

When is a null effect no effect?

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When is a null effect no effect?

- Study duration
- Intent to treat analysis
- Nature of the control or comparison group

Study duration

- Too short:
 - Outcome: not enough time to event
 - Intervention: dose effect necessary
- Too long:
 - Secular trends (introduction of a new intervention; demographic shifts)
 - Cohort effect may apply: (likelihood of bias may increase over time)

Cohort effect

- Time-dependent selection bias
 - Heterogeneity in susceptibility or frailty
 - Behavior change over time
- Censored data or waning compliance
- Both may differential or non-differential
 - May violate initial randomization over time
 - May result in bias to null

Study duration at design stage

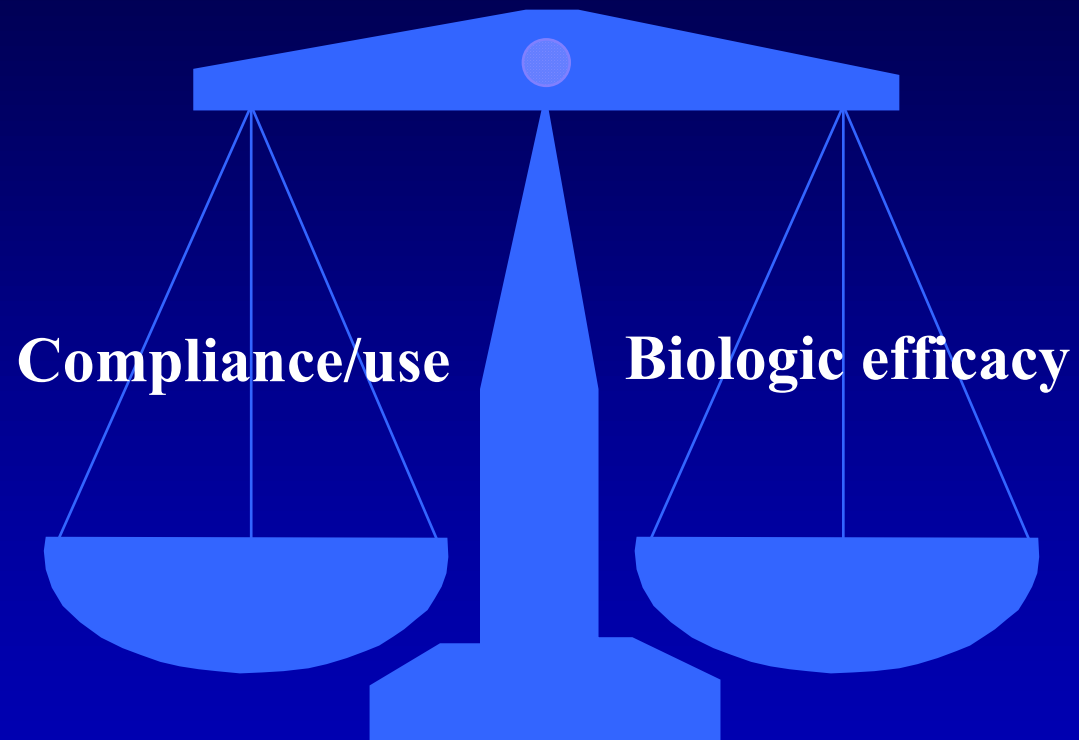
- Control for cohort effect
 - Susceptibility (biological and behavioral)
 - Only enroll susceptibles
 - Homogeneous sample
 - Measure and control in recruitment or as covariate in analyses
 - Compliance discussed in context of ITT
 - Shorter/larger study

Study duration at implementation and analysis

- During implementation:
 - Sequential monitoring and interim analyses including conditional power calculations*. If no effect or a marginal one, may decide to continue study longer or increase sample
- During analysis:
 - Marginal structural models that control for informative drop out, time-dependent confounding

*requires appropriate adjustment in sample size planning

Intent to Treat



Strict ITT

- ITT in the presence of non-compliance estimates effectiveness rather than efficacy
- Who cares?
 - Does disentangling the proportion of effectiveness attributable to efficacy and to compliance matter?
 - Should use, compliance, or adherence be assessed?
 - What about other effect modifiers?

When individual use and compliance are less relevant (strict ITT makes sense)

- DOT
- DOP (vaccine, prophylactic drugs)
- Community-level or structural intervention
- Participants are actively seeking care or treatment for a medical condition

When use/compliance should be considered

- Researchers are actively seeking participants
 - Participation is voluntary; prevention motivates people less than treatment
- Use not 100% under the participant's control
- Choice or compliance intrinsic to the intervention; requires individual volition
- Compliance/use are unobserved

Don't throw out the baby....

- Effectiveness varies by:
 - Compliance, (aspects of which may be modifiable), dependent on:
 - social and cultural context
 - sexual activity/type of partner
 - protocol requirements
 - Other effect modifiers (e.g frequency of exposure and product use)
- Strict ITT would mask this phenomenon

Microbicide tested among sex workers

- Found ineffective, yet product deemed safe
- Null effect may be due to:
 - 1 No biological efficacy
 - 2 Frequency of use and sexual activity
 - 3 Poor compliance
- #'s 2 and 3 merit further testing
- Null effect may not be generalizable

Compliance during design and implementation

- During Design:
 - Minimize compliance issues
 - Run-in to enroll compliant people
- During implementation:
 - Ensure access and acceptability

Compliance during analysis: ITT Plus

- During Analysis:
 - Even in an ITT- check if compliance and other known effect modifiers differ by arm
 - Statistical techniques if differential
 - Per-protocol
 - Adjust measure of effect by compliance factors or other effect modifiers*
 - Marginal structural models

*(Sheiner and Rubin, 1995; Mark and Robins, 1993; Rosenberger, 1996)

Measurement!!!!

- Social desirability
- Mode
- Reliability
- Validity

Compared to what or whom???

- Different control/placebo groups yield different results
- Which comparison has clinical or PH significance?

Control Groups/Placebo Arms

- Comparison may make it difficult to detect an effect
 - Standard of care comparison (e.g., condoms) highly effective
 - Few people only use the product
 - Unknown effect of comparison (e.g. placebo not inert)
- Use of multiple control groups

Project Respect

Kamb et al. JAMA, 1998

- Counseling to prevent HIV/STDs
 - 4 session, 2 session, information only
 - No difference between 4 and 2
 - 4 and 2 significantly better than information (condom use, incident STDs)
- No effect without information only arm
 - Unknown effect of information only

Microbicide Trials

- Intensity of condom counseling
- Placebo
 - Control for behavior
- Non-placebo control
 - Control for unanticipated protective effects of placebo
 - Control for secular trends

Multiple Arms

- Larger sample to compensate for loss in power
 - QA more difficult
 - More expensive
 - Possibly longer study
- Refine the research question(s): be certain multiple arms are necessary

What is reality???

- Study duration: Goldilocks Principle
 - Time enough to see an effect
 - Cohort effect
- To whom can results be generalized?
- Compared to what or whom?
- Additional study versus acting on study results

