Clinical Trials

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Lecture 1
RCT design

Major types of experimental studies

Placebo vs active comparison

Superiority vs non-inferiority

Blinded vs unblinded studies,

Single/double/triple blinding

Randomization methods

Individual vs group randomization

Controlled trials

A control group is used – to compare the effect of a new intervention against standard therapy (‘positive control’) or no therapy (placebo).

Can be assigned purposely – MD selects treatment based on patient characteristics,

Assigned quasi-randomly – based on day of week, or chart number

Randomly - best way to assign participants to control and intervention groups

Non-Randomized Concurrent Controlled Trial

Comparative study with intervention and control group

Subjects are treated at the same time;

But **the assignment is not done by a random process**.

In truth this is simply two case series.

Non-randomized concurrent trials – example:

A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in MDR-TB

G.B. Migliori, B. Eker, M.D. Richardson, G. Sotgiu et al

Comparison of efficacy end-points for treatment of MDR TB

	Linezolid	No Linezolid	P-Value
Patients n	45	110	
Sputum smear conversion Time days			
Mean ± SD	102.9 ± 74	65.4 ± 80.1	0.007
Culture conversion time Days			
Mean ± SD	109 ± 71	69 ± 63	0.007
Treatment outcome			
Success Failure Death	36 (80.0) 0 9 (20)	90 (81.8) 1 (0.9) 19 (17.3)	0.88 0.65

Non-Randomized Concurrent Controlled Trial

Advantages	Disadvantages
•Easier to select patients (increased investigator and subject acceptance); • More inclusive;	• Many potential biases • Patient selection • MD selection

Non-randomized and Non-concurrent (Historical Controlled) Trial

Comparative study with an intervention and a control group where a new intervention is used in a series of subjects and the results are compared to the outcome in a previous series of comparable subjects; Essentially two case series

Non-randomized and Non-concurrent Controlled trial – example: MDR-TB Treatment outcomes.

Edward D. Chan, Valerie Laurel, Matthew J. Strand, Julanie F. Chan, Mai-Lan N. Huynh, Marian Goble, and Michael Iseman

- **Retrospective comparison of MDR-TB patients treated in 2 time periods at NJMC**
- **205 patients in 1984-1998, vs 171 in 1975-83**
- **Initial favorable response: 85% recent cohort vs 65% prior cohort.**
- **Long term success: 75% versus 56%.**
- **TB deaths: 12% versus 22%.**

Non-randomized and Non-concurrent (Historical Controlled) Trial

Advantages	Disadvantages
• All new subjects can receive the new intervention; • Easier to select patient (increased investigator and subject acceptance); • Ethical aspects; • Rapid and relatively inexpensive.	• Potential bias introduced by time changes in the nature of the patient population, in exposure to pathological agents, or in supportive care and diagnostic criteria; • Missing data.

Randomized experimental controlled clinical trial

Prospective study comparing the effect and value of intervention(s) against a control in human subjects

RCT are considered the design that offers the best control of all possible confounding factors

Evidence from Non-randomized vs randomized trials

Systematic review of 145 papers in the treatment of acute MI over 35 years:

- Non-randomized trials: 14 times more likely to find a difference in case fatality rates than Randomized Trials

Randomized Controlled Trial

Comparative study with intervention and control groups; Assignment is by **formal procedure of randomization**

Advantages	Disadvantages
• Removes the potential of bias in the allocation of subjects to the study groups • Tends to balance study groups in covariates • Guarantees the validity of statistical tests of significance	• Emotional and ethical aspects • Can only study one thing at a time • Complex, expensive and time-consuming

Ethical Considerations

Randomized controlled trials entail important ethical issues.

A randomized control study can be undertaken when :

• There is uncertainty about the value of a new therapy or dispute about the relative merits of existing therapies. This is termed equipoise

Although studies might not actually prove the superiority of a new treatment, they can show that new or existing treatment are of no benefit, or even cause harm. This is important to discover.

Clinical trial phases (drugs)

Phase I Studies: *Pharmaco/Toxicity*

– Usually healthy volunteers.

– Pharmacological action, and safety – usually with escalating doses

– Best dose = maximal action with minimal side effects

Phase II Studies: *Treatment effect*

– Evaluate whether the drug has any effect in patients with a specific disease

– Monitor the rate of adverse events in these patients.

– Usually short term studies in small groups

Clinical trial phases (drugs)

Phase III: *Efficacy and Effectiveness*

Designed to assess the effectiveness of the new intervention, and thereby, its role in clinical practice.

Phase IV: *Post-marketing surveillance*

Surveillance for previously undetected adverse events. No control groups

Seed Trials (‘Marketing trials’): Large scale multi-centre studies. Small numbers of patients per centre (<10). Primary objective - marketing

Types of Study Designs

Simple randomization

- The simplest design is Group A gets active drug
- And Group B gets Placebo
- They get the placebo/drug for equal length of time.
- Then both stop
- Outcomes measured. Rate of outcomes compared
- Risk ratio = Incidence of outcome Group A/Group B

Simple randomization – example

Efficacy and Safety of a 4-Drug Fixed Dose Combination Compared with Separate Drugs Lienhardt, et al JAMA

Treatment Outcomes

Response	FDC (n=591)	Separate Drugs (n=579)
Favorable response		
Culture negative No. (%)	555 (93.9%)	548 (94.6%)
Unfavorable response		
Treatment failure (N)	9	8
Relapse (N)	23	19
Death (N)	4	4

Simple randomization – example
Feasibility...of Gene Xpert testing for TB in Africa
Theron et al, Lancet ID 2014

- Pragmatic Randomised multicentre trial
- Adults suspected of TB at primary care facilities
- Patients randomly assigned to Gene Xpert or AFB smear
- Outcome – TB related morbidity at 2 months and 6 months

Outcomes of the study

Days to start of TB treatment	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
All patients	1 (0-4)	0 (0-3)	0.0004
In culture-positive patients	1 (0-3)	0 (0-1)	<0.0001
In culture-negative patients	2 (0-5)	1 (0-4)	0.12
In patients treated empirically	1 (1-6)	1(0-5)	0.38

Cross-Over Design

Each subject serves as own control.

Each subject receives intervention or control first, and then crosses over to the alternative next. Usually a ‘wash-out’ period between.

The order of intervention or control is randomized

Advantages	Disadvantages
• Within-subject estimates means less variability. So need smaller sample size to detect a specific difference in treatment response.	• Effect of the intervention during the first period must not carry over into the second period; • Cannot be used for treatment of an acute disease.

Cross-Over Design - example

- New analgesic vs. Placebo for headache
- Consenting subjects enrolled
- Phase 1 – Randomization – ORDER of interventions:

  Group A – Placebo

  Group B – New analgesic

  Phase 1 ends – All subjects stop treatment
- Wash out phase – No drug for any subject for N weeks
- Phase 2 – No Randomization, just take the other:

  Group A – New analgesic

  Group B -- Placebo
- End of study – all drugs stopped

Cross-Over Design – example

Oral Bioavailability of H,R,E,Z, in a 4-Drug FDC compared to separate pills. Xu, et al

- Randomized single dose two period crossover trial
- PK studies with blood samples collected over 24 hours
- Healthy volunteers randomized to take FDC or separate drugs first
- Washout period of one week
- After one week all volunteers took the opposite formulation

Withdrawal Studies

Subjects on a particular treatment for chronic disease are taken off or have dosage reduced;

Advantages	Disadvantages
• Evaluate the duration of benefit of an intervention already known to be useful; • Alternate way to assess intervention that is believed but never proven to be beneficial.	• Highly selected sample is evaluated, e.g. only subjects who had benefited from the intervention, AND never had a major side effect. Tends to overestimate benefit and underestimate toxicity.

Example

***A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus*.**
The Canadian Hydroxychloroquine (HCQ) Study Group

47 patients with stable SLE on HCQ

at least 6 mos on drug (average was 3 years)

and at least 3 months stable

Randomized to stop drug (switch to placebo) or continue. Duration of study intervention period was 24 weeks. Most patients stayed on same therapy (drug or none) for 3 years after

Major disease flare: 50% if placebo. 28% if active drug

Factorial Design

Two interventions tested at same time:

Group A – Intervention A, Placebo B

Group B – Intervention A, Intervention B

Group C – Placebo A, Placebo B

Group D – Placebo A, Intervention B

Factorial Design Comparisons

Intervention A vs. Placebo A

Intervention B vs. Placebo B

Advantages:

- Can test two interventions for “same price,”
- meaning sample size as for one.

