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Stepped-Wedge Studies:  
The THRio Experience

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Protecting Health, Saving Lives—*Millions at a Time*



It's Friday the 13<sup>th</sup>...



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# Outline

- The Problem: Can we have our cake and eat it too?
- The Proposed Solution: Phased implementation designs
  - Stepped wedge as a prototype
- The Challenges: Stepped wedge as angel food or fruitcake?



# The Problem

- **Novel diagnostics for infectious diseases create an ethical quandary.** Dowdy DW, Merritt MW, Gounder C, Corbett EL, Chaisson RE, under review.
  - Diagnostics are designed to detect the presence or absence of disease, not improve population-level health.
  - They are often approved on the basis of accuracy, but then may be recommended on the untested assumption that they improve health.
  - To know whether these recommendations are appropriate, we need to evaluate whether diagnostics impact population health.
    - Cluster-randomized trials as the ideal design
- **Is it ethical to randomize someone to a diagnostic test that you know is inferior?**



# The Elephant in the Room



# The Elephant in the Room



**Would you recommend that middle-income countries pay Cepheid over \$100 million per year if you knew Xpert MTB/RIF had no impact on population-level health outcomes? Is it just another PSA – gives you a diagnosis, but doesn't reduce morbidity or mortality?**



“All I can say is, if you’re randomizing people to LED microscopy vs. Xpert, I know which arm I want to be in.”

Chris Dye, Amsterdam, Sept. 2011





# Phased-Implementation Designs: The Theory

- Parallel designs are ethically troublesome because, even if you provide access at the end of the study, you are withholding an intervention known to be superior.
  - Is superiority of diagnostic accuracy sufficient to break equipoise over population health?
- Interventions cannot realistically be rolled out at one point in time.
- Given this, why not randomize the order in which groups obtain access to the intervention?
  - Might make roll-out more equitable
  - Might also make it possible to study the intervention as it is rolled out:
    - “Have your cake and eat it too”





