# Lessons Learned from the NIH Collaboratory Biostatistics and Design Core up to 2016

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# Outline

- Common themes across Collaboratory Studies
  - Study Design
  - Analysis/Sample Size
    - Implications of Variable Cluster Size on Estimation and Power
  - Randomization
  - Outcome Ascertainment

- Conclusions/Next Steps

# STUDY DESIGN

# Study Design: Cluster RCT

- Mostly Cluster RCTs (except one)
  - Randomization Unit:
    - Provider < Panel < Clinic < Region < Site
- Average Size of Cluster
  - Initial Proposals: Most large clinic level clusters
  - Goal: Smallest Unit without contamination
    - More clusters are better if possible
  - Smaller number of clusters increase sample size along with estimation issues (GEE)
  - Potential Solutions: Panel-level or physician-level

# Study Design: Which Cluster Design?

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- Cluster
  - Randomize at cluster-level
  - Most common, but not necessarily the most powerful or feasible
  - Advantages:
    - Simple design
    - Easy to implement
  - Disadvantages:
    - Need a large number of clusters
    - Not all clusters get the interventions
    - Interpretation for binary and survival outcomes:
      - Mixed models within cluster interpretation problematic
      - GEE marginal estimates interpretation, but what if you are interested in within cluster changes?

# Study Design: Which Cluster Design?

- Cluster with Cross-over
  - Randomize at cluster but cross to other intervention assignment midway
  - Feasible if intervention can be turned off and on without "learning" happening
  - Alternative: baseline period without intervention and then have half of the clusters turn on

# Study Design: Which Cluster Design?

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| | Cluster | Period 1 | Period 2 |
|---|---|---|---|
| **Simple Cluster** | 1 | INT | |
| | 2 | UC | |
| | 3 | UC | |
| | 4 | INT | |
| | | | |
| **Cluster With Crossover** | 1 | INT | UC |
| | 2 | UC | INT |
| | 3 | UC | INT |
| | 4 | INT | UC |
| | | | |
| **Cluster With Baseline** | 1 | UC | INT |
| | 2 | UC | UC |
| | 3 | UC | UC |
| | 4 | UC | INT |

# Study Design: Which Cluster Design?

- Cluster with Cross-over
  - Advantages:
    - Can make within cluster interpretation
    - Potential to gain power by using within cluster information
  - Disadvantages:
    - Contamination can yield biased estimates especially for the standard cross-over design
    - May not be feasible to switch assignments or turn off intervention
    - Not all clusters have the intervention at the end of the study

# Study Design: Which Cluster Design?

- Stepped Wedge Design
  - Randomize timing of when the cluster is turned **on** to intervention
  - Staggered cluster with crossover design
  - Temporally spaces the intervention and therefore can control for system changes over time

# Study Design: Which Cluster Design?

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| | Cluster | Baseline | Period 1 | Period 2 | Period 3 | Period 4 |
|---|---|---|---|---|---|---|
| Stepped Wedge | 3 | UC | INT | INT | INT | INT |
| | 2 | UC | UC | INT | INT | INT |
| | 1 | UC | UC | UC | INT | INT |
| | 4 | UC | UC | UC | UC | INT |

# Study Design: Which Cluster Design?

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- Stepped Wedge Design
  - Advantages:
    - All clusters get the intervention
    - Controls for external temporal trends
    - Make within cluster interpretation if desired
  - Disadvantages:
    - Contamination can yield biased estimates
    - Heterogeneity of Intervention effects across clusters can be difficult to handle analytically
    - Special care of how you handle random effects in the model
    - Relatively new and available power calculation software is relatively limited

# ANALYSIS/SAMPLE SIZE

# Analysis: Variable Cluster Size

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- Analysis Implications
  - What are you making inference to?
    - Compare intervention across clinics
      - Marginal cluster-level effect
    - Compare within-clinic intervention effect
      - Within-clinic effect
    - Compare intervention effect across patients
      - Marginal patient-level effect
    - Compare an in-between cluster and patient-level effect

DeLong, E, Cook, A, and NIH Biostatistics/Design Core (2014) Unequal Cluster Sizes in Cluster-Randomized Clinical Trials, *NIH Collaboratory Knowledge Repository*.

