The High Statistical Cost of Loss to Follow-up

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Outline

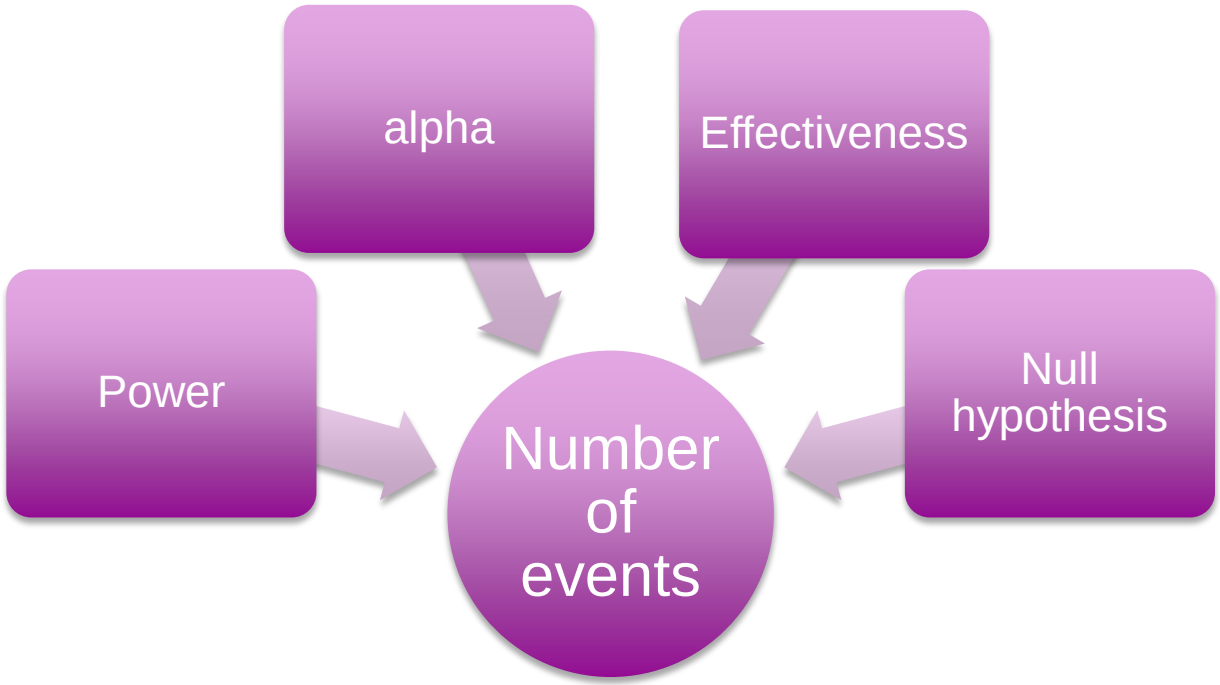
- Preliminaries
  - Study design
  - Intent-to-treat analyses
  - Efficacy vs. Effectiveness
- Examples
  - How can a product be efficacious but not effective?
  - How could this affect future trials (ASPIRE)?
- Conclusions