Disadvantage:

- Assumes NO interaction between interventions
- If Intervention A enhances or reduces effect of B, could make results invalid

Factorial Design Example

Moxifloxacin versus EMB in the first 2 months of treatment for TB *Burman et al, AJRCCM*

- Adults with smear positive pulmonary TB
- Randomized in factorial design:
  - Received Moxi or EMB
  - And randomized to: 5 days/week or 3 days/week
- 2 month in culture conversion:
  - Moxi = EMB
  - 5/week = 3/week
- Four week culture conversion: Moxi > EMB, 5/wk = 3/wk

Placebo vs. Positive Control

Placebo is justified if there is uncertainty regarding whether the standard therapy helps (e.g.. Headache, common cold).

or

Placebo / New drug may be added to an existing standard regimen. Test if the new drug adds to standard therapy. (eg New anti-TB or Placebo added to current MDR-TB regimen)

Positive Control – the new drug is compared directly to the standard therapy.

- Used when the standard therapy is known to be effective.

Superiority Studies

- Test New Interventions against a standard or placebo.

- Hypothesis: New intervention is better.

- New intervention will be adopted if patients' outcomes are better.

Superiority Study: Example

Placebo controlled trial of Isoniazid for inactive TB:

Large study of 28,000 participants

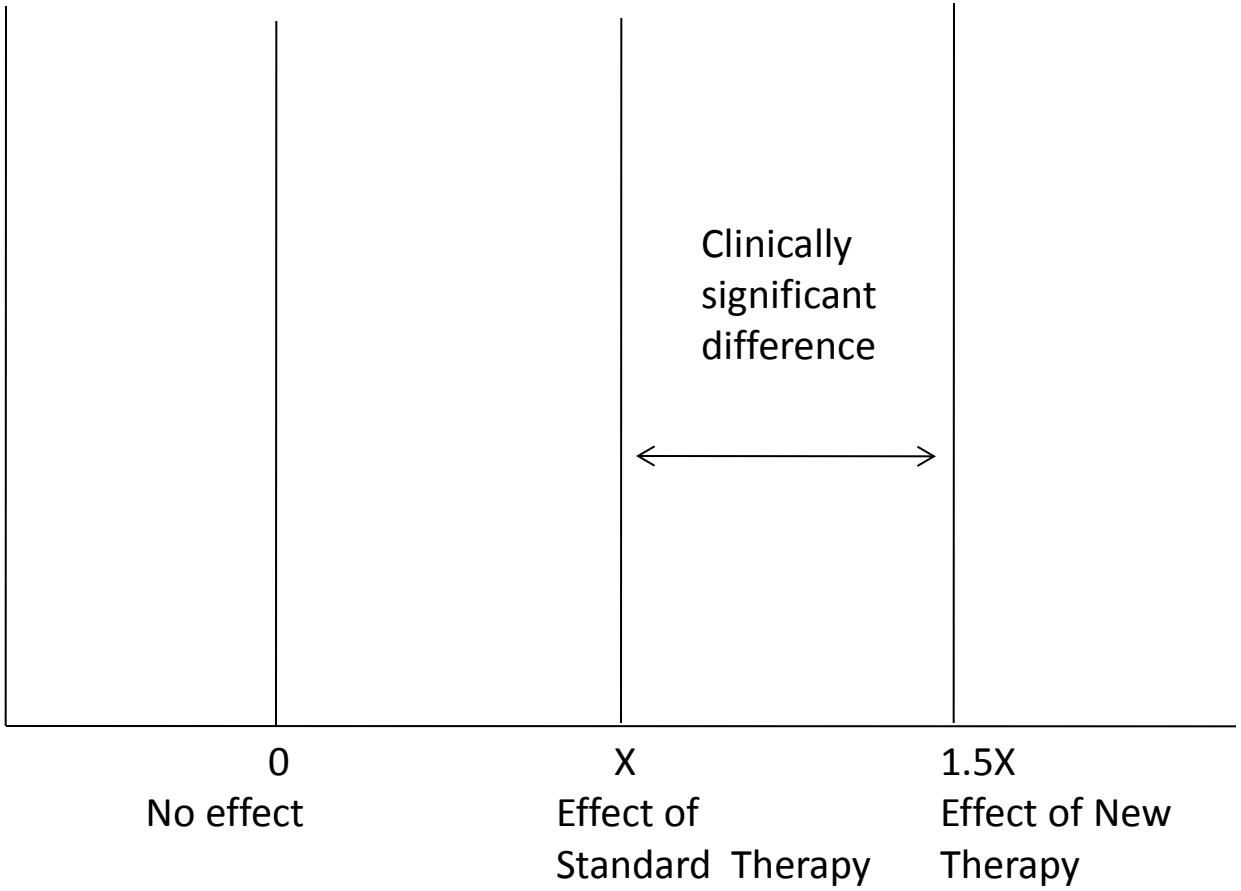
- Conducted in Eastern Europe, in 1968-1975
- **7,000 in each group**

Randomized to: placebo, 3 months INH, 6 months INH, or, 12 months INH

Hypothesis:

INH for 3, or 6 or 12 months would be more effective than placebo in preventing active TB. (Each INH group of 7,000 compared to same placebo group of 7,000)

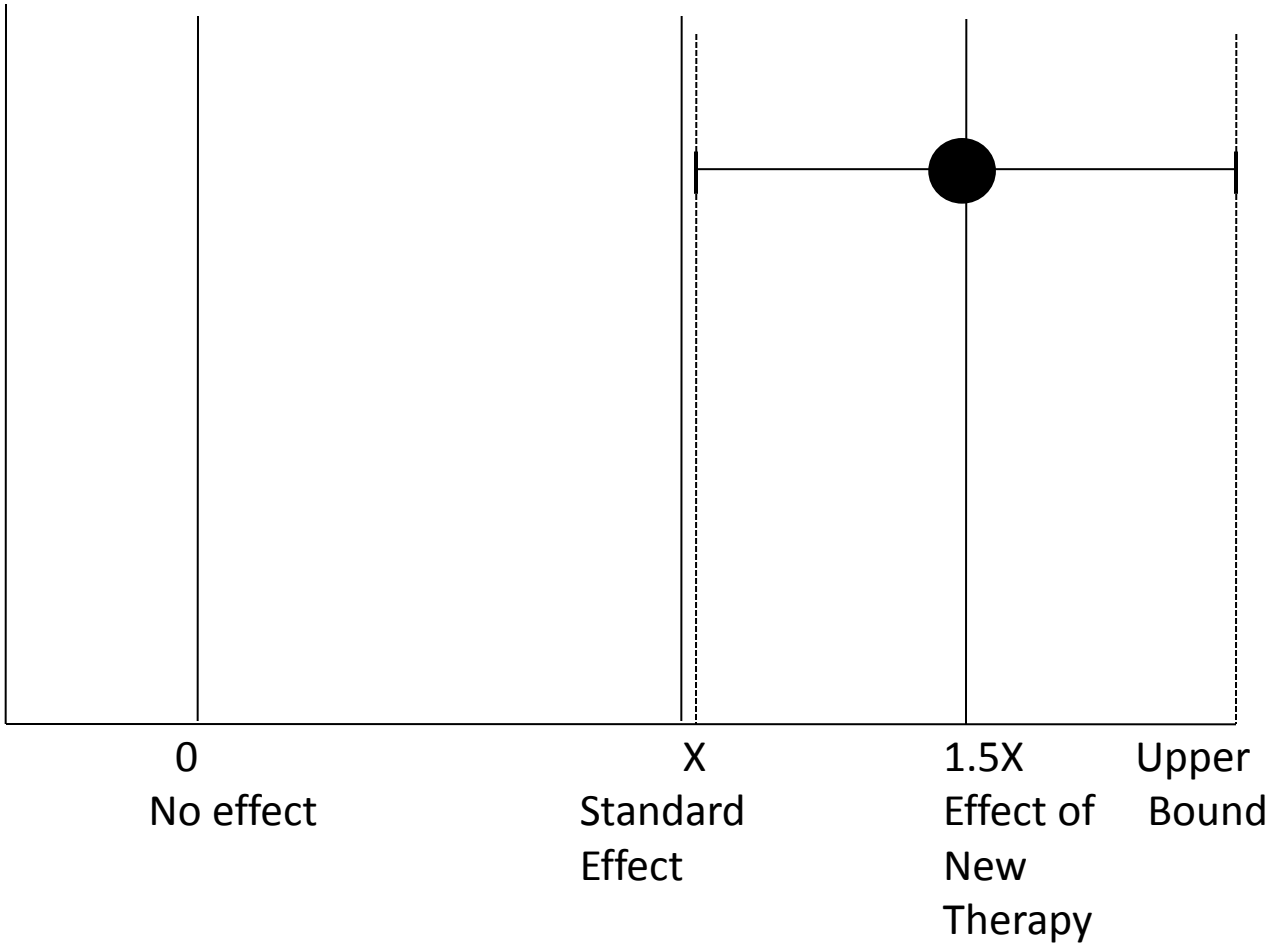
Superiority studies – Concept: Selection of estimates of effect



