Challenges in NMA Methodology Based on Re-Randomization and Treat-through Trial Designs

Svenja Petersohn[1], Melissa Ho[2], Claire Ainsworth[2], Susanne Hartz[3], Tommaso Panni[3].

[1]OPEN Health HEOR & Market Access, Rotterdam, Netherlands, [2]OPEN Health HEOR & Market Access, London, UK, [3]Eli Lilly and Company, Indianapolis, USA

OBJECTIVE

- This study explores the methodological challenges affecting network meta-analyses (NMAs) involving re-randomized (RR) and treat-though (TT) trial designs and potential methodological solutions, using ulcerative colitis (UC) and Crohn's disease (CD) as an example

DISCUSSION AND CONCLUSIONS

- TT and RR trials differ in their purpose and research approach. As a result, they often generate maintenance outcomes that cannot be used in an NMA without prior alignment
- Evidence from active arms can generally be aligned to some degree using different adjustment approaches, while evidence for maintenance placebo arms remains substantially heterogeneous and may not be suitable for inclusion in mixed design NMAs
- Different methodologies have been utilized to combine evidence from RR and TT trials. Approaches incorporating adjustment to individual patient data (IPD), generally, required fewer assumptions than approaches using aggregate data and external evidence, and may be more robust
- The presence of differing active treatment carry-over effects in RR trials may pose challenges to meeting necessary consistency assumptions to enable NMA and should be considered in future NMA feasibility assessments of emerging UC and CD treatments

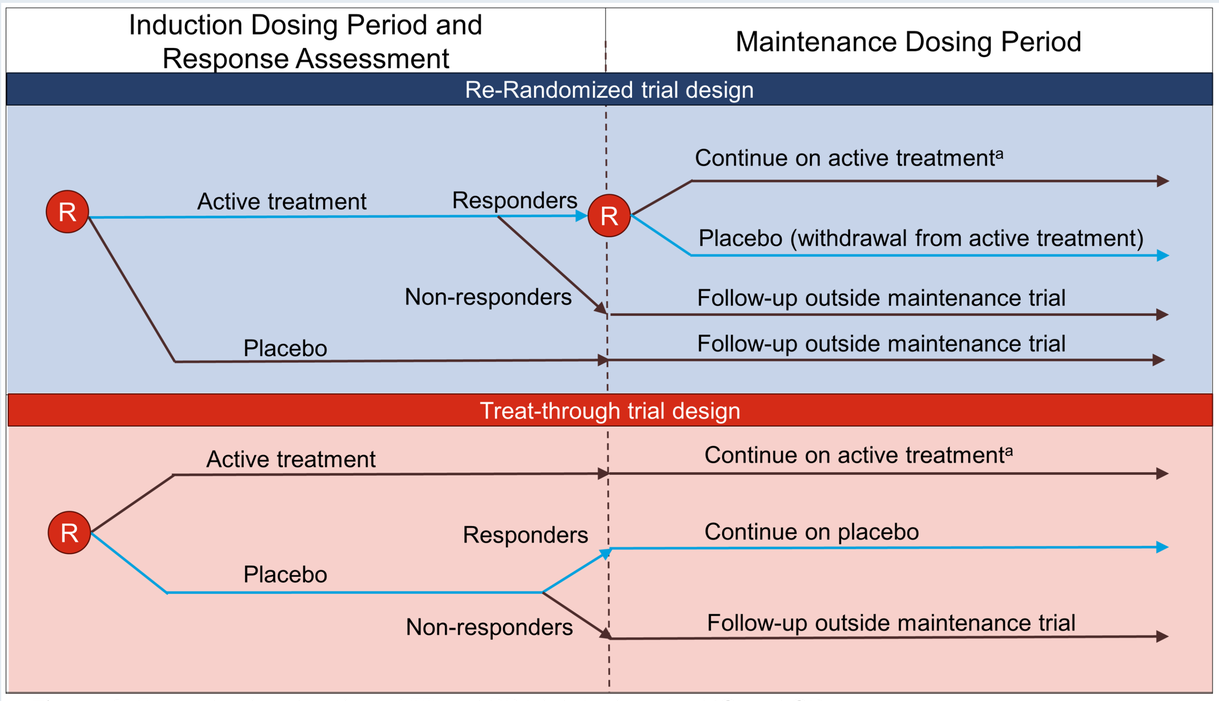

Figure 1: Example visualization of TT and RR trial designs for UC and CD
Abbreviations: R, randomization
[a]Patients who continue on active treatment are having maintenance dosing of active treatment
Note: Blue lines illustrate the path of patients receiving placebo in maintenance

