Una breve discussione degli studi sperimentali randomizzati e controllati

FS

Studi sperimentali

- Sono caratterizzati dalla somministrazione attiva di un intervento da parte dello sperimentatore
- Lo studio può riguardare: a. le sole unità sperimentali trattate
- b. prevedere un confronto tra trattati e non trattati: b1 assegnazione del trattamento decisa dallo sperimentatore b2 assegnazione casuale

Studi sperimentali controllati randomizzati (randomized controlled trial RCT)

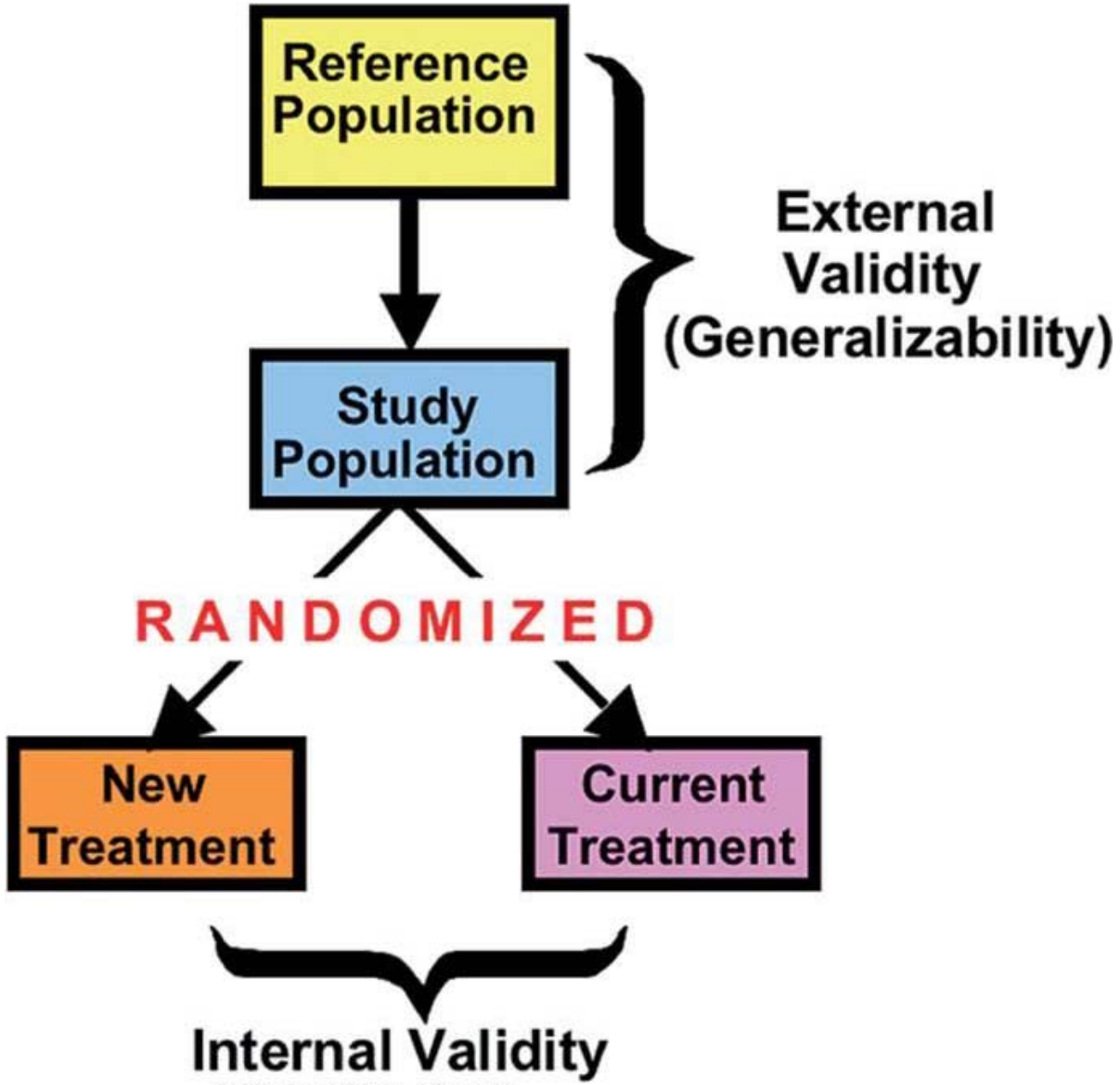
- Lo studio con assegnazione casuale delle unità sperimentali a due (trattato verso non trattato o trattamento A verso trattamento B) o più gruppi è il disegno in grado di fornire le evidenze scientifiche più solide
- È un disegno prospettico
- Quando possibile al gruppo di controllo si somministra un falso trattamento che differisce dal vero per la sola assenza del principio attivo detto placebo

Protocollo dello studio

1. Base scientifica o razionale
2. Obiettivo
    1. Primario
    2. Eventuali obiettivi secondari
3. Disegno dello studio
4. Selezione delle unità sperimentali
    1. Criteri di inclusione
    2. Criteri di esclusione
5. Definizione operativa dell'intervento

Protocollo dello studio

6. Misurazioni – variabili che vengono misurate nel corso dello studio inclusi
    1. Eventi o end-point dello studio (semplice o composto)
    2. Eventi avversi
7. Documentazione (cartelle cliniche, questionari, modelli di segnalazione)
8. Procedure (modalità di misurazione delle variabili)
9. Uscita dallo studio
10. Consenso informato
11. Piano di analisi statistica



Gordis: Epidemiology, 4th Edition.

