a condom.

## TWO OPTIONS

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- Allow for a run-in period and only take in study participants who do not use a condom despite intensive counselling.
- Take in everybody regardless of condom use.

## PROBLEMS WITH OPTION 1

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Run-in period and only take in study participants who do not use a condom despite intensive counselling.

- Study participants may start using condoms later.
- An effect of the microbicide in consistent condom users may be missed.

## PROBLEMS WITH OPTION 2

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Take in everybody regardless of condom use.

- The sample size needs to be increased.
- Possibly problems with analysis of the data: sub group analysis?

## HYPOTHETICAL DATA 1

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<u>Condom use</u>	HIV incidence ( <i>per 100 py</i> )		
	<u>Placebo</u>	<u>Microb</u>	<u>RR</u>
Never	15	7	0.5
Sometimes	10	5	0.5
Often	8	4	0.5
Always	5	2	0.4

## HYPOTHETICAL DATA 2

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<u>Condom use</u>	HIV incidence ( <i>per 100 py</i> )		
	<u>Placebo</u>	<u>Microb</u>	<u>RR</u>
Never	15	7	0.5
Sometimes	10	5	0.5
Often	8	4	0.5
Always	5	2	1

## POSSIBLE EXPLANATIONS FOR THE DIFFERENCE IN RR ACCORDING TO CONDOM USE

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- Chance finding → test for interaction
- There is statistical interaction:
  - the microbicide does not provide additional protection over and above the condom
  - study participants who misreport condom use are not compliant with microbicide use

# HYPOTHETICAL SCENARIO 1

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Intent-to-treat analysis

→  $RR = 0.5$  regardless of proportion of study participants who consistently use a condom

## HYPOTHETICAL SCENARIO 2

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Intent-to-treat analysis:

<u>Consistent condom use</u>	<u>RR</u>
30%	0.58
50%	0.67
70%	0.77

A large effect may be missed in the **population of interest.**

## HOW TO DEAL WITH THIS PROBLEM ?

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- Preempt the % of consistent condom users in the trial population → adapt sample size calculation **not only** to expected lower incidence of HIV but also to sub group analysis.
- Stratified analysis (sub group analysis).

## CONCLUSION

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When testing the efficacy of a microbicide one should not do 1 trial at a time, but several trials (one for each stratum of condom use) !