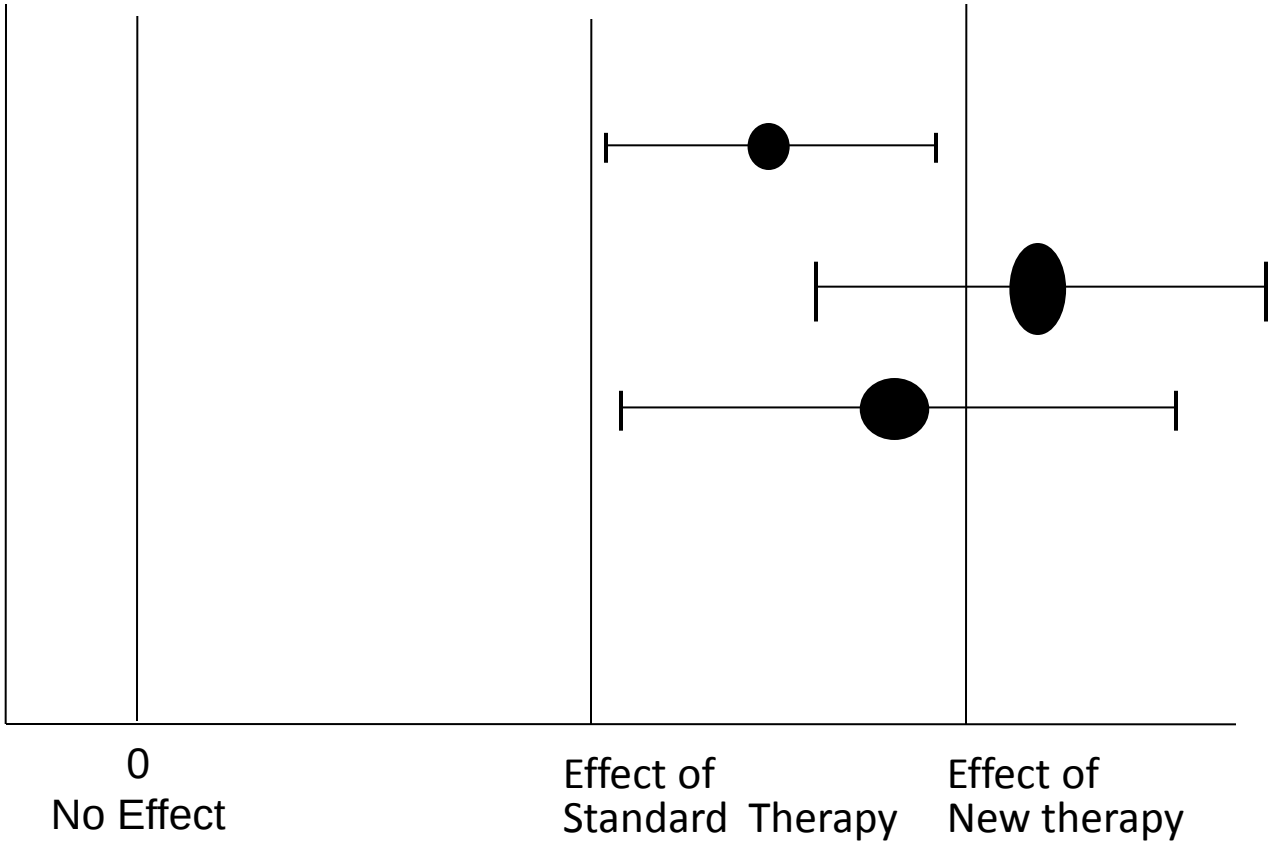
Superiority: New treatment must be at least 50% times more effective than existing treatment.

Superiority studies – Design

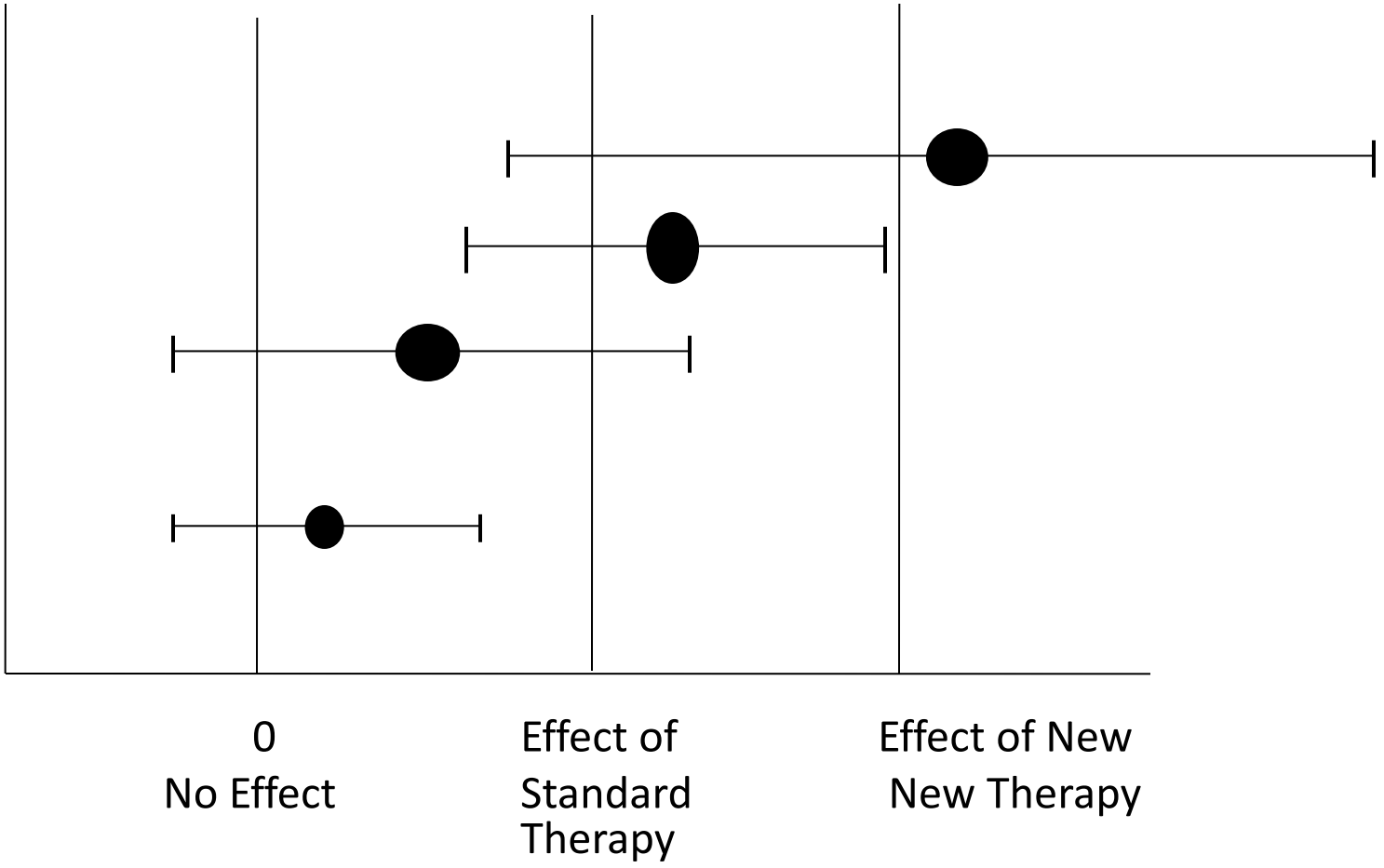
Setting 95% confidence intervals



Superiority studies:
Results: CAN conclude superiority



Superiority studies:
Results: CANNOT conclude superiority



Non-inferiority Studies

If current therapy is effective

- But is very costly, or lengthy
- Or has major side effects

Alternate therapies must be cheaper, shorter, or safer.