The Design of Randomized Clinical Trials in Critically Ill Patients*

Chest. 2002;121(4):1290-1300. doi:10.1378/chest.121.4.1290

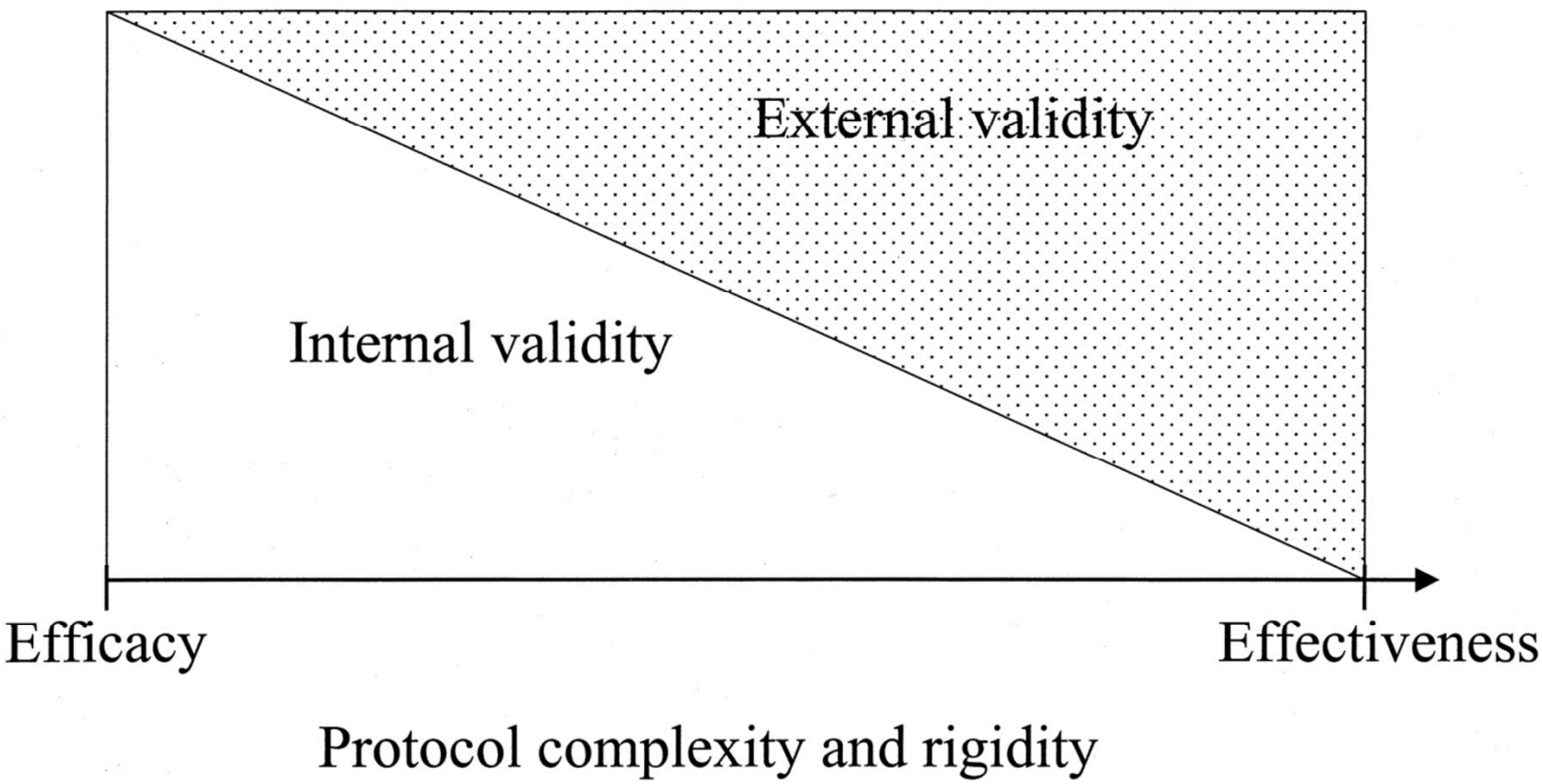


Figure Legend:

Implication of design approaches on internal and external validity.

