Statistical Design and Analysis of a Non-Inferiority Clinical Trial

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Background

Non-inferiority (NI) trials are increasingly used in clinical research, particularly when placebo control is unethical. Despite their widespread adoption, NI trials are frequently misdesigned and misinterpreted, often due to poorly justified margins, inappropriate control selection and misunderstanding of statistical conclusions. This combination of issues may lead to misleading evidence with consequences for clinicians, regulators and the wider public.

What is a Non-inferiority Trial?

A non-inferiority trial aims to demonstrate that a new treatment is not unacceptably worse than an active control by more than a pre-specified margin (Δ). NI is concluded if the estimated treatment effect and its confidence interval lie entirely within this margin.

The NI margin must be justified on both clinical and statistical grounds, preserving a clinically meaningful proportion of the control treatment's established effect.

Aims & Objectives

1. To define and justify an NI margin for the case study using historical and published evidence.
2. To develop statistically appropriate NI trial design parameters from a bio statistical perspective.
3. Develop a Shiny app to determine and visualize different sample size requirements under varying design assumptions and inferiority margins.
4. To analyse and interpret simulated trial data and evaluate NI conclusions.
5. To critically reflect on the limitations and assumptions inherent to NI designs.

Case-study: Biomimics 3D stent

We will use a simulated 2008 clinical and regulatory setting to examine the statistical design of a pivotal NI trial for the BioMimics 3D vascular stent. The case study is based on the original development of the device, led by Kevin Heraty, lead scientist on BioMimics 3D.

The BioMimics 3D stent is a peripheral vascular stent implanted in the leg or arm to improve blood flow in patients with peripheral vascular disease (narrowing of the the peripheral blood vessels). Unlike conventional straight stents, it features a three-dimensional helical design, intended to improve vascular performance and blood flow patterns in the affected areas.

To reflect a real-world trial planning scenario, we meet with Kevin Heraty to discuss key statistical decisions, including endpoint selection, performance goals, and sample size requirements. This ensures the statistical design is informed by clinical and device-specific considerations.

The BioMimics 3D stent is treated as the investigational device in a hypothetical NI trial, with established peripheral stents used as the active control. Evidence available from up till 2008 is used to guide the design, and simulated trial data will be used to assess non-inferiority conclusions and highlight common sources of misinterpretation.

Meta-Analysis & Evidence base

Evidence-Based Safety Performance Goals (30 Days)

Endpoint	Pooled Estimate	95% CI	Recommended Performance Goal	Justifiable Range
Amputation	0	[0.0000, 1.0000]	1%	0-1%
Death	0	[0.0000, 1.0000]	1%	0-1%
Target Vessel Revascularisation (TVR)	0.0517	[0.0234, 0.1104]	11%	2-11%

Evidence-Based Efficacy Performance Goals (12 Months)

Endpoint	Outcome Category	Pooled Estimate	95% CI	Recommended Performance Goal	Justifiable Range
Rutherford Classification Change	Improved or No Change	0.9583	[0.8786, 0.9865]	87%	87–99%
Rutherford Classification Change	Increase by One Class	0.0441	[0.0143, 0.1280]	1%	1–13%

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Margin-Jinn

Margin-Jinn is an interactive Shiny application we developed as a part of this project in order to support statistical planning for NI trials. The app supports visual exploration of sample size requirements across different assumptions, highlighting the sensitivity of NI designs to choices that are often fixed or under-examined during trial planning.

In this study, Margin-Jinn is applied to the BioMimics 3D case study to justify and critically assess sample size decisions under realistic design scenarios.

WIP LOGO

GitHub: https://github.com/FilipMKgit/Margin-Jinn

Next Steps

- Extend the BioMimics 3D case-study through simulation of non-inferiority trial data.
- Analyse simulated trial outcomes to assess NI conclusions.
- Further explore the assumptions, limitations, and interpretational caveats inherent to NI trials.

References

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