Statistical design of a study

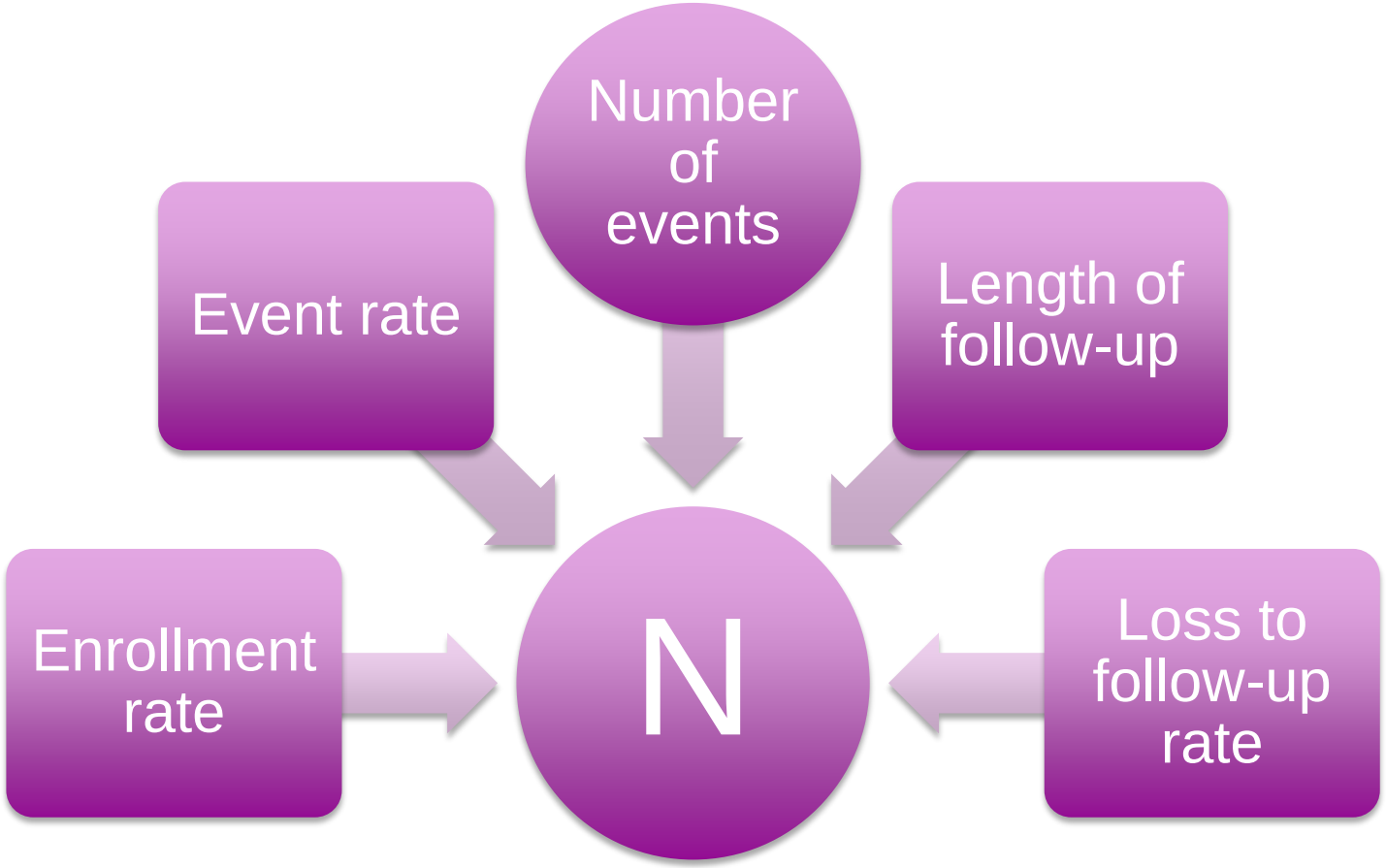
Or how do we decide how many participants to enroll?

- First, we calculate the number of events
  - Effect size of the intervention
  - Power
    - The probability of having a positive result given that the intervention is effective
  - False positive rate (alpha level)
  - Null hypothesis
- Next the number of participants

