

Non-Inferiority Trials in Stroke Research: What Are They, and How Should We Interpret Them?

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Review

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COMMENTATOR

Scheme of presentation

- Types of clinical trials
- Hypothesis and type of errors for different clinical trials
- Setting of non- inferiority margin
- Interpretation of non-inferiority trial results
- Challenges to consider in interpretation

Types of trial

- **Superiority trial** - a new treatment or intervention is superior to an existing standard treatment or placebo
 - Investigator choose the expected difference between two comparison group
 - Accepted type 1 error rate
 - Power to decide the sample size

Types of trial

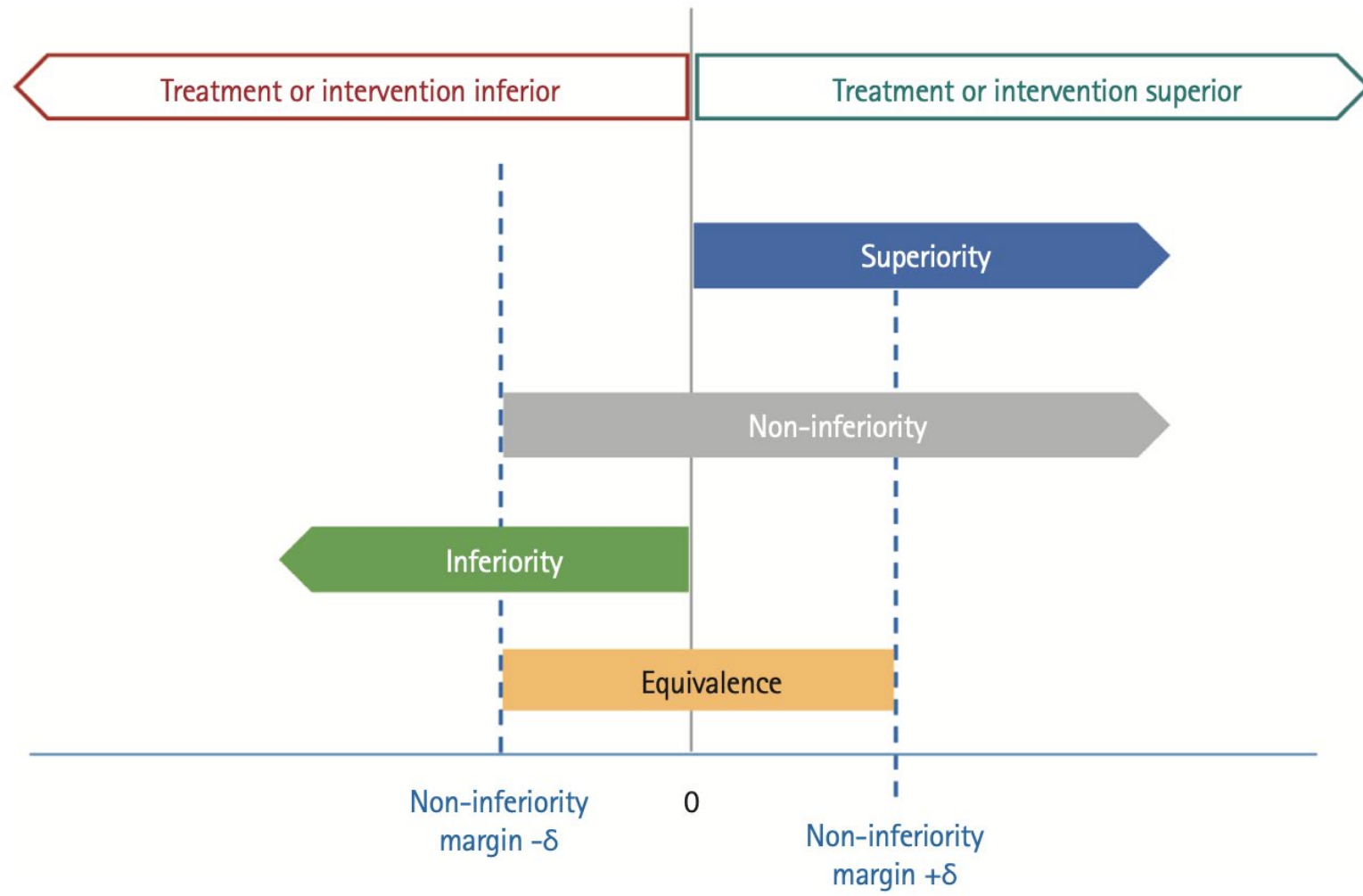
- **Equivalence trial** – two treatments have similar effectiveness within predefined margin of difference
 - Equivalence in terms of clinical outcomes
 - Two sided 90%CI is typically used in this trial ($-\delta, +\delta$)
 - Sample size is usually much larger than superiority and non inferiority trials