Cook, AJ, Delong, E, Murray, DM, Vollmer, WM, and Heagerty, PJ (2016) Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Health Care Systems Collaboratory Biostatistics and Design Core *Clinical Trials* **13(5)** 504-512.

# Analysis: Variable Cluster Size

- What is the scientific question of interest?
  - Marginal cluster-level effect
    - "What is the average expected clinic benefit if all clinics in the health system changed to the new intervention relative to Usual Care?"
  - Within-clinic effect
    - "What is the expected benefit if a given clinic implements the new intervention relative to Usual Care?"
  - Marginal patient-level effect
    - "What is the average expected patient benefit if all the clinics in the health system changed to the new intervention relative to Usual Care?"

# Analysis: Variable Cluster Size

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- Simplified Example:
  - $Y_{ci}$ is a binary outcome for patient *i* at clinic *c*
  - $n_c$ is the number of patients at clinic *c*
  - $X_c$ is 1 if clinic *c* was randomized to intervention or 0
  - Estimate a simple marginal clinic-level effect (difference in clinic means amongst those randomized to intervention relative to those not randomized)

$$\hat{\Delta}^c = \frac{\sum_{c=1}^{N} \hat{\mu}_c X_c}{\sum_{c=1}^{N} X_c} - \frac{\sum_{c=1}^{N} \hat{\mu}_c (1 - X_c)}{\sum_{c=1}^{N} (1 - X_c)}$$

where $\hat{\mu}_c = \sum_{i=1}^{n_c} \frac{Y_{ci}}{n_c}$ is the mean outcome at clinic *c*

# Analysis: Variable Cluster Size

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$$\hat{\Delta}^p = \frac{\sum_{c=1}^{N}\sum_{i=1}^{n_c} Y_{ci}X_c}{\sum_{c=1}^{N} X_c\, n_c} - \frac{\sum_{c=1}^{N}\sum_{i=1}^{n_c} Y_{ci}(1-X_c)}{\sum_{c=1}^{N}(1-X_c)\, n_c}$$

Patients are weighted equally and clustering is really just nuisance in terms of variance and not of interest

# Analysis: Variable Cluster Size

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- Some ways to estimate these quantities in practice
  - Marginal cluster-level effect
    - GEE with weights the inverse of the cluster size with independent correlation structure and robust variance
  - Compare within-clinic intervention effect
    - GLMM but need to get correlation structure correct but most often just a cluster random effect
  - Marginal patient-level effect
    - GEE with no weights with independent correlation structure and robust variance
  - In-between cluster and patient-level effect
    - GEE with no weights but exchangeable cluster correlation structure and robust variance
    - Exchangeable weights based on statistical information, but not necessarily the most interpretable

# Sample Size: Variable Cluster Size

- Sample Size calculations need to take variable cluster size into account
  - Design effects (amount sample size is inflated due to cluster randomization relative to individual patient randomization) are different
  - Depends on the analysis of choice and the estimate of interest

- Example: Estimating marginal clinic-level mean difference
  - Design effect:

$$1 + \left( \frac{\sum_{c=1}^{N} {n_c}^2}{\sum_{c=1}^{N} n_c} - 1 \right) \rho > 1 + (n_c - 1)\rho \text{ where } n_c \text{ is a constant}$$

DeLong, E, Lokhnygina, Y and NIH Biostatistics/Design Core (2014) The Intraclass Correlation Coefficient (ICC), *NIH Collaboratory Knowledge Repository*.

Eldridge, S.M., Ashby, D., and Kerry, S. (2006) Sample size for cluster randomized trials: effect of coefficient of variation of size and analysis method. *Int J Epi* **35**:1292-1300.