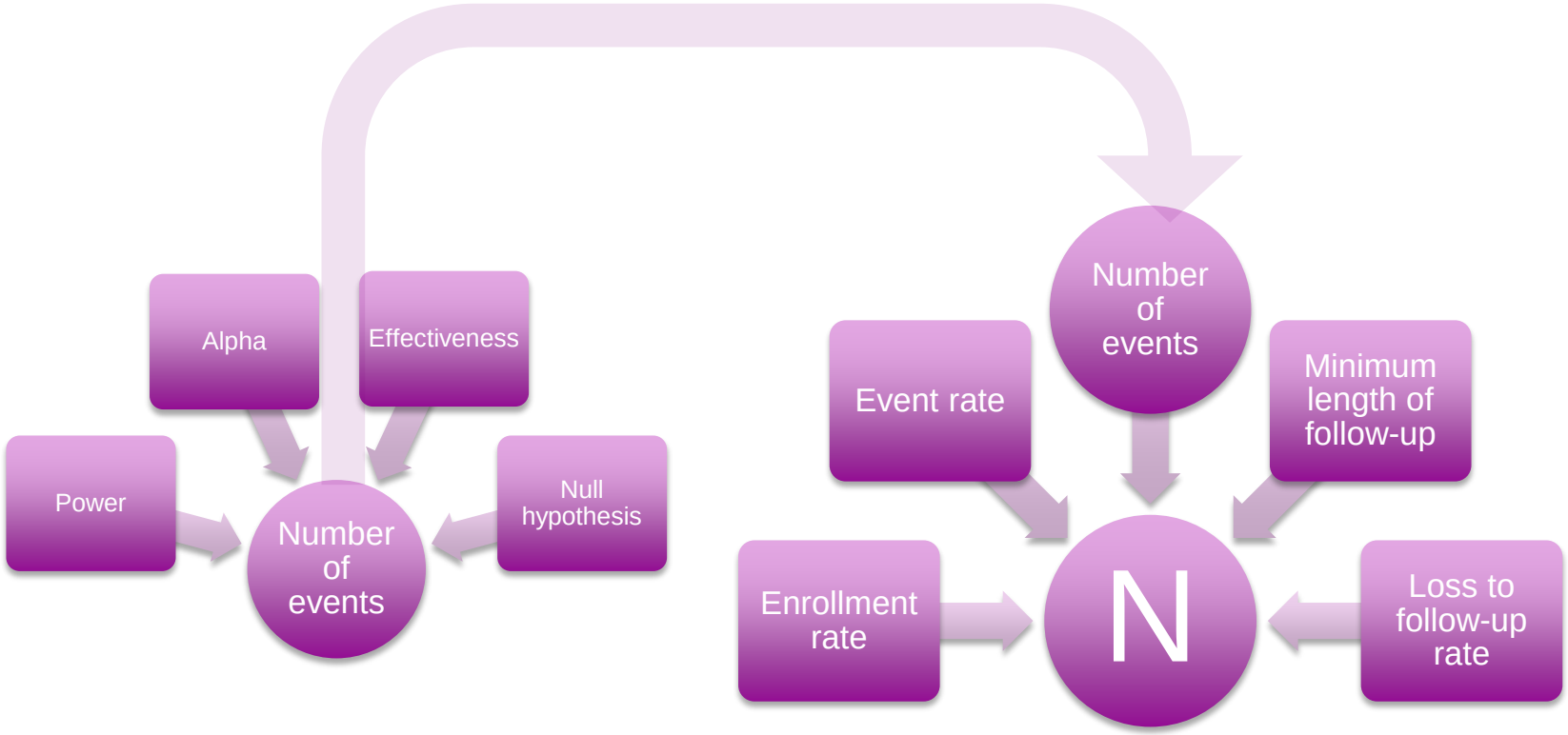
Getting to the number of events



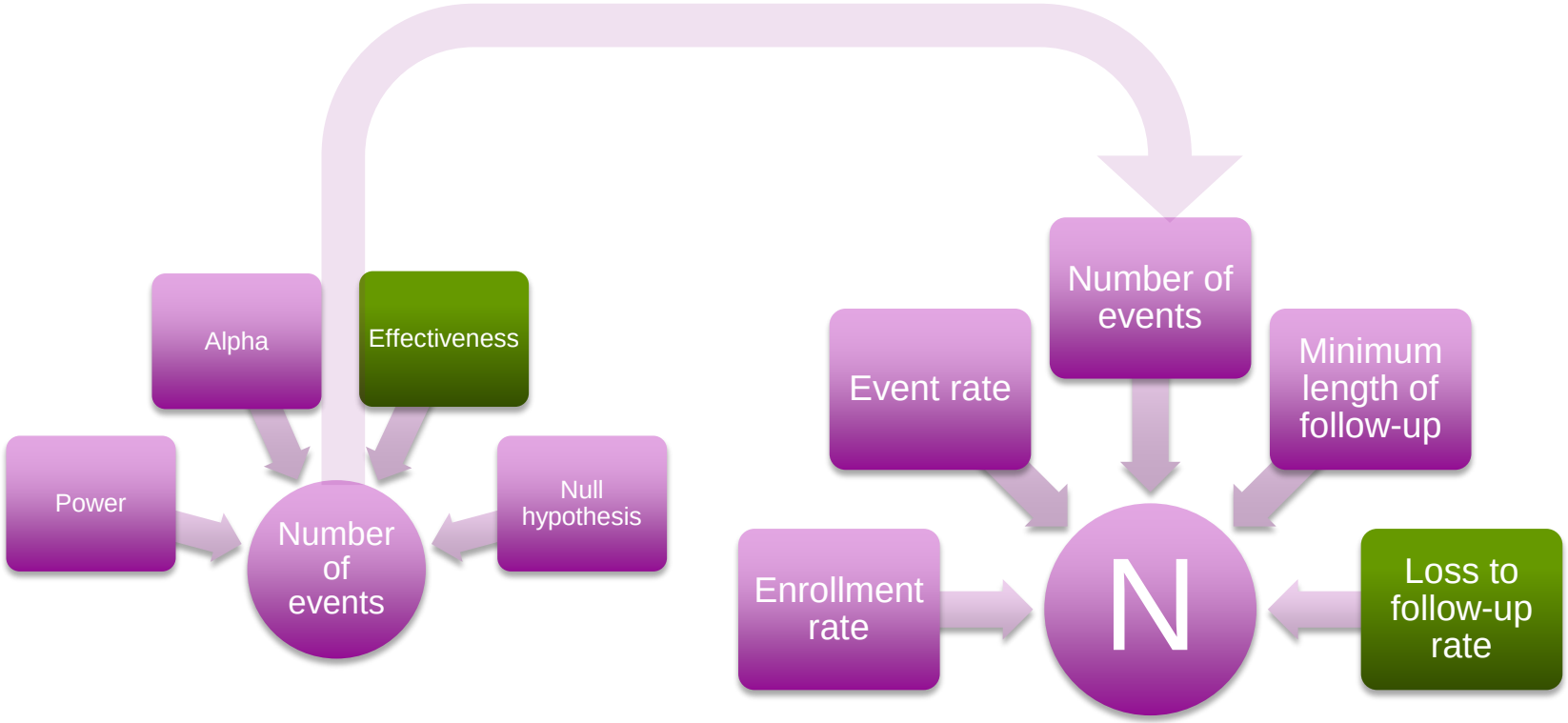
Number of participants



Design summarized



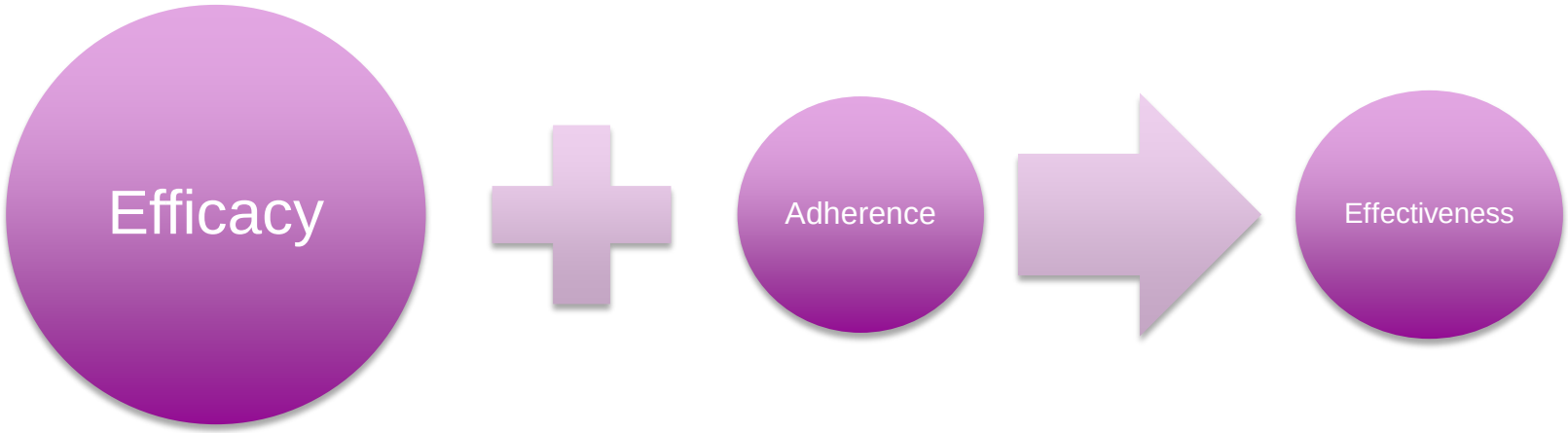
Design summarized



Efficacy vs. effectiveness

