INTERNAL PILOT DESIGNS FOR CLUSTER SAMPLES

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OUTLINE

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3. Cluster Example (IP Design)
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MOTIVATING CLUSTER EXAMPLE

- Debilitating disease condition requiring intravenous therapy
- Concerns due to high infection rates of current protocol.
- New protocol has been developed that leads to dramatically reduced infection rates in preliminary work conducted at a single site.
- Investigators wish to plan a randomized clinical trial to further evaluate the efficacy of the new protocol.

MOTIVATING CLUSTER EXAMPLE

- For practical purposes, randomization will take place at the hospital level.
- Hospitals will be randomly assigned to utilize the existing or the new protocol for IV treatment.
- Hence, all patients at the same hospital will receive the same protocol.
- Need to account for correlation among patients within the same hospital.

MOTIVATING CLUSTER EXAMPLE

Assumptions:

- Infection rate w/ old protocol = 0.35 cases/yr
- Infection rate w/ new protocol = 0.07 cases/yr
  (i.e., 80% reduction in infection rate)
- Assume 20 patients per clinic with an average follow-up of one year.
- Assume ρ (intraclass correlation coefficient) = 0.1.
- Would like to use internal pilot design to reassess assumptions at an interim time point.

MOTIVATING CLUSTER EXAMPLE

Based on normal approximation to Poisson distribution:

- Pooled variance = (0.35+0.07)/2 = 0.21
- Old protocol subjects ~ N(0.35, 0.21)
- New protocol subjects ~ N(0.07, 0.21)
- Hence, $\delta = 0.28$ and $\sigma = 0.46$
- Would like to obtain 90% power to detect the effect above at the 5% significance level
- Hence, 10 hospitals per treatment group are required (20 hospitals total)

INTERNAL PILOT DESIGNS

Note MANY assumptions made during study planning.

If any assumption is incorrect, the power of the study may be greatly affected.

Table shows impact of mis-specifying ρ (for a study with 10 hospitals and 20 patients per hospital).

Under-estimating ρ can severely impact the power of the study

ρ	Power
0.01	>99
0.1	90
0.2	75
0.4	50

INTERNAL PILOT DESIGNS

Internal pilot (IP) designs (Wittes & Brittain, 1990) allow re-estimation of nuisance parameters and adjustment of the sample size.

For this study, an IP design would allow an evaluation of the validity of these assumptions and make any necessary changes to the sample size at some interim time point.

INTERNAL PILOT DESIGNS

IP Designs for cluster samples:

- Lake et al. (2002) examined an unadjusted test for IP designs with cluster sampling
  - Evaluated several scenarios via simulation
  - Substantial gain in power if original estimates too low
  - Impact on type I error rate is minimal with moderate to large sample sizes

INTERNAL PILOT DESIGNS

IP Designs for cluster samples:

- Gurka et al. (2007) transform mixed models with no missing or mistimed data and compound symmetry within independent sampling units to an equivalent univariate linear model
  - Univariate model provides *exact* inference for power analysis
  - Allows utilizing known distributional results for IP designs in the univariate setting.
  - Applies to hospital-based cluster samples, if willing to assume equal cluster sizes and equal correlation within clusters.

CLUSTER EXAMPLE (IP DESIGN)

Using results in Gurka et al. (2007) :

- Allows implicitly defining a set of 2 distinct univariate linear models with i.i.d. errors.

Source	d.f.	Variance
Grand Mean	**1**	
Treatment	**1**	
Error Between	***N*-2**	$\lambda_1 = \sigma^2 \cdot [1+(p-1)\rho]$
Patient	**19**	
Error Within	**19·(*N*-2)**	$\lambda^2 = \sigma^2 \cdot (1-\rho)$
Total	**20*N***	

CLUSTER EXAMPLE (IP DESIGN)

Based on transformation approach:

- Effect of interest: $\delta = (20)^{1/2} \cdot 0.28 = 1.25$
- Variance: $\lambda_1 = \sigma^2 \cdot [1+(p-1)\rho] = 0.78$
- Again, implies 10 hospitals per group are required (20 hospitals total – 400 total patients)
- Would like to utilize an IP design to allow for corrections if original estimates are mis-specified.

CLUSTER EXAMPLE (IP DESIGN)