# Figure: Power Curve
# ICC is 0.03 and effect size 0.1$\sigma$

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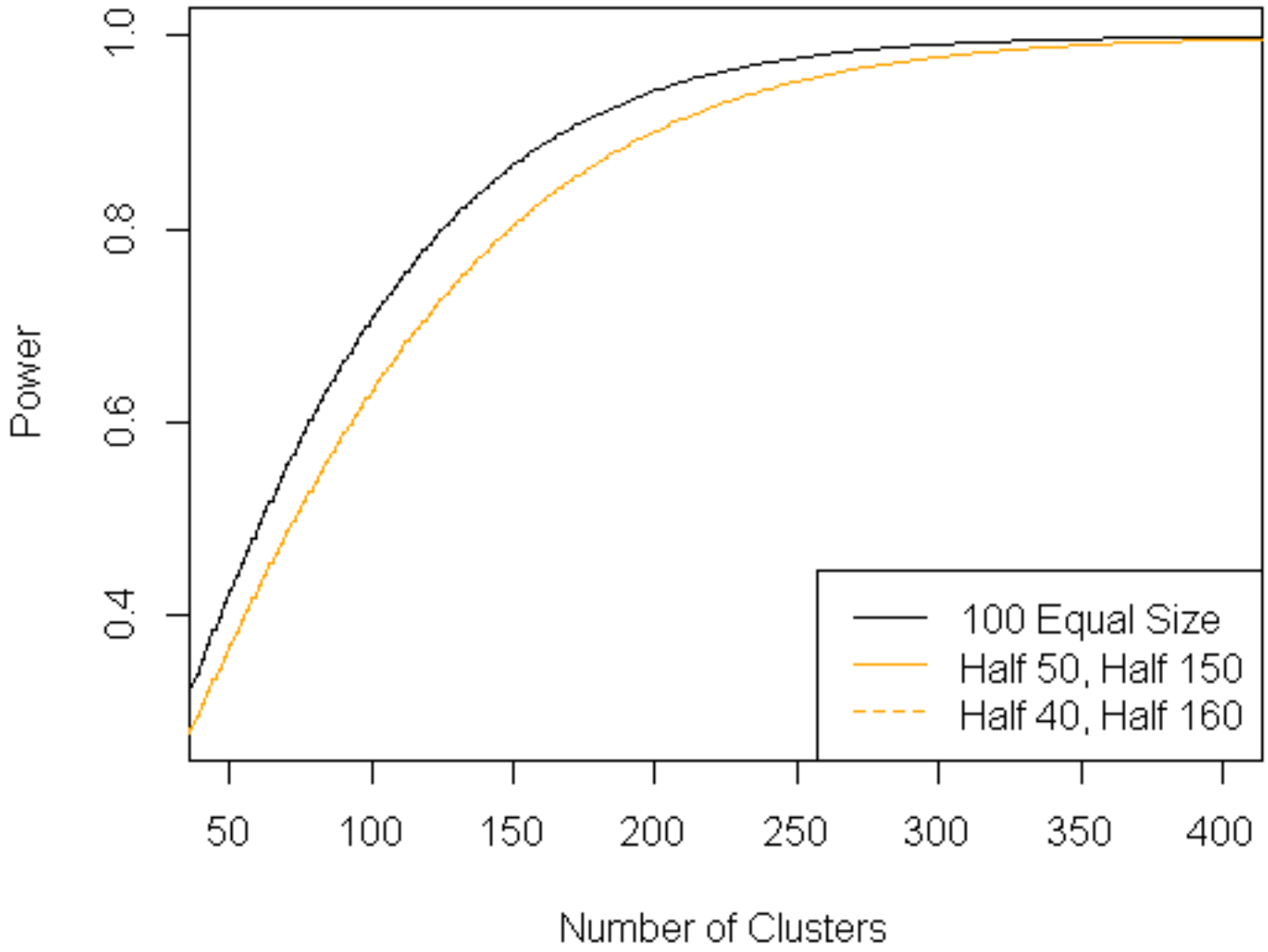