- Efficacy is a person-level measure (The biomedical impact of the drug on risk)
- Effectiveness is a population-level measure

Efficacy vs. effectiveness, cont.



What is adherence?

- Ideally, adherence reflects how a woman would use a product when it is provided.
- Full adherence is not possible when a woman does not have the product.
- Two types
  - Study adherence: Adhering to the protocol
  - Product adherence: Adhering to the product when provided
- We cannot have full product adherence without full study adherence!

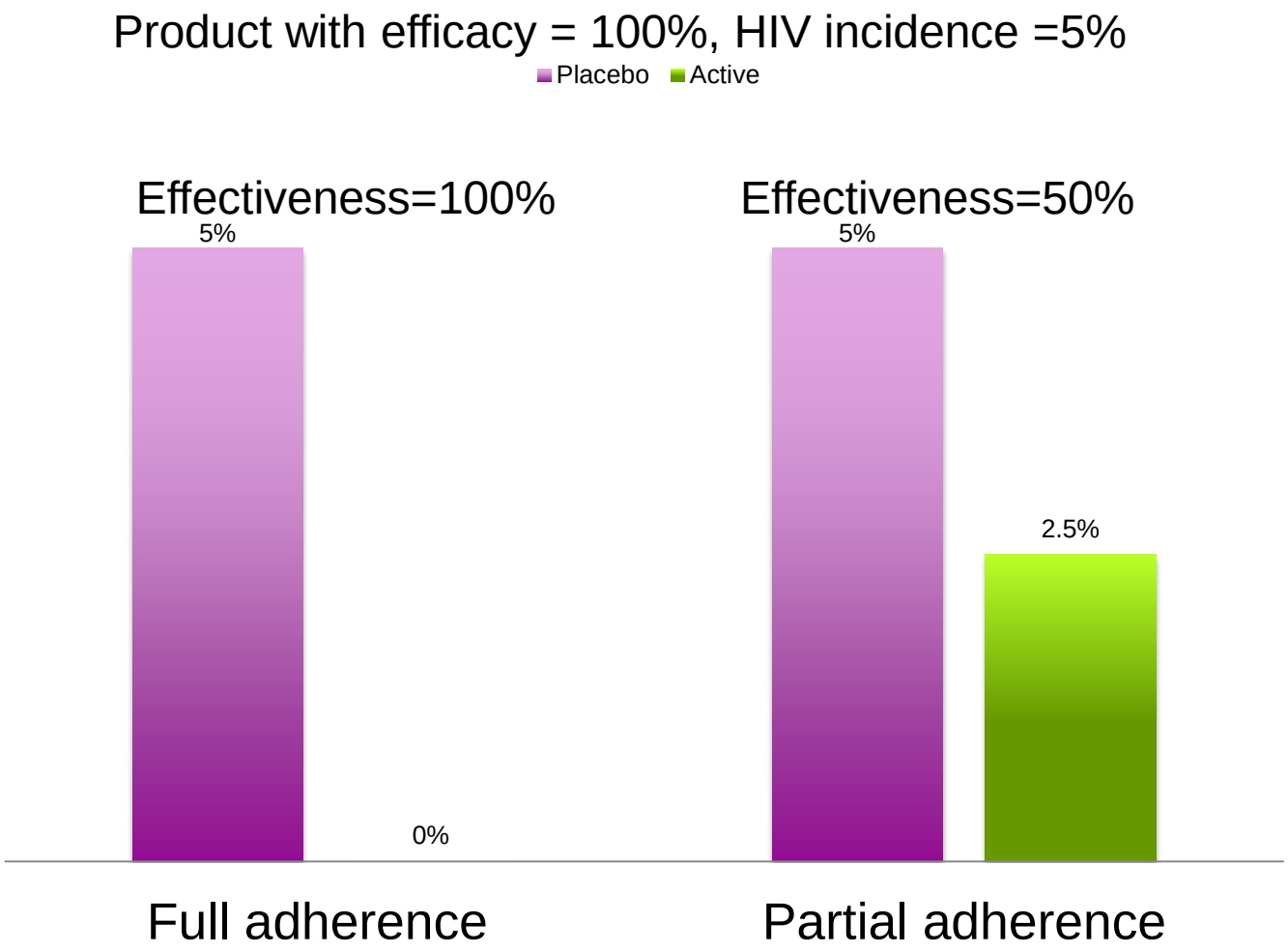
Why does adherence matter?