Assegnazione casuale ai gruppi

- È probabile che i gruppi formati mediante allocazione casuale risultino simili in termini di frequenza di comparsa dell'end-point dello studio in assenza di intervento
- Fattori che condizionano la probabilità di sviluppare l'evento tendono a distribuirsi in modo omogeneo tra i gruppi; questo vale sia per fattori noti sia per fattori non noti

Assegnazione casuale ai gruppi 2

- È tuttavia possibile che i gruppi formati risultino sbilanciati
- Il bilanciamento dei gruppi può essere controllato per i fattori noti registrati
- Tanto maggiore è la dimensione dello studio e tanto meno risultano probabili squilibri rilevanti tra i gruppi

Analisi per assegnazione

- L'analisi viene effettuata in base all'appartenenza ai gruppi e non alla effettiva somministrazione dell'intervento (analisi per intenzione di trattamento, *intention to treat*)
- Questo da un lato può riflettere l'accettabilità dell'intervento e la presenza di effetti collaterali (tollerabilità) ma certo conduce ad una sottostima dell'eventuale efficacia dell'intervento
- L'analisi per trattamento, d'altronde, inficerebbe la randomizzazione, rendendo possibili differenze sistematiche tra i gruppi

Esecuzione in cieco

- L’esecuzione dello studio nell’ignoranza del trattamento somministrato ai gruppi evita possibili distorsioni (effetto placebo, distorsione legata all’osservatore)

- Numero di ciechi:
- Singolo: unità sperimentali ignorano trattamento
- Doppio: sperimentatore ignora il trattamento
- Triplo: analista ignora trattamento