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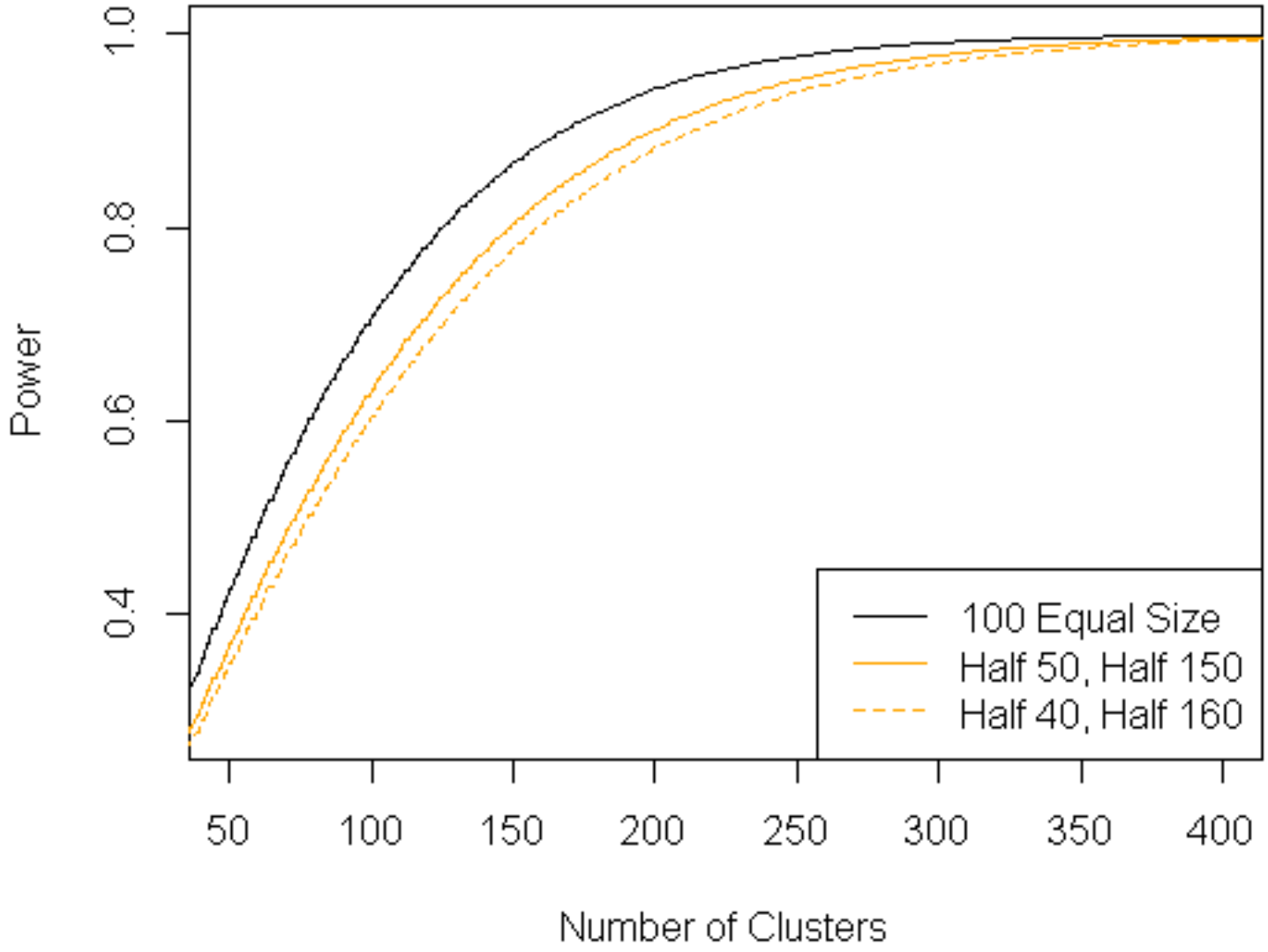