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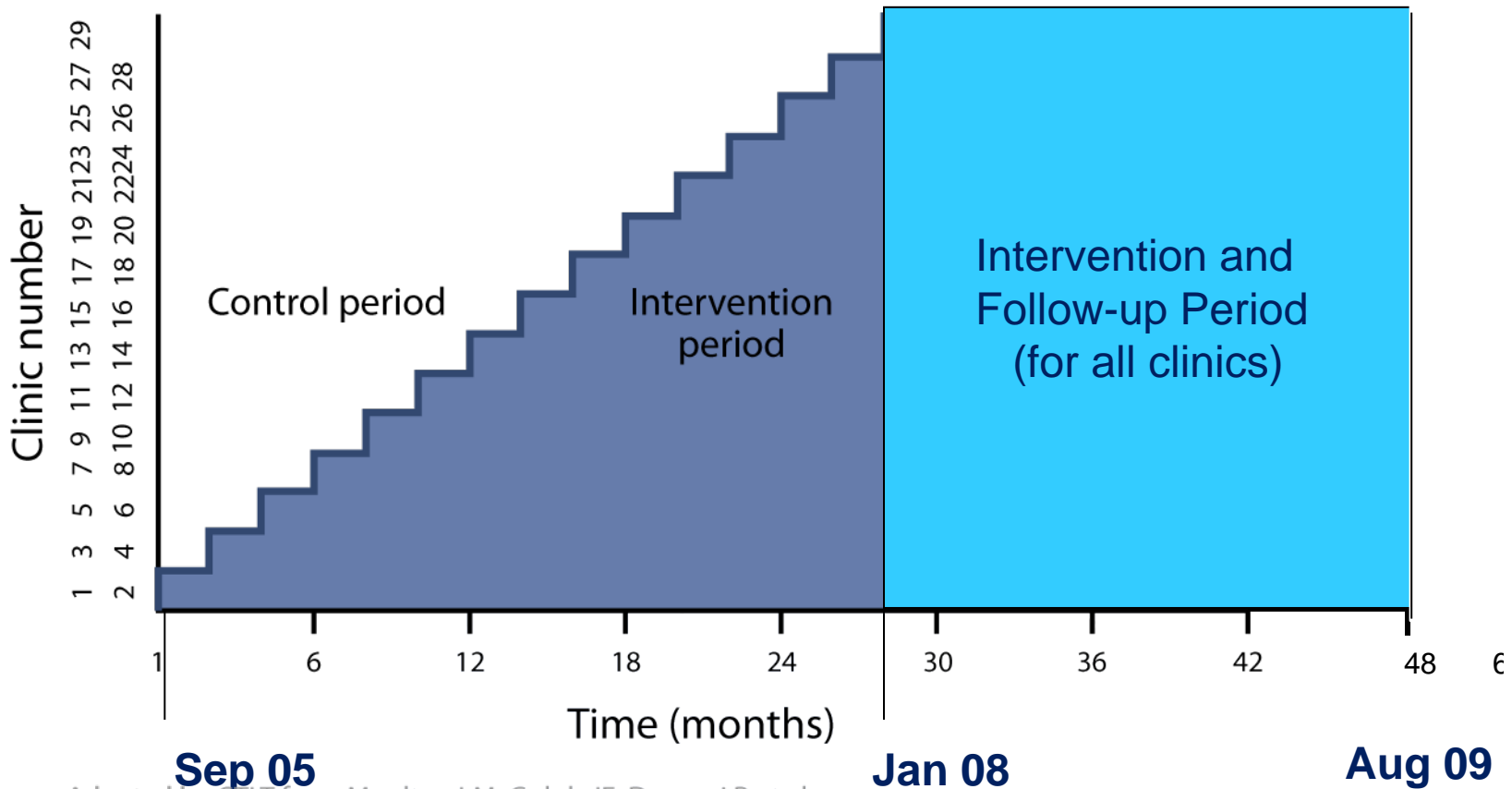
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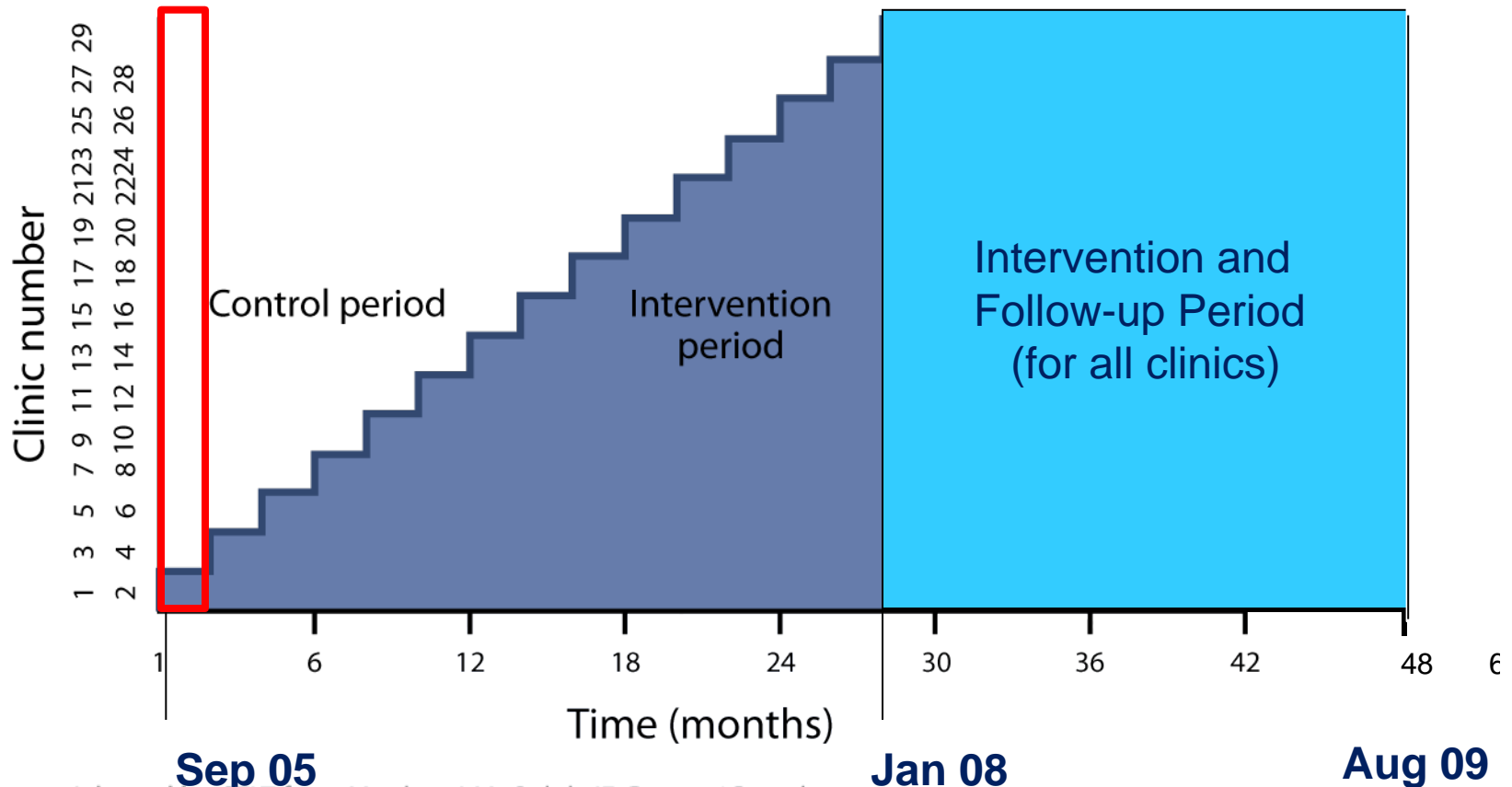
# Stepped-Wedge Design



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*Clinical Trials* 2007;4:190.