- The primary analysis in a clinical trial is always *intent-to-treat*
- Other ways to think of this:
  - What is the effect of the randomization on HIV acquisition in the population?

  Or

  - What affect does providing a woman an HIV prevention strategy and counseling her to follow it have on HIV incidence?
- This is different than “does the product protect against HIV?”

Why the difference?



Impact on a clinical trial

To investigate the impact of intermittent loss to follow-up on the results of a study like ASPIRE, we

- Simulated data according to the design parameters in ASPIRE
- Varied the levels of drop-out and return to study
- Graphical summaries of the impact on the study results focusing on power and efficacy estimates

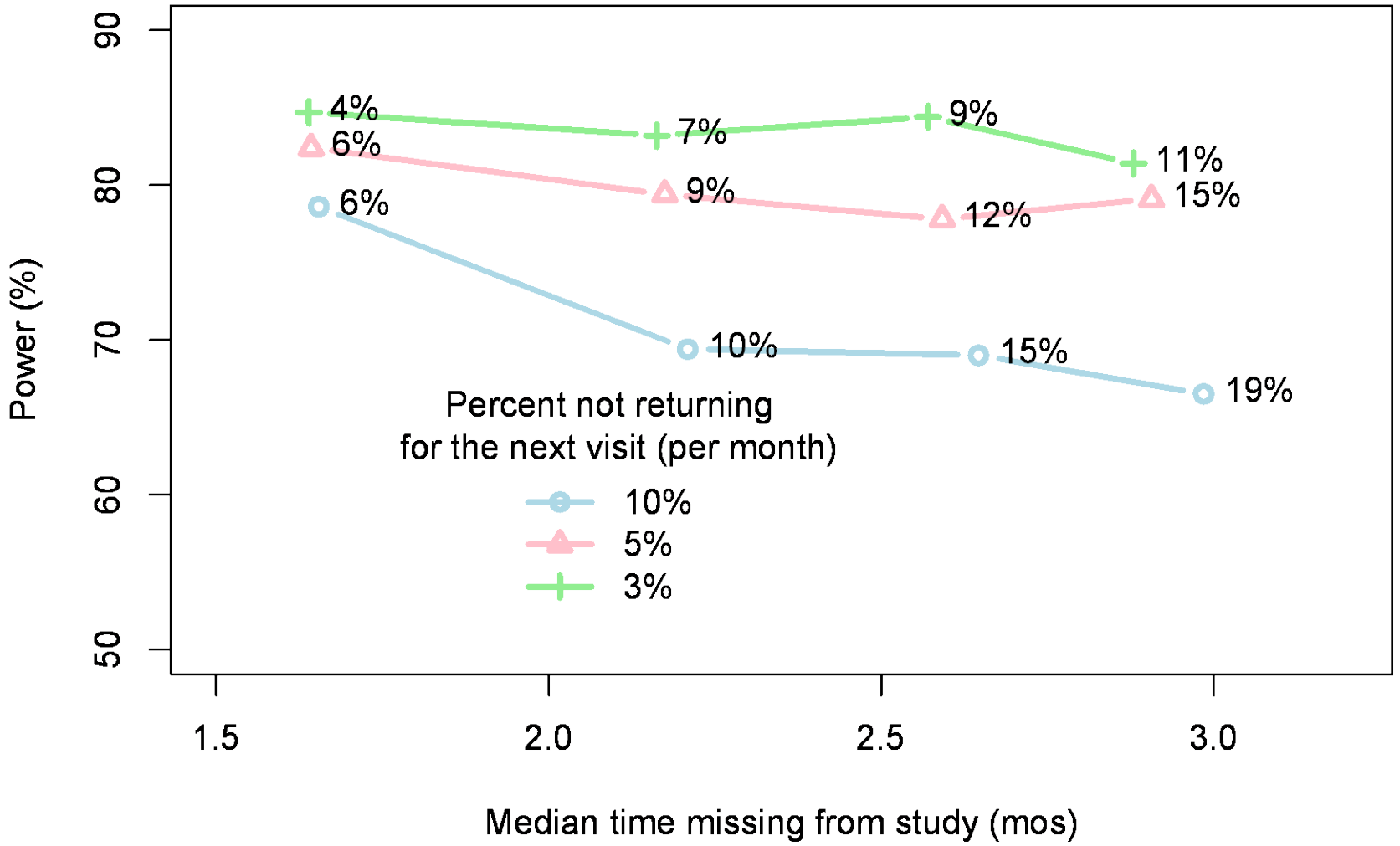
MTN-020 ASPIRE

- Baseline infection rate: 3.9%/year
- Effectiveness: 60%
- Loss-to-follow-up rate: 1%/mo (15% overall)
- Power=90%, alpha=0.05
- Events=120
- N=3476
- Null hypothesis: rule out effectiveness<25%

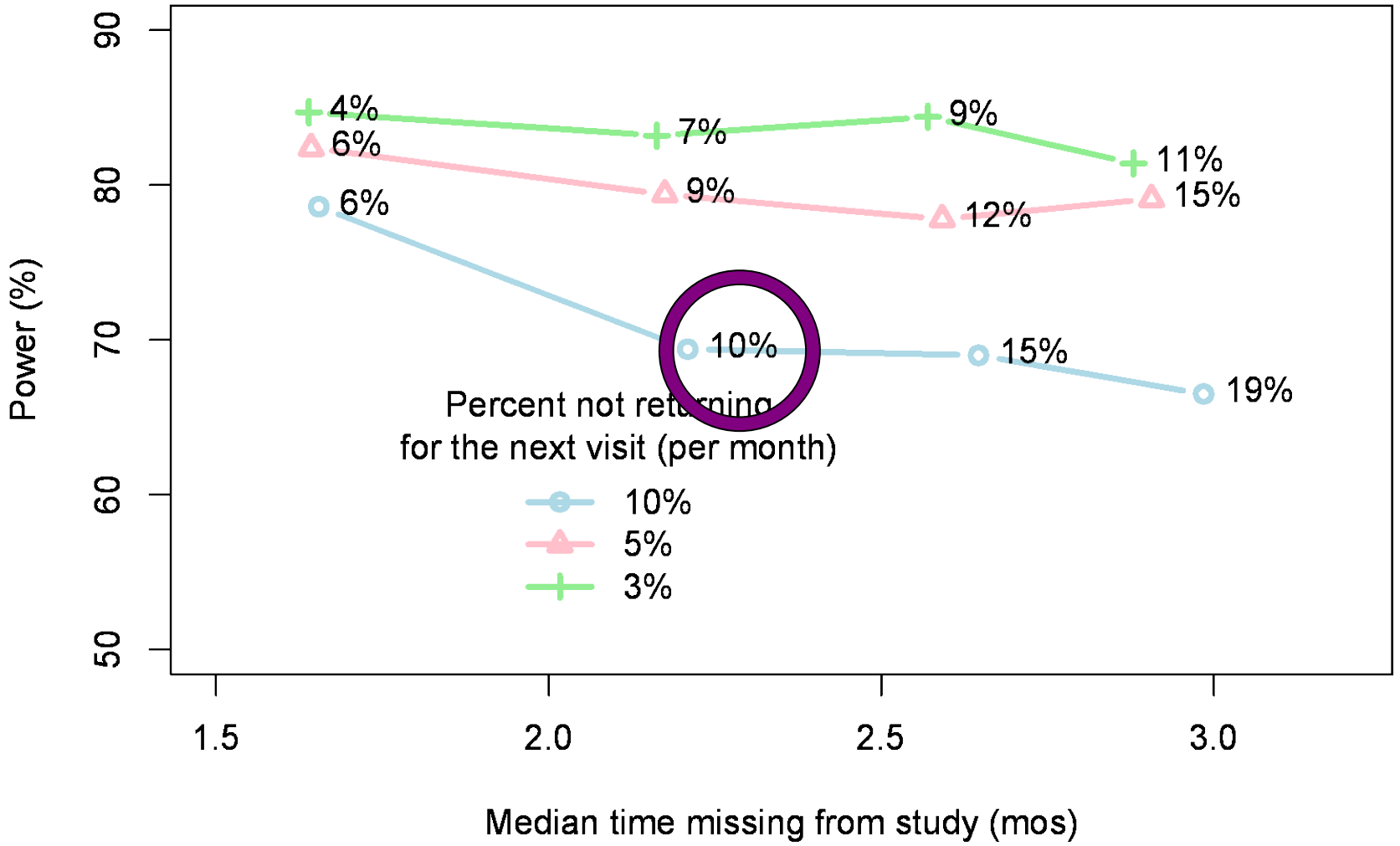
Nowhere in these calculations do we allow for intermittent loss to follow-up.

