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The role of estimands in academic trials – present and future

Estimands in clinical trials: Current practice and future directions

Estimands in clinical trials: Current practice and future directions: Outline

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- A brief look back before estimands
- Some evidence on the use and need for estimands in recent published literature:
  - “Estimands in published protocols of randomised trials: urgent improvement needed” (Kahan 2021)
  - “Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands” (Cro 2022)
  - Spoiler Alert: Past usage was underwhelming
- Survey amongst (bio-)statisticians working in academia to assess current and future usage

Estimands in clinical trials: Current practice and future directions: Frameworks for Evidence Synthesis

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(Davies 2011)

Components of the Different PICO-based Frameworks

	Patient / Population	Intervention	Comparison	Outcome	Timeframe	Context	Type of Question	Type of Study Design	Professionals	Health Care Setting	Exposure	Duration	Results	Environment	Stakeholders	Situation
Richardson et al., 1995	■	■	■	■												
Fineout-Overholt & Johnson, 2005	■	■	■	■	■											
Petticrew & Roberts, 2005	■	■	■	■		■										
Schardt et al., 2007	■	■	■	■			■	■								
ADAPTE Collaboration, 2009	■	■		■					■	■						
Dawes et al., 2007	■		■	■							■	■	■			
Schlosser & O'Neil-Pirozzi, 2006	■	■	■	■										■	■	
DiCenso, Guyatt, & Ciliska, 2005	■															■

Review of current literature

Estimands in published Protocols

(Kahan 2021)

- Reviewed 50 trial protocols published October 2020
  - Inclusion: full protocol of an RCT in humans
  - Exclusion: (i) pilot/feasibility trial, (ii) phase I/II trial,(iii) dose-finding study, (iv) trial in patients with COVID-19
- Determined whether the estimand for the **primary outcome** was:
  - Explicitly stated
  - Not stated but inferable
  - Not inferable
- Results:
  - **Explicitly stated: 0%**
  - Not stated but inferable: 26%
  - Not inferable: 74%

Kahan *et al. Trials* (2021) 22:686
https://doi.org/10.1186/s13063-021-05644-4

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.

Results: None of the 50 trials explicitly described the estimand for the primary outcome, and in 74% of trials, it was impossible to infer the estimand from the information included in the protocol. The population attribute of the estimand could not be inferred in 36% of trials, the treatment condition attribute in 20%, the population-level summary measure in 34%, and the handling of intercurrent events in 60% (the strategy for handling non-adherence

Review of current literature

Estimands in published Protocols

(Kahan 2021)

Estimand attributes

Population	
Stated	0 (0%)
Inferable	32 (64%)
Not inferable	18 (36%)
Treatment condition(s)	
Stated	0 (0%)
Inferable	40 (80%)
Not inferable	10 (20%)
Outcome	
Stated	50 (100%)
Inferable	0 (0%)
Not inferable	0 (0%)
Population-level summary measure	
Stated	0 (0%)
Inferable	33 (66%)
Not inferable	17 (34%)
Handling of intercurrent event(s)	
Stated	0 (0%)
Inferable	20 (40%)
Not inferable	30 (60%)

Number of attributes not inferable	
0	13 (26%)
1	14 (28%)
2	9 (18%)
3	13 (26%)
4	1 (2%)
5	0 (0%)

Review of current literature

Estimands in published RCTs

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(Cro 2022)

- Reviewed 255 RCTs in February 2021
  - Inclusion: Phase 2-4 RCTs in humans
  - Exclusion: Cluster randomized, crossover, non-inferiority, equivalence trials, phase I, pilot or feasibility trials, primary outcome of cost effectiveness, interim- and meta-analyses
- Determined whether the estimand for the **primary outcome** was:
  - Explicitly stated
  - Not stated but inferable
  - Not inferable
- Results:
  - **Explicitly stated: 0%**
  - Not stated but inferable: 46%
  - Not inferable: 54%

Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands

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

ABSTRACT

OBJECTIVES

To evaluate how often the precise research question being addressed about an intervention (the estimand) is stated or can be determined from reported methods, and to identify what types of questions are being investigated in phase 2-4 randomised trials.

DESIGN

Systematic review of the clarity of research questions being investigated in randomised trials in 2020 in six leading general medical journals.

