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## **The impact of co-enrollment in clinical trials**

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## ***Background***

- **Co-enrollment:** the enrollment of a patient into 2 or more studies that overlap in time
- For today, I will focus on the enrollment of a patient into more than 1 randomized controlled trial that overlap in time

## ***Background***

- **Clinicaltrials.gov accessed on October 20<sup>th</sup>, 2009**
  - Search Term: **intensive care/critical care**
  - # of Trials: 1103 with **532** open for recruitment
  
  - Search Term: **sepsis**
  - # of Trials: 527 with **265** open for recruitment
  
  - Search Term: **severe sepsis**
  - # of Trials: 152 with **79** open for recruitment

## ***Background***

- **Many ideas → many interventions → many trials**
- **Finite patient pools & sites**
- **Limited human and \$ resources**
- **In 2009, limited outcomes?**
  - Especially in the climate of meeting a definition of “clinically important”
    - death & organ failure
- **Not surprising that co-enrollment is on the agenda**
  - reasonable to consider impact/considerations

## ***Background: What's out there?***

### **“Co-enrollment or Coenrollment” on PubMed : 4 references**

- The unique challenges of enrolling patients into multiple clinical trials. Randolph AG. Crit Care Med. 2009 Jan;37(1 Suppl):S107-11.PMID: 19104209 [PubMed - indexed for MEDLINE]
- ~~Coenrollment for students who are deaf or hard of hearing: friendship patterns and social interactions. Bowen SA. Ann Deaf. 2008 Summer;153(3):285-93. PMID: 18807402 [PubMed - indexed for MEDLINE]~~
- Enrollment of intensive care unit patients into clinical studies: a trinational survey of researchers' experiences, beliefs, and practices. Cook DJ, Blythe D, Rischbieth A, Hebert PC, Zytaruk N, Menon K, Erikson S, Fowler R, Heels-Ansdell D, Meade MO. Crit Care Med. 2008 Jul;36(7):2100-5. PMID: 18552686 [PubMed - indexed for MEDLINE]
- ~~Evaluation of human immunodeficiency virus biomarkers: inferences from interval and clinical cohort studies. ~~... D, George S.J. Kirk GD, Moore RD. Epidemiology. 2009 Sep;20(5):664-72. PMID: 19478669 [PubMed - in process]~~~~

## ***Background: What's out there?***

### **“Co-enrollment or Coenrollment” on Google October 11<sup>th</sup>,2009**

- **Fair amount on co-enrollment policies in AIDS/HIV research**
  - Concentrate on the ethical and logistical issues
  - Much cited paper by Ellenberg et al “Statistical Issues Arising in AIDS Clinical Trials” J Amer Stat Assoc, 1992
- **Cook et al.’s tri-national survey**
- **And then...**

[PDF] [Tuesday, October 27, 2009](#)

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**The impact of co-enrollment in clinical trials.** 15:50-16:10 T Thompson. The control group in non-pharmacologic trials. 16:10-16:30 B Kavanagh ...  
[www.criticalcarecanada.com/.../CCCF%202009%20Advance%20Program%20Tuesday.pdf](http://www.criticalcarecanada.com/.../CCCF%202009%20Advance%20Program%20Tuesday.pdf) - [Similar](#)

## Background

Table 1. Strategies to increase enrollment of intensive care unit patients into randomized trials

	Effective Median [IQR]	Feasible Median [IQR]	Ethical Median [IQR]
<b>To enhance recruitment efficiency</b>			
More participating centers	7 [6, 7]	6 [5, 7]	7 [7, 7]
Weekend enrollment	7 [6, 7]	5 [3, 6]	7 [7, 7]
Afterhours enrollment	7 [6, 7]	5 [3, 6]	7 [6, 7]
<b>Coenrollment of one patient in two RCTs</b>	<b>6 [4, 7]</b>	<b>5 [4, 6]</b>	<b>5 [4, 7]</b>
<b>To consider alternative designs</b>			
Factorial RCTs	5 [4, 6]	5 [4, 6]	6 [4, 7]
Cluster RCTs	4 [4, 6]	5 [4, 6]	6 [4, 7]
<b>To modify the consent process</b>			
Deferred consent	7 [6, 7]	6 [5, 7]	6 [4, 6.5]
Waived consent	7 [6, 7]	6 [4, 7]	4 [2, 6]
Two independent physicians consent	6 [5, 7]	5 [3, 6]	4 [2, 5]

In this table, we present several strategies to enhance recruitment efficiency, to consider alternative study designs, and to modify the consent process, with the overall goal of increasing the enrollment of critically ill patients into randomized trials. Respondents rated these strategies in terms of their effectiveness (1, ineffective, 7, effective), feasibility (1, infeasible, 7, feasible) and ethics (1, unethical, 7, ethical). IQR, interquartile range; RCT, randomized clinical trial.

