National Translational Medicine and
Clinical Trial Resource Center
國家轉譯醫學與臨床試驗資源中心

臨床試驗之基礎研究設計

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報告摘要

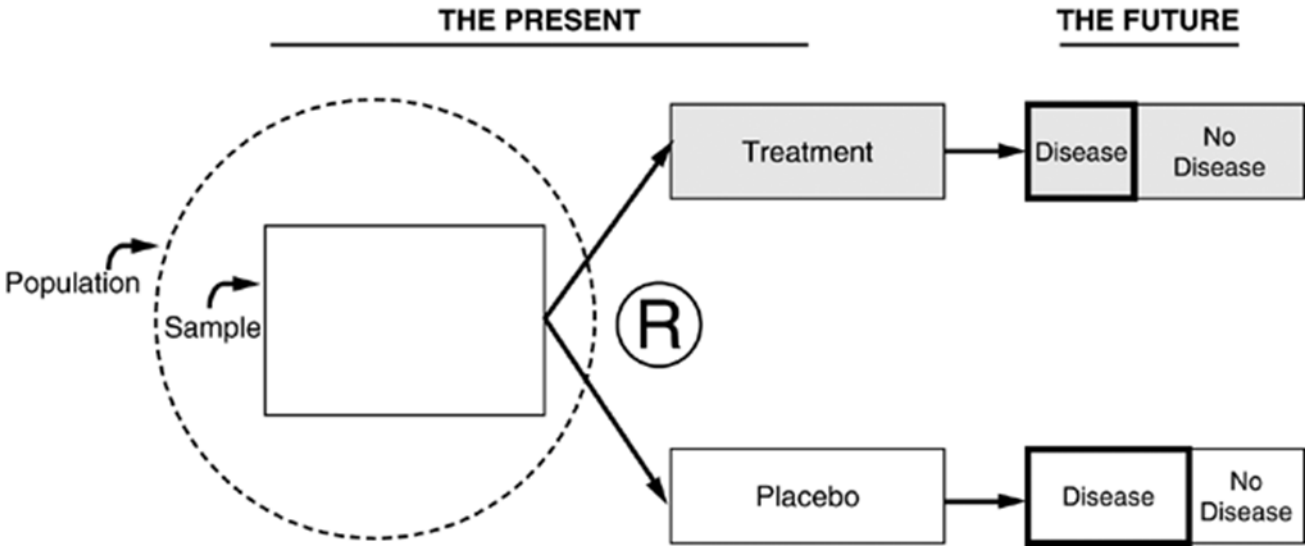
- 參考來源：
  - Lawrence M. Friedman, Curt D. Furberg, David L. DeMets; Fundamentals of Clinical Trials; Fourth Edition
    - Chapter 5 Basic Study Design
    - Chapter 6 The Randomization Process
- 摘要：
  - 本章簡介臨床試驗的基本研究設計，除了隨機分派的方式，其他設計包含資料庫或病例對照、交叉研究設計、退出型試驗、矩陣型研究設計等。

報告大綱

- Randomized Control Trials 隨機分派臨床試驗
- Nonrandomized Concurrent Control Studies
  非隨機分派的同期試驗
- Historical Controls and Databases 資料庫或病例對照
- Cross-Over Designs 交叉研究設計
- Withdrawal Studies 退出型試驗
- Factorial Design 矩陣型研究設計
- Group Allocation Designs 集束隨機分派試驗
- Hybrid Designs 混合設計
- Large, Simple and Pragmatic Clinical Trials 大樣本臨床試驗
- Studies of Equivalency and Noninferiority 不劣勢試驗
- Adaptive Designs 適應性設計

RANDOMIZED CONTROL TRIALS
隨機分派臨床試驗

- FIGURE 10.1. In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants (R), (d) applies interventions (one should be a blinded placebo, if possible), (e) measures outcome variables during follow-up (blinded to randomized group assignment).