DATA SOURCE

PubMed search in February 2021.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Phase 2-4 randomised trials, with no restrictions on medical conditions or interventions. Cluster randomised, crossover, non-inferiority, and

trial reports so that all stakeholders, including clinicians, patients and policy makers, can make fully informed decisions about medical interventions.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42021238053.

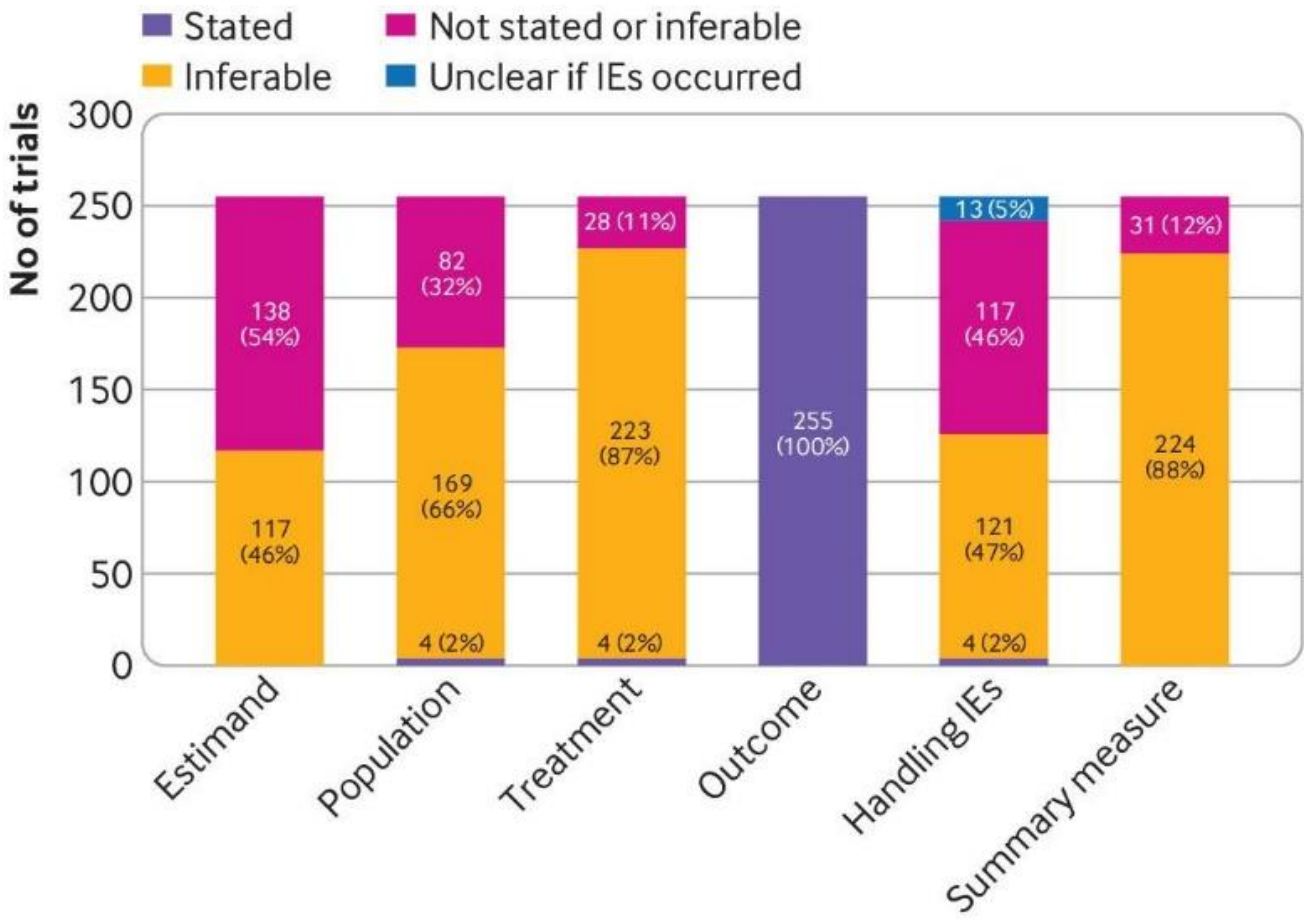
Introduction

The results of randomised controlled trials are used in policy making and clinical practise to make decisions about which medical interventions to use. However, informed decision making requires an understanding of the precise question being investigated in a trial, because different questions can lead to different conclusions about the usefulness of an intervention.[1-9] For example, a trial in type 2 diabetes[10] compared a once weekly insulin regimen with a once daily regimen on the change from baseline in glycated haemoglobin, and asked two