## ***The attraction of co-enrollment***

- **Need for numbers**
- **Efficiency (logistics)**
  - Reasonable given multiple studies in pts that require multiple treatments
- **Obligation to offer a patient all potential beneficial therapies**
- **Success of national disease-oriented trial groups**
  - # of trials, # of large trials
  - # large trials assessing important outcomes with limited patients
- **Potential to look at interactions between interventions (even if exploratory)**

## ***Impact of Co-enrollment: considerations***

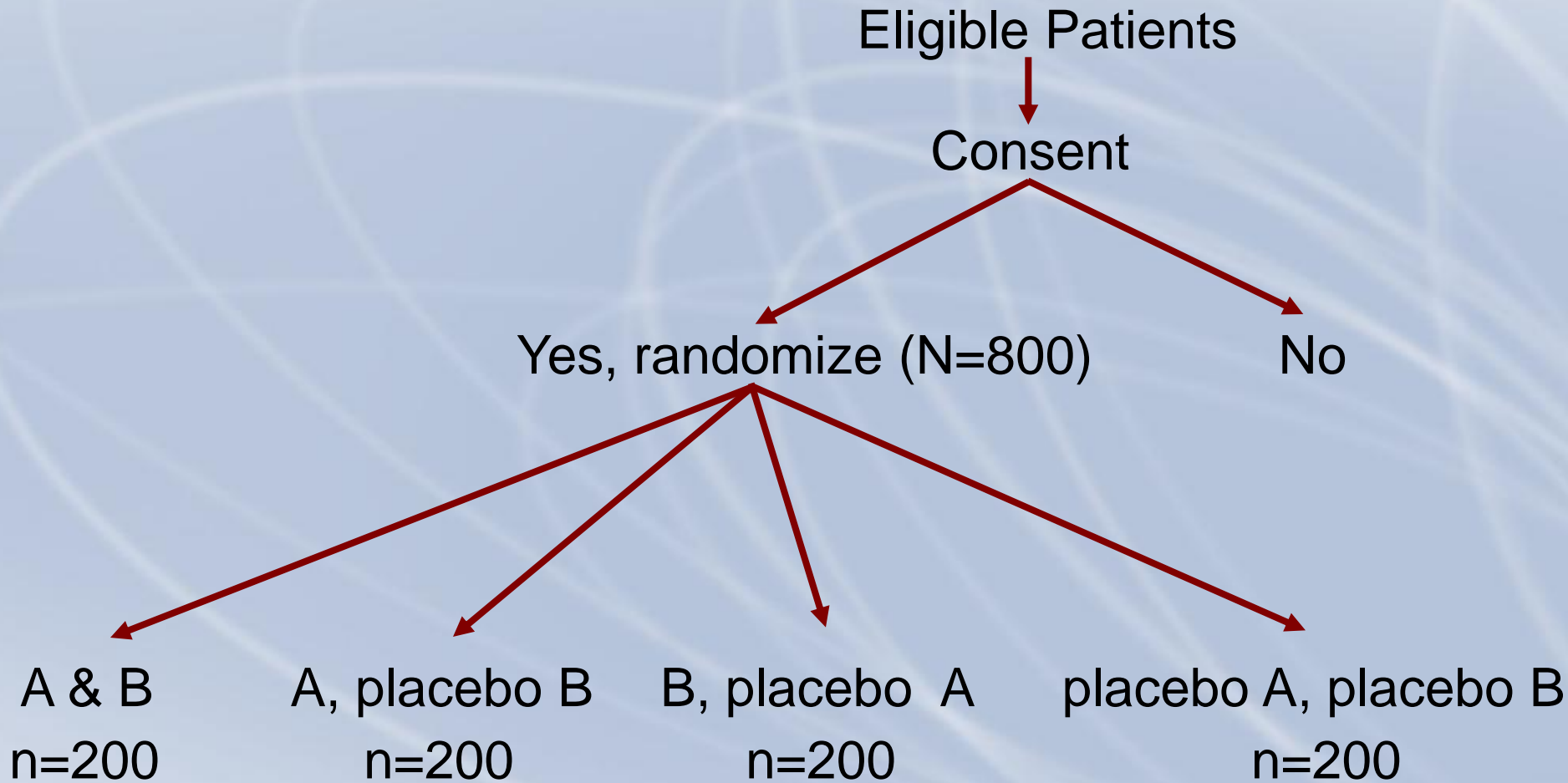
- **Ethical**
- **Logistical/Planning**
- **Methodological**
- **Analytical**