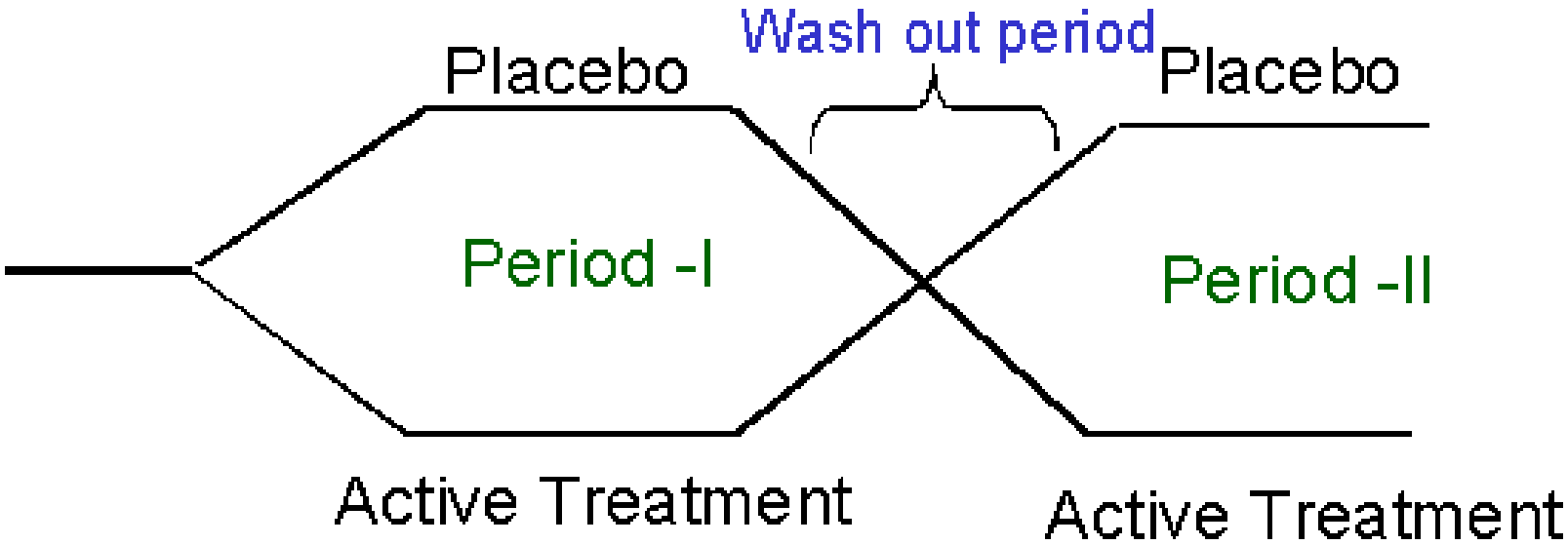
Disegni

Gruppi paralleli

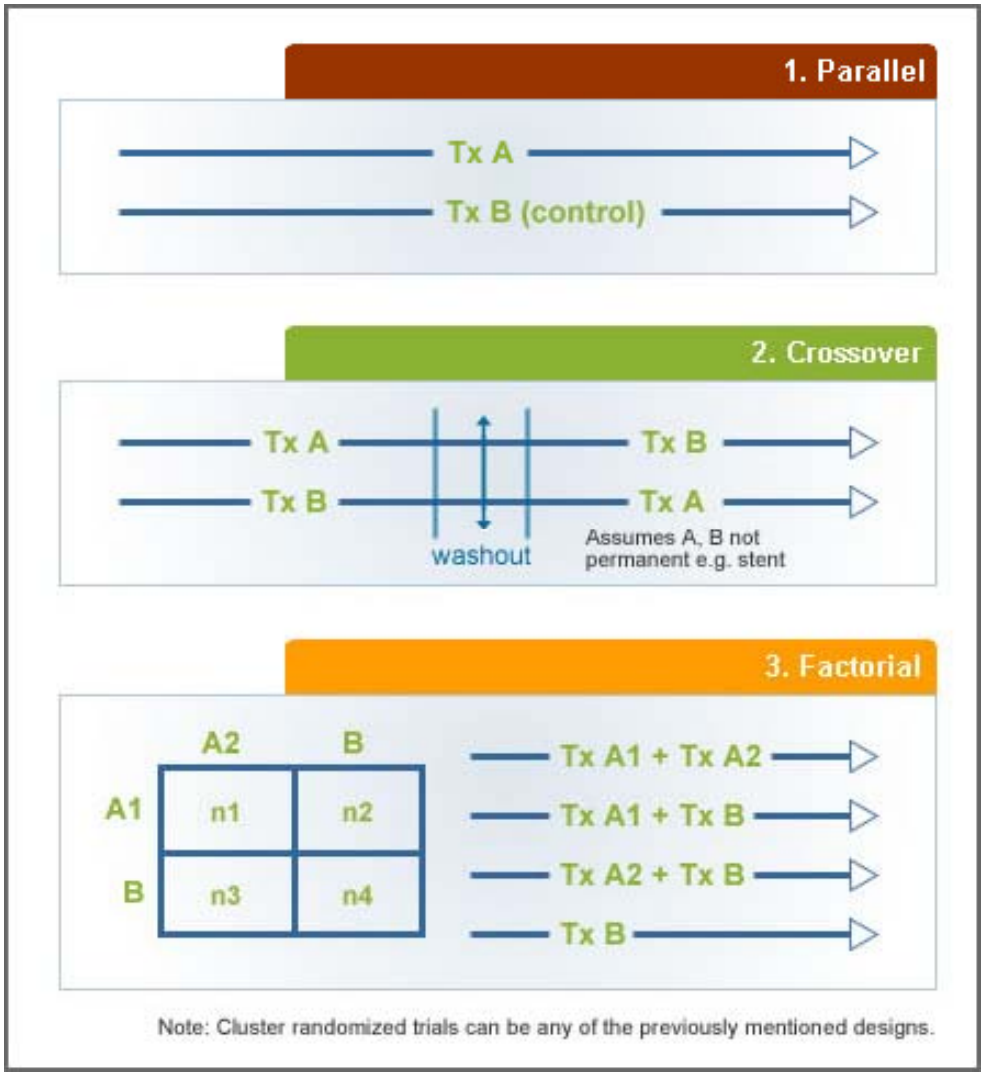
- Ciascun gruppo di solito di eguale numerosità riceve un diverso intervento e la comparsa di eventi viene messa a confronto

Studio incrociato (Cross-over)

- Ogni soggetto riceve i diversi trattamenti in tempi differenti; questo disegno consente di valutare l'effetto del periodo e la variabilità entro e tra soggetti
- *(il disegno cross-over può essere adottato per condizioni durature che richiedono trattamenti cronici)*
- *Effetto trascinamento (carry-over): l'influsso di un intervento può protrarsi nel tempo riducendo la differenza apparente tra i trattamenti; possibile periodo di depurazione (wash out) per evitare carry over effect.*
- Disegno sequenziale ed analisi intermedie (interim)



Crossover design



Cluster randomized trials are performed when larger groups (e.g., patients of a single practitioner or hospital) are randomized instead of individual patients - Cluster trials can be any of the previously mentioned designs.

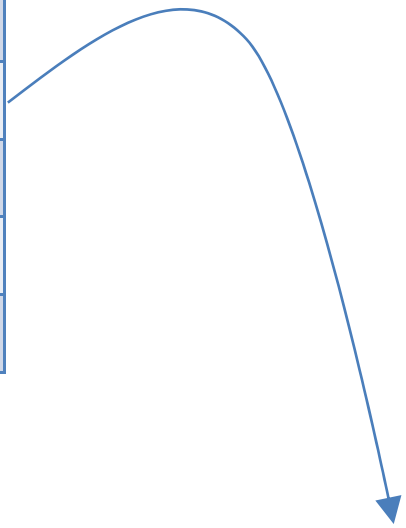
Randomizzazione

- Completa
  - Assegnazione casuale di ogni soggetto (n_A può differire da n_B)
  - *Esempio* ***A, A, B, A, B, A, A, B, B, A***
- Alternata
  - Assegnazione casuale del primo incluso
  - Esempio ***B****, A, B, A, B, A …*
- Blocchi