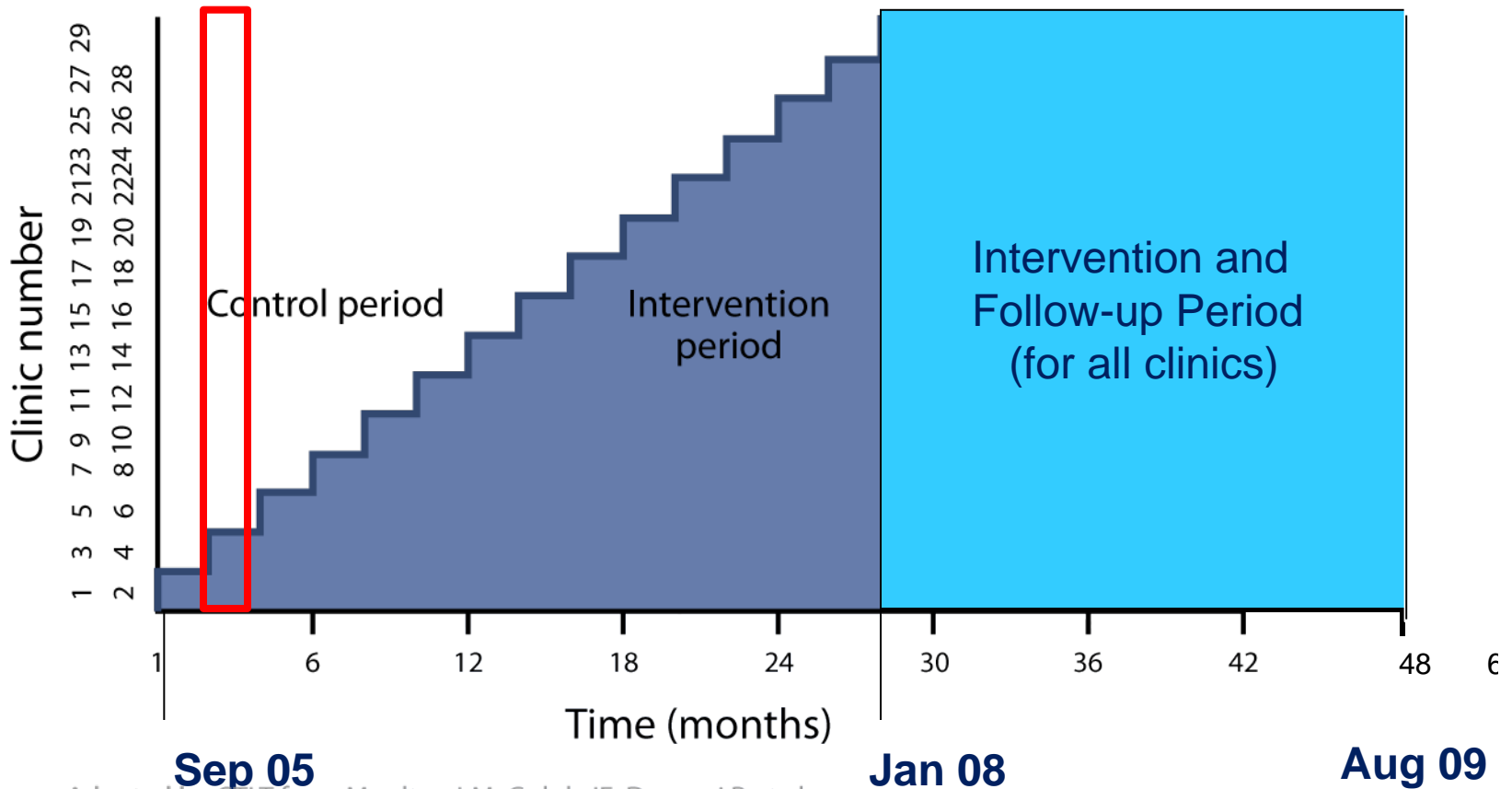
# Analysis: Automatically Adjusts for Secular Trends