Review of current literature

Estimands in published RCTs

(Cro 2022)



Survey Results

Survey of (Bio-)Statisticians working in Academia

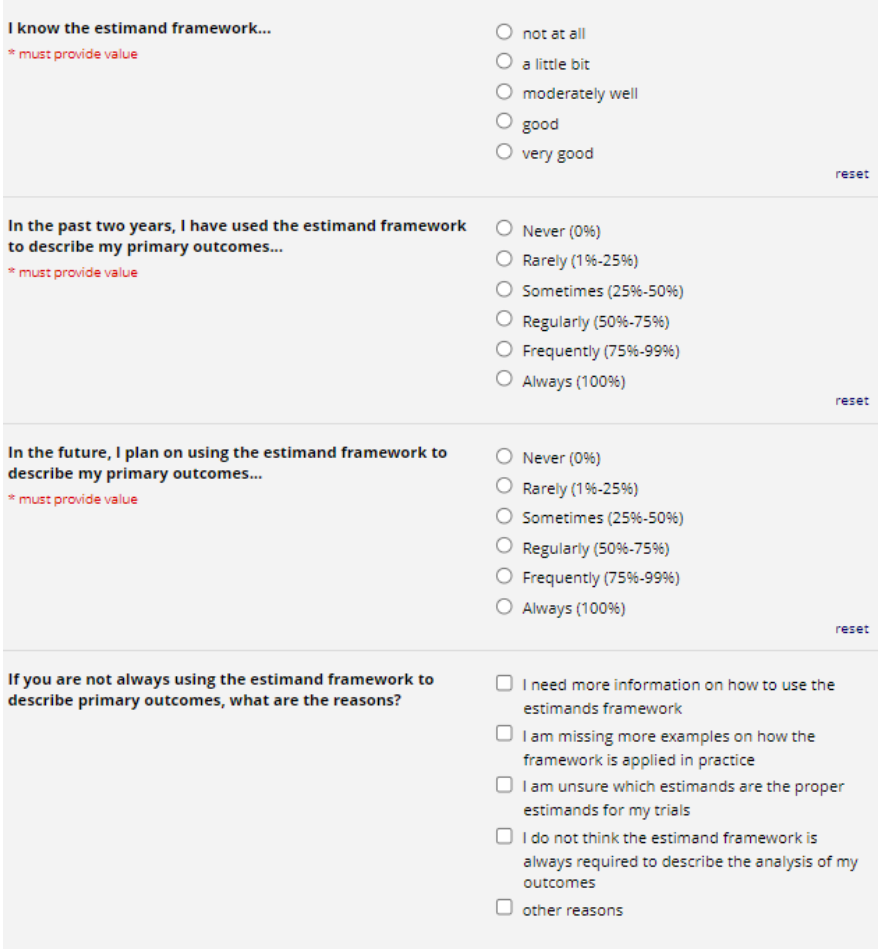
https://www.kks-netzwerk.de/

- KKS = “Koordinierungszentren für Klinische Studien” ≈ Clinical Trials Unit
- Research partners at university medical centers
- Support and design of clinical trials in academia
- Consists of multiple working groups:
  - Education & Training
  - **Biostatistics**
  - Data Management
  - IT
  - Monitoring
  - Project Management
  - Quality Management
  - Vigilance
  - Clinical Trial Management (with TMF)

Survey Results
Survey of (Bio-)Statisticians working in Academia

- Anonymous Online Survey within the Working group for Biostatistics
- 5 Questions on past and current usage of the estimand framework
- N=19 respondents (≈25% of the mailing list)

- **I work as a (bio-)statistician in…**
  - Academia: 95%
  - Industry: 0%
  - Other: 5%



I know the estimand framework...
* must provide value

- ○ not at all
- ○ a little bit
- ○ moderately well
- ○ good
- ○ very good

reset

In the past two years, I have used the estimand framework to describe my primary outcomes...
* must provide value

- ○ Never (0%)
- ○ Rarely (1%-25%)
- ○ Sometimes (25%-50%)
- ○ Regularly (50%-75%)
- ○ Frequently (75%-99%)
- ○ Always (100%)

reset

In the future, I plan on using the estimand framework to describe my primary outcomes...
* must provide value

- ○ Never (0%)
- ○ Rarely (1%-25%)
- ○ Sometimes (25%-50%)
- ○ Regularly (50%-75%)
- ○ Frequently (75%-99%)
- ○ Always (100%)

reset

If you are not always using the estimand framework to describe primary outcomes, what are the reasons?