Then we want to show that the new treatment is not worse.

This is called a Non-inferiority study.

Non-inferiority- Example

9 months INH- now the current standard for TB prevention.

- Greater than 90% efficacy in preventing TB
- but 9 months duration - reduces compliance
- And significant side effects

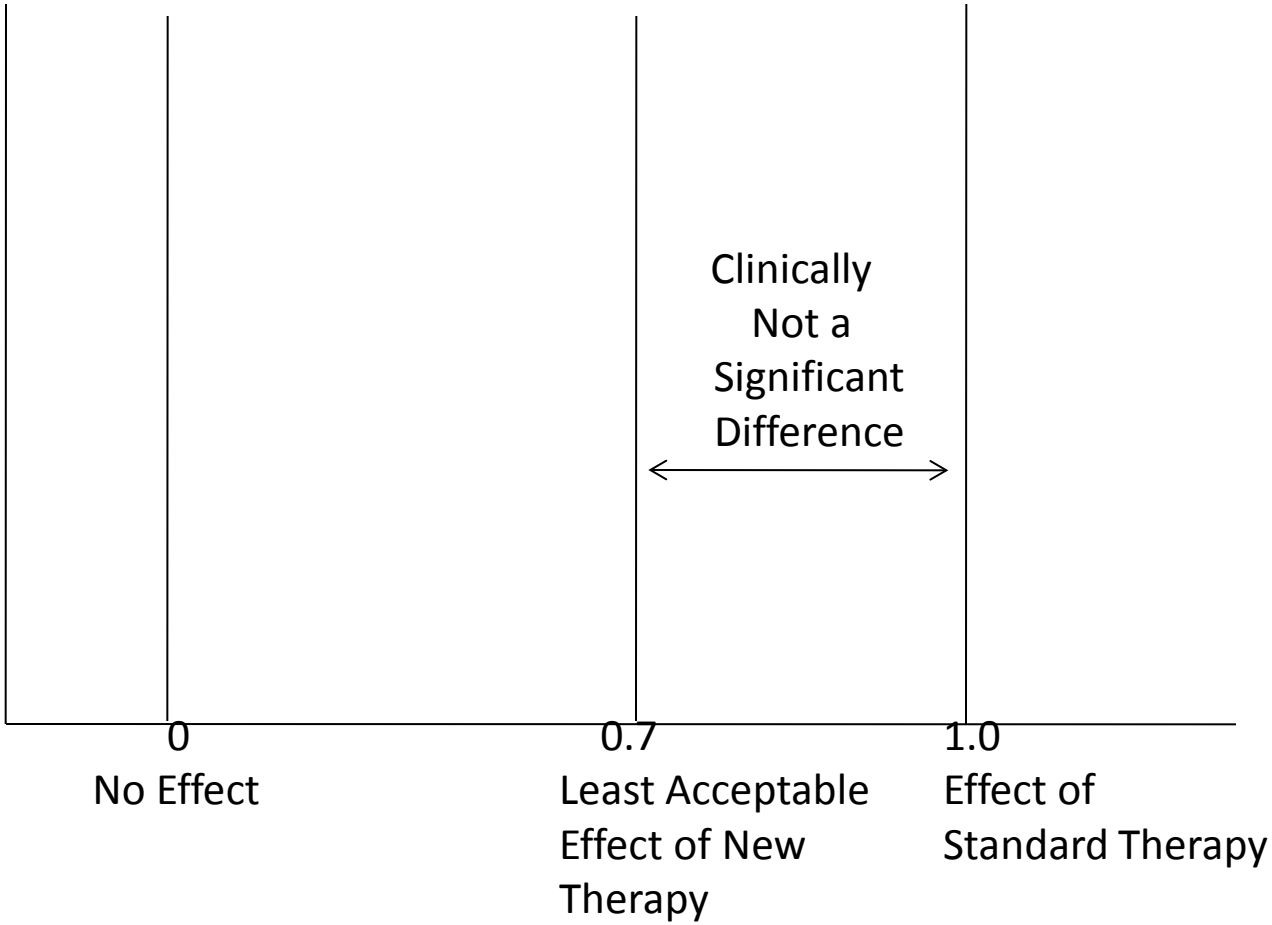
4 months Rifampin - much better compliance

- and lower rates of serious adverse effects

Therefore, objective is to demonstrate efficacy that is NOT (a lot) worse than 9 INH.

- because it is hard to beat 90% efficacy!

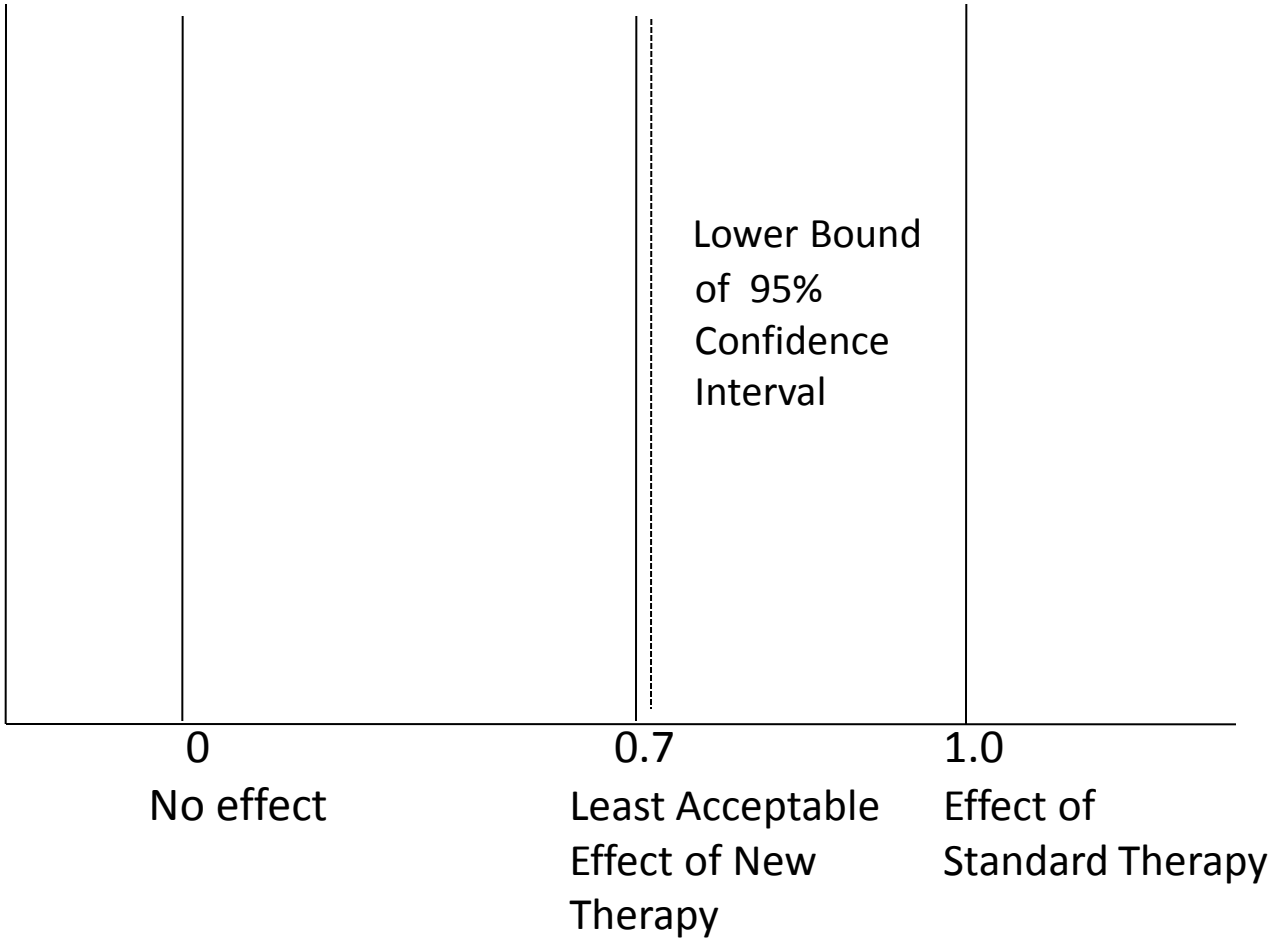
Non-Inferiority studies - concept



Inferiority: New treatment could be 30% worse and still acceptable.