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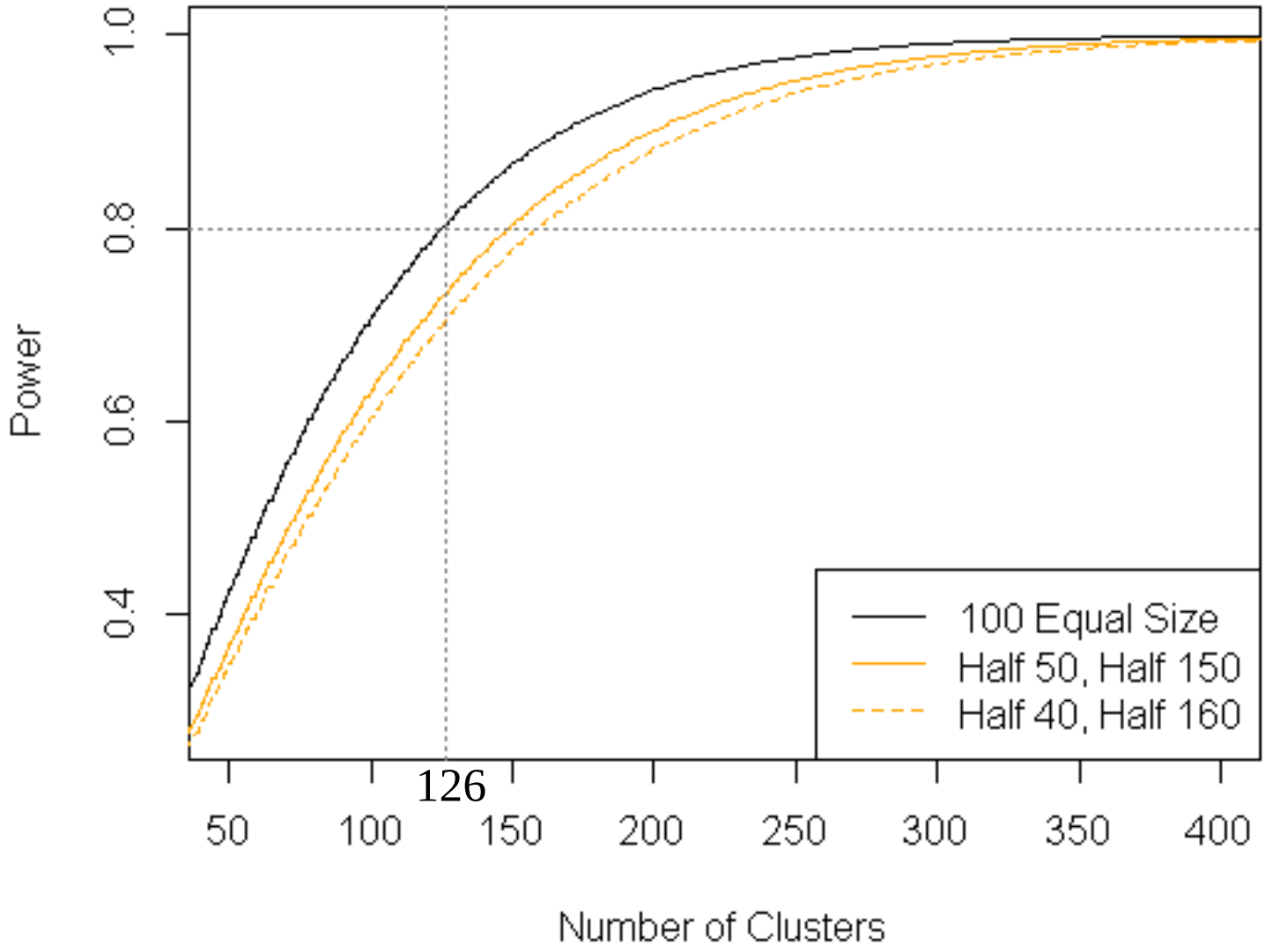