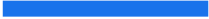
Types of trial

- **Non- Inferiority trial** – new treatment is not inferior to the comparison group
 - Not acceptably worse than the established treatment by predefined margin
 - Lower boundary of 95% CI should be above δ
 - Difference from equivalence is that only one side of the confidence interval matter

The hypothesis and the types of errors in statistics for the different clinical trial concepts

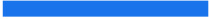
Trial concept	Null hypothesis	Alternative hypotheis	Type_1 error (False positive)	Type-II error (False negative)
Superiority	New treatment is not better than SoC or placebo	New treatment is better than SoC or placebo	Concluding superiority without superiority	Non concluding superiority
Equivalence	New intervention is either superior or inferior to SoC	New intervention is equivalent to SoC	Concluding new treatment is equivalent	Concluding new treatment is not equivalent
Non-inferiorty	New treatment is worse than the SoC by more than a pre-specified margin	New treatment is not worse to the SoC within the non-inferiority margin	Concluding new treatment is not inferior	Concluding inferiority for a new treatment





Why do we need non-inferiority trials

- Ethically inappropriate to include a control arm
- New treatments or interventions that might not be expected to be more effective than an existing approach
- But may have some other advantages,
 - Such as greater availability
 - Reduced cost
 - Better safety profile, or easier administration.
- Allow the introduction of new treatments for conditions with effective but suboptimal existing therapies

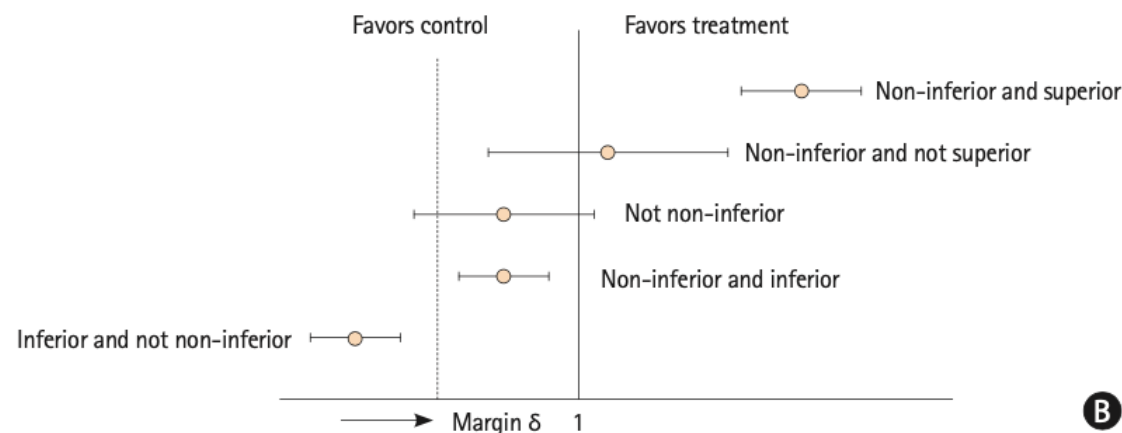
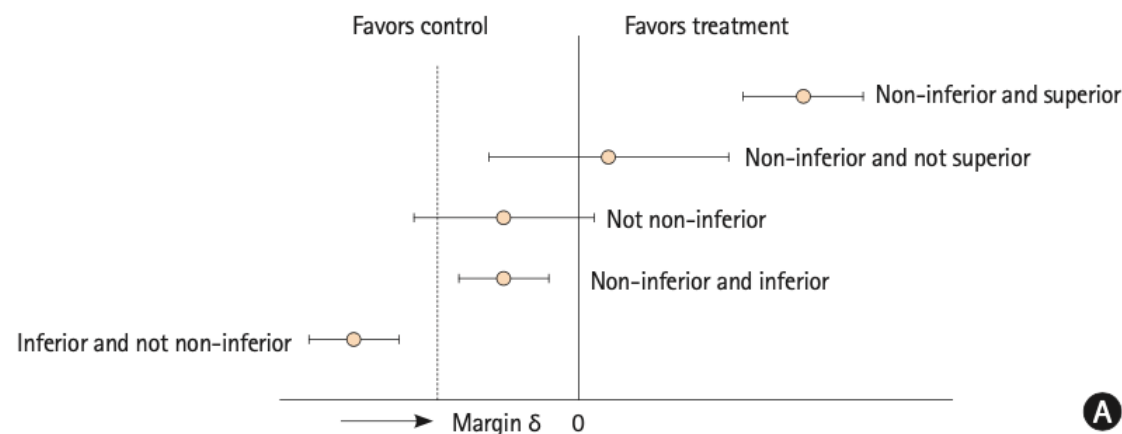


