How Do Meta-Analyses Handle Treatment Switching? A Systematic Review

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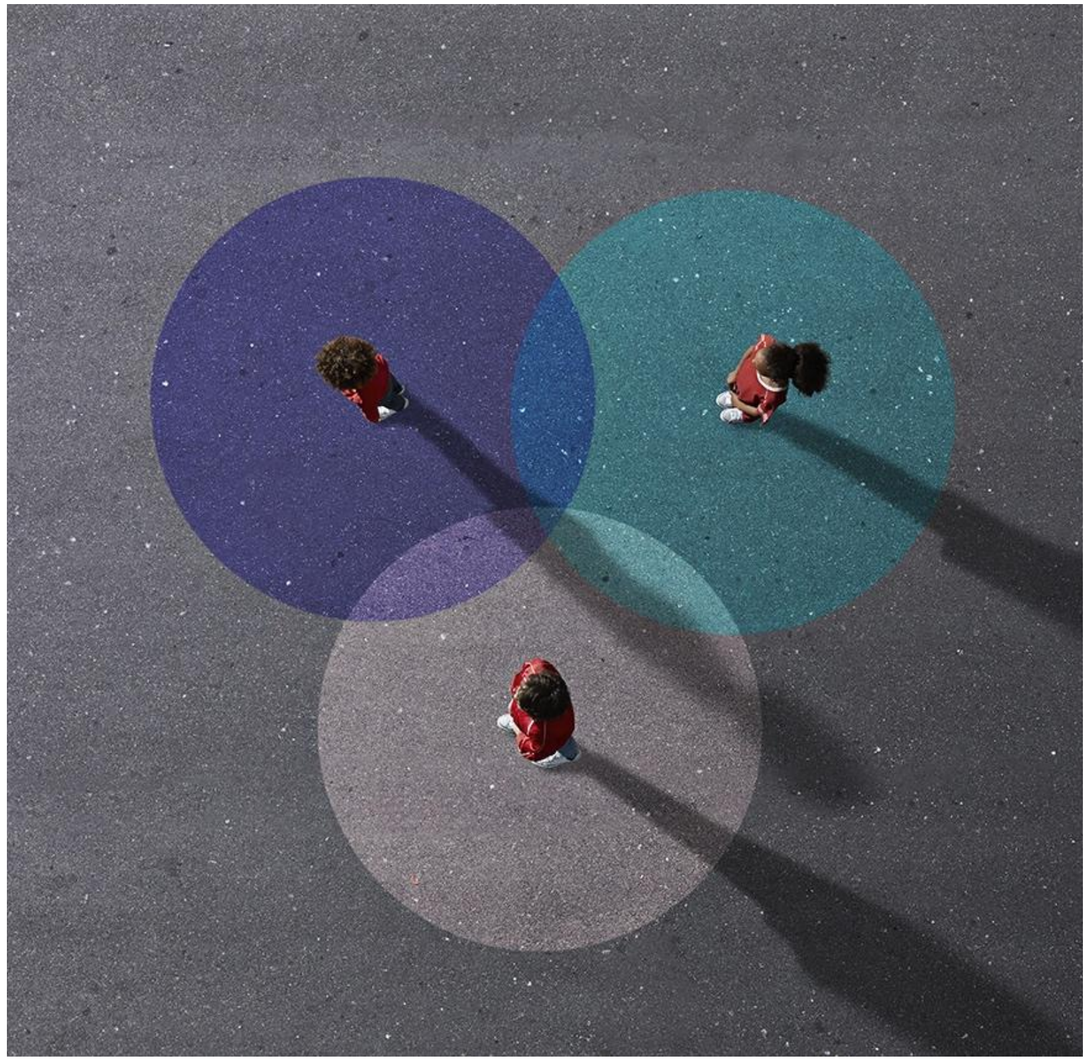
Overview

- Background and rationale
- Methods
- Findings
- General conclusions
- Future directions



Did you know the 2019 ICH E9(R1) addendum….

1. Highlights the importance of estimands including specifying post-randomization events that may affect the interpretation of clinical trial outcomes (i.e., intercurrent events; ICEs) and strategies to handle these events