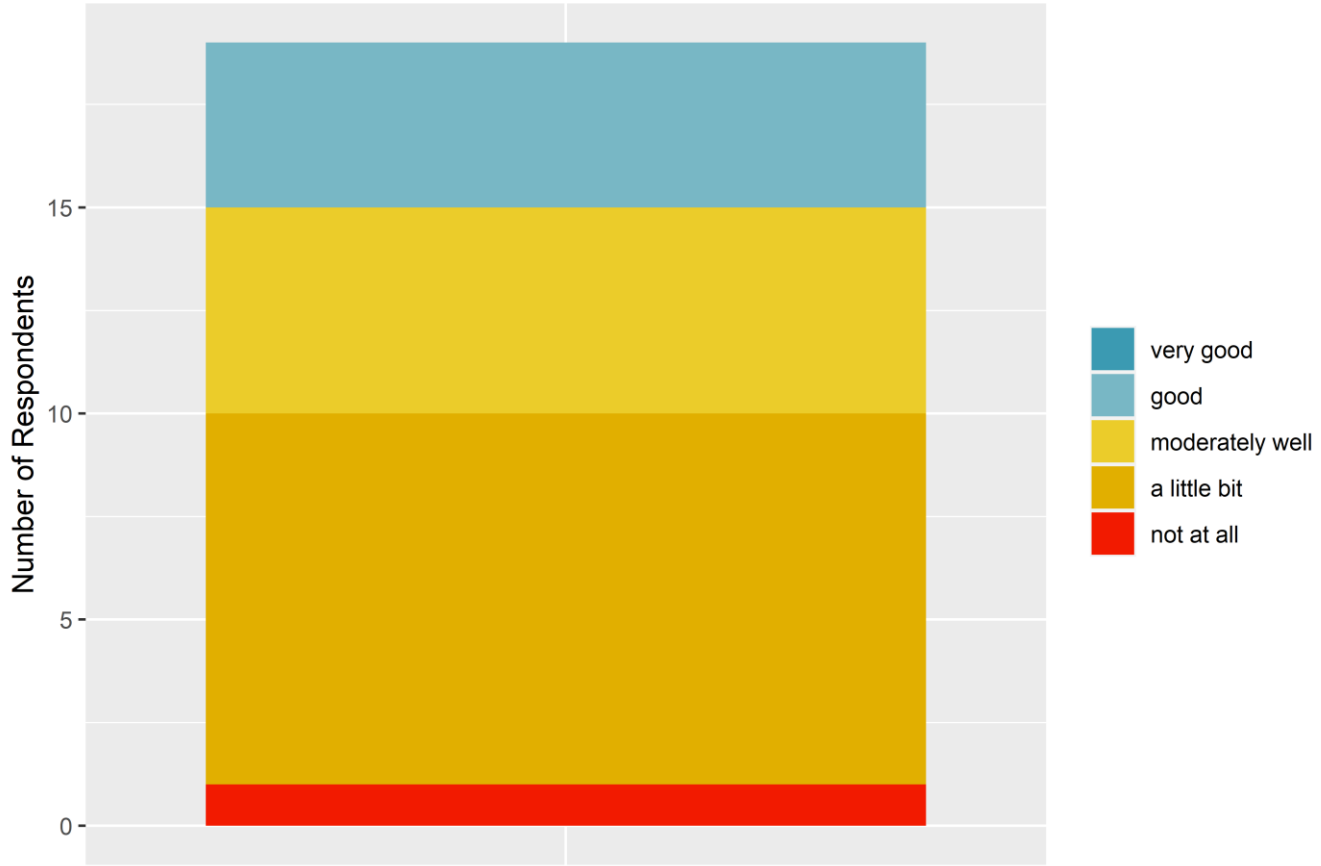
- ☐ I need more information on how to use the estimands framework
- ☐ I am missing more examples on how the framework is applied in practice
- ☐ I am unsure which estimands are the proper estimands for my trials
- ☐ I do not think the estimand framework is always required to describe the analysis of my outcomes
- ☐ other reasons

Survey Results

Survey of (Bio-)Statisticians working in Academia

I know the estimand framework…

- Very good: 0%
- Good: 21%
- Moderately well: 26%
- A little bit: 47%
- Not at all: 5%



