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Inserm
La science pour la santé
From science to health

Non-inferiority trials and switch from non-inferiority to superiority

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Disclosures

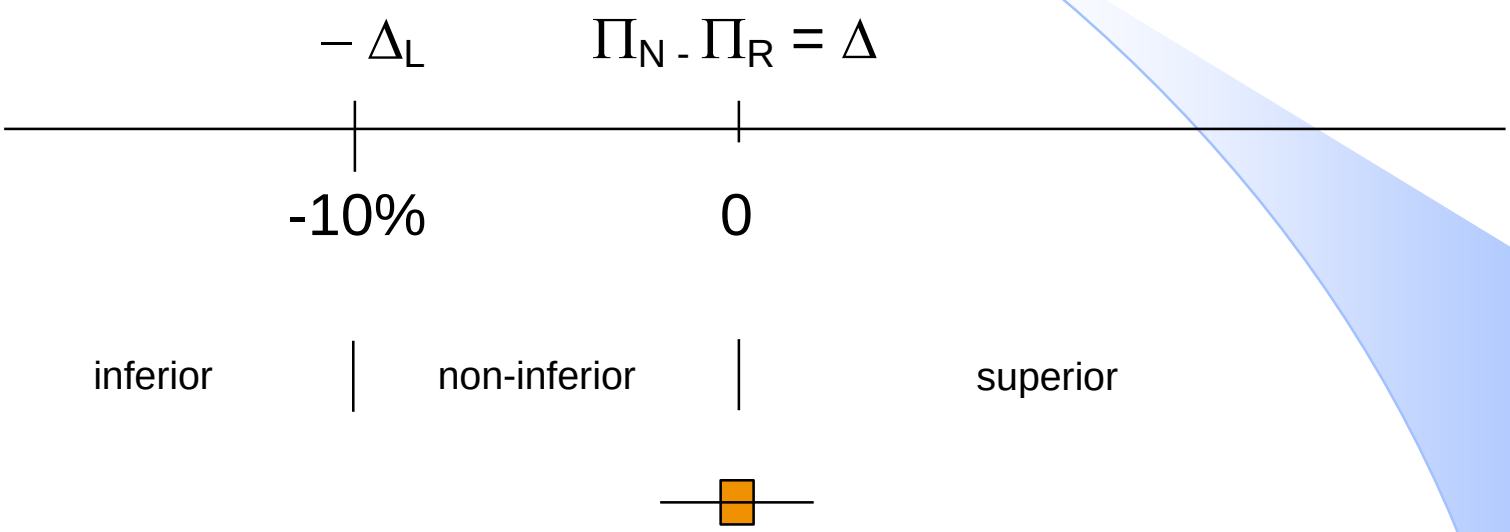
- I have received consultancy fees, honoraria, and my team study grants from:
  - Consultancy Innavirvax (2016), Merck Switzerland (2017)
  - Lectures Janssen (2016, 2018), MSD (2017), Gilead (2018)
  - Grants from Janssen (2017-2018, 2019-2021), MSD (2017)

Clinical trial objectives

- Trials comparing a new treatment (or a strategy) to a reference treatment
  - Showing the superiority of the new treatment
    - Is N better than R ?
      - Pre-treated patients with treatment failure
  - Showing the non-inferiority of the new treatment
    - Is N doing not worse than R ?
      - Naive patients
      - Switch studies
  - Showing the equivalence of the new treatment
    - Is N doing as well as (neither better not worse) R ?
      - Bio-equivalence (different formulation of the same drug)

Definition of non-inferiority

- N is not doing worse than R



Choice of the non-inferiority limit - 1

- Clinical decision, not statistical
- The largest difference clinically acceptable
- < = difference used in superiority trials of the same domain
- To warrant that the new product is doing better than placebo in trials with no placebo

A working case in diabetes: HbA1c the risk of death - 1

- In diabetes, for new drugs the most common endpoint is HbA1C
  - Non inferiority margin usually taken as 0.6 %
  - Superiority trials usually try to demonstrate a 1% difference

A working case in diabetes: HbA1c the risk of death - 2

- Each 1% reduction in updated mean HbA1c was associated with reductions in risk of
  - 21% for any end point related to diabetes (95% confidence interval 17% to 24%),
  - 21% for deaths related to diabetes (15% to 27%),
  - 14% for myocardial infarction (8% to 21%), and
  - 37% for microvascular complications (33% to 41%).
  - No threshold of risk was observed for any end point.

Stratton IM et al. UKPDS 35. BMJ 2000;321:405-412

A working case in diabetes: HbA1c the risk of death - 3

- Is it possible to define a non-inferiority limit clinically acceptable in this context?