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隨機分派的優點

1. 隨機分派可以移除潛在的偏差
2. 增加對照組的可比較性
3. 確保統計上顯著差異的效力

隨機分派

- 研究要注意 allocation bias，這會使對照組變得無意義。
- 研究會以不同的隨機分派方式(Simple、Blocked、Stratified Randomization)或是統計分析處理干擾因素。

blocked randomization

Assignment	Random number	Rank
A	0.069	1
A	0.734	3
B	0.867	4
B	0.312	2

In the case of block size 4, there are six possible combinations of group assignments: AABB, ABAB, BAAB, BABA, BBAA, and ABBA.

Table 6.1 Stratified randomization with block size of four

Strata	Age	Sex	Smoking	Group assignment
1	40–49	M	Current	*ABBA BABA*…
2	40–49	M	Ex	*BABA BBAA*…
3	40–49	M	Never	etc.
4	40–49	F	Current	
5	40–49	F	Ex	
6	40–49	F	Never	
7	50–59	M	Current	
8	50–59	M	Ex	
9	50–59	M	Never	
10	50–59	F	Current	
11	50–59	F	Ex	
12	50–59	F	Never	
	(etc.)			

As an example of stratified randomization with a block size of 4, suppose an investigator wants to stratify on age, sex, and smoking history. the design has $3 \times 2 \times 3 = 18$ strata.