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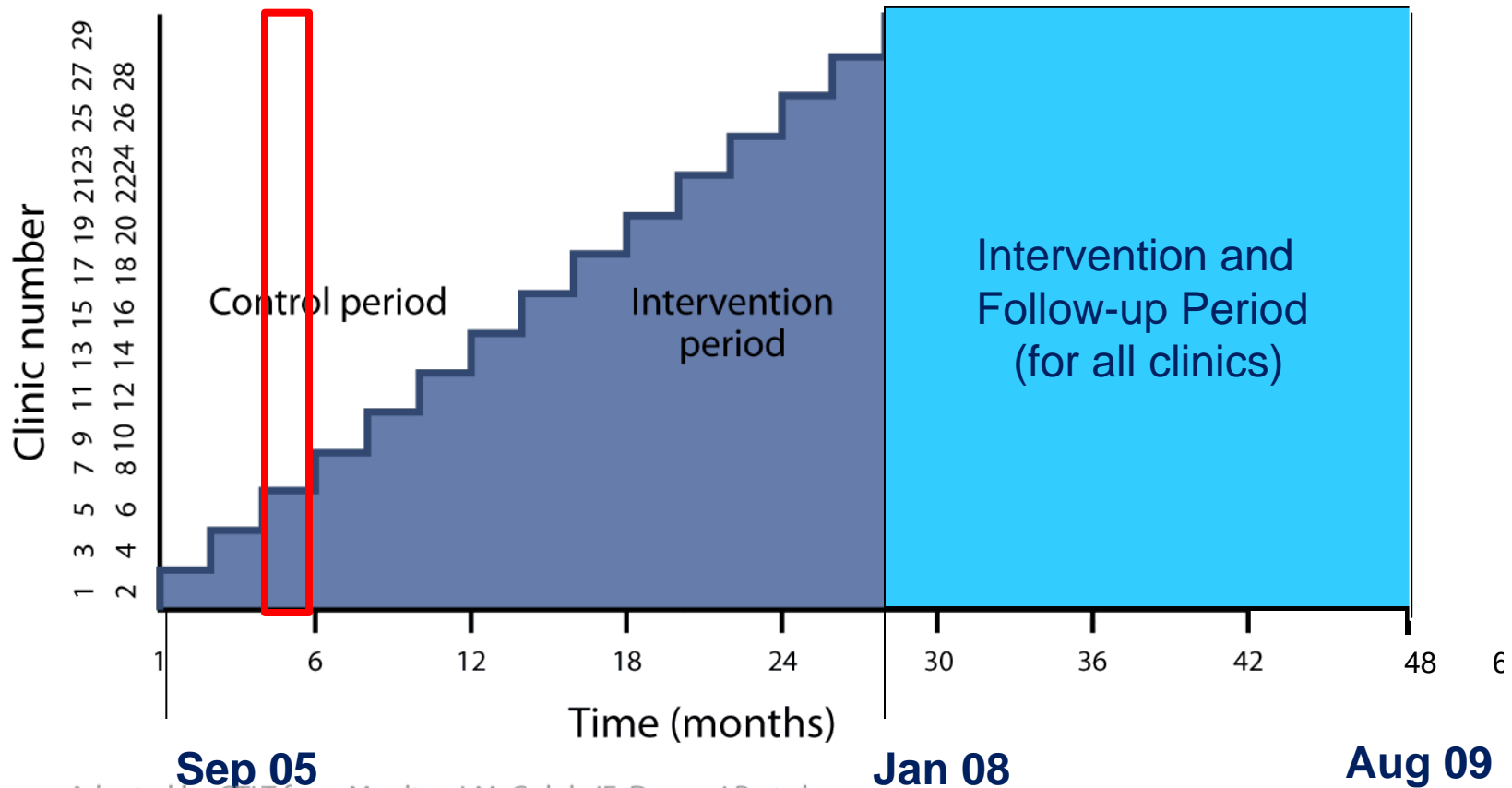
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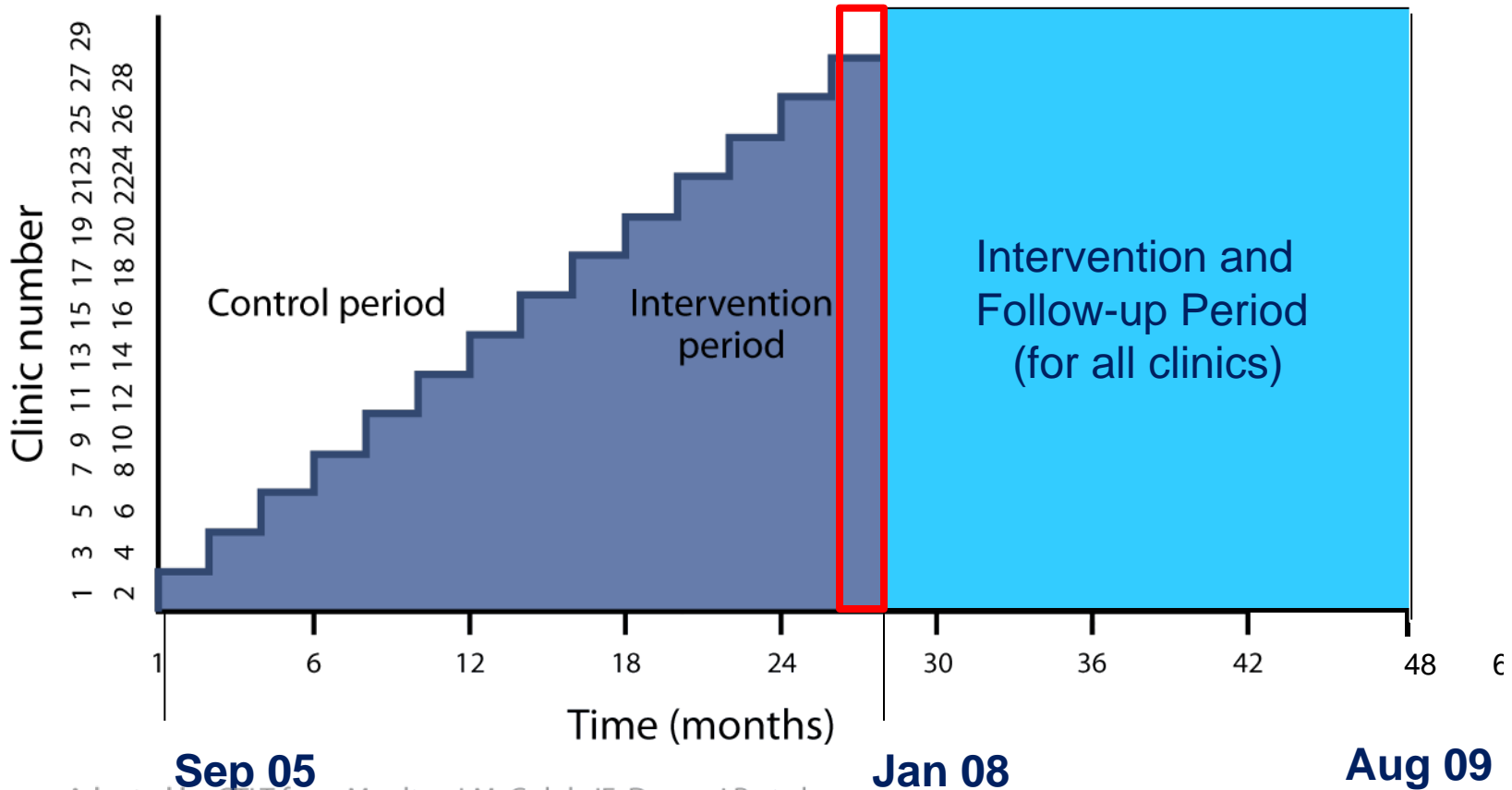