What is the potential effect of this on the study?

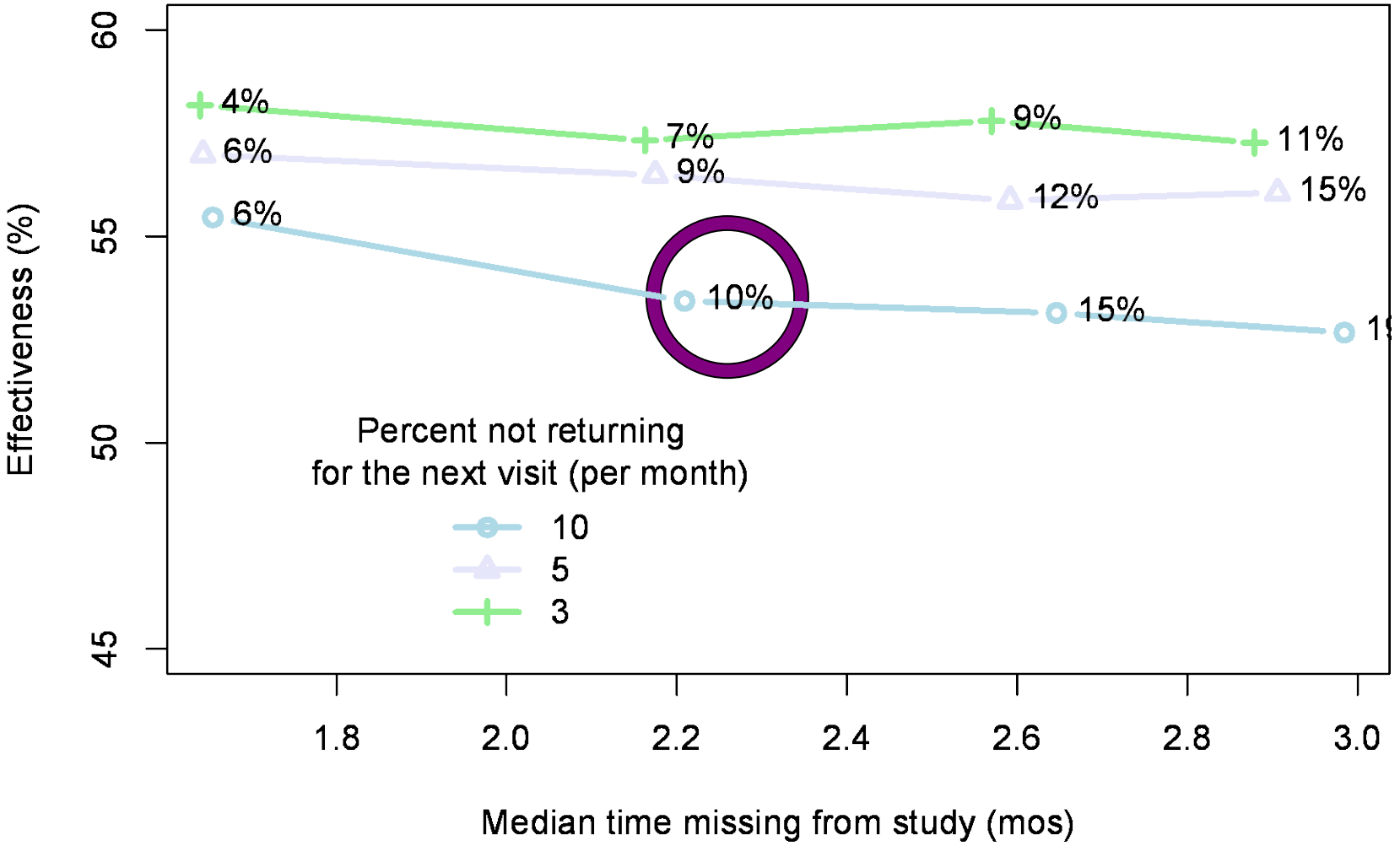
Results


Power (%)
90
80
70
60
50
4%
7%
9%
11%
6%
9%
12%
15%
6%
10%
15%
19%
Percent not returning
for the next visit (per month)
10%
5%
3%
1.5
2.0
2.5
3.0
Median time missing from study (mos)