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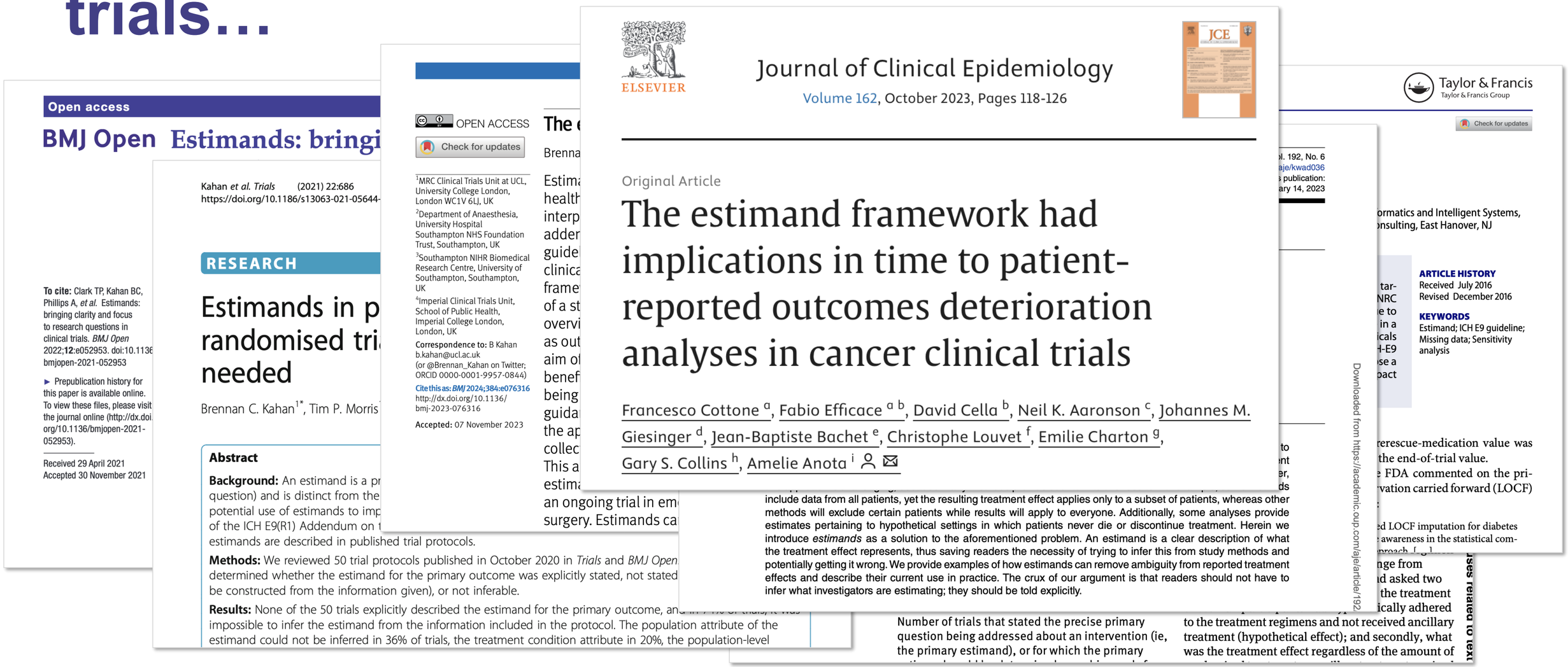
1. Highlights the importance of estimands including specifying post-randomization events that may affect the interpretation of clinical trial outcomes (i.e., intercurrent events; ICEs) and strategies to handle these events

AND

2. **Explicitly notes that integration of data from multiple trials without consideration and specification of the estimand targeted by each trial**, which includes handling of intercurrent events, **can be misleading**

Yet there has been much attention to individual trials…



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BMJ Open Estimands: bringi

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RESEARCH

Estimands in p
randomised tri
needed

Brennan C. Kahan[1*], Tim P. Morris

Abstract

Background: An estimand is a pr
question) and is distinct from the
potential use of estimands to imp
of the ICH E9(R1) Addendum on t
estimands are described in published trial protocols.

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

Results: None of the 50 trials explicitly described the estimand for the primary outcome, and
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

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Journal of Clinical Epidemiology

Volume 162, October 2023, Pages 118-126

Original Article

The estimand framework had implications in time to patient-reported outcomes deterioration analyses in cancer clinical trials

Francesco Cottone [a], Fabio Efficace [a b], David Cella [b], Neil K. Aaronson [c], Johannes M. Giesinger [d], Jean-Baptiste Bachet [e], Christophe Louvet [f], Emilie Charton [g], Gary S. Collins [h], Amelie Anota [i]

include data from all patients, yet the resulting treatment effect applies only to a subset of patients, whereas other methods will exclude certain patients while results will apply to everyone. Additionally, some analyses provide estimates pertaining to hypothetical settings in which patients never die or discontinue treatment. Herein we introduce *estimands* as a solution to the aforementioned problem. An estimand is a clear description of what the treatment effect represents, thus saving readers the necessity of trying to infer this from study methods and potentially getting it wrong. We provide examples of how estimands can remove ambiguity from reported treatment effects and describe their current use in practice. The crux of our argument is that readers should not have to infer what investigators are estimating; they should be told explicitly.

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Estimand; ICH E9 guideline; Missing data; Sensitivity analysis

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to the treatment regimens and not received ancillary treatment (hypothetical effect); and secondly, what was the treatment effect regardless of the amount of

Number of trials that stated the precise primary question being addressed about an intervention (ie, the primary estimand), or for which the primary

…and relatively little to meta-analysis

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COMMENTARY

Statistics in Medicine WILEY

Some considerations on target estimands for health technology assessment

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First and foremost, I would like to thank an anony
ing discussion around my article, "Target estiman
prior exchange with Phillippo et al.[2-4] I extend my
et al,[9] for their additional contributions.

This rejoinder discusses the potential developm
health technology assessment (HTA). I consider th
treatment comparison or a network meta-analysis
multiple randomized controlled trials (RCTs).[10-12]
ing authorization setting, and has target estimand
are not exclusively based on RCTs and HTA decisi

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Methodology

Is Intention to Treat Still the Gold Standard or Should Health Technology Assessment Agencies Embrace a Broader Estimands Framework?