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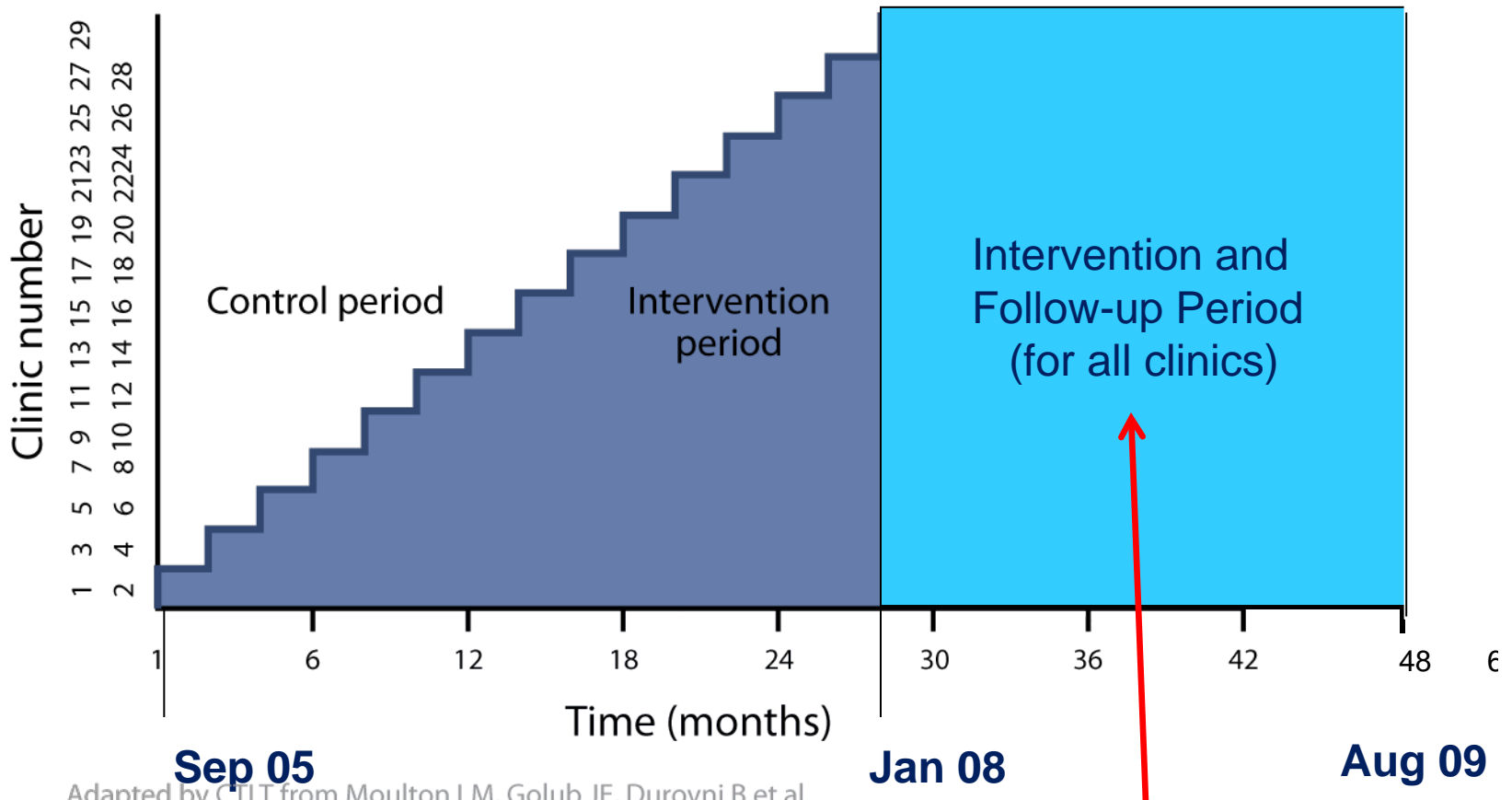
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Study End: Everyone gets the intervention!