NONRANDOMIZED CONCURRENT CONTROL STUDIES 非隨機分派的同期試驗

- 同期性的，不經由隨機分派分組，對照組是未做試驗組之介入的受試者。
- 舉例：實驗組是接受新手術者，對照組是傳統醫療照護，觀察存活。

非隨機分派同期試驗之優缺點

- 優點：可以依受試者提供一個最適合的醫療介入，並且因為有給予治療，也較容易選擇對照組，選擇時也偏好配對。

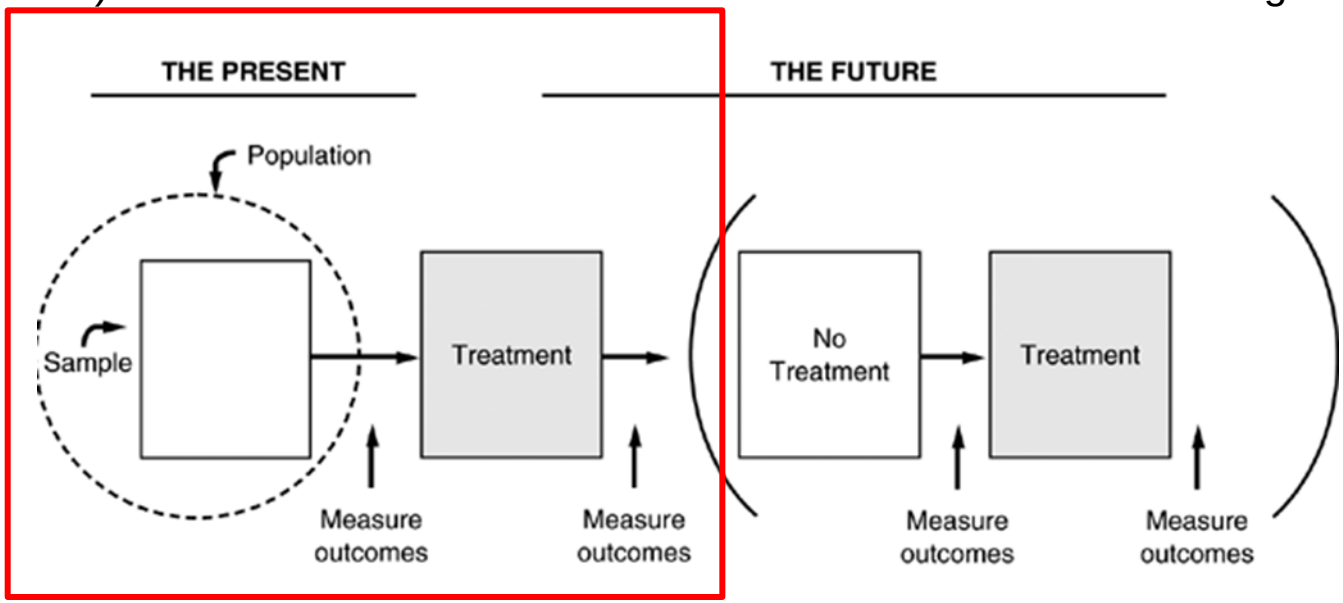
- 缺點：可比較性差。

HISTORICAL CONTROLS AND DATABASES 資料庫或病例對照

- 以過去的資料作為對照組，是非隨機分派、非同期的

  如：接受新的介入後之結果與接受前的結果作比較。

FIGURE 11.2. In a time-series trial, the investigator (a) selects a sample from the population, (b) measures baseline and outcome variables, (c) applies the intervention to the whole cohort, (d) follows up the cohort and measures outcome variables again, (e) (optional) removes the intervention and measures outcome variables again, and so on.



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資料庫或病例對照研究

- 適用於疾病診斷已明確的特殊病例或致死率高的疾病。
- 資料來源可以是
  1. 過去的文獻
  2. 電腦資料或病例

資料庫對照研究之優缺點

- 優點：全部的受試者皆可以接受新的治療。
  a. 沒有倫理道德選擇的問題。
  b. 受試者是在確定介入治療之內容的情況下進入研究，研究的意願會比較高。
  c. 招募的時間幾乎可以減半。
- 可建立大型資料庫進行研究，注意刊登偏差、資訊不足等問題

資料庫對照研究之限制(1)

1. 所觀察的outcome不應隨著時間改變
   - 圖5.2 疾病並未依時間有很大的變化
   - 圖5.3 肝炎的發生在不同年代有不同

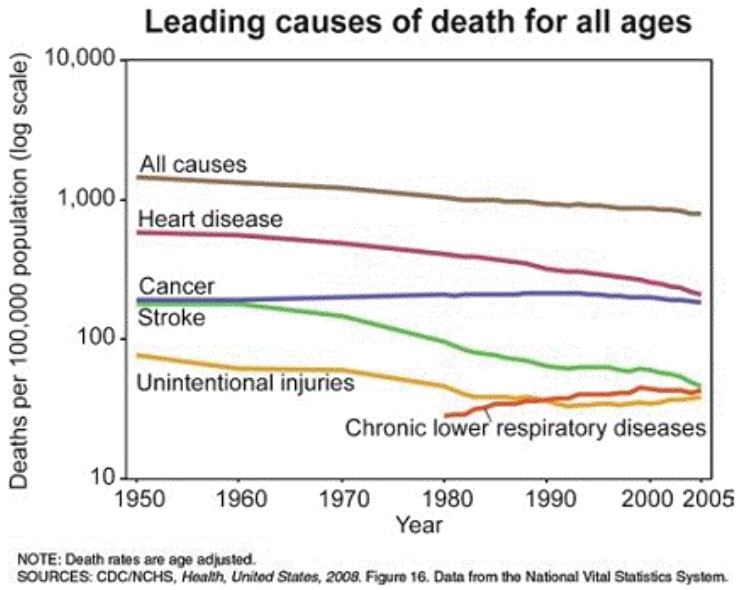


Fig. 5.2 Trends in causes of death in the U.S.