# ***Methodological Considerations***

- **Keeping it simple...**
  - Consider two novel treatments: A and B
  - Both hypothesized to reduce mortality in severe sepsis
  - Assessment of main effects of A and of B vs placebo is the primary aim
- **What are our design options?**
  - Factorial trial (100% “co-enrollment”)
    - Impact on generalizability, numbers, timing
  - 3-arm trial (co-enrollment not an issue)
  - Two separate 2-arm Trials prohibiting co-enrollment
  - **Two separate 2-arm Trials allowing co-enrollment**
- **Among others, each choice has sample size/power implications**

**The implications of:  
Two 2-arm Trials allowing co- enrollment design**

## 2 x 2 Factorial Design assessing main affects of A and of B versus placebo



## ***When do we conduct Factorial Trials?***

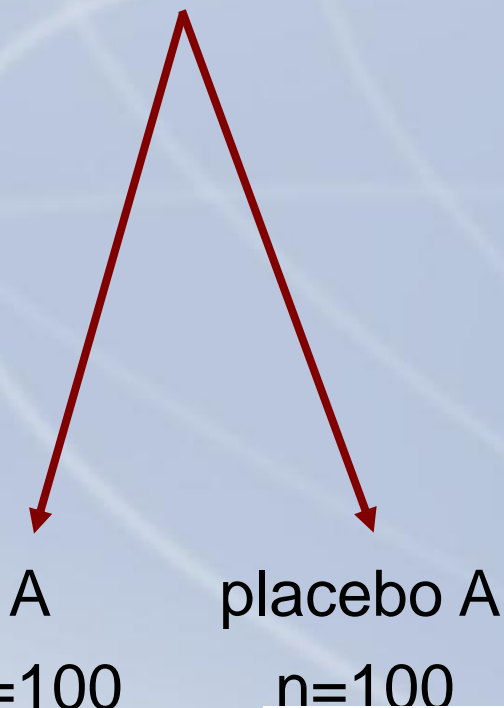
- **When statistical interaction not present**
  - (design becomes very efficient)
- **When there is a hypothesized clinically important interaction**
  - (sample size is considerable)
    - Fisher, *The Design of Experiments*, 1971
- **Best when we have 2 separate questions with 2 separate unrelated outcomes**
- **What happens when there is a “mild to moderate” interaction but interest is in main effects?**
  - **Sample size needs to be increased if interaction leads to a dilution of main effects**
    - NB: Increase in sample not to detect interaction BUT main effect

## 2 Parallel Trials assessing A & B

### TRIAL 1

Randomize

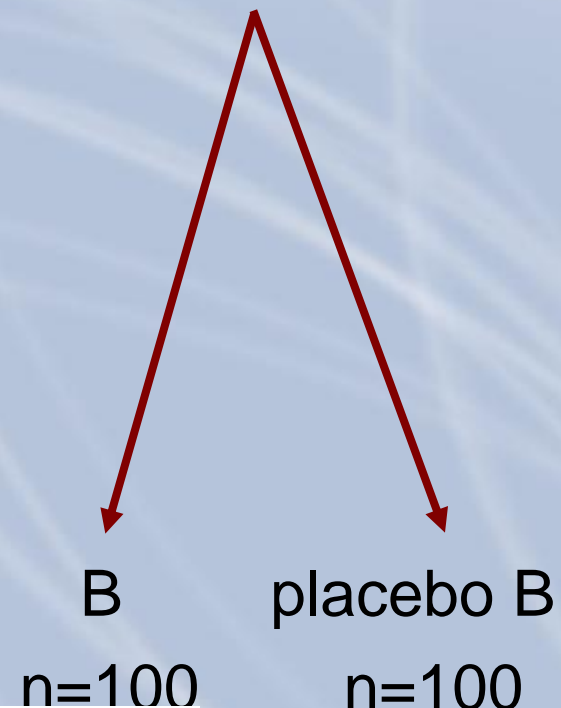
(N=200)