BACKGROUND

- RR and TT are trial designs to assess outcomes for treatments with an induction phase aiming for a rapid reduction of disease symptoms and severity, and a maintenance phase maintaining or further improving outcomes
- NMAs enable a comprehensive comparison of treatment options, when head-to-head trials are not available. To perform NMA, similarity assumptions (amongst others) need to be met, including on study design, population, and outcomes
- As shown in Figure 1, RR and TT trial designs have key differences. This heterogeneity presents challenges when NMAs include both trial designs, especially in the maintenance phase
  - In RR trials, maintenance patients have a history of response to active treatment, this means patients randomized to placebo during induction usually do not enter maintenance and instead get followed-up outside the maintenance trial
  - In TT trials, induction patients on active treatment continue treatment in the maintenance phase independent of induction response. In the placebo arm, usually, only induction responders continue on placebo into maintenance, non-responders are followed-up outside maintenance trial

METHODS

- A targeted literature review was conducted to identify recent submissions to the National Institute for Health and Care Excellence (NICE) and NMA publications in UC and CD where TT and RR trials are included, as well as methodological publications exploring key sources of uncertainty and approaches addressing these challenges
- Based on the literature identified, we summarized findings, considering different scenarios of data availability

RESULTS

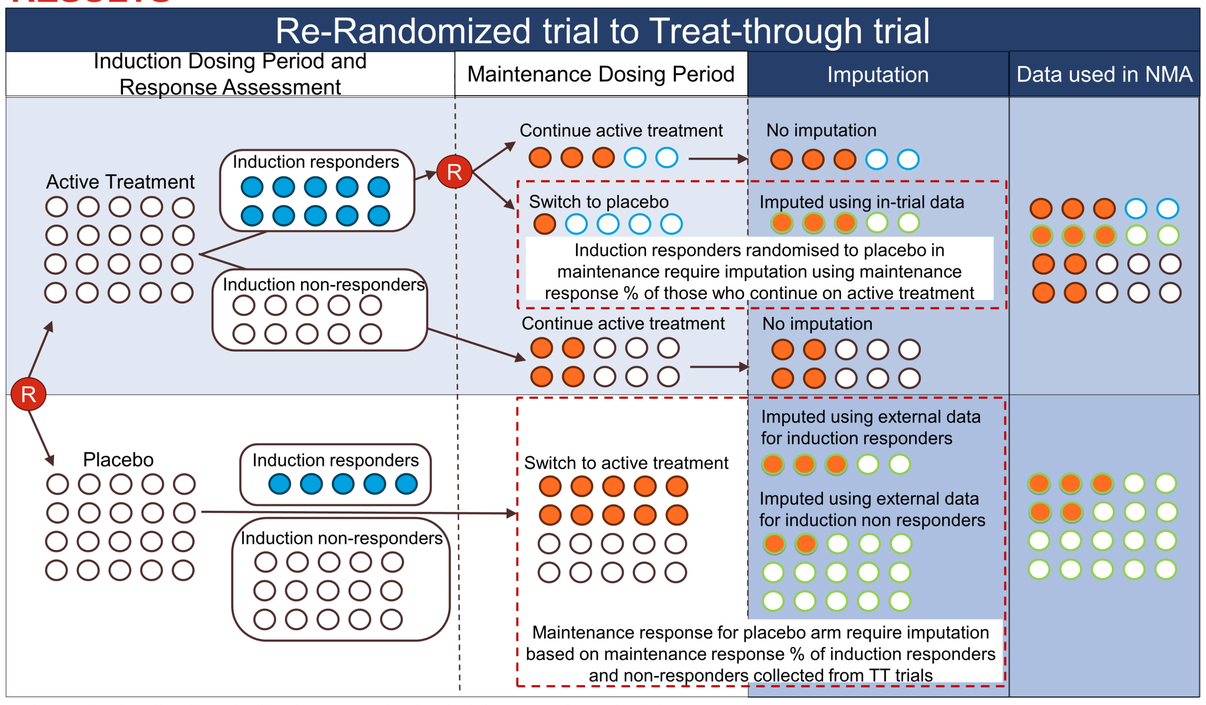

Figure 2: Visualization of adjusting re-randomized trial to treat-through trial
Abbreviation: TT: treat-though; R: randomization
= induction responders; = maintenance responders; = induction responders in maintenance; = imputed data; = patient entering the trial