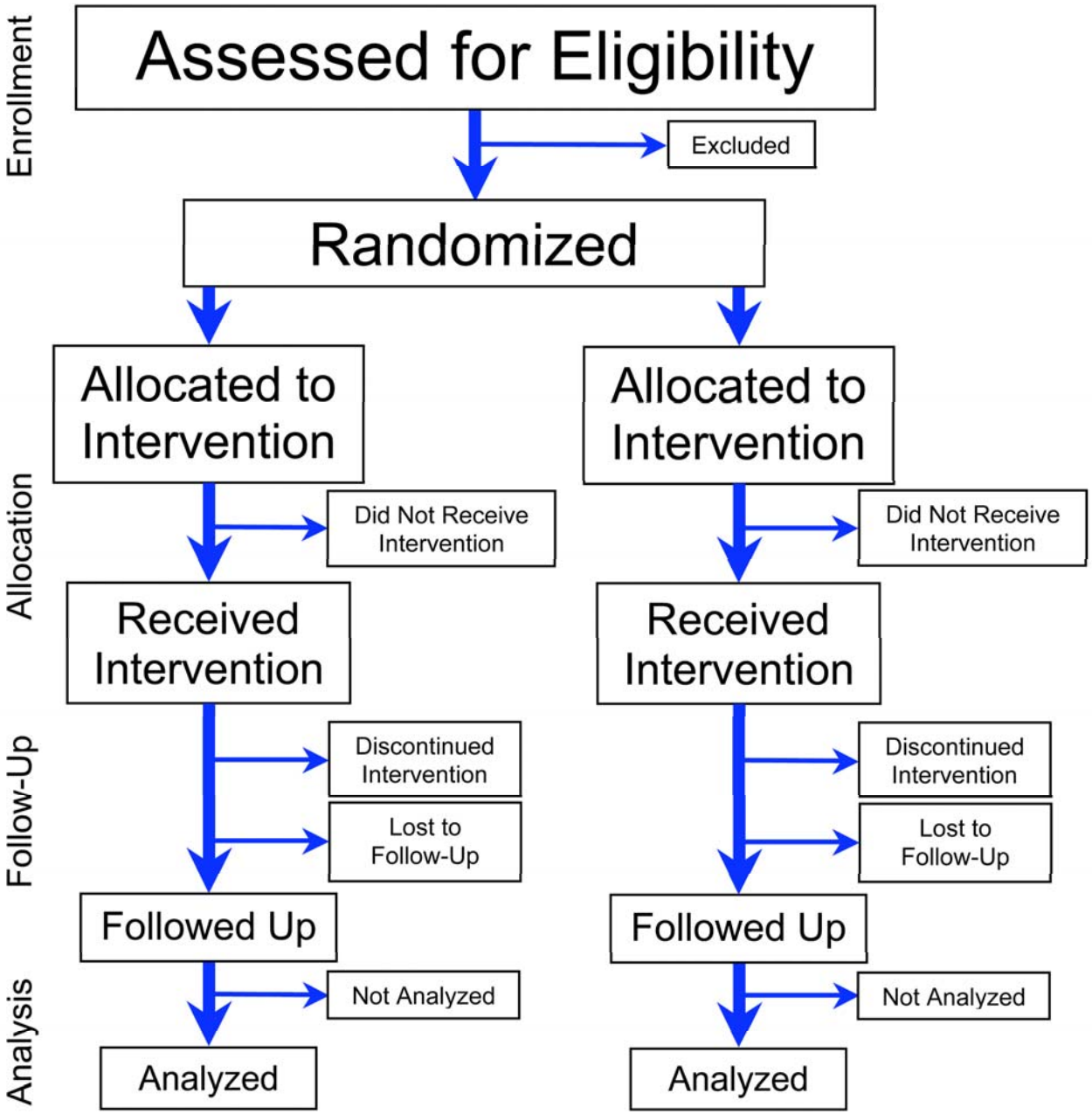
- Semplice
- Stratificata (assegnazione casuale all'interno di strati di variabili in grado di influire sul rischio di sviluppare l'evento)
- A grappolo (cluster)

Possibili blocchi (n=4)