### TRIAL 2

Randomize

(N=200)



**Factorial within 2 Trials**

**Co-enrollment = 80 pts**

**A,B =20**

**A, placebo B =20**

**B, placebo A =20**

**placebo A, placebo B =20**

**But, this is the best case scenario!**

Reasonable to expect selection bias  
in sequential enrollment

***Given the “best case scenario” &  
Given the potential for interaction in those  
co-enrolled...***

- Reasonable to expect that it may have an impact on a study's power for main effects
  - potential to dilute main effects
  - albeit less than a true factorial design
- So, let's assess!

## ***The beef...***

Simulated 2 RCTs with a dichotomous outcome (mortality)

### **Trial 1:**

- average baseline probability of mortality of 15%
- relative risk associated with the treatment was 0.60 (40% RRR)
- Sample size: 1030
- Power: 80% to detect main effect

### **Trial 2:**

- average baseline probability of mortality of 25%
- relative risk associated with the treatment was 0.80 (20% RRR)
- Sample size: 2060
- Power: 80% to detect main effect

## ***Simulations***

- **Baseline outcome probabilities were drawn from two beta distributions with means of 0.15 and 0.25, respectively**
- **Defined so that there was some overlap between the baseline outcome probabilities.**
  - modeled to simulate a situation where some of the patients recruited into the first RCT (which targeted patients at relatively lower risk of the outcome) were also eligible for the second (which targeted patients with a relatively higher risk of the outcome)

## ***Simulations: 2 scenarios***

**Scenario 1: 20% of Trial 1 patients co-enrolled in Trial 2**

**Scenario 2: 50% of Trial 1 patients co-enrolled in Trial 2**

- **Simulated 10,000 pairs of RCTs under each of 2 scenarios to examine the effect of co-enrollment on risk estimates and power**
- **Each patient in a given RCT had a 50% chance of being given the treatment or the control**
- **A patient simultaneously enrolled in both RCTs and received both active treatments would have a relative risk of experiencing an outcome equal to  $0.6 \times 0.8 = 0.48$  (52% RRR)**

## ***Simulations: Results***

- Found no bias in the measure of effect due to co-enrollment
- But, there was a moderate effect on power in the second set of simulations

### **Scenario 1: 20% co-enrolled**

- power was essentially unaffected (<0.5%)

### **Scenario 2: 50% co-enrolled**

- power for the 1<sup>st</sup> RCT was reduced by 3% (80% to 77%)

For Trial 1, this translates into an increase in sample size of approximately 100 patients to compensate

## ***Why the decrease in power for Trial 1?***

- **Can't provide a definitive answer (WIP)**
- **Trial 2 mortality diluted effect of mortality in Trial 1?**
  - The 20% RRR diluted the 40% RRR in Trial 1
  - The higher mortality rate from Trial 2 patients diluted expected effect in Trial 1

## ***Further work needed***

- **Implications on sample size for range of:**
  - co-enrollment
  - baseline risks
  - expected effects
- **Implications on sample size for variety of design choices (Factorial vs Parallel)**
- **If relevant, develop simple rules for when to adjust and how to adjust sample size**

## ***Other considerations***

- **I have kept the scenarios straightforward**
- **What if dilution of effect is not protected by randomization?**
  - may differ for multi-centre trials with low numbers at sites
  - preference of one arm over another to enter a second trial
- **Is my usual care the same as yours?**
- **Influence of types of RCT maneuvers**
  - Blinding vs non-blinding may influence participation (selection bias)
- **Types of outcomes**
  - Same (competing)
  - Different but in the same pathway

## ***What to do?***

- **For ongoing studies, unless co-enrollment rates are high ( $>50\%$ ), we can “ignore” effect of co-enrollment**
- **At design stage, if co-enrollment expected to be high ( $>50\%$ )**
  - merit in listing assumptions and adjust sample size/power calculations if dilution expected
  - run simulation based sample size estimates
- **Compare with other design choices (sample size and logistics)**
- **Prudent to identify patients co-enrolled on CRFs**
- **If sufficient numbers, treat co-enrolled as subgroup analyses**
  - “protected” by randomization (ie. balanced)
  - any insights gained at no or very little cost

***Thank you***

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