Use of estimands in the published literature
&
Current practise

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Outline

- Evidence on the use and need for estimands in the published literature;

  - A review of protocols published in October 2020
  - A review of trial results articles published in 2020

- Your thoughts and experiences on using estimands...

Evidence from published protocols

How often can we tell the primary question clinical trials are designed to address from their published protocol?...

Trials

RESEARCH   **Open Access**

Estimands in published protocols of randomised trials: urgent improvement needed

Brennan C. Kahan[1*], Tim P. Morris[1], Ian R. White[1], James Carpenter[1] and Suzie Cro[2]

Abstract

Background: An estimand is a precise description of the treatment effect to be estimated from a trial (the question) and is distinct from the methods of statistical analysis (how the question is to be answered). The potential use of estimands to improve trial research and reporting has been underpinned by the recent publication of the ICH E9(R1) Addendum on the use of estimands in clinical trials in 2019. We set out to assess how well estimands are described in published trial protocols.

Methods: We reviewed 50 trial protocols published in October 2020 in *Trials* and *BMJ Open*. For each protocol, we determined whether the estimand for the primary outcome was explicitly stated, not stated but inferable (i.e. could be constructed from the information given), or not inferable.

Evidence from published protocols

- A review of 50 trial protocols published in October 2020 in *Trials* and *BMJ Open*

- Was the estimand for the primary outcome:
  - explicitly stated
  - not stated but inferable (from the information on the *estimator*/methods)
  - not inferable

Evidence from published protocols

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- In 37/50 (74%) trials, could not infer the estimand (≥1 attribute not inferable)

For most trials, it was impossible to understand the precise clinical question (estimand) targeted

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Evidence from published results

- How often can we tell the primary question clinical trials address from their published results articles? & what questions are being assessed?

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- Review of phase II-IV RCTs published in 2020 in *6* leading general medical journals

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Evidence from published results

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- 162 (64%) had an academic or not-for-profit sponsor; 93 (36%) had a pharmaceutical or for-profit sponsor;

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- Total of 255 trials identified

- 162 (64%) had an academic or not-for-profit sponsor; 93 (36%) had a pharmaceutical or for-profit sponsor;

- None of the 255 results articles completely stated the primary estimand

- 4 (2%) attempted to define an estimand but missed one or more attribute

- In 138 (54%) trials, we could not infer the estimand (one or more attribute not inferable)

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Evidence from published results

- Could only determine how intercurrent events were handled in 125 (49%) trials (N=4 stated strategy, N=121=inferable)

- Where stated or inferable (N=125):
  - 96 (76%) used treatment policy
  - 17 (14%) used hypothetical
  - 12 (10%) used composite

Evidence from published results

In most trials, it was impossible to understand precisely what clinical question had been addressed

Different questions can result in different views on treatment benefit,

Different effects → different conclusions

- What was the mean difference in glycated haemoglobin for a once-weekly insulin regimen compared to a once-daily regimen...

....if all participants had hypothetically adhered to the treatment regimens and not received ancillary treatment?

-0.18 percentage points (95% CI -0.38 to 0.02, p=0.08)

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Different effects → different conclusions

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….if all participants had hypothetically adhered to the treatment regimens and not received ancillary treatment?
-0.18 percentage points (95% CI -0.38 to 0.02, p=0.08)

…regardless of the amount of randomised treatment or ancillary treatment received?
-0.09 percentage points (95% CI -0.29 to 0.20, p=0.35)

Are you using estimands today?