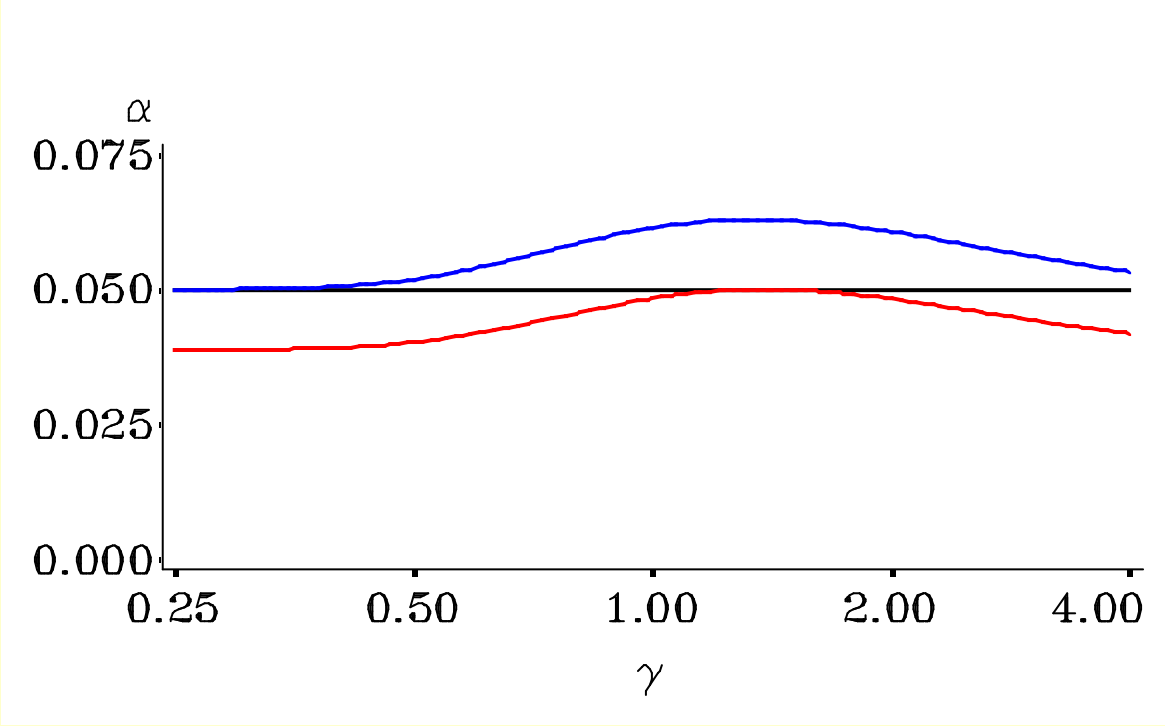
Consider IP design with:

- First 6 hospitals serving as the IP sample ($n_1 = 6$ – assumes hospitals will be enrolled in waves)
- Allow reducing the final number of hospitals
- Impose a finite maximum of 50 hospitals (25 per group)
- Use bounding approach described by Coffey and Muller (2001) to account for possible small sample bias

CLUSTER EXAMPLE (IP DESIGN)

Due to small # of hospitals, unadjusted test (blue line) leads to possible inflation of type I error rate.

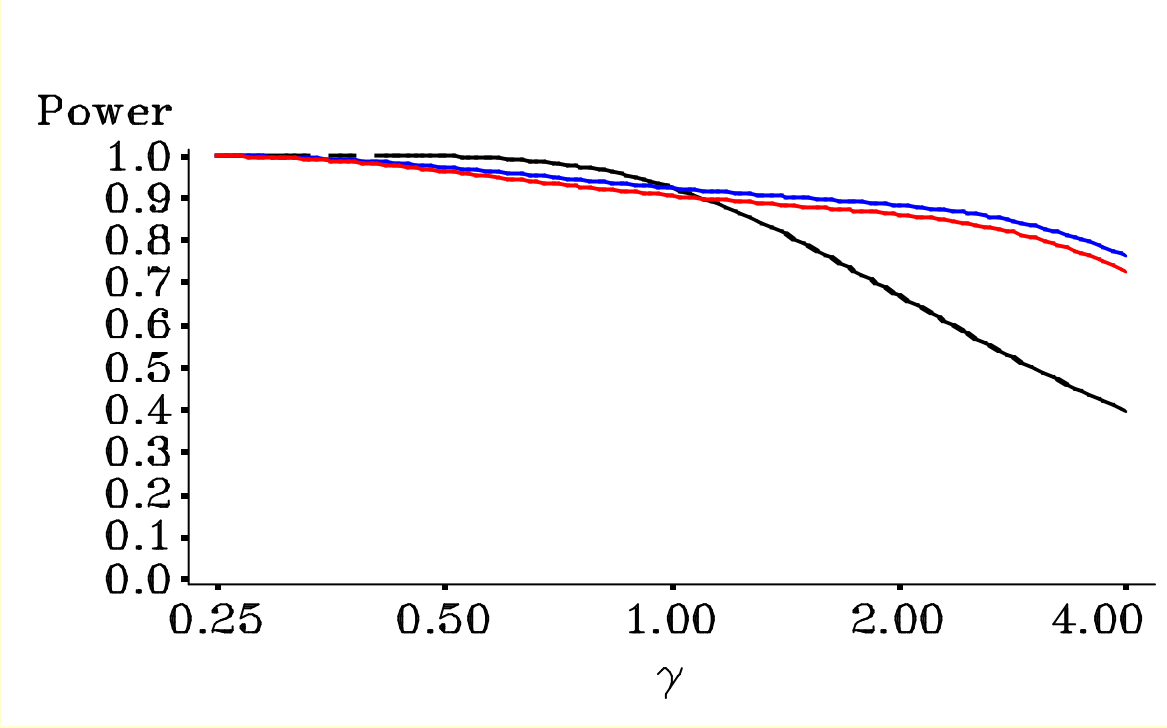
Type I error rate controlled for bounding test (red line).