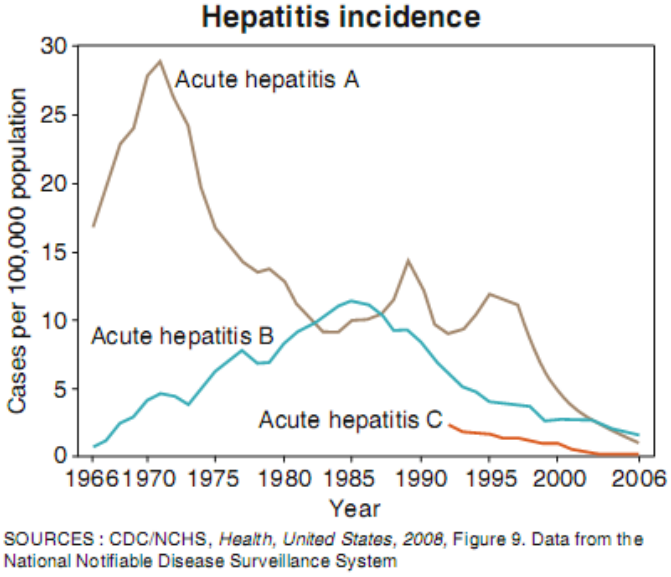
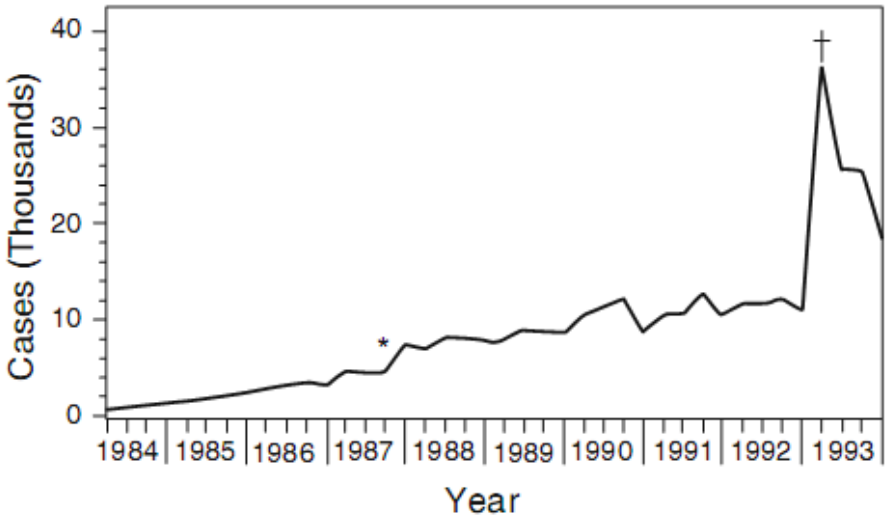


Fig. 5.3 Changes in incidence of hepatitis, by type, in the U.S.

資料庫對照研究之限制(2)