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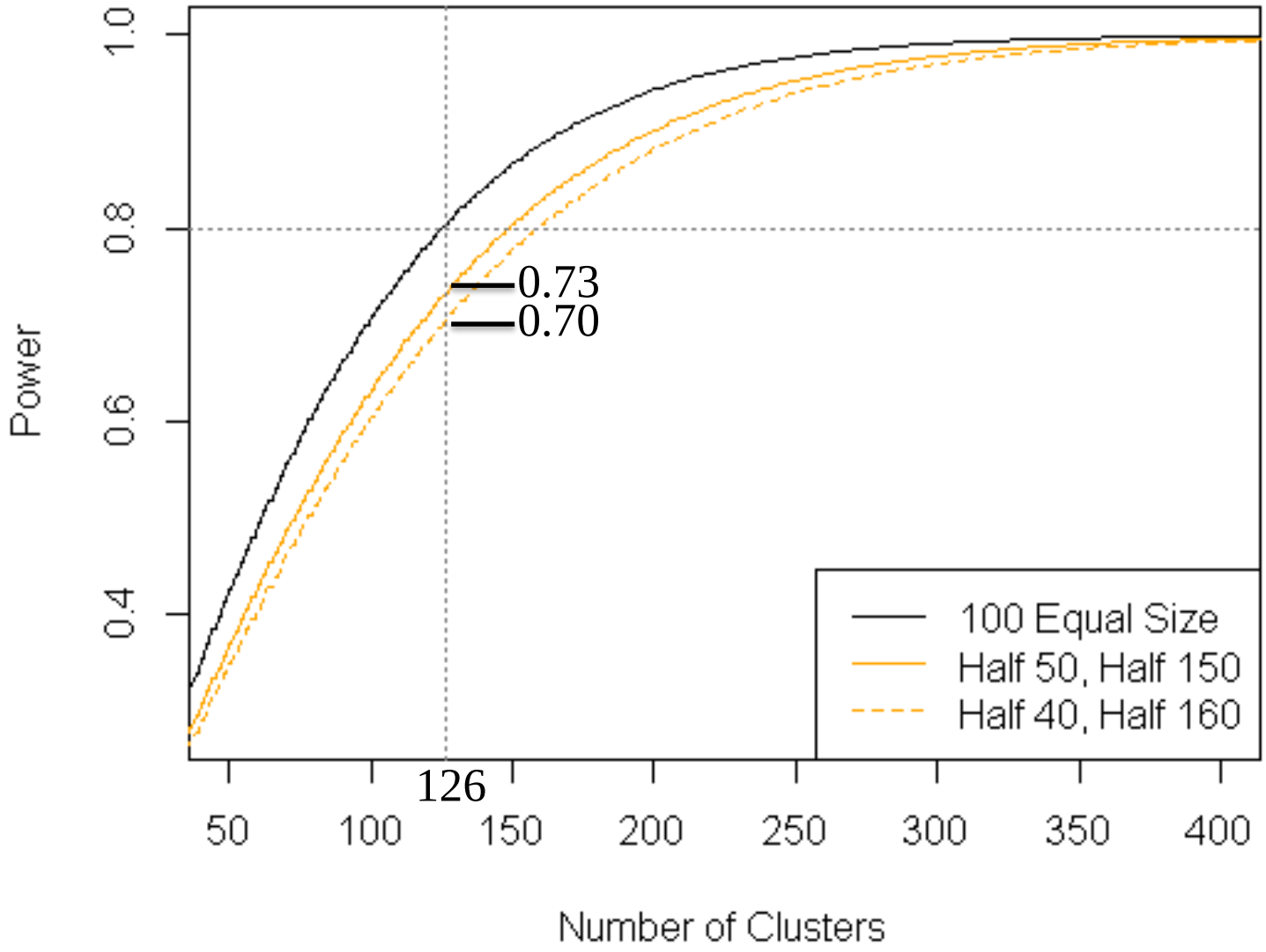