Insights and Perspectives From the National Institute for Health and Care Excellence and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E9 (R1) Addendum

Antonia Morga, DPhil, Nicholas R. Latimer, PhD, Martin Scott, MSc, Neil Hawkins, PhD, CStat, Michael Schlichting, MSc, Jixian Wang, PhD

Research Synthesis Methods

DISCUSSION

Broad versus narrow research questions in evidence synthesis: A parallel to (and plea for) estimands

This article relates to:

orst-Rasmussen

tps://doi.org/10.1002/jrsm.1741 | Citations: 2

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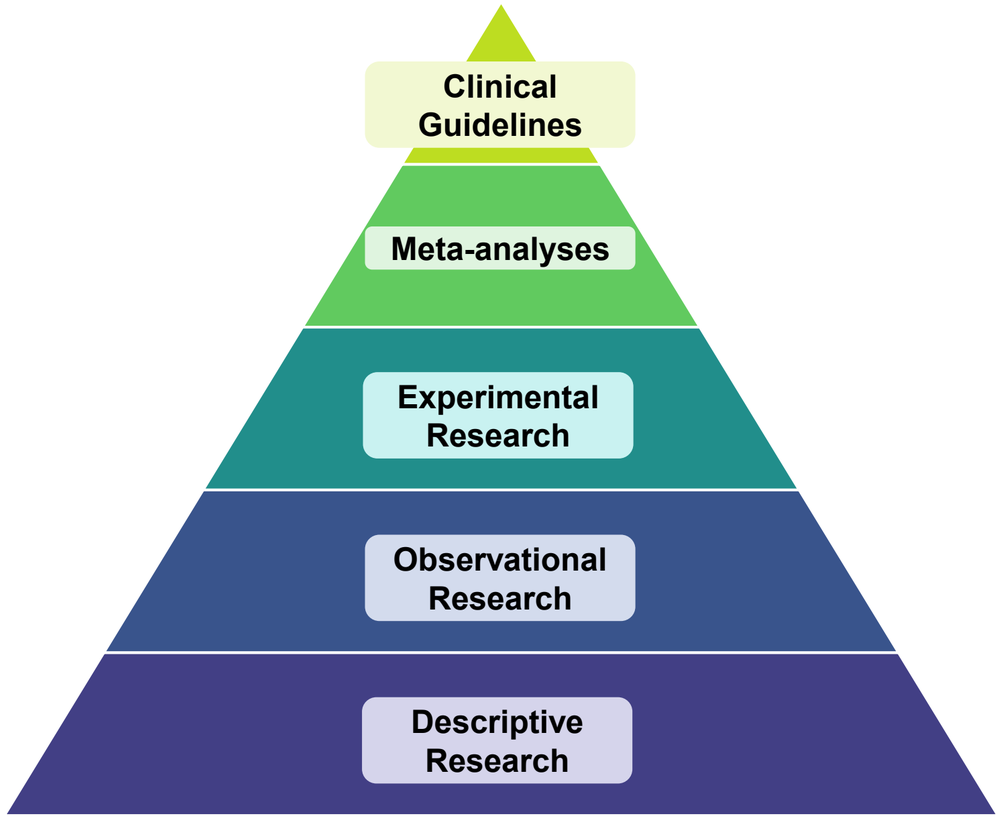
rom broad to more specific research questions in the
alysis (NMA). Such convergence is also taking place in the
tional trials, following the recent introduction of the
s impacting the design, data collection strategy, analysis and

Meta-analyses shape health care

- Health technology assessment (HTA) determines what treatments patients have access to

- Clinical guidelines determine what treatments are actually delivered



We asked:

How are meta-analyses handling different estimands?