1.	A	A	B	B
2.	A	B	A	B
3.	A	B	B	A
4.	B	A	A	B
5.	B	A	B	A
6.	B	B	A	A

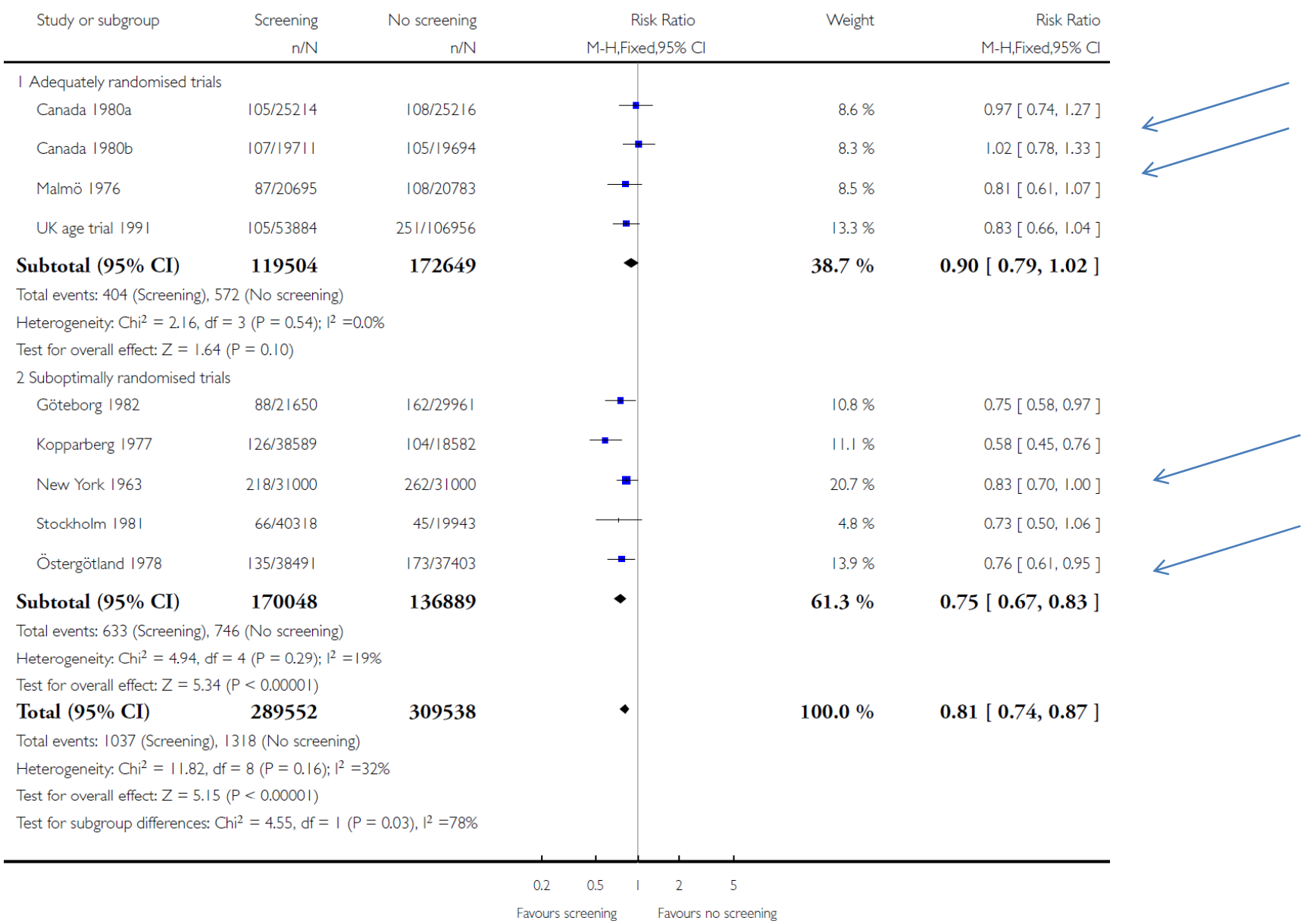


Selezione casuale dei blocchi
6, 3, 1, 2, 6, …


Enrollment
Assessed for Eligibility
Excluded
Randomized
Allocation
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Follow-Up
Discontinued Intervention
Lost to Follow-Up
Followed Up
Analysis
Not Analyzed
Analyzed
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Discontinued Intervention
Lost to Follow-Up
Followed Up
Not Analyzed
Analyzed

I trial per la valutazione dello screening mammografico

- eight eligible trials (Canada 1980; Edinburgh 1978; Göteborg 1982;Malmö 1976; New York 1963; Stockholm 1981; Two-County 1977; UK age trial 1991)
- An additional trial in the UK…This is an age extension cluster
- randomised trial, recruiting women aged 47-49 or 71-73 years old, and aiming for a sample size of 3 million women. It started in 2010 and is expected to run till the end of 2026
- The Canadian trial was the only one in which the women were individually randomised after invitation and gave informed consent;
- the others used a variety of procedures based on a prespecified segment of the female population that was randomised to invitation for screening or to a control group



Comparison 1 Screening with mammography versus no screening, Outcome 2 Deaths ascribed to breast cancer, 13 years follow up

The New York trial (New York 1963**)**

- women who were members of an insurance plan and aged 40 to 64 years

Randomisation

- an individual randomisation within pairs matched by age, family size and employment group (Shapiro 1985)…The largest published exact number of women invited is 31,092 (Fink 1972)

Likelihood of selection bias

- We classified the trial as suboptimally randomised

New York 2

Comparability of groups

- Postrandomisation exclusions of women with previous breast cancer occurred but this status "was most completely ascertained for screened women," whereas women in the control group "were identified through other sources as having had breast cancer diagnosed before their entry dates" (Shapiro 1988).
- …853 women were excluded from the screened group because of previous breast cancer compared with only 336 in the control group…*
- This creates a bias in favour of screening for all-cause mortality and likely also for breast cancer mortality though the authors have written, without providing data, that ascertainment of cases of previous breast cancer was "nearly perfect" in those women who died from breast cancer (Shapiro 1988)

Assignment of cause of death

- We found no data on the autopsy rate. Assignment of cause of death was unblinded for 72% of the women with breast cancer (Shapiro 1988)**.
- In the New York trial, differential misclassification might be responsible for about half of the reported breast cancer mortality benefit

The Two-County trial (Kopparberg 1977; Two-County 1977; Östergötland 1978)

Population studied

- This trial recruited women 40 years of age and over in Kopparberg and Östergötland; the two subtrials were age-matched and cluster randomised (21 and 24 clusters, respectively).
- The selection of clusters was stratified to ensure an even distribution between the two groups with respect to residency (urban or rural), socioeconomic factors and size (Kopparberg 1977; Tabar 1979; Östergötland 1978).
- The randomisation process and the definition of the date of entry have been inconsistently described;
- It is not clear how many women were randomised and reported numbers vary considerably, both for numbers randomised (Table 1) and for numbers of breast cancer deaths, despite similar follow up (Gøtzsche 2004).

