55

Determining the non-inferiority margin in light of the ICH E9(R1) estimand framework.

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Sunita Rehal
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Sunita worked at the Medical Research Council Clinical Trials Unit at UCL from 2012 as a Statistician working in respiratory, dermatology and tuberculosis studies. Sunita completed a PhD in Medical Statistics in the same institution from 2015-2018. The PhD focused on investigation missing data methods for binary outcomes within non-inferiority studies. She then moved to industry in 2018, first working for Roche as a Statistician on studies in Alzheimer's and Spinal Muscular Atrophy before moving to GSK in 2020 where she worked in respiratory. In 2021, Sunita joined the Statistical Methodology group at GSK headed by Nicky Best.

Helle Lynggaard
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Helle Lynggaard is a Statistical Director at Novo Nordisk, based in Copenhagen, Denmark. She obtained her MSc from the University of Aalborg in 1994 and her PhD in 2005 from the University of Copenhagen. Helle has 25+ years of experience in the pharmaceutical industry working in different roles. Currently, she holds the subject matter expert role on estimands in Novo Nordisk. In 2019, she joined the EFPIA and EFSPI co-sponsored Estimand Implementation Working Group (EIWG), where she leads the sub-team on estimands in non-inferiority trials.

Marian Mitroiu
Please provide a brief biography for the Presenting author(s)
Marian is from Romania. In 2015-2016 he did a traineeship at EMA in London at the Biostatistics and Methodology Office. In 2017, he started his doctoral studies at Julius Center, UMC Utrecht and Utrecht University. He worked in parallel at CBG-MEB, being part of the Methodology Working Group. He joined Biogen as a biostatistician in August 2021 and continues the estimand methodology research, implementation and application in clinical drug development, being a member of various estimand-related working groups. In December 2022, Marian successfully defended his PhD thesis entitled "Estimands in clinical drug development: from design to regulatory assessment" at Utrecht University, The Netherlands.

Tobias Muetze
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Tobias Mütze is currently a statistical methodologist at Novartis Pharma AG in Basel, Switzerland, where he supports teams in the design, conduct, and analysis of clinical trials. Previously, he worked as a CMC statistician in vaccines development. His current research interests include estimands, missing data handling, recurrent event methodology, and monitoring of clinical trials. He received his PhD in biostatistics from the University of Göttingen, Germany, and holds a BSc and MSc in mathematics.

David Wright
Please provide a brief biography for the Presenting author(s)
Dr Wright became the Head of Statistical Innovation at AstraZeneca in September 2016. David leads a team of expert statistical methodologists who advise colleagues within AstraZeneca on novel trial design and analysis issues. Between 1999 and 2016 David worked for the Medicines and Healthcare products Regulatory Agency (MHRA) (formerly the

Medicines Control Agency (MCA)) as a Statistical Assessor. David was Chair of the Biostatistics Working Party at the European Medicines Agency from 2011-2016. He is current chair of the Board of Directors of PSI, one of the Editors-in-Chief of Pharmaceutical Statistics and a member of the EFSPI/EFPIA Estimands Implementation Working group (and has published a number of papers on Estimands).

Single topic, multi-speaker session, Workshop or Single presentation submission

A single presentation/poster

Single presentation or poster submission

Determining the non-inferiority margin is critical when designing a non-inferiority trial. This margin represents the largest clinically acceptable difference between the test treatment and the reference treatment, and its choice should be a combination of both clinical judgement and statistical reasoning. ICH E9(R1) has been adopted by all major regulatory agencies. However, there is no regulatory guidance yet on how to determine the NI margin using the outlined estimand framework.

The FDA guidance on non-inferiority trials outlines approaches for determining the non-inferiority margin. As part of this approach, the effect of the reference treatment compared with placebo should be estimated based on historical trials (e.g. via a meta-analysis). This effect is named M_1 and the final non-inferiority margin, named M_2, cannot be larger than M_1.

In this presentation, we first outline how the M_1 effect of the reference treatment versus placebo depends on the targeted estimand, specifically on the strategies for addressing intercurrent events. We conclude that theoretically, any meta-analysis performed to determine M_1 needs to be based on the same estimand that is targeted in the new non-inferiority trial. We then illustrate the practical implications of this through reported clinical trials on weight-loss drugs.

In practice, many historical trials that might be relevant for determining the margin M_1 pre-date the ICH E9(R1) addendum and it is often unclear which estimand was of interest and was actually estimated. We will discuss approaches for how the non-inferiority margin could be determined in these cases using simulated trial data.