Novel cancer therapies where treatment switching is common

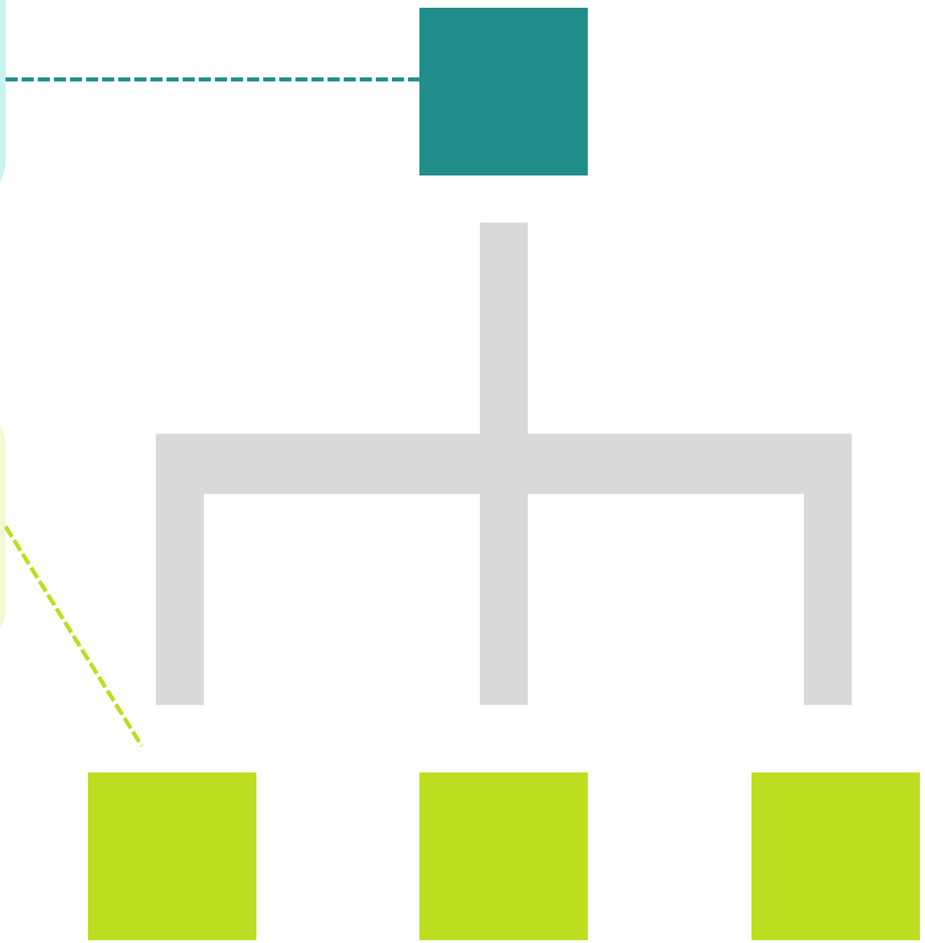
Cochrane meta-analyses of randomized trials published since 2021

Category	Criteria
Population	Patients with any cancer site or class, and of any stage or treatment setting
Intervention	• Immunotherapies • Hormone therapies • Targeted therapies • Other novel pharmacology therapies
Comparators	No restrictions
Outcomes	At least one of the following outcomes: • Progression free survival (PFS) • Overall survival (OS)
Study design	Meta-analyses randomized clinical trials identified through a systematic review
Other	Published in Cochrane Library in or after 2021

Two-stage Approach

Step 1:
Review meta-analyses and see what was done

Step 2:
Review included trials and see what could have been done



Key Elements Reviewed

Meta-Analyses

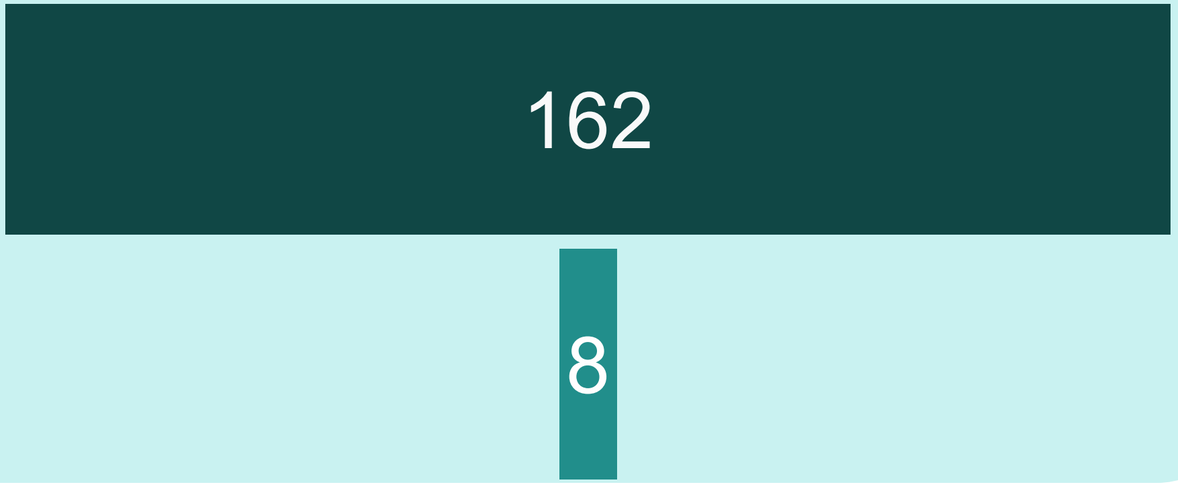
- Outcomes (PFS and/or OS)
- Consideration of treatment switching in risk of bias assessment
- Stated strategies for handling treatment switching in the evidence synthesis

Clinical Trials

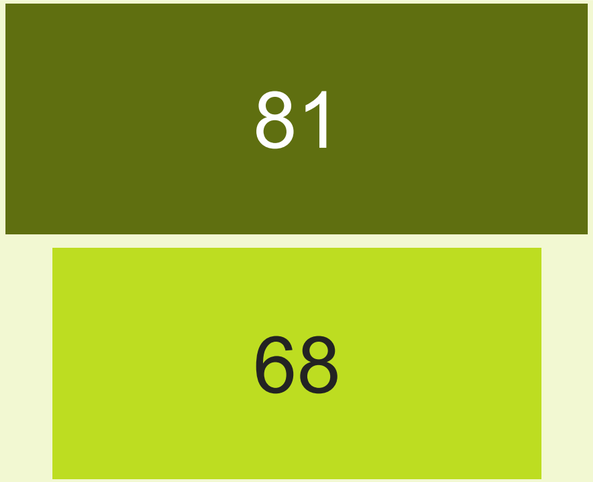
- Reported outcome definitions of PFS and OS and their related censoring mechanism
- Analytical framework (i.e., per protocol or intention to treat)
- Treatment switching
  - Was it allowed?
  - When?
  - For whom? (i.e., direction of switch)