Two-County trial 2

- …assessment of cause of death is susceptible to bias. The authors of the Two-County trial assessed cause of death openly and reported a 24% reduction in breast cancer mortality for Östergötland *(E)* (Tabar 2000), whereas
- a meta-analysis of the Swedish trials based on an official cause of death register reported only a 10% reduction for Östergötland (Nyström 2002).
- The trial authors reported 10 fewer deaths from breast cancer in the study group despite slightly longer follow up, and 23 more deaths in the control group.

Two-County trial 3 - Holmberg L, Duffy SW, Yen AM, Tabár L, Vitak B, Nyström L, Frisell J.Differences in endpoints between the Swedish W-E (two county) trial of mammographic screening and the Swedish overview: methodological consequences. J Med Screen. 2009;16:73-80.

- *Method* A Review Committee compared the original data files from W *(=Kopparberg)* and E county *(=Ostergotland)* and the first and second OVC. The reason for a discrepancy was determined individually for all non-concordant cases or breast cancer deaths.
- *Results* Of the 2615 cases included by the W-E Trial or the OVC, there were 478 (18%) disagreements. Of the disagreements 82% were due to inclusion/exclusion criteria, and 18% to disagreement with respect to cause of death or vital status at ascertainment. For E-County, the OVC inclusion rules and register based determination of cause of death (second OVC) rather than individual case review (W-E Trial and 1st OVC) resulted in a reduction of the estimate of the effect of screening, but for W-County the difference between the original trial and the OVC was modest

Two-County trial 3

- But it is not convincing (Holmberg 2009).
- There was no blinding; it was not an independent audit

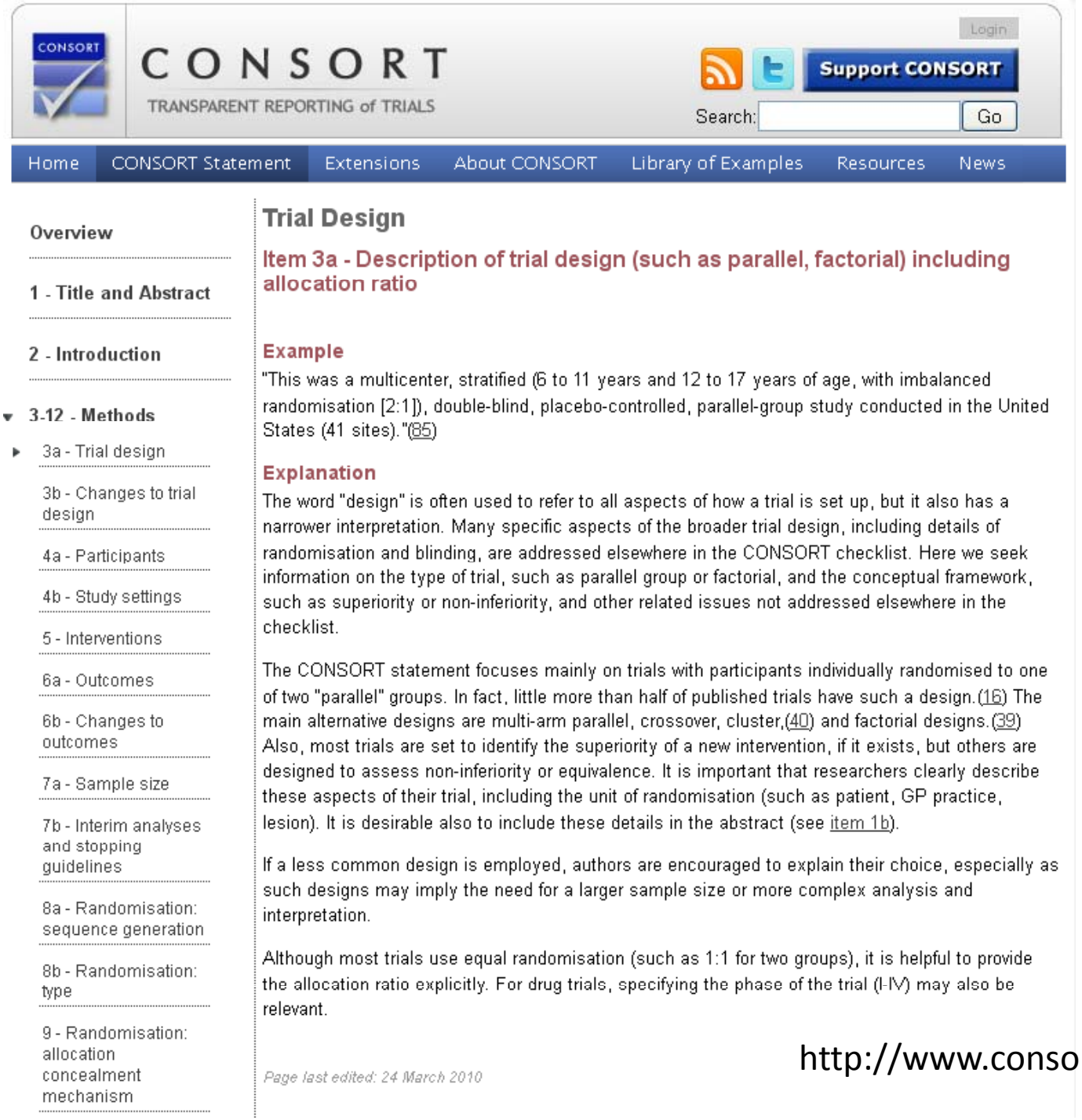
Risk of bias

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	High risk	See text, information inconsistent and incomplete.