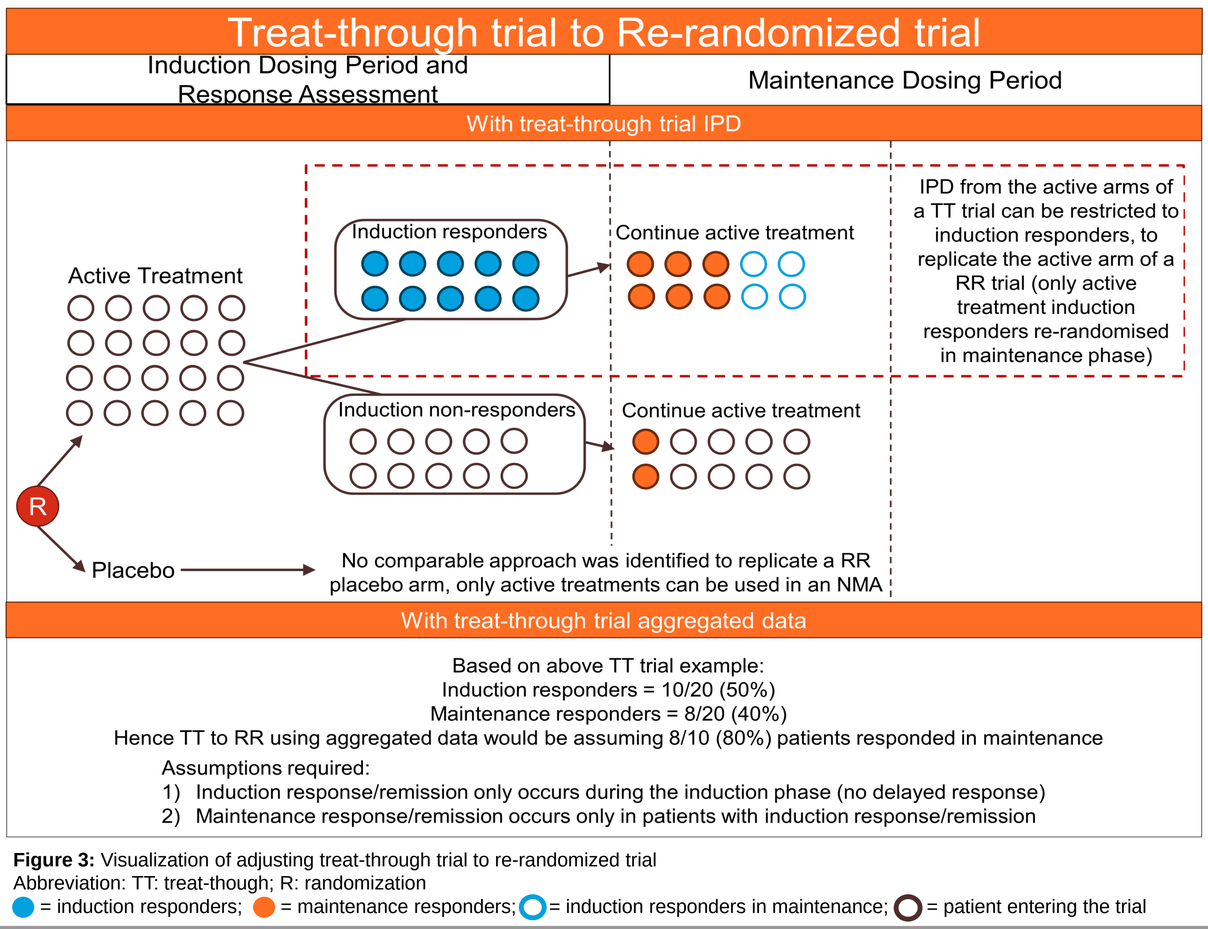

Figure 3: Visualization of adjusting treat-through trial to re-randomized trial
Abbreviation: TT: treat-though; R: randomization
= induction responders; = maintenance responders; = induction responders in maintenance; = patient entering the trial

- The review identified 7 recent NICE submissions assessing treatments of UC[1-7] and 4 submissions for CD[8-11], and a further 3 NMA publications (2 for UC[12,13] and 1 for CD[14]) providing information of interest
- A summary of methodological challenges and potential solutions discussed in the identified sources is presented in **Table 1**

Table 1: Overview of limitations and solutions

Methodological challenges	Solutions
Incomparable maintenance outcome data across trial designs (see Figure 1). **Previous NMAs excluded trials, restricting to either TT or RR trials.[8 10 11]**	Depending on available data (aggregate versus IPD) and trial design mix, different data adjustment approaches enabling inclusion of all evidence in an NMA, see Figure 2 and Figure 3. - RR to TT using IPD: not identified. - RR to TT using aggregate data: requires imputation using in-trial and external evidence.[12] Uses strong assumptions - TT to RR using IPD: IPD from the active arms of a TT trial can be restricted to induction responders, to replicate the active arm of a RR trial. No comparable approach was identified to replicate a RR placebo arm (withdrawal from induction active treatment), only active treatments can be used in an NMA.[5] - TT to RR using aggregate data: Requires assumptions, e.g.: patients with induction outcomes in the TT trial serve as proxy for patients entering maintenance, assuming 1) induction outcome only occurs during the induction phase, there is no delayed outcome; 2) maintenance outcome occurs only in patients with induction outcome.[1-7] Estimated maintenance outcomes may lack face validity if underlying assumptions are violated. Difficult to implement.