Included Studies

162 Cochrane meta-analyses of which, 8 were eligible



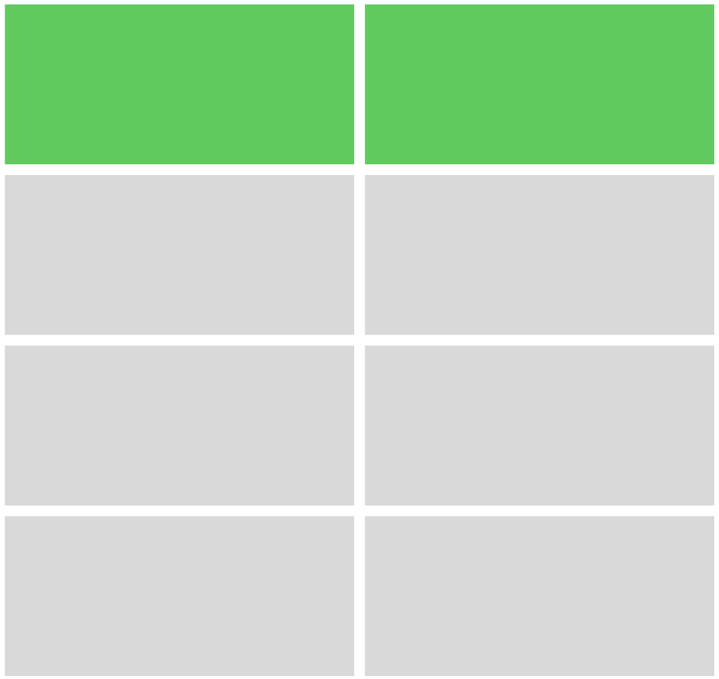
Containing 81 clinical trials, of which 68 were eligible



Meta-Analyses: Risk of Bias Assessment Based on Intercurrent Event

2 of 8 studies considered intercurrent events in the risk of bias assessment

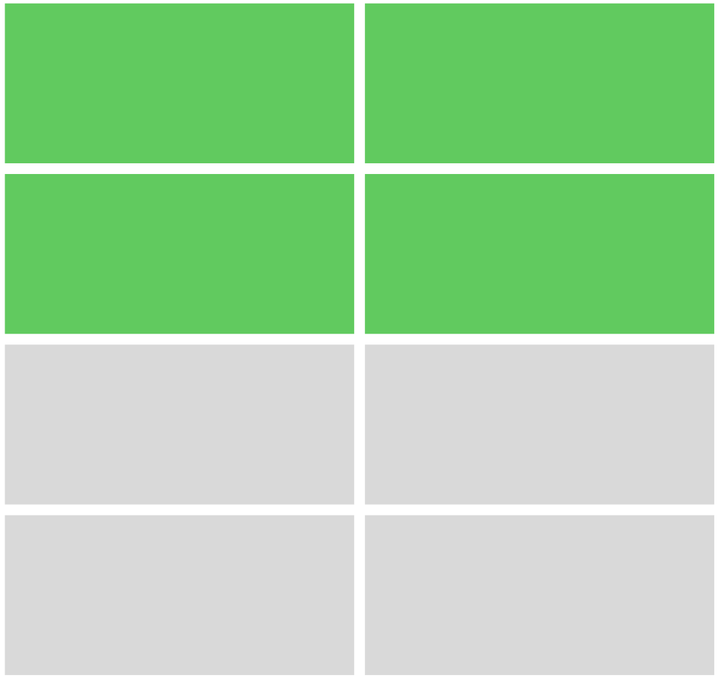
- Taylor et al. 2021, considered the impact of intercurrent events, and specifically treatment cross-over, on estimates of OS
- Ferrara et al. 2021, considered intercurrent events in their RoB 2 assessment of one included trial, where they noted that intercurrent illness could introduce bias into the study analysis