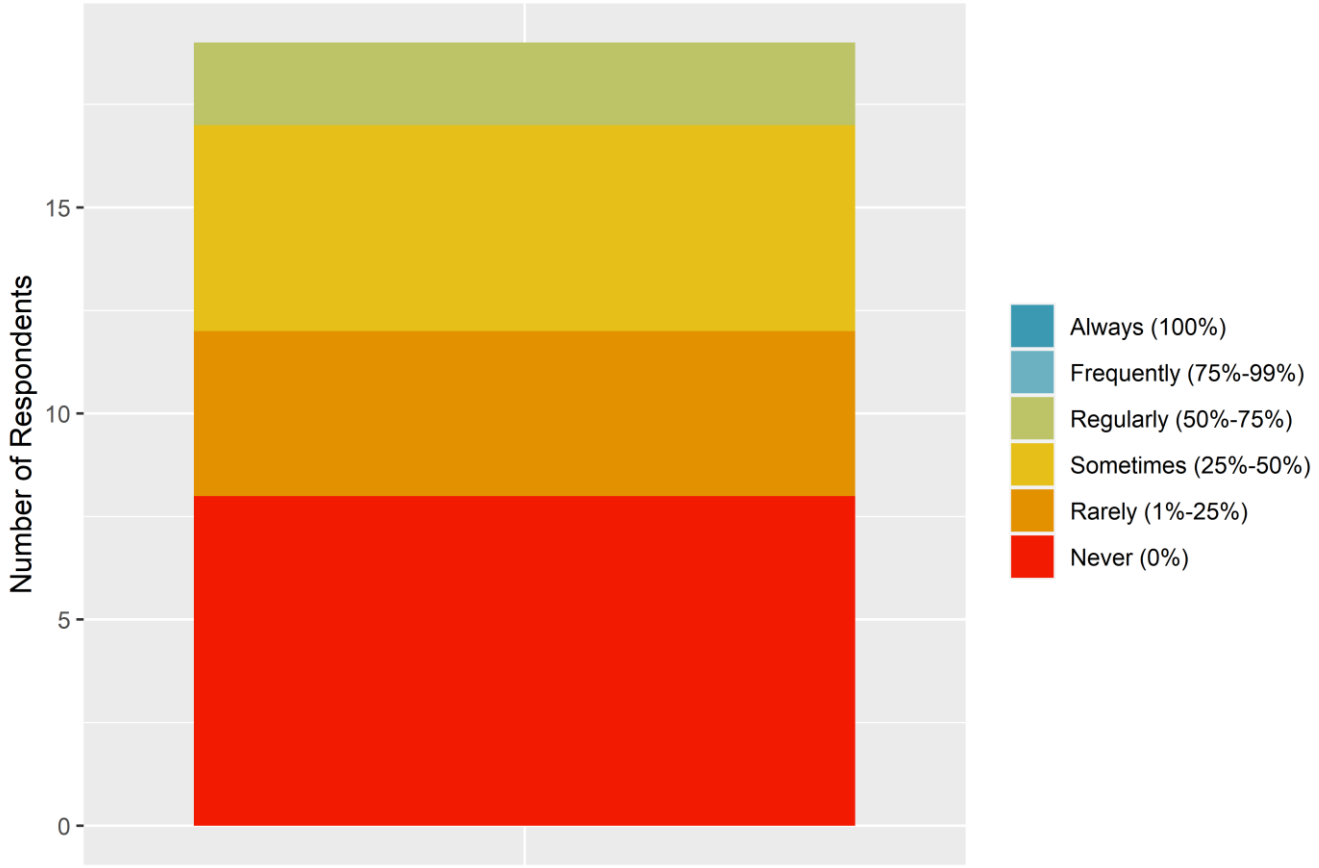
Survey Results

Survey of (Bio-)Statisticians working in Academia

In the past two years, I have used the estimand framework to describe my primary outcomes…

- Always: 0%
- Frequently: 0%
- Regularly: 10%
- Sometimes: 26%
- Rarely: 21%
- Never: 42%

