Imperial College London

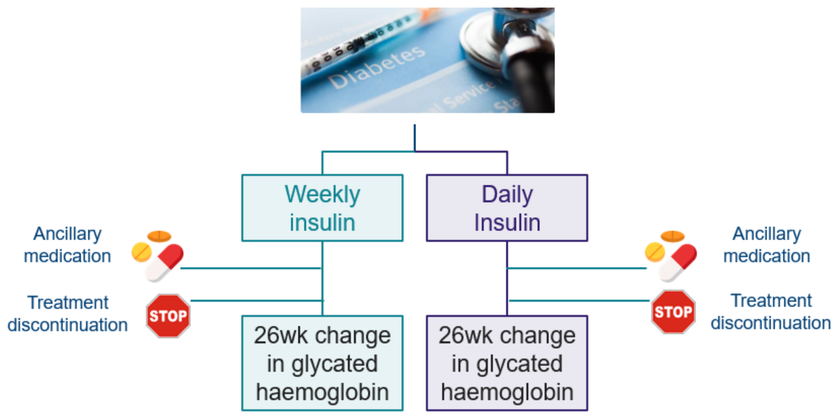
Are randomised trials addressing clear and useful questions?

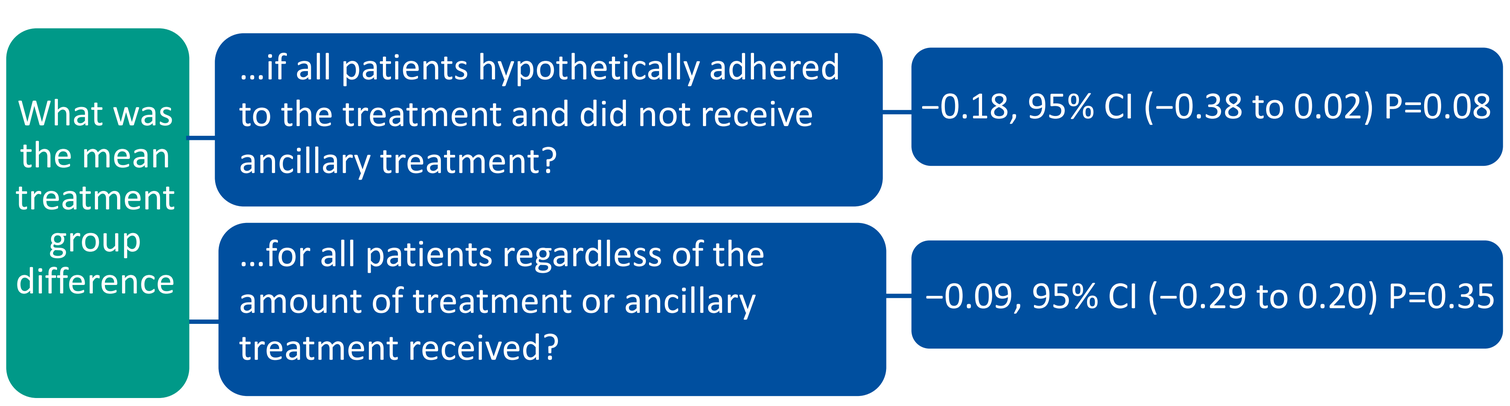
Suzie Cro[1], Brennan Kahan[2], Sunita Rehal[3], Anca Chis Ster[4], James Carpenter[2,5], Ian White[2], Victoria Cornelius[1]

[1]Imperial Clinical Trials Unit, Imperial College London, [2]MRC CTU at UCL, [3]GSK, [4]KCL, [5]London School of Hygiene & Tropical Medicine

Introduction

- Asking different questions in trials can lead to different conclusions on treatment benefit:





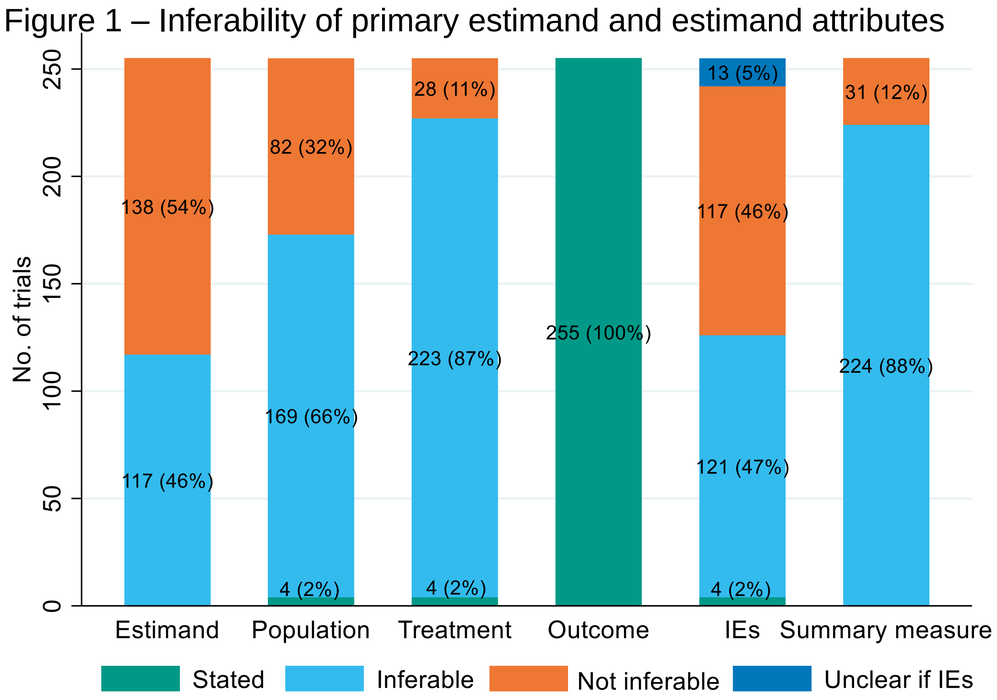
- ICH E9(R1) calls for trialists to define ***estimands*** in order to precisely describe the targeted treatment effects
- An estimand is a precise description of a treatment effect specifying the patient population, treatment conditions, outcome, handling of intercurrent events and population level summary measure
- We aimed to establish whether reporting estimands in trial reports is necessary to fully understand the questions being investigated

Methods

- A systematic review of phase II-IV randomised trials published in 2020 in six leading general medical journals
- Two statistical reviewers independently assessed whether each estimand attribute was explicitly stated, not explicitly stated but unambiguously inferable based on the statistical methods (estimator) or other reported methods, or not inferable

Results

Figure 1 – Inferability of primary estimand and estimand attributes



- The primary estimand could not be determined for 138/255 (54%) trials
- 242/255 (95%) trials reported intercurrent events, but the strategy for handling these could only be determined for 125/255 (49%)
- Where this could be determined, most trials (96/125, 77%) addressed the effect of the treatment regardless of intercurrent events (treatment policy)
- 17/125 (14%) investigated hypothetical questions
- 4/99 (4%) trials with treatment non-adherence due to adverse events estimated the hypothetical effect as if patients continued treatment despite adverse events
- 19 (79%) of 24 trials where some patients died estimated the treatment effect in a hypothetical setting, if patients could not die

Discussion

- The precise question addressed in most trials is unclear
- This is mainly due to lack of clarity in handling intercurrent events
- While 46% primary estimands could be inferred by our statistical reviewers, inferability will be lower for non-methodologists, and patients
- We couldn't tell whether the question addressed by the methods corresponded with what trial investigators wanted to know
- Reporting of estimands is necessary to fully understand the questions clinical trials address
- CONSORT should be updated to mandate reporting of estimands
- For more details and results publication see:

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MRC Clinical Trials Unit

UCL

King's College London

London School of Hygiene & Tropical Medicine

ICTU Imperial Clinical Trials Unit