Choice of the non-inferiority limit - 2

- As defining a non-inferiority limit implies to accept some loss
  - There must be some advantage to use the new product
    - easyness
    - safety
    - costs
    - …

Choice of the non-inferiority limit - 3

- FDA recommendations in HIV
  - 4% in switch studies
  - 10% in naive studies

Other issues

- Internal validity
  - Limited
    - protocol deviation,
    - lack of adherence,
    - lost to follow-up,
    - and missing data
  - Because they biased the result towards no difference
- External validity
  - **Choice of the reference treatment**
    - Known efficacy
    - Placebo group when possible
  - Study population
    - Same as the one in which the reference treatment was shown efficacious
  - Endpoint(s)
    - Same as the one(s) used to show the reference treatment efficacy
  - Expected efficacy from the reference treatment observed in the current trial

Sample size

Table 2. Sample sizes per arm for noninferiority trials, by power, delta and expected response rate in the control arm; the efficacy of the new drug is assumed to be equivalent for the purposes of calculating sample sizes.

Expected response rate in control arm	Delta 12% 80% power	90% power	Delta 10% 80% power	90% power
50%	273	365	393	526
55%	270	362	389	521
60%	262	351	377	505
65%	249	333	358	479
70%	229	307	330	442
75%	205	274	295	395
80%	175	234	252	[illegible]
85%	139	187	201	268
90%	99	132	142	190

Hill A AIDS 2008;22:913-921

Analysis plan

- Results
  - Confidence intervals of the difference
  - More rarely a p-value
- Both ITT and per protocol analyses should be conducted and give the same results
  - As ITT analysis is no longer conservative
- Analysis of compliance to treatment and protocol deviation (+++)

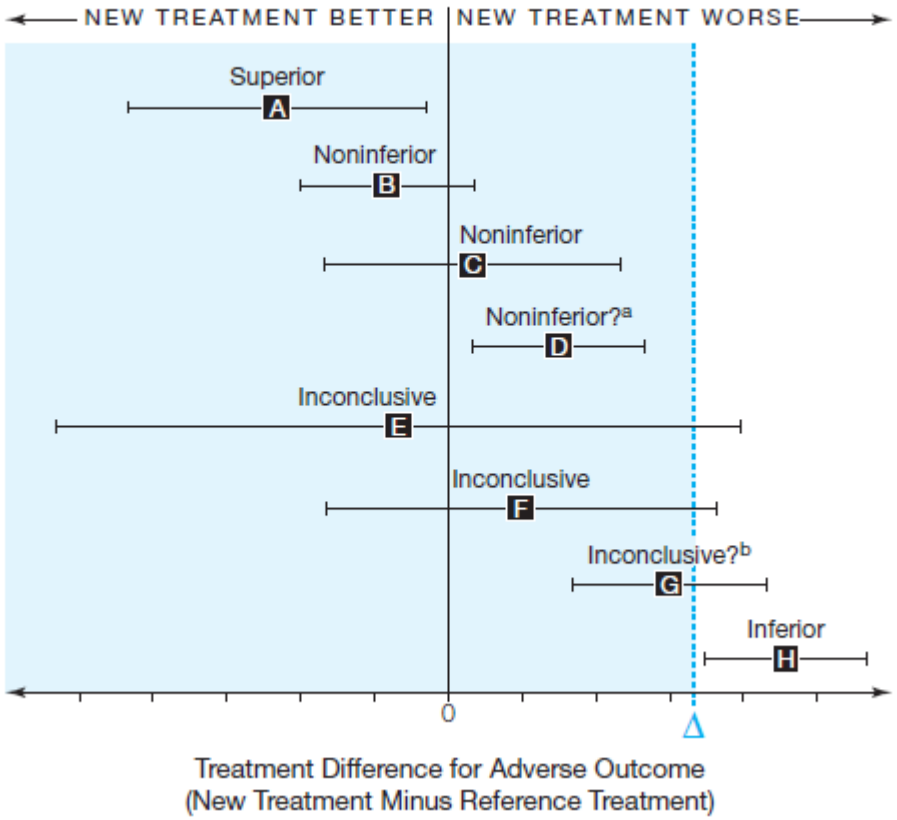
The conclusion is based on

- The lower limit of the confidence interval of the estimated difference compared with the non inferiority limit Δ_L

Reporting of Noninferiority and Equivalence Randomized Trials

Extension of the CONSORT 2010 Statement

Figure 1. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



Interpreting a non-inferiority trial as a superiority trial

- No majors issues, but is the difference of clinical significance ?
  - Depending on
    - The reference treatment
    - The power
    - The effect size
    - The analysed population
    - The trial quality
  - The p value for the superiority test is derived from the ITT analysis

Conclusion

- If one accepts a loss of chance, what is the expected gain?
- The choice of the non-inferiority limit is critical
  - It is a clinical, not a statistical decision
  - Should warrant that the new product is better than placebo
  - Typically 4-10% in the recent trials or recommendations in HIV
- The ITT analysis is no longer the main analysis
  - Both ITT and per protocol are important
  - The difference in the number of patients included in each analysis is an indicator of the study quality
- No major issues in switching from non-inferiority to superiority
  - However, is the difference clinically relevant?