≈ 21% of primary outcomes were described



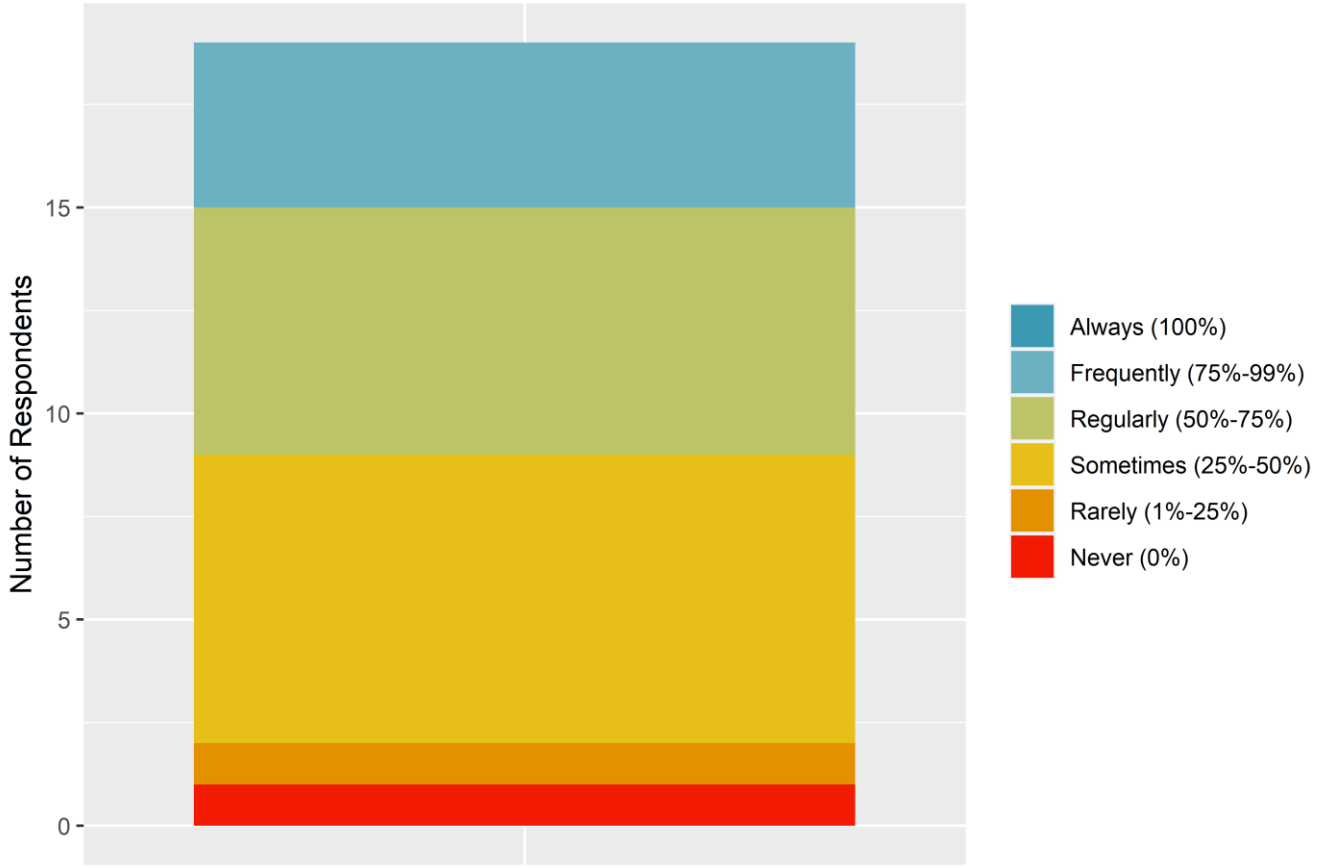
Survey Results

Survey of (Bio-)Statisticians working in Academia

In the future, I plan on using the estimand framework to describe my primary outcomes...

- Always: 0%
- Frequently: 22%
- Regularly: 28%
- Sometimes: 39%
- Rarely: 5%
- Never: 5%