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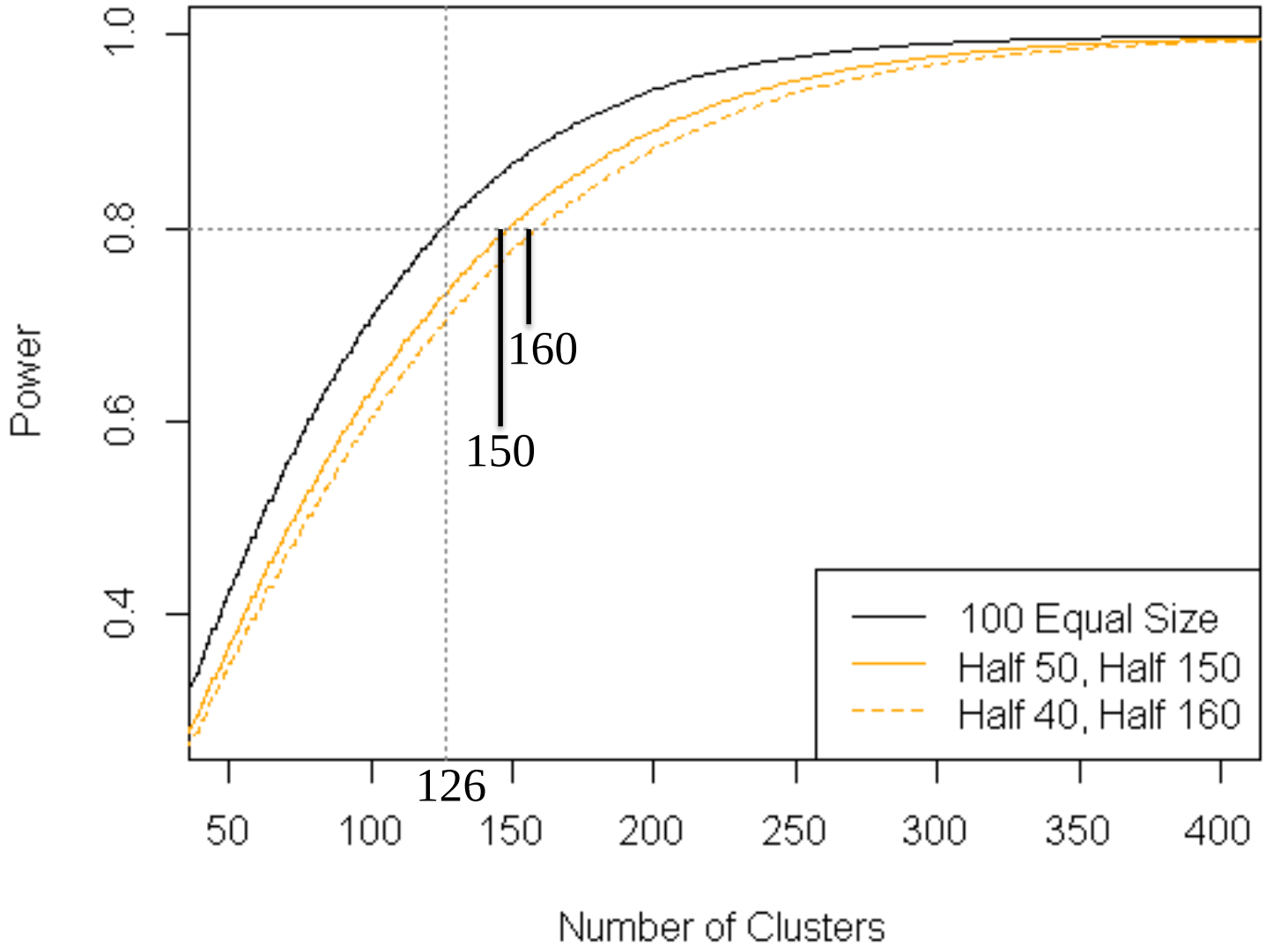

# RANDOMIZATION

# Randomization

- Crude randomization not preferable with smaller number of clusters or need balance for subgroup analyses
- How to balance between cluster differences?
  - Paired
    - How to choose the pairs best to control for important predictors?
    - Implications for analyses and interpretation
  - Stratification
    - Stratify analysis on a small set of predictors
    - Can ignore in analyses stage if desired
  - Other Alternatives

DeLong, E, Li, L, Cook, A, and NIH Biostatistics/Design Core (2014) Pair-Matching vs stratification in Cluster-Randomized Trials, *NIH Collaboratory Knowledge Repository*.