Meta-Analyses: Strategies for Treatment Switching

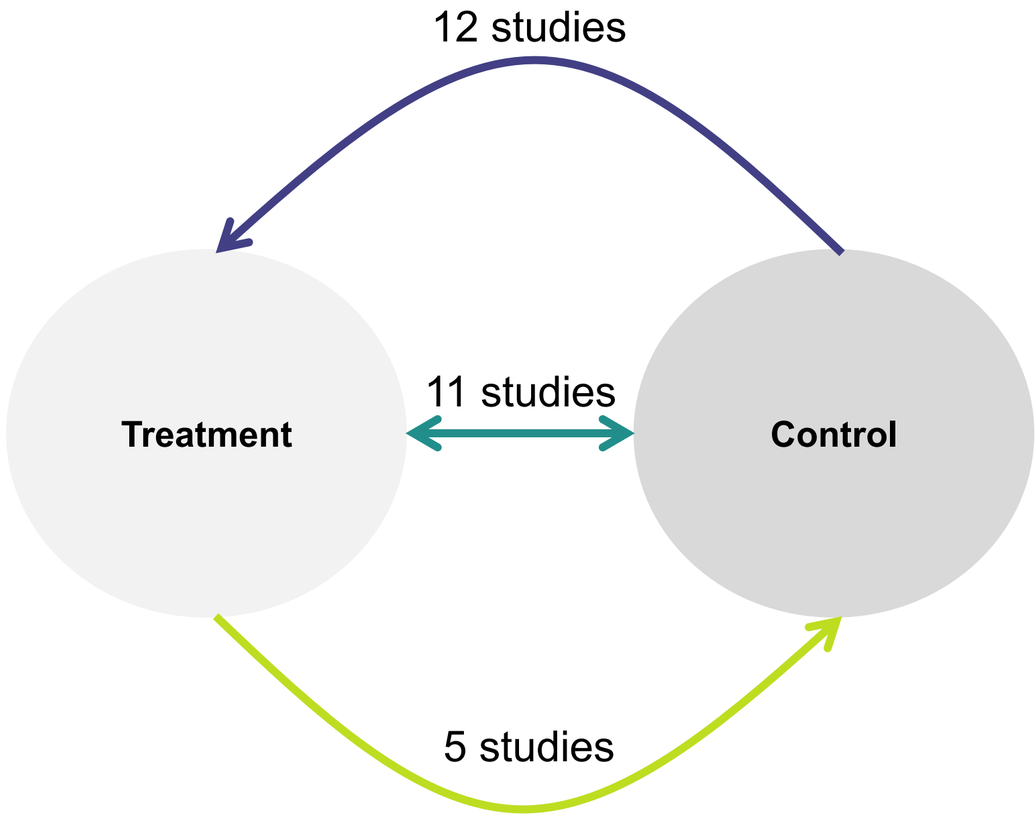
4 of 8 studies reported any strategy for addressing treatment switching

- Cameron et al. 2022 contextualized findings by reporting median length of survival time and rate of cross-over
- Taylor et al. planned sensitivity analyses to address crossover but necessary data were not available
- Zhu et al. 2022 & Ferrara et al. 2021 planned strategies for formal crossover trials but none were included in their meta-analyses



Clinical Trials: Direction of Treatment Switching

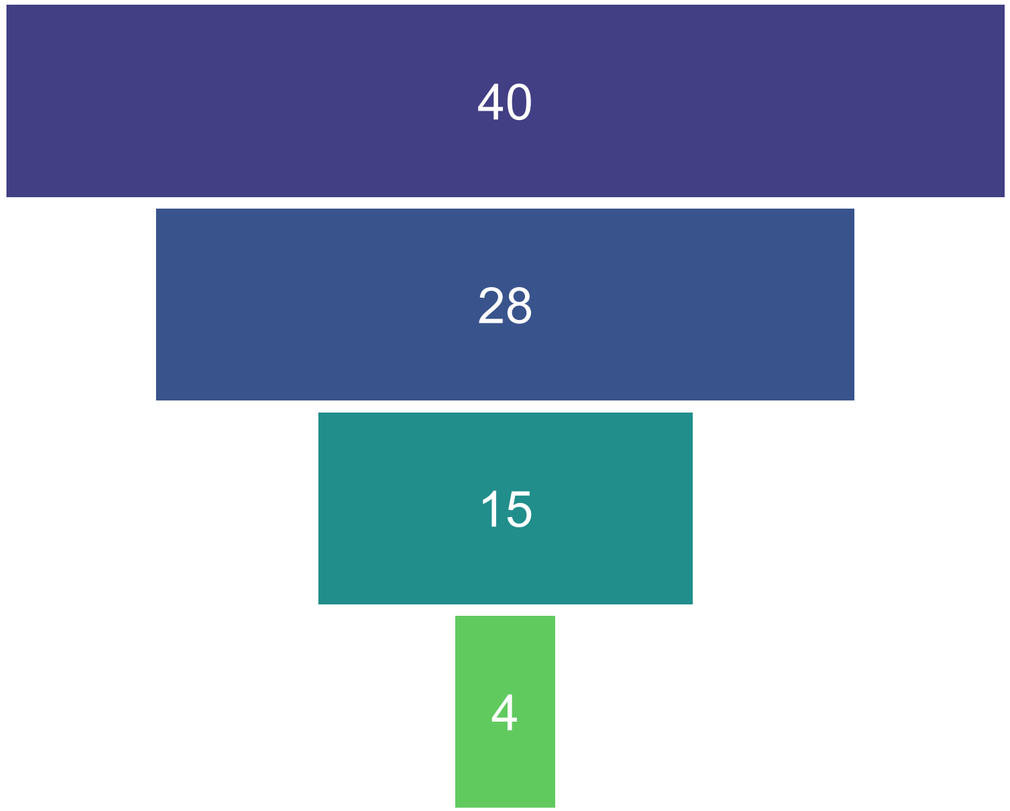
- 28 of the 40 trials that allowed treatment switching allowed cross-over between trial arms
- 27 of these reported the rate of treatment switching between trial arms