2. 被選入的受試者不同會有很大的影響。
   - 舉例：排除嚴重究疾病個案，使死亡率低於期望值。
3. 隨著科技的進步，診斷的能力及標準有所不同。

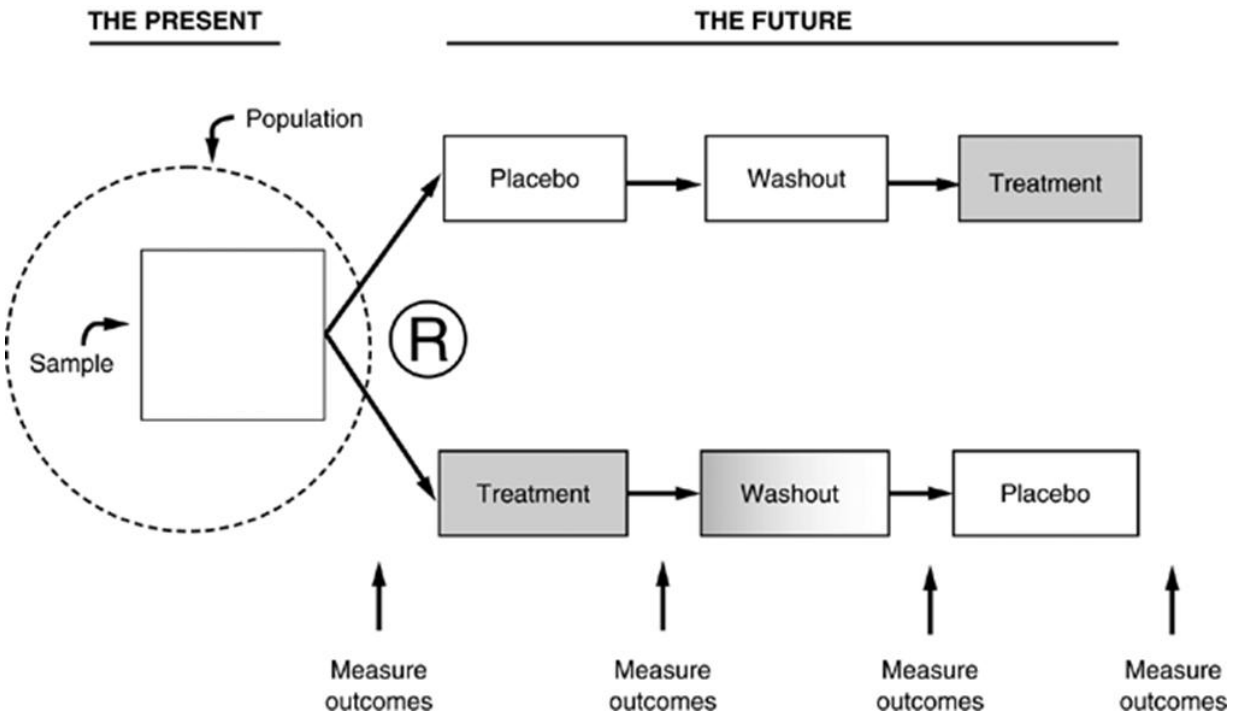


[#] Case definition revised in October 1987 to include additional illnesses and to revise diagnostic criteria (3).
[†] Case definition revised in 1993 to include CD4+ criteria and three illnesses (pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer) (1).

Fig. 5.4 AIDS cases, by quarter year of report – United States, 1984–1993 [61]

CROSS-OVER DESIGNS 交叉研究設計

- FIGURE 11.3. In a crossover randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline and outcome variables, (c) randomizes the participants (R), (d) applies interventions, (e) measures outcome variables during follow-up, (f) allows washout period to reduce carryover effect, (g) applies the intervention to former placebo group and placebo to former intervention group, (h) measures outcome variables again at the end of follow-up.



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CROSS-OVER DESIGNS優缺

- 優點：
  1. 變異降低：由同一個個案接受不同介入治療
  2. 所需樣本數較小
- 嚴格的假設：

  兩治療期間及結果應要獨立
  - 第一期間的治療效應不能帶到第二期的治療研究。
- cross-over study 一般用於藥物不良反應評估，對象為健康人，觀察藥理作用。