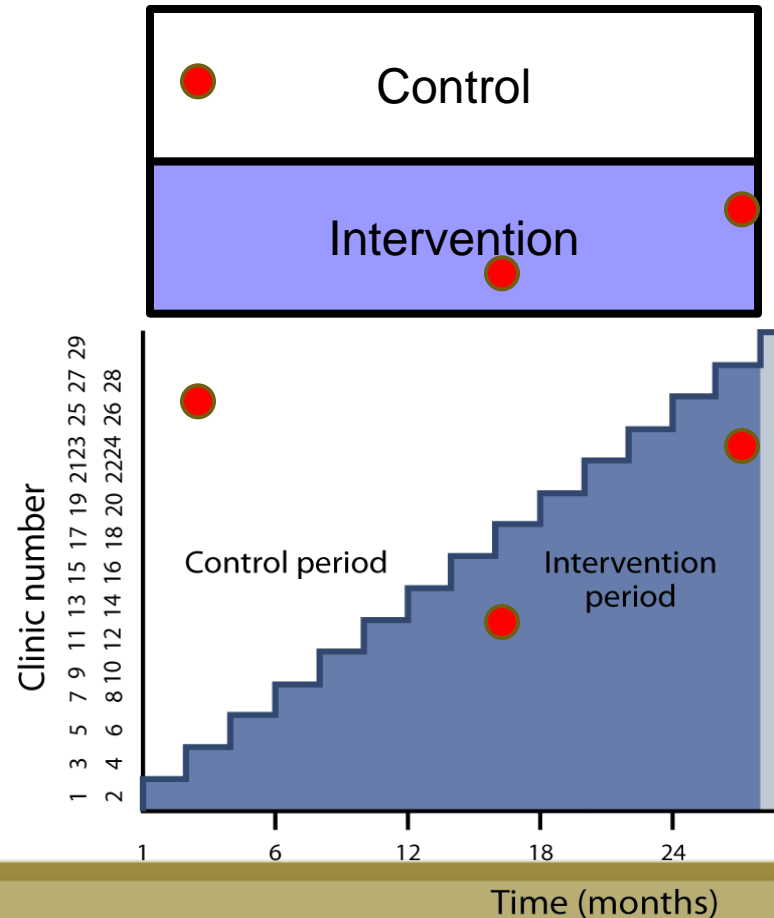
# Phased Implementation Designs: Angel Food?