What is the non-inferiority margin δ ?

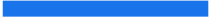
- Represents the minimal clinically and/or statistically acceptable difference in efficacy between the new treatment and the active control where the new treatment would be considered as “not unacceptably worse” or “non-inferior.”
- Non-inferiority margin δ and can be chosen as an absolute risk difference or relative risk difference (risk ratio).
- Established active control from RCTs
- Thus serving as a solid benchmark against which new treatments can be compared by non-inferiority analysis.
- The selection of δ should be based upon a combination of statistical reasoning and clinical judgment as suggested by international guidelines.

Interpretation non-inferiority trial results

Possible scenarios to interpret the findings of a non-inferiority trial. (A) Absolute difference. (B) Relative risk.

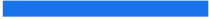


Name of trial	Patients	Intervention comparision	Outcome	Inferior margin (δ)	Results	Remarks
ARISTOTLE	Atrial fibrillation	Apixanvan vs warfarin	Stroke prevention	RR < 1.38	RR 0.79 (0.66-0.95)	Non-inferior and superiority
TRACE-2	Acute ischaemic cerbrovascular events	Tenecteplase vs Alteplase	mRS score of 0-1 at 90 days	RR < 0.937	RR 1.07(0.98-1.16)	Non inferior and non not superior
-	Atrial fibrillation	Idraparinux vs oral Vit K agonist	Stroke	HR- 1.5	HR 0.71(0.39-1.30)	Non-inferior and inferior
INSURE	Acute ischaemic stroke	Indobufen vs aspirin	New stroke	HR- 1.25 (upper limit 95% CI)	HR 1.23 (1.01-1.5)	Not non-inferior and inferior
SoSTART	Atrial fibrillation with spontaneous itracarnial hge	Oral anticoagulant vs SOC	Recurrent hemorrhage	HR< 3.2 (upper limit 95% CI)	HR 2.42 (0.72-8.09)	Inconclusive



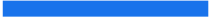
Challenges to consider interpreting non-inferiority trials

- Absolute or relative risk difference
 - Constancy assumption is difficult to assess
 - Baseline event or rate is expected to vary between studies or population
 - RRD approach to account the changes
 - If absolute risk difference is used in original trial both approach can be used to conclude
- Quality of trial conduct
 - Important in RCTs
 - Poor adherence, loss to follow up or treatment cross over less likely to show difference in superiority trial
 - In non inferiority trial make the two groups similar, false positive results will be concluded



Challenges to consider interpreting non-inferiority trials

- Choices of analytic approach
 - ITT is recommended by guidelines in superiority trials
 - Can be resulted in false positive results
 - Per-protocol analysis might be helpful
 - Both IIT as a primary approach and per-protocol analysis as sensitivity analysis
- Power deflation
 - Statistical power of decreases if new treatment perform unexpectedly better



Challenges to consider interpreting non-inferiority trials

- Evolution of standard of care
 - Drug A after superiority becomes the SOC
 - Drug B compare to drug A in non inferiority prove to be non- inferior with cost advantage
 - Drug C compare to drug B as SOC in non inferiority design with δ may further worsening compare to drug B to drug A
 - Comparing with drug D may not be ethical



thank
you