WITHDRAWAL STUDIES 退出型試驗

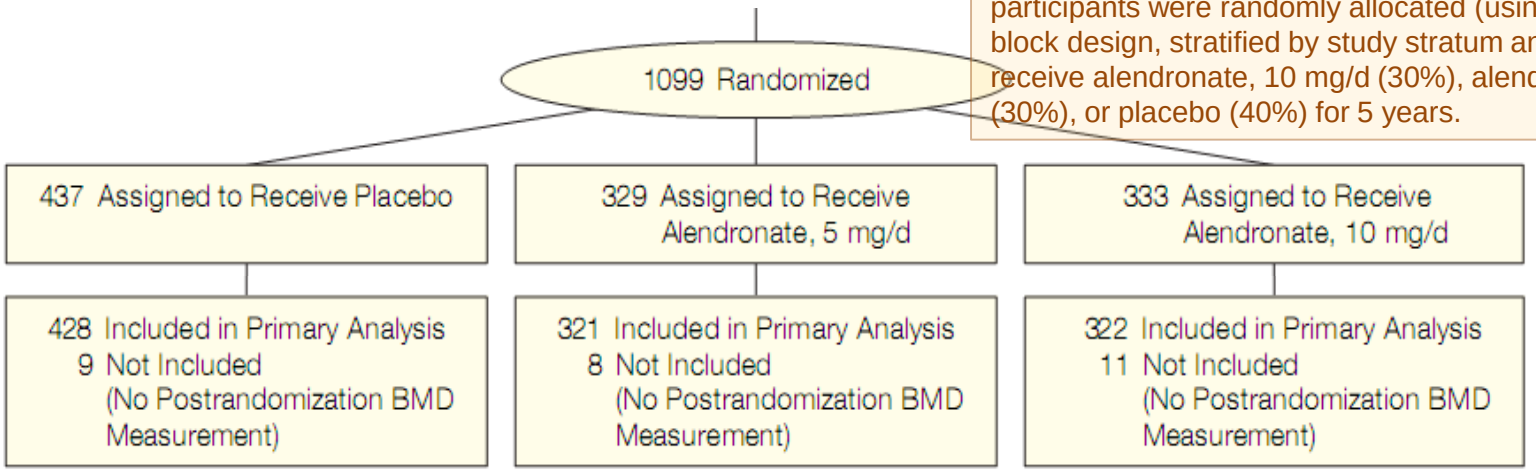
- 考慮如慢性病的長期治療會因個人狀況有停藥或藥物減量的情形。
- 研究設計的目的為評估停藥或減量的反應。
- 對樣本的高選擇性，因為研究將不良反應者排除，可能會高估成效、低估毒性。

FRACTURE INTERVENTION TRIAL LONG-TERM EXTENSION (FLEX)

- **Objective** To compare the effects of discontinuing alendronate treatment after 5 years vs continuing for 10 years.

Participants One thousand ninety-nine postmenopausal women who had been randomized to alendronate in FIT, with a mean of 5 years of prior alendronate treatment.

participants were randomly allocated (using a permuted-block design, stratified by study stratum and center) to receive alendronate, 10 mg/d (30%), alendronate, 5 mg/d (30%), or placebo (40%) for 5 years.



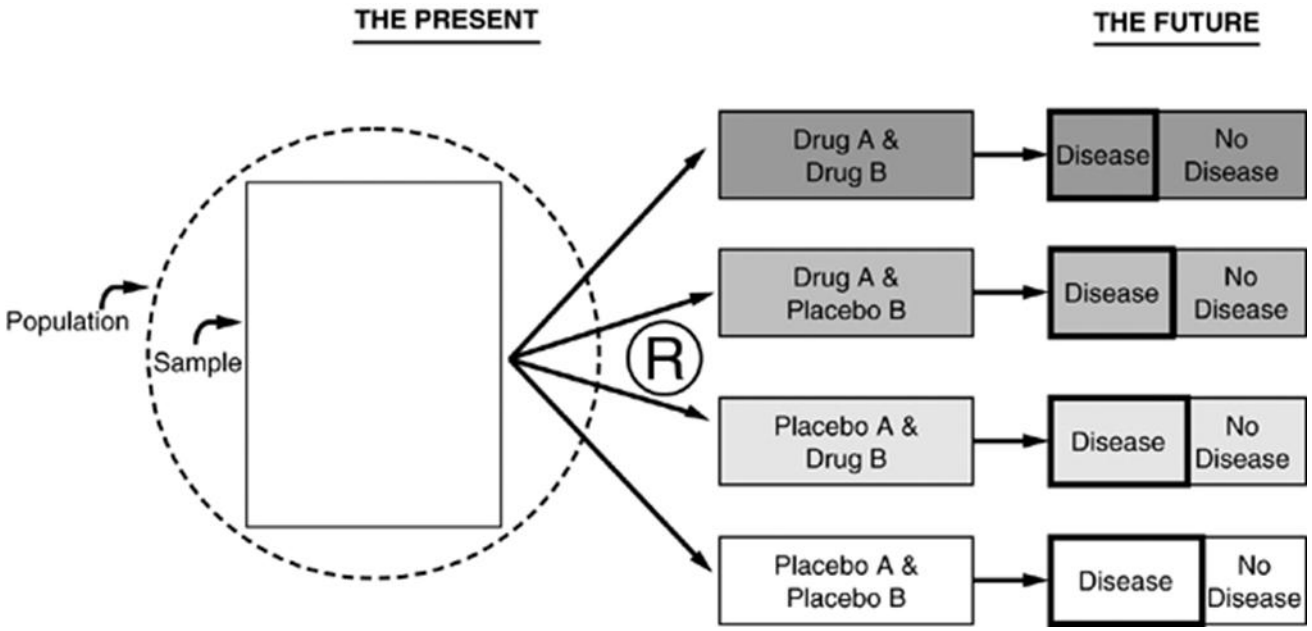
BMD indicates bone mineral density; FIT, Fracture Intervention Trial; FLEX, Fracture Intervention Trial Long-term Extension.

