Inferiority Complex: Challenges in Clinical Equivalence and Non-Inferiority Trials in Health Technology Assessment

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INTRODUCTION

In many cases, it is desirable to demonstrate that new health technologies are superior to existing technologies via a superiority clinical trial. However, a new technology may still be accepted if it is equally as effective as an existing technology (e.g. if it reduces costs or has other benefits). This concept is termed non-inferiority or clinical equivalence and should be demonstrated using specific types of clinical trials.

A non-inferiority clinical trial aims to show that the effectiveness of a new technology is not 'worse' than an existing comparator technology by more than a clinically meaningful amount (the non-inferiority margin). A clinical equivalence trial aims to show that there is an absence of a clinically meaningful difference between two or more technologies.

There is a substantial body of literature discussing the methods employed in non-inferiority and clinical equivalence trials, alongside guidelines published by regulatory and health technology assessment (HTA) bodies. Within existing research, there is considerable variation in definitions and practice, which can make it challenging to robustly demonstrate or assess claims of non-inferiority of clinical equivalence.

This study aimed to evaluate the current body of literature and guidelines and provide actionable recommendations regarding the appraisal of non-inferiority and clinical equivalence claims during HTA.

METHODS

Figure 1: Methods

Pragmatic literature review

Review conducted in May 2024 to how non-inferiority and equivalence studies are being reported. Reviews from 2010 to 2023 were included.

Review of HTA and regulatory body documents

Review conducted in May 2024 to identify guidelines and methods published by HTA/regulatory bodies.

Expert stakeholder panel

A panel with five experts from NICE to identify methodological issues.

Recommendations

The results of the previous 3 stages were synthesis to produce a list of best-practice recommendations for appraising non-inferiority/equivalence during HTA.

The methods for the project are illustrated in Figure 1. During the project, information regarding the non-inferiority margin, confidence intervals, uncertainty, indirect treatment comparisons, economic evaluations, non-adherence, and diagnostics were extracted.

In the second stage of the project, the regulatory bodies that were searched included the UK Medicines and Health products Regulatory Agency (MHRA), the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA). The HTA bodies that were searched included the National Institute for Health and Care Excellence (NICE) in the UK, the Scottish Medicines Consortium (SMC), Haute Autorité de Santé (HAS) in France, the Institute for Quality and Efficiency in Health Care (IQWIG) in Germany, Canada's Drug Agency (CDA-AMC), and the Institute for Clinical and Economic Review (ICER) in the US.

RESULTS

Published guidelines were identified from all regulatory bodies (MHRA, FDA and EMA). There was limited guidance published by HTA bodies, with the exception of HAS in France and IQWIG in Germany.

The guidelines on conducting non-inferiority and clinical equivalence studies could be summarised into two key areas: how non-inferiority margins should be set and how the analysis should be conducted. The majority of guidelines (13/14) discussed, to varying extents, these two key areas. Despite this, the rationale for the margin was not reported in over 50% of 273 blinded randomised controlled trials between 1966 and 2015 [1].

The main methods for determining the non-inferiority margins in clinical trials were to base it on historical evidence of the effectiveness of the active comparator, use expert opinion, use historical margins, or use margins that are stated in specific guidelines.

The panel interviewees reported that evidence of non-inferiority or clinical equivalence presented in NICE Medical Technology Evaluation Programme appraisals (for health technologies) is often of lower quality than in Technology Appraisal appraisals (for pharmaceuticals). It is increasingly concluded that further evidence generation is required.

The results from the reviews and expert panel were synthesised into actionable recommendations for HTA bodies. These are listed in Table 1.

Table 1: Recommendations for appraising claims of non-inferiority and clinical equivalence during HTA

Recommendation 1
The terminology in HTA guidelines requires more precision around non-inferiority and clinical equivalence. The terms **non-inferiority** and **equivalence** should not be used interchangeable.
Recommendation 2
Before looking at non-inferiority evidence, the patient pathway in which the technology will be placed and all aspects of the pathway whether the technology will impact on patient outcomes and costs needs to be determined. Evidence on non-inferiority needs to be provided against all aspects of the patient pathway where the technology could negatively change patient outcomes. Where evidence against any of these aspects suggests that an assessed technology is inferior to existing technology, a conclusion of non-inferiority or equivalence should not be drawn.
Recommendation 3
Assessment of non-inferiority and equivalence should not be based on trial evidence alone; it should first be based upon an assessment of the technological, biological and/or pharmacokinetic reasons to support the assumption that a new technology would not be inferior to the existing comparator. Without this rationale, the reasons for undertaking a non-inferiority trial should be challenged.
Recommendation 4
In circumstances where a non-inferiority or equivalence study is required, a poor-quality and/or under-powered study is likely to lead to inconclusive results or a failure to correctly identify the new technology is inferior to an existing technology. When an RCT was not possible, observational study designs may be accepted. The methods used to undertake the analysis must be rigorous and transparent.
Recommendation 5
Although they are similar in some respects, equivalence and non-inferiority studies are not the same. The similarities and differences in the interpretation of the statistics generated between these trials need to be understood and recognised to correctly interpret findings and ensure that the conclusions correctly reflect trial design. Statistical inference from non-inferiority and equivalence trials should be based upon an assessment of confidence intervals and whether they do/do not cross the non-inferiority/equivalence margins. In cases where either a clinical equivalence or non-inferiority study shows that trial technology is statistically inferior (compared with the non-inferior margin), clinical equivalence or non-inferiority can be ruled out.
Recommendation 6
Reporting of non-inferiority or equivalence trials should be assessed against the CONSORT checklist for such studies published in 2012 [2].
Recommendation 7
Failure to show statistical significance in a superiority study should not in itself be presented as evidence of non-inferiority or equivalence to the comparator intervention. In such cases, supporting evidence on the underlying reasons to suspect at equivalence/non-inferiority should be presented and statistical testing performed, noting that the trial may be insufficiently powered to show non-inferiority.
Recommendation 8
The method of determining a non-inferiority margin should be based upon a historical appraisal of evidence on the effectiveness of the active comparator, preferably through a statistical appraisal of variance in effectiveness. If the preserved fraction of effectiveness is a factor in the margin, this should be determined by clinicians.
Recommendation 9
Regardless of the method used to derive the non-inferiority margin, the margin needs to have been set so that it reflects no clinically meaningful change in patient outcomes. There should be no trade-off in setting the margin or preserved fraction if the benefits of the technology are only hypothesised (i.e. perceived benefits).
Recommendation 10
In assessing non-inferiority and equivalence for diagnostic tests, the same considerations on non-inferiority and equivalence apply as for other technologies. However, non-inferiority and equivalence evidence for both the sensitivity and specificity of the diagnostic test will be required.

CONCLUSIONS

Despite clear guidance, the quality of reporting in non-inferiority and clinical equivalence trials is consistently poor. Prior to presentation of trial evidence, HTA submissions that claim non-inferiority or equivalence should present the technical, biological and/or pharmacokinetic reasonings that support the claim. HTA bodies should introduce more precise definitions of non-inferiority and clinical equivalence so that evidence standards are more likely to be met.

REFERENCES

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