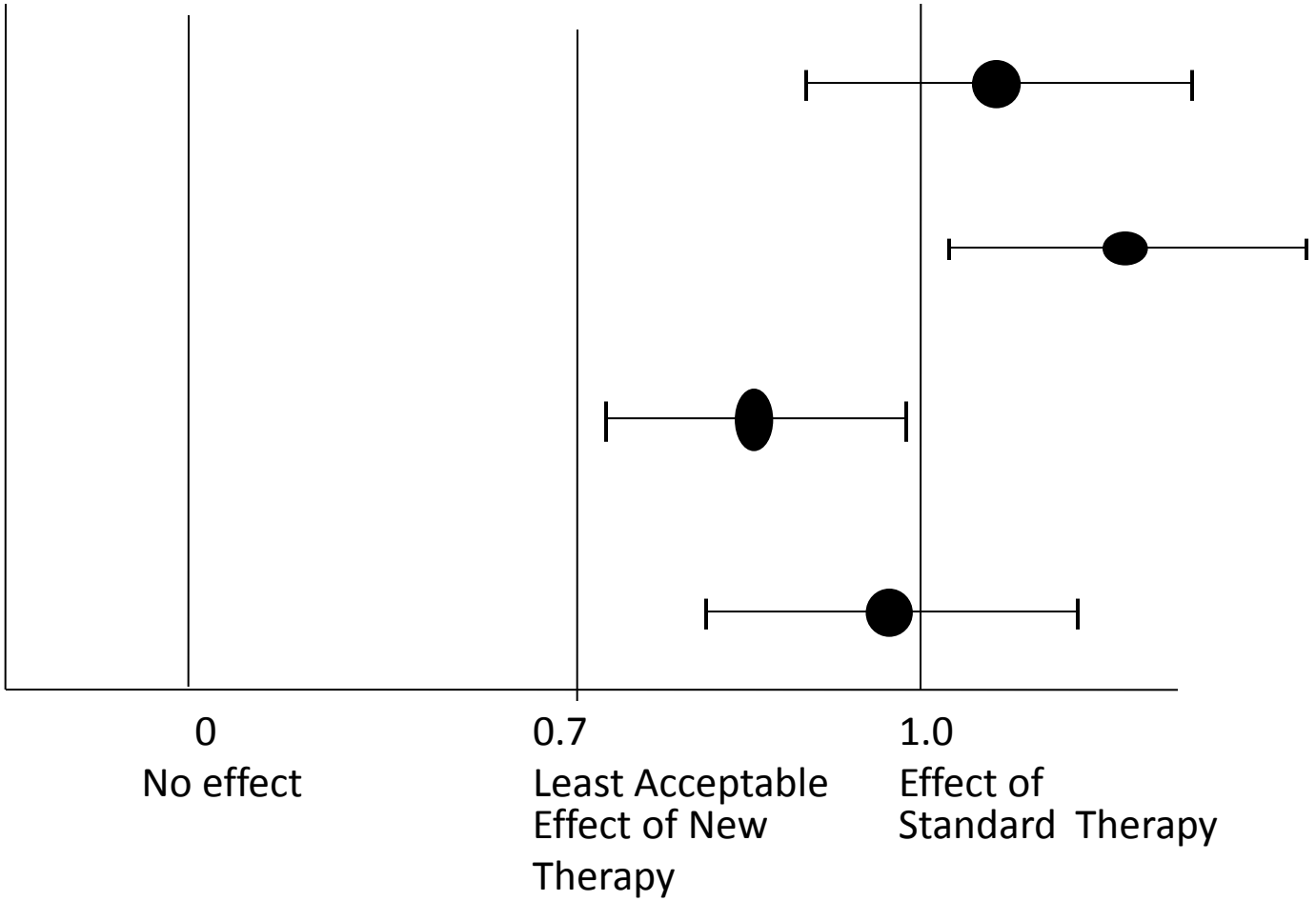
Non-Inferiority studies - design

Setting 95% confidence interval for non-inferiority



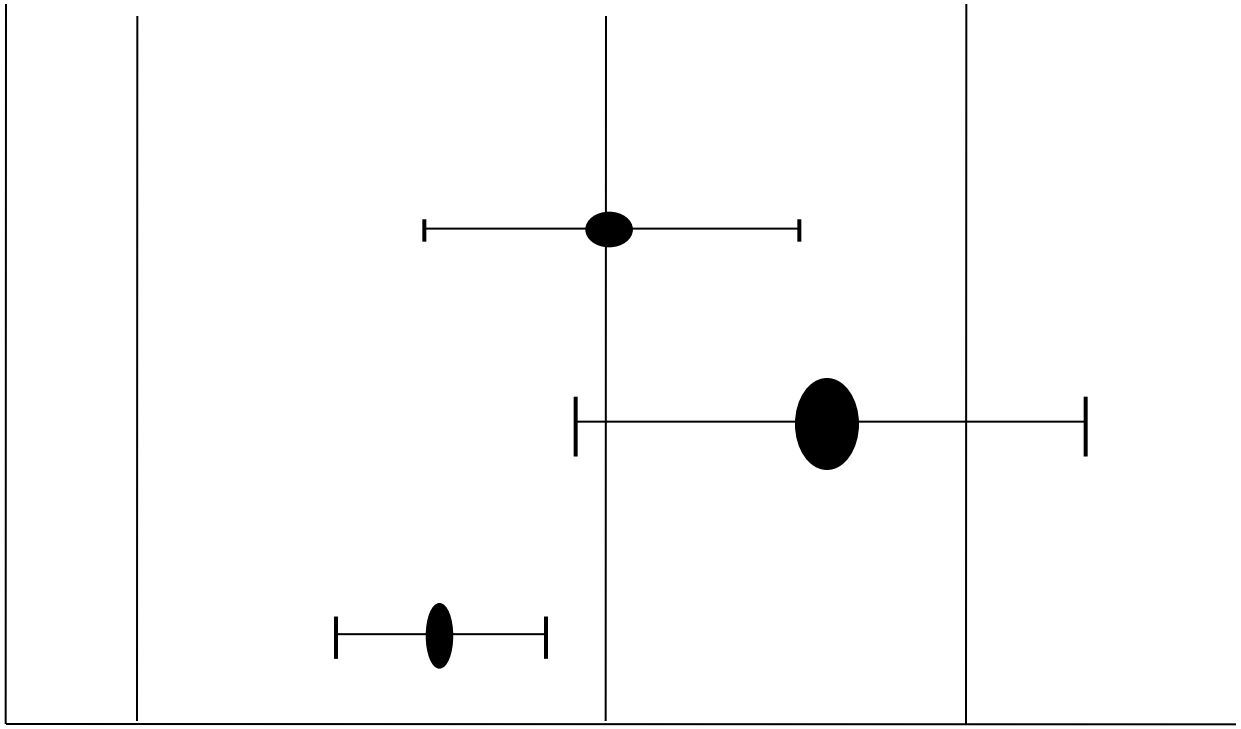
Non-Inferiority studies - Results

CAN conclude non-inferiority



Non-Inferiority studies - Results

CANNOT conclude non-inferiority



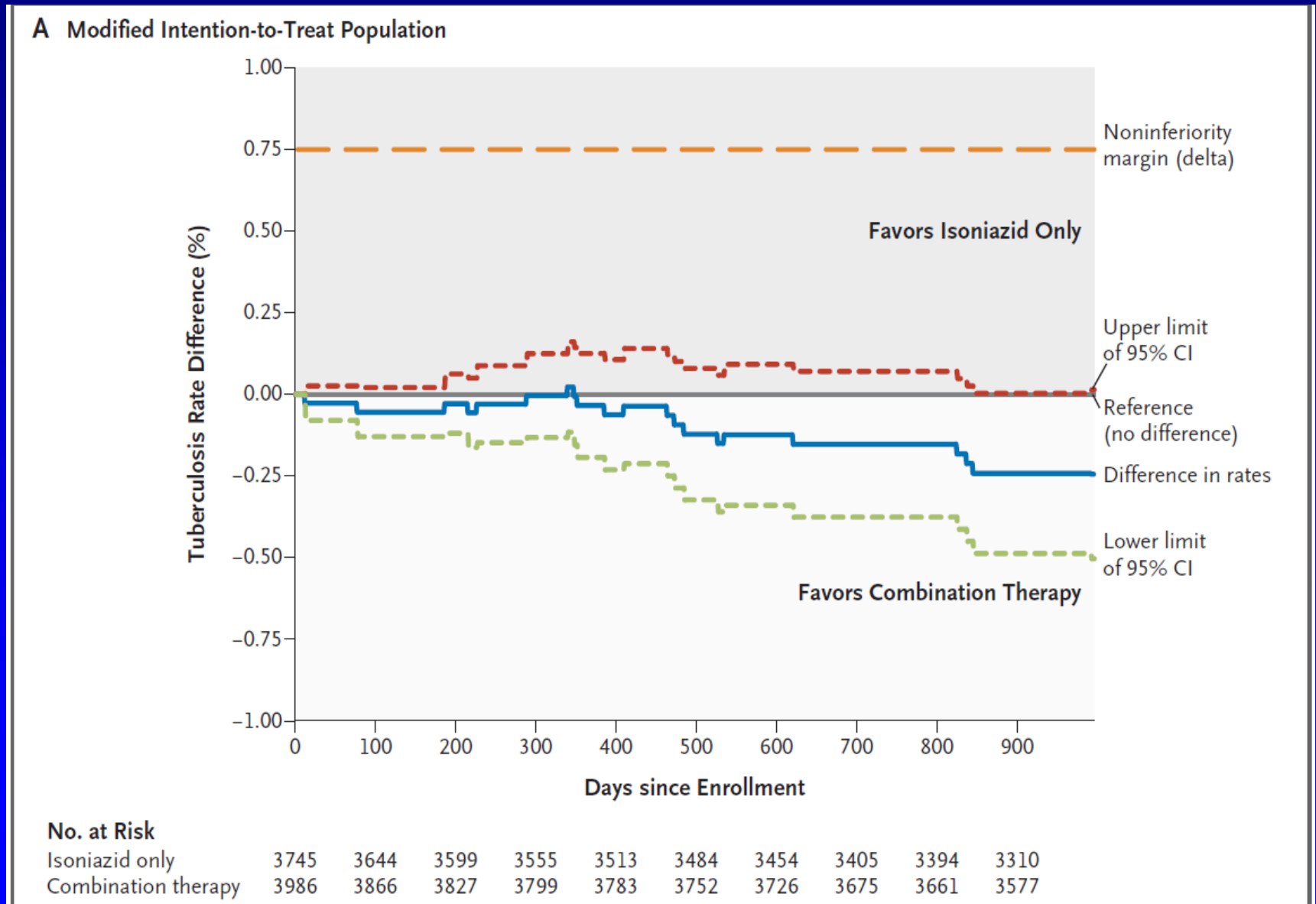
3 months once weekly INH & Rifapentine – Incidence of active TB

Sterling et al NEJM, 2011