- **Conclusions** The group that was randomized to discontinue alendronate had a modest increase in vertebral fractures but no increase in nonvertebral fractures.

Dennis M. Black et al. JAMA. 2006;296:2927-2938

FACTORIAL DESIGN 矩陣型研究設計

- FIGURE 11.1. In a factorial randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomly assigns two active interventions and their controls to four groups as shown, (d) applies interventions, (e) measures outcome variables during follow-up, (f) analyzes the results, first combining the two drug A groups to be compared with the two placebo A groups and then combining the two drug B groups to be compared with the two placebo B groups.



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FACTORIAL DESIGN優缺

- 優點：

  可以同時評估兩種以上的介入組合。

- 缺點：

  1. 不同介入間的交互作用
  2. 樣本數可能較少

GROUP ALLOCATION DESIGNS
集束隨機分派試驗

- 或稱cluster allocation designs。
- 隨機分派的單位為一組人，如社區或學校，有效應用於媒體傳播等的影響評估。

RESTRICTED RANDOMIZATION OF ZAMSTAR: A 2 X 2 FACTORIAL CLUSTER RANDOMIZED TRIAL

- **Purpose** We present the randomization scheme used in the ZAMSTAR trial of tuberculosis control interventions in Southern Africa.
- **Methods** We used stratification and restriction to randomize 24 clusters (16 Zambian, 8 South African) into four intervention groups in a 2 X 2 factorial design. Stratification was by country and tuberculous infection prevalence and restriction by tuberculous infection prevalence, HIV prevalence, urban/rural, social context, and geographical location.

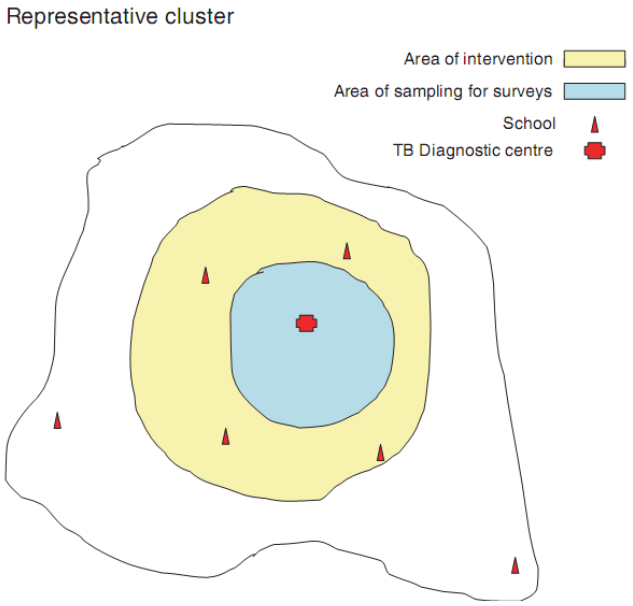


Figure 1 Schematic representation of a typical ZAMSTAR cluster and the 'fried egg' sampling design

Table 1 ZAMSTAR 2 × 2 factorial design of the enhanced case finding (ECF) and the household (HH) interventions

		HH	
		–	+
ECF	–	Control* (Group A)	HH (Group B)
	+	ECF (Group C)	HH + ECF (Group D)

*Control = the WHO package of TB/HIV collaborative activities, provided as standard to all 24 clusters.