A generated allocation schedule should be implemented by using **allocation concealment**,(23) a critical mechanism that **prevents foreknowledge of treatment assignment** and thus shields those who enroll participants from being influenced by this knowledge. **The decision to accept or reject a participant should be made**, and informed consent should be obtained from the participant**, in ignorance of the next assignment in the sequence**.

Ignoranza dello schema di assegnazione del trattamento

- allocation concealment refers to **preventing the next assignment in the clinical trial from being known**
- If the referring health care provider is aware of the next allocation, he/she may (even unknowingly) influence enrollment or selection of participating subjects.
- The allocation concealment should not be confused with blinding. **Allocation concealment seeks to prevent selection bias**, protects the assignment sequence until allocation, and can always be successfully implemented. In contrast, blinding seeks to prevent performance and ascertainment bias, protects the sequence after allocation, and cannot always be implemented.
- **Trials in which the allocation sequence had been inadequately or unclearly concealed yielded larger estimates of treatment effects** than did trials in which authors reported adequate allocation concealment.



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Overview

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- 6b - Changes to outcomes
- 7a - Sample size
- 7b - Interim analyses and stopping guidelines
- 8a - Randomisation: sequence generation
- 8b - Randomisation: type
- 9 - Randomisation: allocation concealment mechanism

Trial Design

Item 3a - Description of trial design (such as parallel, factorial) including allocation ratio

Example

"This was a multicenter, stratified (6 to 11 years and 12 to 17 years of age, with imbalanced randomisation [2:1]), double-blind, placebo-controlled, parallel-group study conducted in the United States (41 sites)."(85)

Explanation

The word "design" is often used to refer to all aspects of how a trial is set up, but it also has a narrower interpretation. Many specific aspects of the broader trial design, including details of randomisation and blinding, are addressed elsewhere in the CONSORT checklist. Here we seek information on the type of trial, such as parallel group or factorial, and the conceptual framework, such as superiority or non-inferiority, and other related issues not addressed elsewhere in the checklist.

The CONSORT statement focuses mainly on trials with participants individually randomised to one of two "parallel" groups. In fact, little more than half of published trials have such a design.(16) The main alternative designs are multi-arm parallel, crossover, cluster,(40) and factorial designs.(39) Also, most trials are set to identify the superiority of a new intervention, if it exists, but others are designed to assess non-inferiority or equivalence. It is important that researchers clearly describe these aspects of their trial, including the unit of randomisation (such as patient, GP practice, lesion). It is desirable also to include these details in the abstract (see item 1b).

If a less common design is employed, authors are encouraged to explain their choice, especially as such designs may imply the need for a larger sample size or more complex analysis and interpretation.

Although most trials use equal randomisation (such as 1:1 for two groups), it is helpful to provide the allocation ratio explicitly. For drug trials, specifying the phase of the trial (I-IV) may also be relevant.

Page last edited: 24 March 2010

http://www.consort-statement.org/home/

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers of women, cancers and deaths vary in the reports of the trial
Selective reporting (reporting bias)	High risk	Numbers of women, cancers and deaths vary in the reports of the trial
Other bias	High risk	Numbers of women, cancers and deaths vary in the reports of the trial, see also main text

The Canadian trial (Canada 1980; Canada 1980a; Canada 1980b)

Canada 1980

Methods	Individual randomisation in blocks of 2 or 4, stratified by centre and 5-year age group (see also text) Cause of death was assessed blinded and independently by two specialists for women with diagnosed breast cancer and for other possible breast cancer deaths
Participants	Women aged 40-59 years. Number randomised: see below.
Interventions	Two-view mammography: cranio-caudal and mediolateral (later medio-lateral oblique except in two centres) 4-5 cycles of screening with yearly interval.
Outcomes	Total mortality. Breast cancer mortality. Surgical interventions.
Notes	Attendance rate: 100% in first round.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization with two block sizes (equalled out the allocations only after every 48 entries; Baines, personal information, June 2011)
Allocation concealment (selection bias)	Low risk	Adequate, see text.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible for a screening trial and not relevant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cause of death was assessed blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few women excluded after randomisation (see text) and none because of previous breast cancer
Selective reporting (reporting bias)	Low risk	This trial has been meticulously reported and documented.

Attrito (bias di selezione)

- or the **loss of eligible participants /**loss of study participants**/**
- Attrition may compromise internal validity by **altering the random composition of groups and their equivalence**
- External validity may be compromised due to the potential for attrition to limit **the generalizability of results to only those who are retained in a study**. For instance, those participants retained in a study may be more persistent or more adherent, or have other characteristics that differ from those who drop-out.
- Attrition may also compromise statistical validity by **reducing sample size and power** or by systematically altering the variability within samples