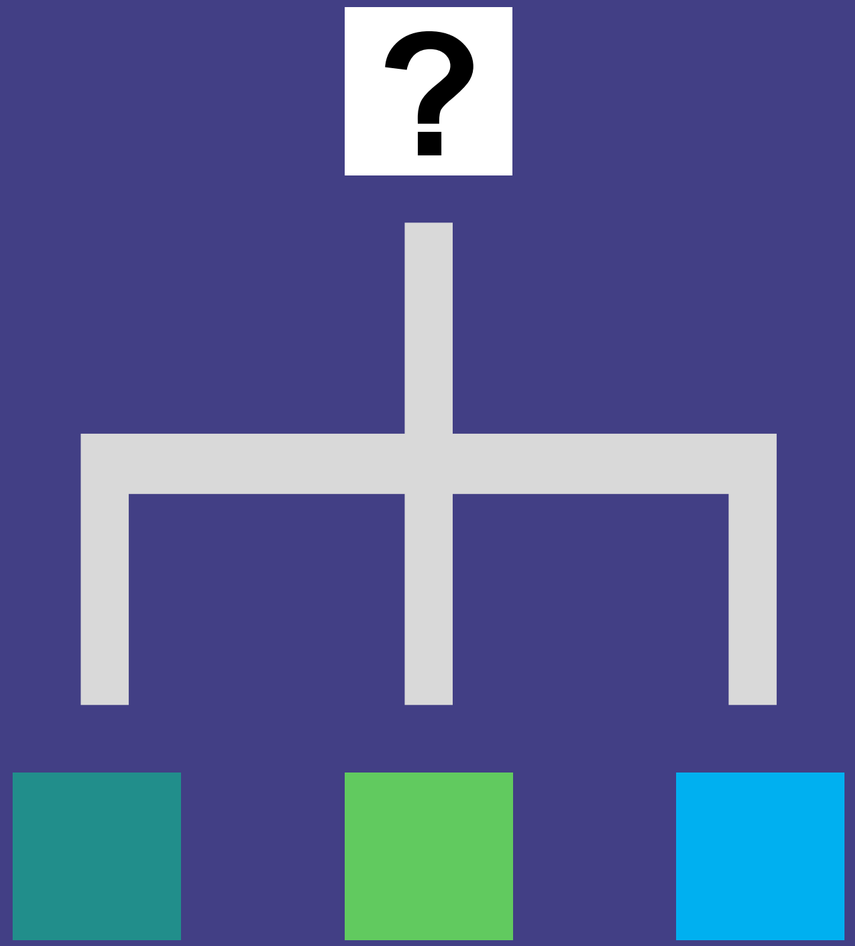
Clinical Trials: Strategies to Address Treatment Switching in PFS

- **28 of the 40 trials** had publicly available protocols or statistical analysis plans
- **15** censored participants from the primary analysis because of treatment switching
- **4** reported any censoring related to treatment switching in the primary publication

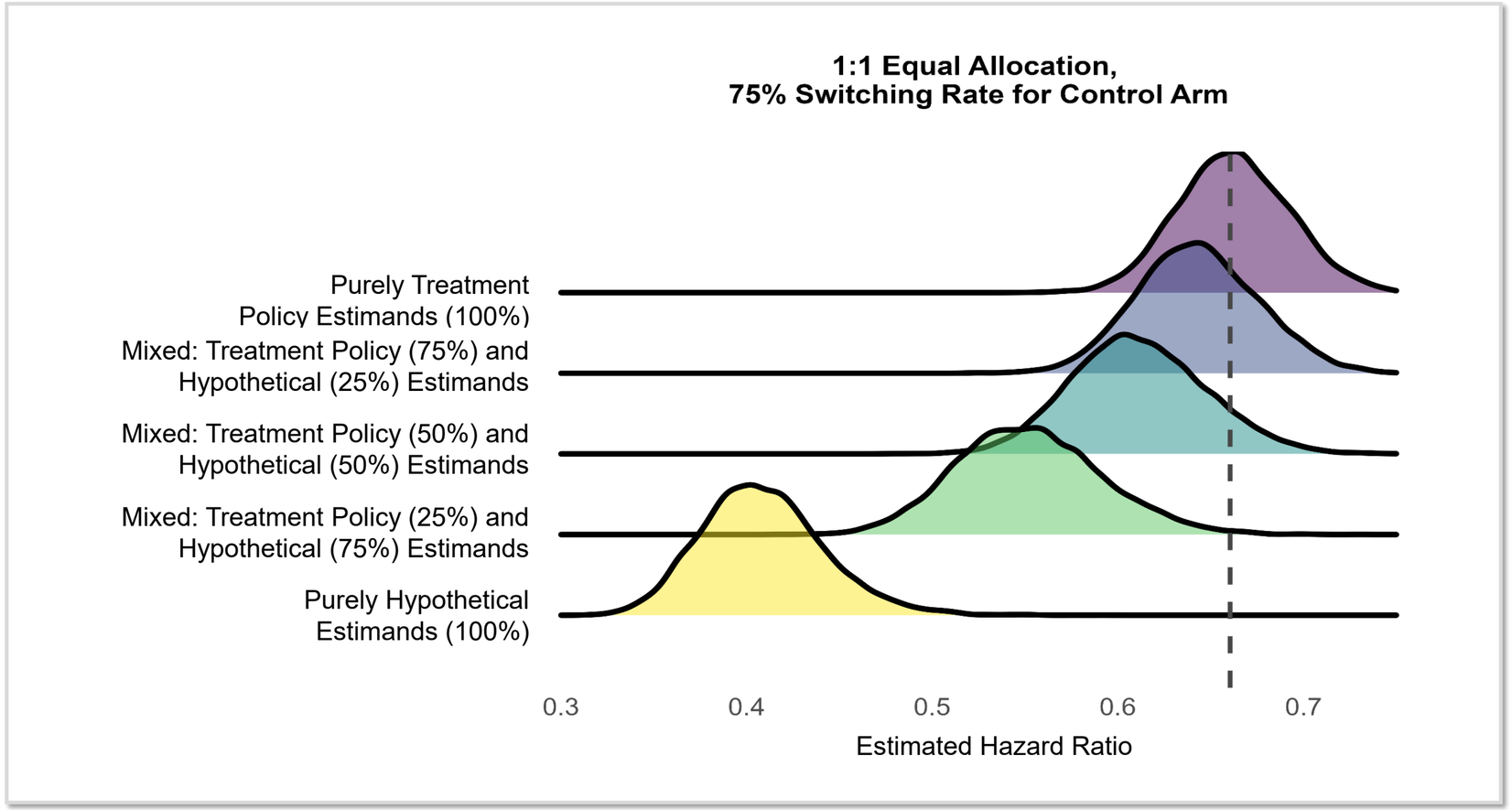
Censoring strategies varied between trials in a single met—analysis.