- Randomized analysis, adjusted for secular trends
- Wouldn't be able to roll out the intervention any faster
  - Nobody is harmed by the study
- Everyone gets the intervention at the study's end
- *IRB paperwork burden is slashed!*
  - Or you can get away with things (e.g., waiver of informed consent) that you otherwise wouldn't



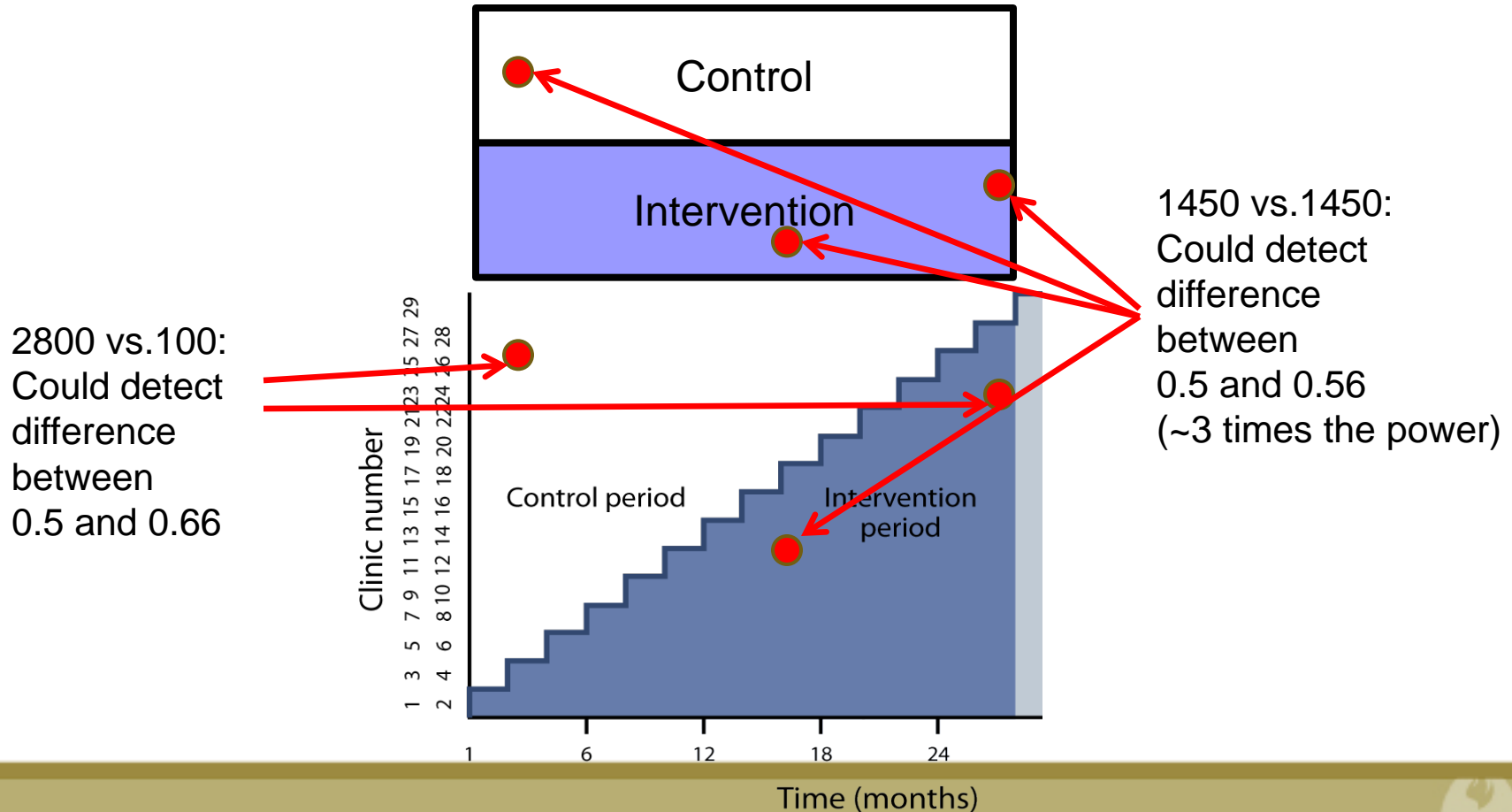
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- Study power is compromised.
  - Assume 100 people in each clinic



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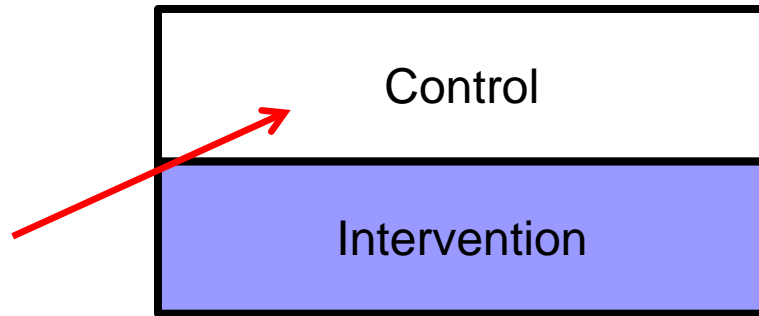


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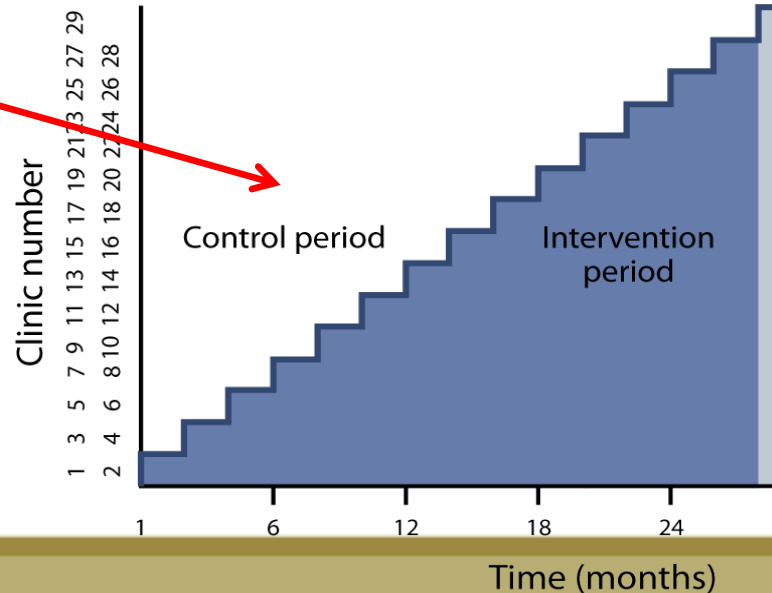
- Does it really make you feel better ethically?

Same amount of person-time in the control period:

Total population morbidity is the same.



Everyone gets the intervention in the end (if shown effective).