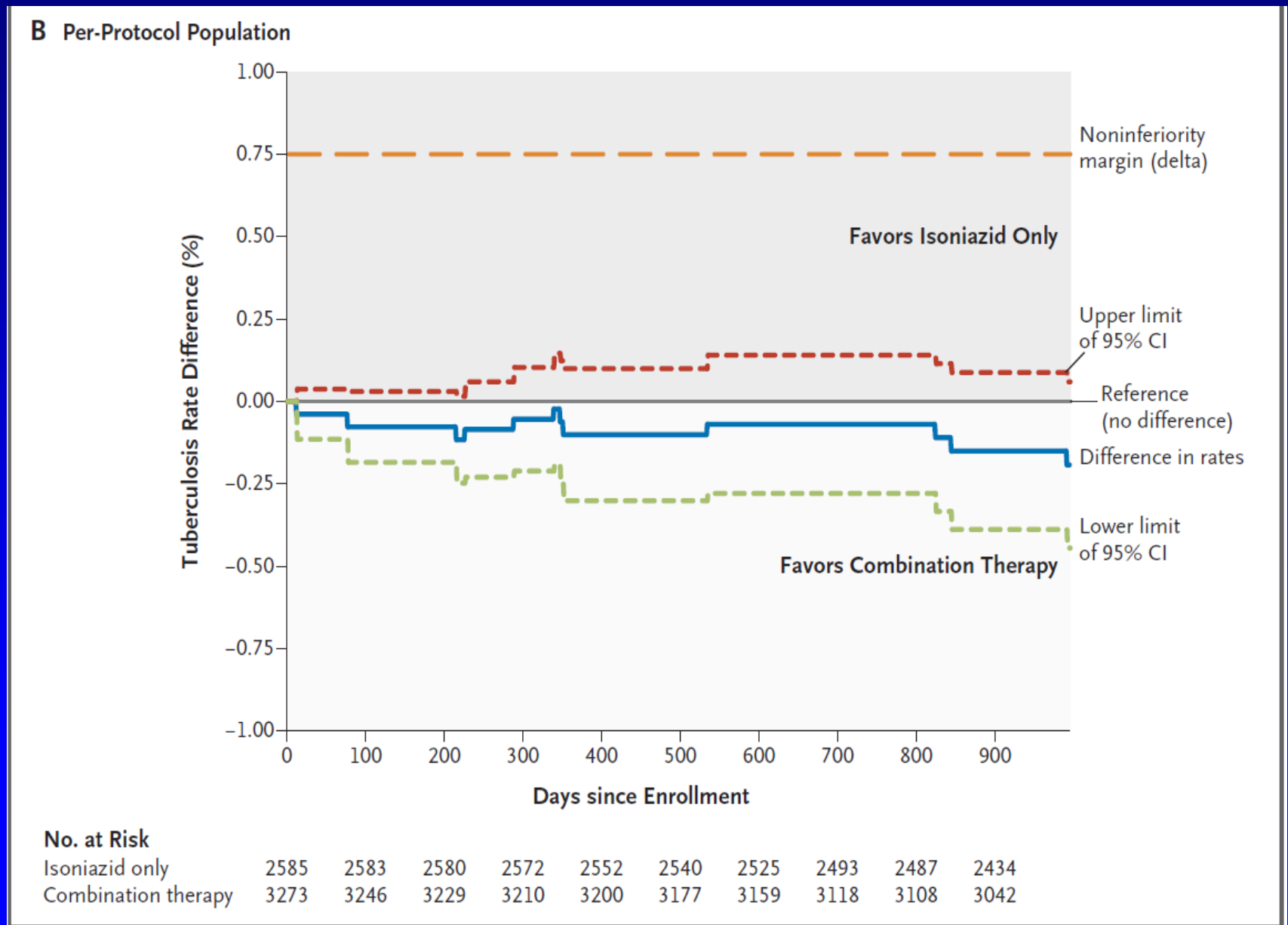
	9INH	3HP
Randomized	3649	3895
Completed	2536 (69%)	3190 (82%)
TB Disease - All patients	12 (0.4%)	7 (0.2%)
- Completed	5 (0.2%)	4 (0.1%)

Non-Inferiority Study design - Example:

9H vs 3HP – *Sterling et al NEJM, 2011*



Non-Inferiority Study design - Example:
9H vs 3HP – Sterling et al NEJM, 2011



Optimal Background Therapy (OBT) trial design:
Example - The enfuvirtide registration trials