Breaking of randomization in maintenance during adjustment from TT to proxy RR outcomes	To mitigate potential confounding from breaking randomization, when TT trial IPD is available, a logistic regression model with inverse probability weighting can be used. This estimates the probability of being in each treatment arm using relevant baseline characteristics based on clinical relevance.
Lack of comparable placebo maintenance arm when adjusting TT to RR	No respective adjustments were identified to mimic active treatment withdrawal in RR trials, even when IPD is available for TT trial. To connect active arms adjusted from TT to RR into an evidence network, a second active arm needs to be present in the TT trial and in one of the RR trials.
Carry-over effects from induction to maintenance in RR placebo arms	Network meta-regression can be used to investigate potential carry-over effects by using induction outcomes as covariates in estimating maintenance outcomes.[15] However, induction data needs to be available for maintenance trials, and a strong carry-over effect may be needed to identify a significant coefficient. Further, this requires a very strong assumption that the carry-over effect is proportional to induction outcomes. Treatment sequence approaches utilizing one placebo-to-placebo arm to replace the placebo arms of all trials have been tested. However, the approach breaks randomization and enables confounding due to differences in settings, treatments, and disease severity across trials.[9]

Acknowledgments: The authors would like to thank Shane Whelan for writing and editorial contributions.
Disclosures: Svenja Petersohn, Melissa Ho and Claire Ainsworth are employees of OPEN Health. Susanne Hartz and Tommaso Panni are employees and minor shareholders of Eli Lilly and Company.

Sponsored by Eli Lilly and Company

ISPOR EU 2024; Barcelona, Spain; November 17 – 20, 2024

References
See supplementary material for full reference list