C Sismanidis et al. Clinical Trials 2008; 5: 316–327

HYBRID DESIGNS 混合設計

- 如果大量的資料可以由歷史資料獲得，則可使用混合性的研究設計。
- 隨機分派時並非均分，而是將分到對照組的比例減少，則可接受介入者比例會更多。
- 混合歷史性資料及隨機分派的研究設計，研究的標準一致，包含受試者的條件、評估的因子等。
- 此設計要注意在非隨機分派的研究中可能的偏差所造成的影響。

LARGE, SIMPLE AND PRAGMATIC CLINICAL TRIALS 大樣本的臨床試驗

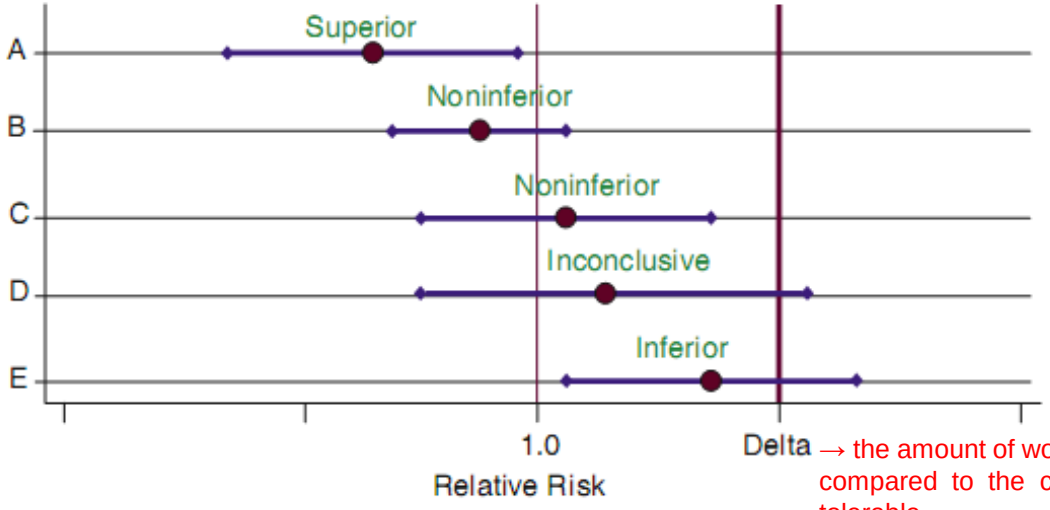
實用性的臨床試驗，應用於大族群的研究：

1. 組間異質性大
2. 研究時間相對會較短
3. 對象族群大，研究的
    a. 介入要簡單，容易實施
    b. 所觀察的outcome，要容易檢測
4. 研究的經費會較高

STUDIES OF EQUIVALENCY AND NONINFERIORITY
不劣勢試驗

- 研究假設：

1. 有適當的控制組
2. 受試者間的一致性不隨時間改變
3. 實驗前的資料是可以獲得的
4. 需評估敏感性，確認差異的真實性



→ the amount of worse effect of the intervention compared to the control that was chosen as tolerable.

Fig. 5.5 Possible results of noninferiority trials; modified from [132]

ADAPTIVE DESIGNS 適應性設計

- 一個理想的研究設計，在不同階段的臨床試驗有所不同：
  - 藉由第一期試驗不斷的修正得到適當的劑量，後期試驗再修正並評估成效。
  - 有適當的樣本數。
- 若介入結果不如預期或有其他安全性的考量，則研究可以提早終止或修改內容等。
  - Various designs (response adaptive)、trend adaptive designs、Group sequential designs…