Study population

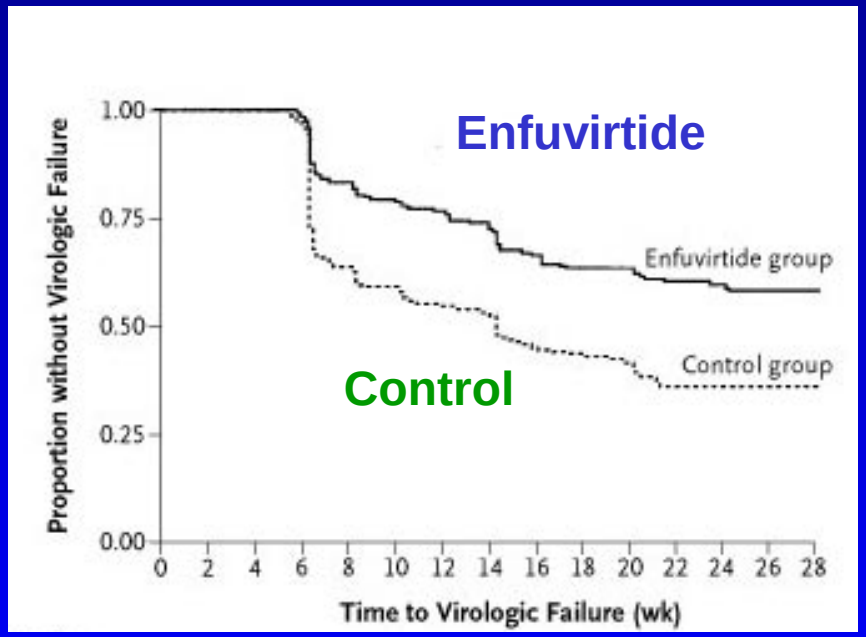
- –Prior therapy with 3 drug classes (NRTI, NNRTI, PI)
- –Virological failure of current therapy: VL > 5000

Randomization

- –OBT (could include other investigational or expanded access drugs) + placebo
- – vs OBT + enfuvirtide

Enfurvirtide trial – results from OBT trial

(% with viral load > 5000 copies/ml)

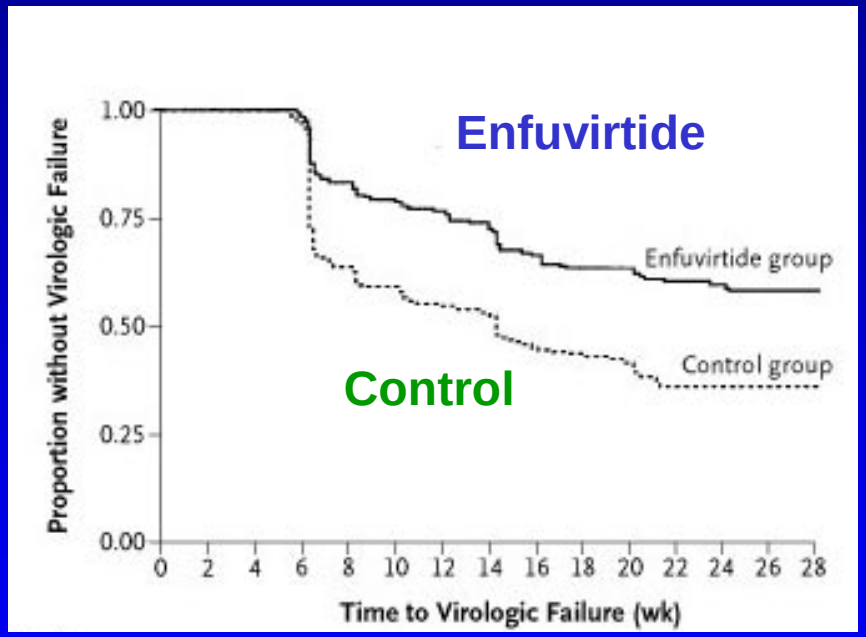


N = 501

N Engl J Med 2003; 348: 2175-85,

Results from two OBT Enfurvirtide trials

(% with viral load > 5000 copies/ml)



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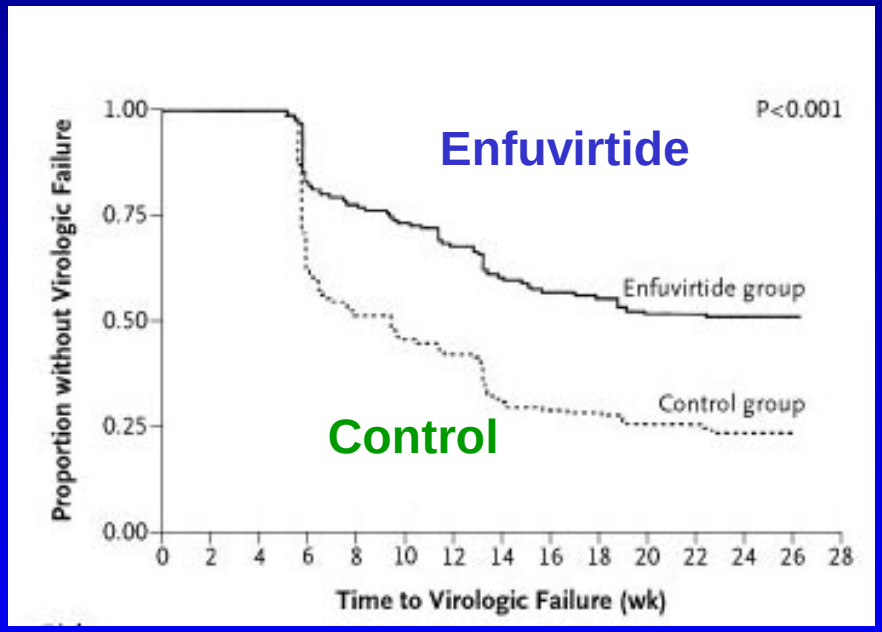
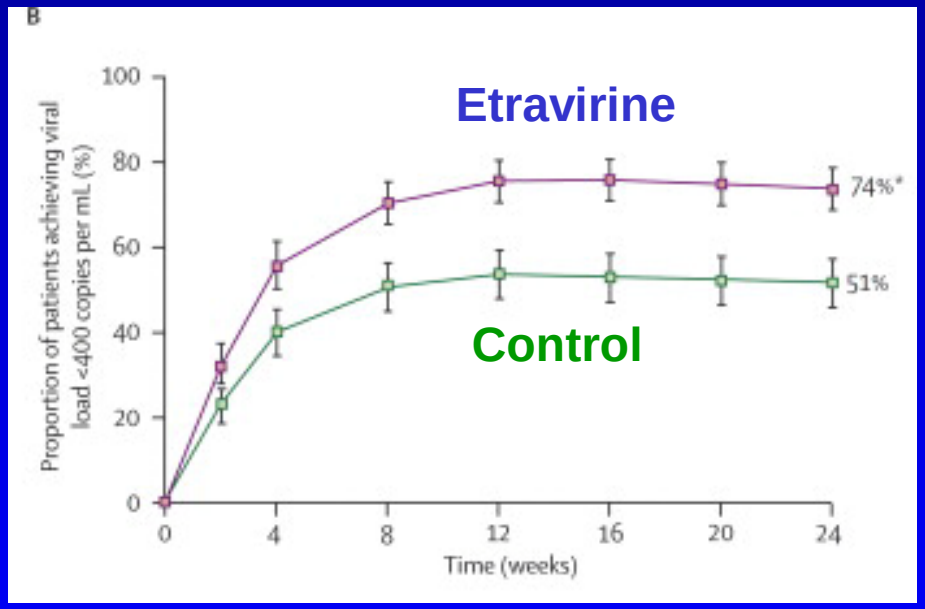