CLUSTER EXAMPLE (IP DESIGN)

Big payoffs:

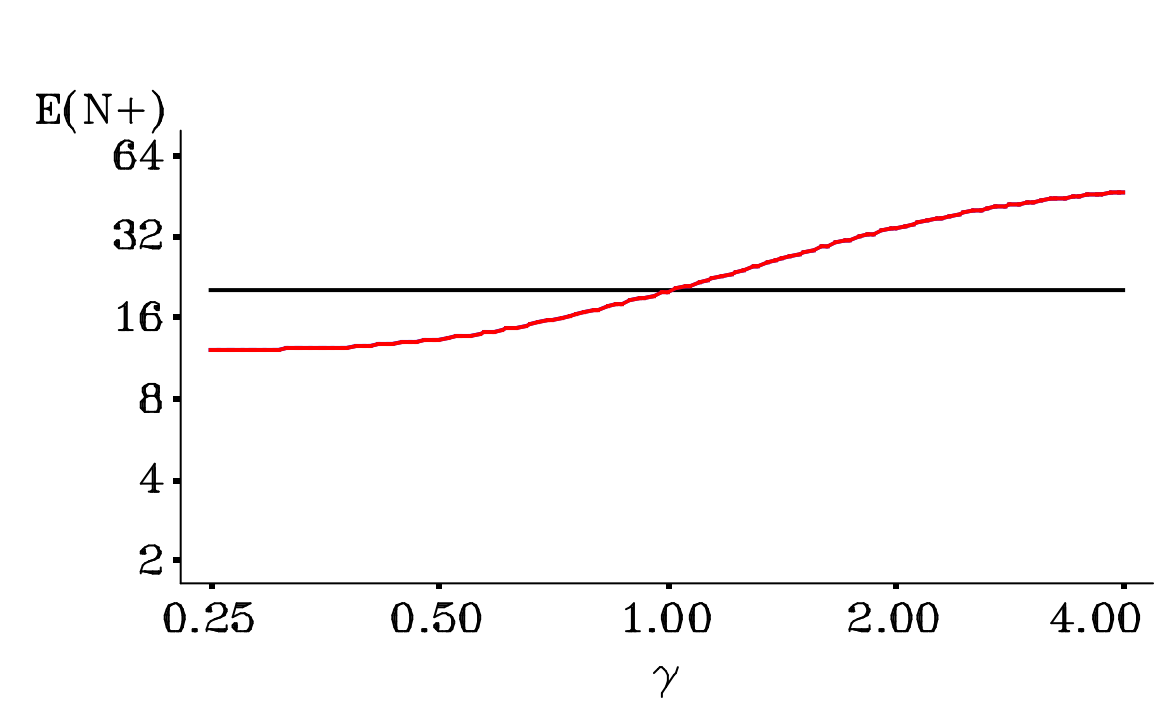
- Protect against power loss if ‘variance’ under-estimated
- Finite maximum on # of clusters somewhat limits gains that can be achieved for extreme values



CLUSTER EXAMPLE (IP DESIGN)

Big payoffs:

- Can reduce sample size if ‘variance’ over-estimated (Both approaches use same SSR procedure)



WHERE DO WE GO FROM HERE?

Current approach seems justified when planning group randomized trials where investigators can only provide average number enrolled per site.

When this is the case, seems appropriate to assume equal cluster sizes for initial planning.

However, future research should address some of the limitations of this approach.

WHERE DO WE GO FROM HERE?

Limitations to this approach:

1) Current approach only allows adding clusters.
   - Might also want to add observations within existing clusters
   - Might also want to add both additional clusters and additional observations within existing clusters
   - Impact on operating characteristics not known

WHERE DO WE GO FROM HERE?

Limitations to this approach:

2) Realistically, we are not likely to observe equal cluster sizes at the end of the trial.

- One might consider an IP design to evaluate validity of this assumption and make any necessary changes to the design at some interim time-point.
- Additional work needed to allow IP designs for studies with unequal cluster sizes
- Suggested technique for power analysis described in previous talk seems to be a good starting point

WHERE DO WE GO FROM HERE?

Limitations to this approach:

3) Assumes that all patients are examined for first group of hospitals before any are enrolled in the second group.

- Additional work needed to allow for interim assessment once partial patients are enrolled at all hospitals
- This will require carefully adjusting the variance estimate to account for the fact that # of subjects within a cluster at time of variance re-estimation differs from that at end of trial

$$\lambda_1 = \sigma^2 \cdot [1+(p_1-1)\rho] \text{ at time of interim analysis}$$

vs.

$$\lambda_* = \sigma^2 \cdot [1+(p_*-1)\rho] \text{ at end of study}$$

WHERE DO WE GO FROM HERE?

Recent developments allow the use of IP designs with cluster samples.

However, some of the necessary assumptions may not be realistic in many practical settings.

Additional research is required to better utilize IP designs in such settings.