≈ 53% of primary outcomes will be described



Survey Results
Survey of (Bio-)Statisticians working in Academia

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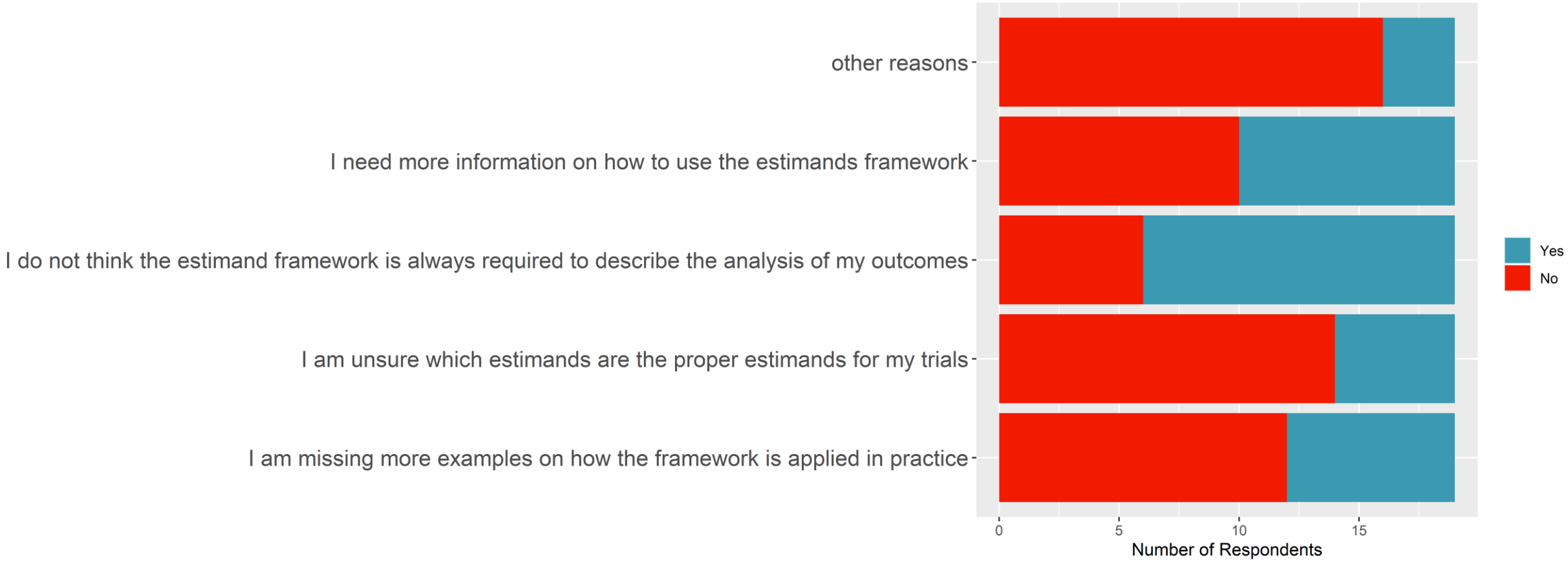
If you are not always using the estimand framework to describe primary outcomes, what are the reasons?



Estimands in clinical trials: Current practice and future directions: Conclusion

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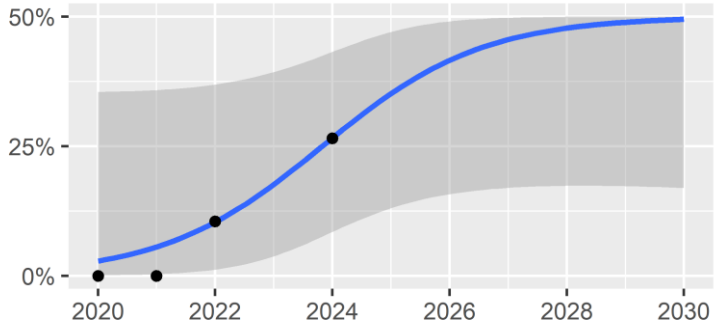
- **In the past**: In a sample from 2021 estimands were not reported explicitly **(0%)**
- The survey showed some improvement over this within the last 2 years **(21%)**

- **In the future:** (bio-)statisticians working in academia want to improve reporting using estimands **(53%)**
- There is still training needed for statisticians (and maybe clinicians?) to apply the framework → How do we get there?
- There is some skepticism on the necessity to use the framework for all clinical trials → When should we use it? Should there be an obligation to use it in certain settings?

Maybe like this…



Referenzen

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2. Kahan BC, Morris TP, White IR, Carpenter J, Cro S. Estimands in published protocols of randomised trials: urgent improvement needed. Trials. 2021 Oct 9;22(1):686. doi: 10.1186/s13063-021-05644-4. PMID: 34627347; PMCID: PMC8500821.
3. Cro S, Kahan B C, Rehal S, Chis Ster A, Carpenter J R, White I R et al. Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands *BMJ* 2022; 378 :e070146 doi:10.1136/bmj-2022-070146