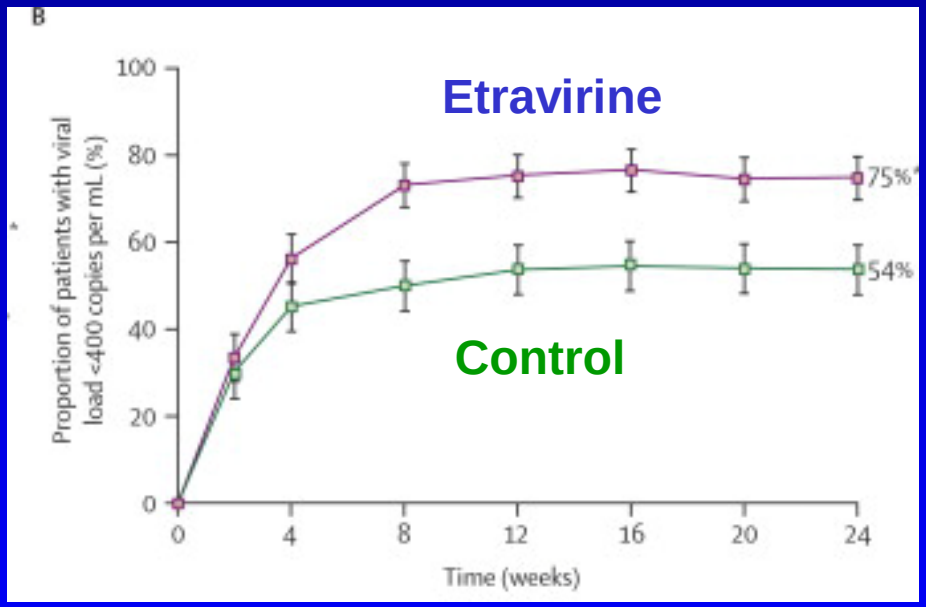
N Engl J Med 2003; 348: 2186-95

Efficacy of etravirine in two OBT trials

(% with viral load < 400 copies/ml)



Lancet 2007;370:29-38



Lancet 2007;370;39-48

Lessons from OBT trials

OBT design can provide highly reproducible estimate of the treatment effect, using a dichotomous endpoint (virological failure)

WHILE

Allowing for the diversity inherent in treating patients with advanced disease or MDR-TB

- **Prior therapy**
- **Degree of baseline resistance**
- **Other drugs used at the time. The optimized regimen is selected by each treating MD, and is highly individualized**

Pragmatic trials

Concept: trial that simulates real practice conditions

- –Non-selective patient selection
- –Realistic follow up

Patient selection should be truly representative

- –Of all patients with target condition
- –Includes patients at risk for adverse events
- –Includes patients at risk for non compliance

Pragmatic trials: follow up

In a typical clinical trial, follow-up is very close and intense

- –Adherence is usually over estimated
- –Serious adverse events often under estimated

In pragmatic trial one attempts to simulate real life conditions

- –Follow up by normal clinic staff and MDs
- –Research staff play observer role
- –Research staff “jump in” if outcome occurs

Intention to treat analysis will be more realistic

- –And quite different from per protocol analysis

What is Pragmatic research? Comparing to "Typical RCT"

	Typical Randomized Trials	Pragmatic research
Question	Efficacy. How well does it work under optimum conditions?	Effectiveness. How well does it work in real practice?
Setting	Well resourced ($$$)	Publicly funded ($)
Participants	Carefully selected. Likely non-adherent excluded	All comers
Adherence	Carefully monitored and enforced	Normal enablers and incentives. (Patients drop out, come late, forget)
Relevance to practice	Indirect	Direct

Pragmatic trials: example

Comparison between MGIT and LJ in detection of TB at public health care facilities...

Moreira, Kritski and others

- Practical clinical trial to evaluate clinical performance and cost effectiveness of two diagnostic methods
- MGIT 960 compared to smear microscopy
- Adults who were TB suspects were enrolled and randomized to one or the other diagnostic method
- Outcomes – change in initial treatment approach within 2 months of randomization
- Unblinded study except outcome assessors blinded

Cluster randomized trials

- Randomization in most RCT is by individual
  - One by one
- Cluster randomization – is by groups
  - Could be towns/villages (fluoridation of water)
  - Could be health facilities (introduction of XPert)
  - Could be school classes (polio)
- Why? – when the intervention is not at individual level, but affects entire group

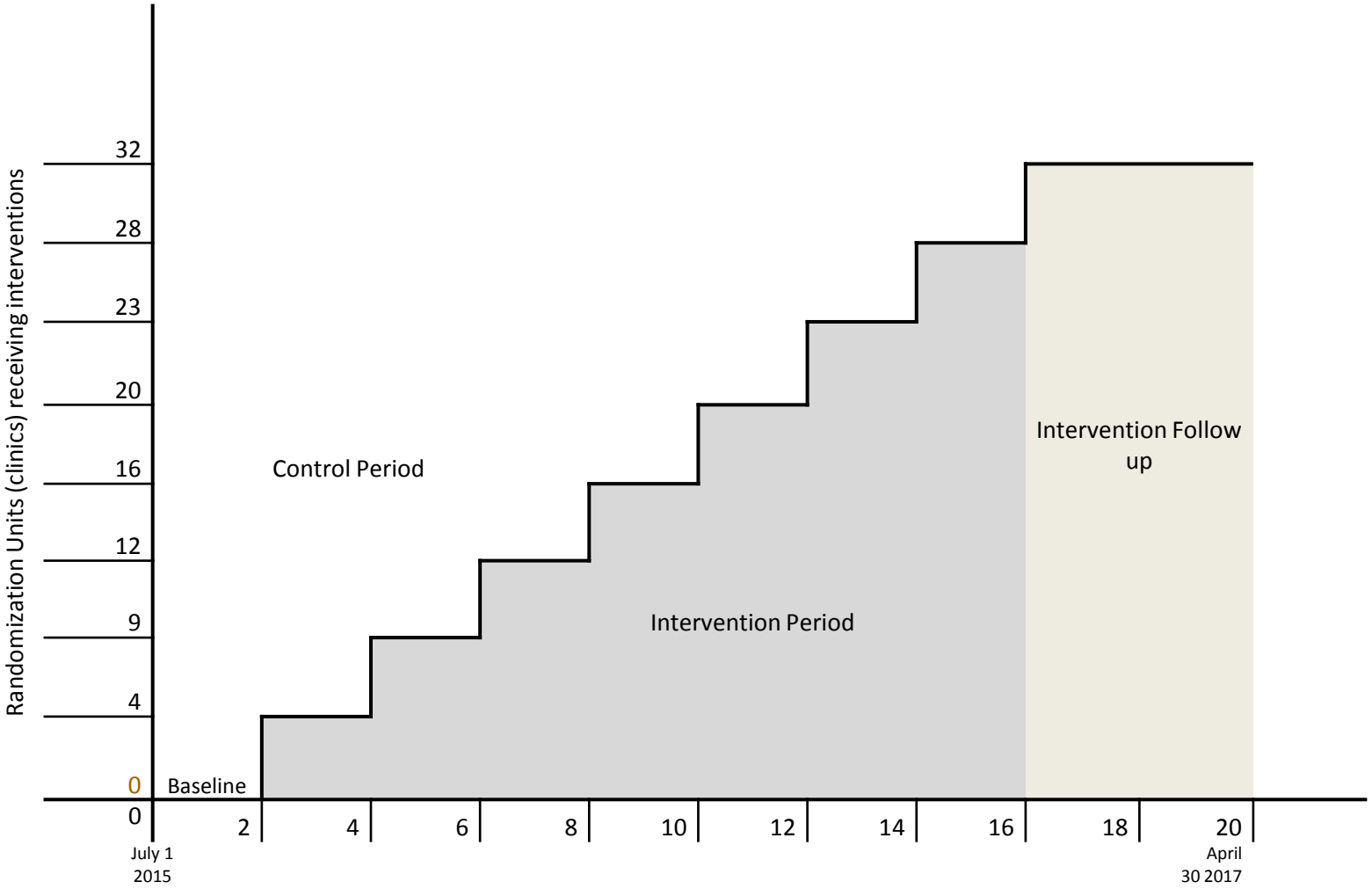
Advantages and disadvantages of cluster randomized trials

- Advantages: For many interventions – it's the only option
- Disadvantages:
  - Sample size must be larger
  - Accounts for group effect
  - May not be able to control confounding as well.
  - May not be able to measure confounding well either
  -

Stepped intervention trials

- Stepped intervention – means interventions are introduced sequentially to different groups (goes with cluster randomized trial)
- Comparison: Outcomes during period before intervention with outcomes after intervention
- Advantage: Everyone eventually gets the intervention – resolves ethical issue
  - Plus – simply more feasible if intervention is complicated and takes time to introduce
- Disadvantage: Temporal effect – if other things change (improve) at same time

Schematic of Stepped intervention design



First 2 months (0-2) No clinics have intervention

Last 4 months (16-20) All clinics have intervention

Thanks