Everyone gets the intervention in the end (if shown effective).



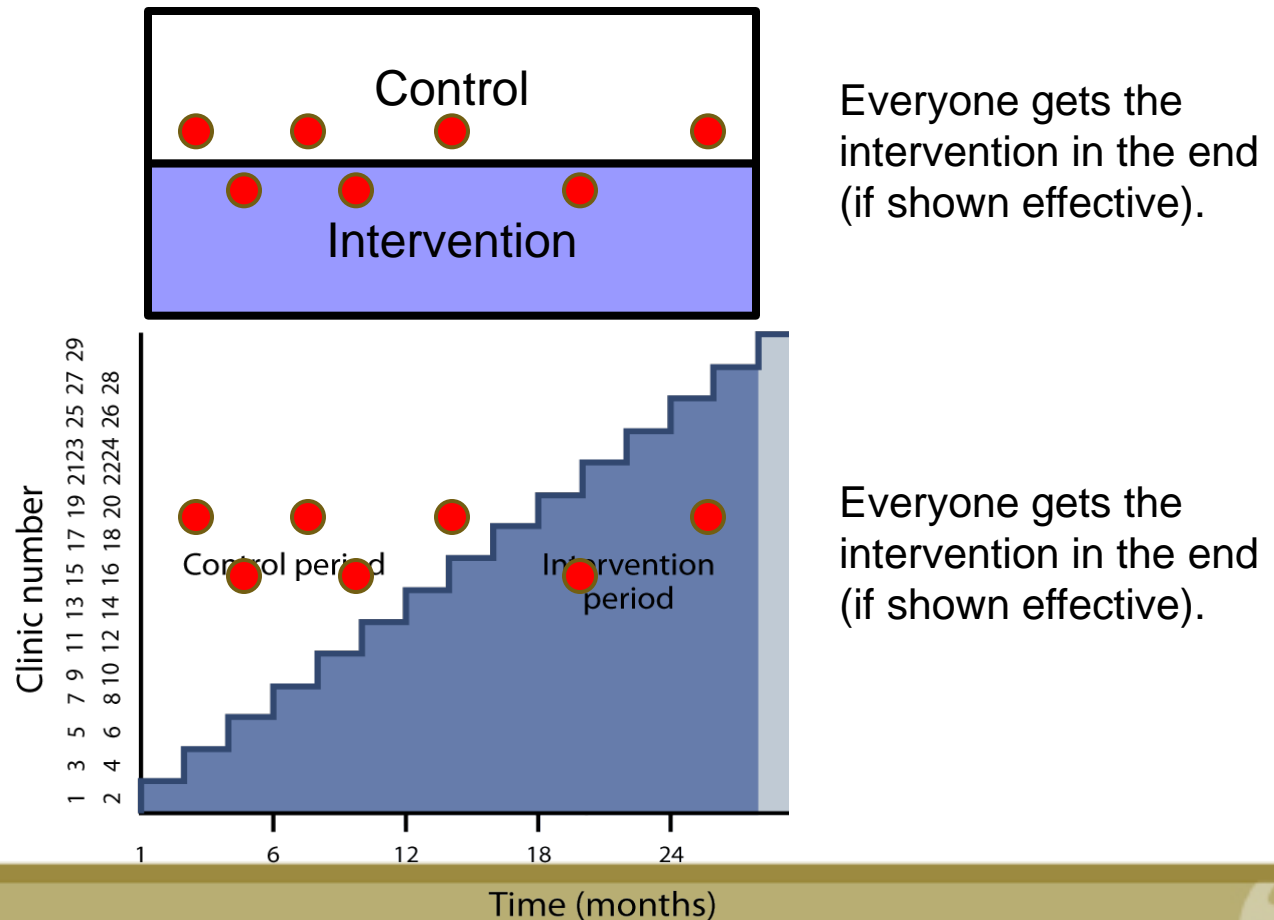
# Phased Implementation Designs: Fruitcake?

- The real problem: secular trends still exist.
  - Expect secular trends any time you're evaluating an implementation – people get better at implementing the intervention over time.
- In a phased implementation study, these trends are harder to manage.
  - More “control period” occurs during the early time period, and more “intervention period” occurs during the late time period.
  - Assuming the RR/OR remains exactly the same over time, are you comfortable comparing “control in 2007” to “intervention in 2011”?



# Phased Implementation Designs: Fruitcake?

- What happens with secular trends?



# Summary Points I

- Diagnostic tests – designed to detect disease but not improve health – represent an ethical dilemma.
- Phased implementation designs are gaining in popularity as a way to manage this ethical challenge.
- The stepped-wedge design is a prototype of the phased implementation study and compares intervention to control phase in “slices of time.”



## Summary Points II

- Phased implementation designs are more attractive to IRBs and do have some conceptual advantages.
- However, they cause loss of study power and do not actually improve morbidity in the study population.
- Phased implementation designs are intended to deal with secular trends, but when those trends are strong, they remain difficult to interpret.





# Thank You!



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