If censoring strategies vary (i.e., estimands differ), how do we interpret the meta-analytic results?



Naively pooling hypothetical and treatment policy estimands increases bias and yields estimates that don't reflect either estimand.



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Statistics > Methodology

[Submitted on 21 Nov 2024]

Estimands and Their Implications for Evidence Synthesis for Oncology: A Simulation Study of Treatment Switching in Meta-Analysis

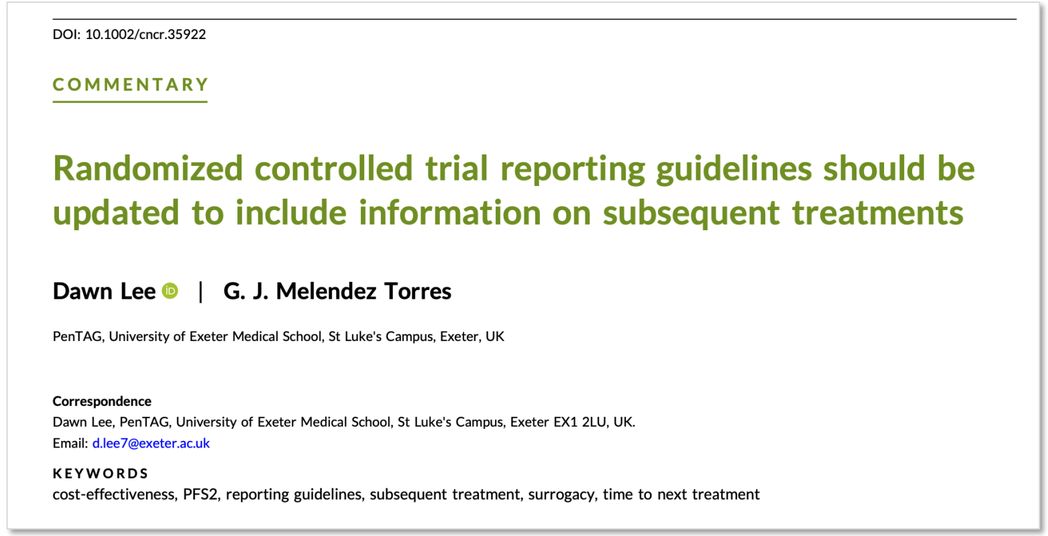
Quang Vuong, Rebecca K. Metcalfe, Antonio Remiro-Azócar, Anders Gorst-Rasmussen, Oliver Keene, Jay J. H. Park

General Conclusions

1. **Consideration of estimands in meta-analyses is limited** even for common and well-established intercurrent events like treatment switching in oncology
2. **Meta-analyses are mixing different estimands** making their interpretation difficult
3. **Limiting meta-analyses to single estimands is not practical**. While this could improve interpretability, it would limit the available evidence and erode the feasibility of meta-analysis

Future Directions

- **More comprehensive reporting of intercurrent events** is needed to enable meaningful meta-analysis in the era of estimands
  - Ideally this would also include more sharing of individual patient data
- **New methods that allow consideration of different estimands in meta-analysis**
  - We have begun early work building on state-based network meta-analysis



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COMMENTARY

Randomized controlled trial reporting guidelines should be updated to include information on subsequent treatments

Dawn Lee | **G. J. Melendez Torres**

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KEYWORDS
cost-effectiveness, PFS2, reporting guidelines, subsequent treatment, surrogacy, time to next treatment

Simulation Study Preprint

Thank you!

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