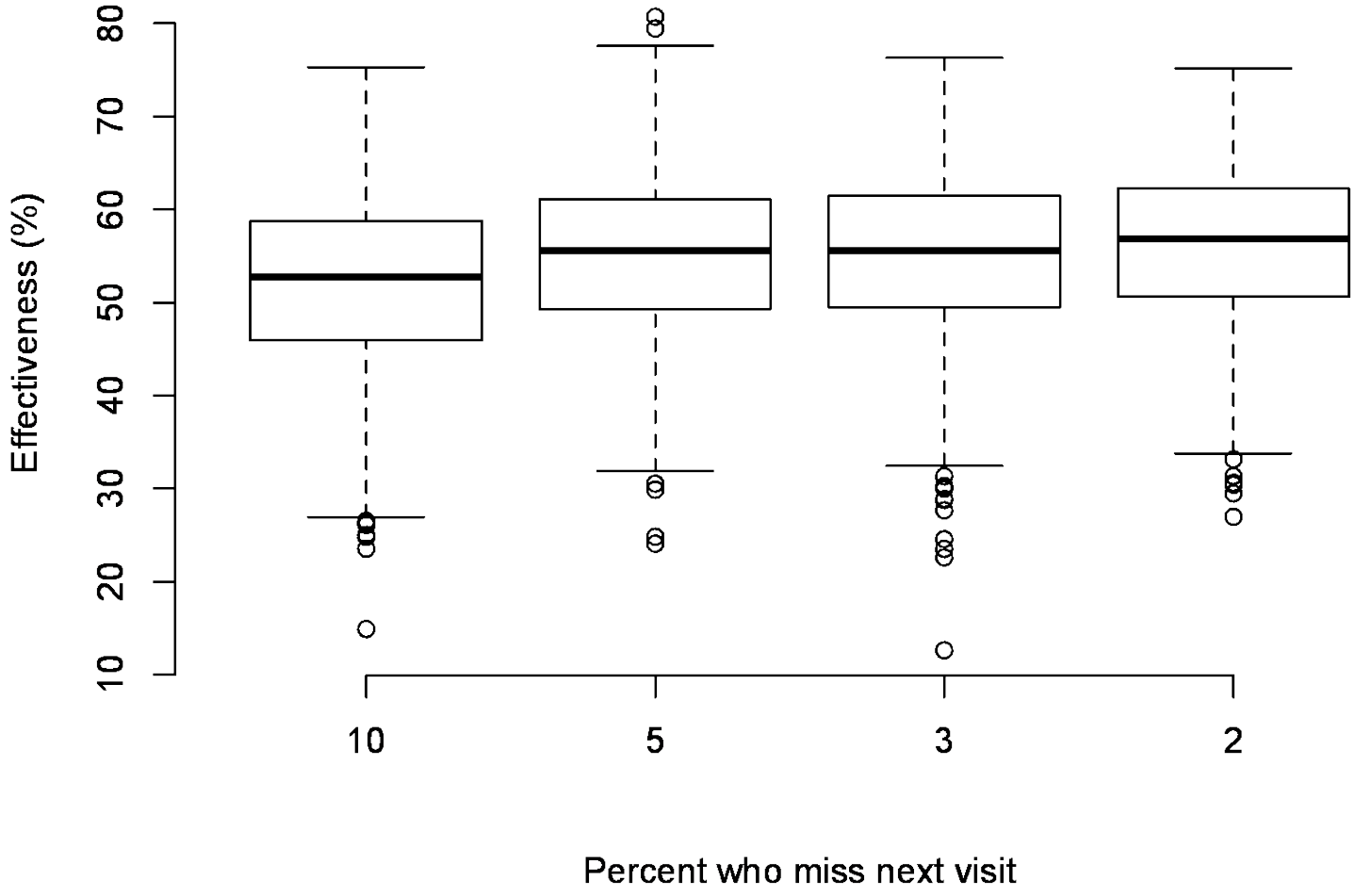
Results


Power (%)
90
80
70
60
50
1.5
2.0
2.5
3.0
Median time missing from study (mos)
4%
7%
9%
11%
6%
9%
12%
15%
6%
10%
15%
19%
Percent not returning
for the next visit (per month)
10%
5%
3%

Results, cont.



Results from 1000 clinical trials with 90% retention



Summary

- Even while maintaining the desired overall retention rate, intermittent loss to follow-up can negatively impact the results of a trial
  - Loss of power
  - Underestimate of potential effectiveness
  - Inability to estimate efficacy
- Ensuring women return for visits or have other arrangements that allow them to stay on product is CRITICAL!

Further comments

- Examples shown are best case scenario
  - More likely that in practice, a woman's ability to adhere to the protocol is related to her HIV risk – this could result in even more severe underestimation of potential effectiveness

Thank you!