# Constrained Randomization

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- Balances a large number of characteristics
- Concept
  1. Simulate a large number of cluster randomization assignments (A or B but not actual treatment)
  2. Remove duplicates
  3. Across these simulated randomizations assignments assess characteristic balance
  4. Restrict to those assignments with balance
  5. Randomly choose from the “constrained” pool a randomization scheme.
  6. Randomly assign treatments to A or B

# Constrained Randomization

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- Is Constrained randomization better then unconstrained randomization
- How many valid randomization schemes do you need to be able to conduct valid inference?
- Do you need to take into account randomization scheme in analysis?
  - Ignore Randomization
  - Adjust for variables in regression
  - Permutation inference

# Constrained Randomization

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⇨ Conduct a simulation study to assess these properties

# Continuous Outcome Simulation Design

- Outcome Type: Normal
- Randomization Type: Simple versus Constrained
- Inference Type: Exact (Permutation) versus Model-Based (F-Test)
- Adjustment Type: Unadjusted versus Adjusted
- Clusters: Balanced designs, but varied size and number
- Correlation: Varied ICC from 0.01 to 0.05
- Potential Confounders: Varied from 1 to 4

Li, F., Lokhnygina, Y., Murray, D, Heagerty, P., and Delong, ER. (2016) An evaluation of constrained randomization for the design and analysis of group-randomized trials *Stat Med* **35(10)**: 1565-1579.

# Continuous Outcome Simulation Results

- Adjusted F-test and the permutation test perform similar and slightly better for constrained versus simple randomization.
- Under Constrained Randomization:
  - Unadjusted F-test is conservative
  - Unadjusted Permutation holds type I error (unless candidate set size is not too small)
  - Unadjusted Permutation more powerful then Unadjusted F-Test
- Recommendation: Constrained randomization with enough potential schemes (>100), but still adjust for potential confounders

# Binary Outcome Simulation Design

- Outcome Type: Binary
- Randomization Type: Simple versus Constrained
- Inference Type: Exact (Permutation) versus Model-Based (F-Test)
- Adjustment Type: Unadjusted versus Adjusted
- Clusters: Balanced designs, but varied size and number
- Correlation: Varied ICC from 0.01 to 0.05
- Potential Confounders: Varied from 1 to 4

Li, F., Turner, E., Heagerty, P., Murray, D., Vollmer, W., and Delong, ER. An evaluation of constrained randomization for the design and analysis of group-randomized trials with binary outcomes (Under Review)

# Binary Outcome Simulation Results

- Adjusted F-test based on maximum likelihood has liberal size
- Adjusted F-test based on linearization and the permutation test are valid and perform similarly and slightly better for constrained versus simple randomization in terms of power
- Under Constrained Randomization:
  - Unadjusted F-test is conservative
  - Unadjusted Permutation more powerful then Unadjusted F-Test
- Recommendation: Constrained randomization with enough potential schemes (>100), but still adjust for potential confounders; avoid using adjusted F-test based on maximum likelihood (PROC NLMIXED) due to its unsatisfactory small sample performance

# OUTCOME ASCERTAINMENT

# Outcome Ascertainment

- Most trials use Electronic Healthcare Records (EHR) to obtain Outcomes
  - Data **NOT** collected for research purposes
- If someone stays enrolled in healthcare system - assume that if you don't observe the outcome it didn't happen
  - In closed system this is likely ok
  - Depends upon cost of treatment (likely to get a bill the more the treatment costs)

# Outcome Ascertainment (Cont)

- Do you need to validate the outcomes you do observe?
  - Depends on the Outcome (PPV, sensitivity)
  - Depends on the cost (two-stage design?)
- How do you handle Missing Outcome Data?
  - Leave healthcare system
    - Type of Missing Data: Administrative missingness (MCAR), MAR or non-ignorable?
    - Amount of Missing Data: how stable is your population being studied?
  - Depends on the condition and population being studied.

DeLong, E, Li, L, Cook, A, and NIH Biostatistics/Design Core (2014) Key Issues in Extracting Usable Data from Electronic Health Records for Pragmatic Clinical Trials, *NIH Collaboratory Knowledge Repository*

# Conclusions

- Pragmatic Trials are important to be able to move research quickly into practice
- Pragmatic Trials add Complication
  - First Question: Can this study be answered using a pragmatic trial approach??
  - Study Design is essential and needs to be flexible
  - Choice of which quantity to estimate should be made based on the scientific question of interest, but statistical trade-offs, including power, must also be considered.
  - Variability in cluster sizes have potentially major implications for power and analysis approach
- Lots of open statistical questions still to be addressed