NIH Pragmatic Trials Collaboratory 2026 Annual Workshop

Endpoint Strategy in Pragmatic Trials

From Big Questions to Meaningful Outcomes

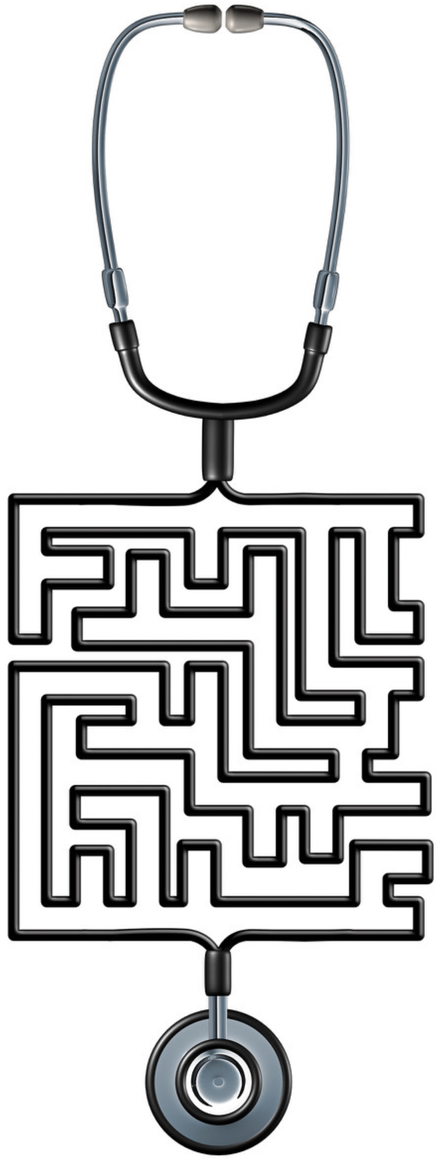
NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

Housekeeping

- Please pose your questions in the Q&A
- Slides and recordings will be posted on rethinkingclinicaltrials.org after the workshop

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Overview of Endpoints in Pragmatic Clinical Trials

Kevin Weinfurt, PhD
Duke University School of Medicine

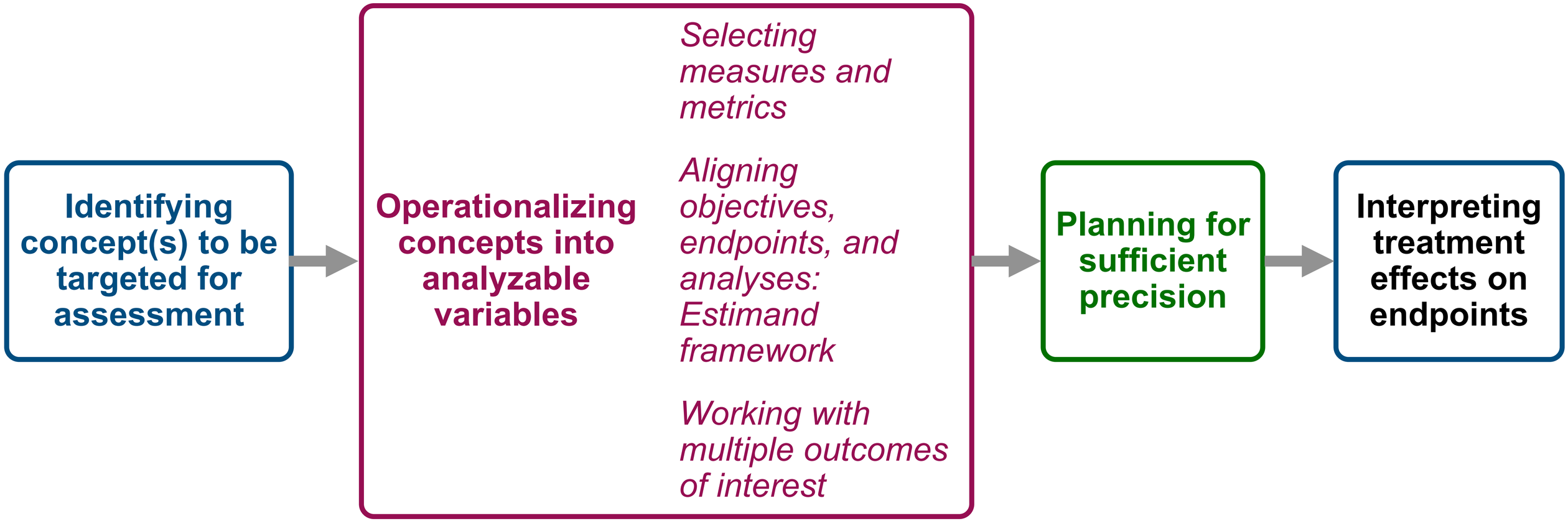
2026 NIH Workshop

Pragmatic clinical trials (PCTs) are *"designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens, and risks of a biomedical or behavioral health intervention at the individual or population level."*

Califf RM, Sugarman J. 2015. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials. 12:436–441. doi:10.1177/1740774515598334. PMID: 26374676.

Idea	Example
Benefit is framed in terms of some health **concept**	Reduced *impact of pain on daily living*
Operationalizing that concept requires specification of…	
Assessment(s) (or "measurements")	PROMIS Pain Interference Short Form 8a
Timing	Baseline and 3 months post-randomization
Statistical operation (if applicable)	Computed change in score
Definition of the **endpoint**, the analyzable variable thought to reflect the health concept	Change from baseline to 3 month post-randomization in PROMIS Pain Interference 8a scores

Key Endpoint Considerations in Pragmatic Clinical Trials



ACP PEACE *Advance Care Planning: Promoting Effective and Aligned Communication in the Elderly*

- Stepped-wedge, cluster-randomized trial testing whether the delivery of a video decision aid to patients and goals-of-care communication skills training to oncology clinicians will increase **advance care planning** in older patients with advanced cancer
- 29 oncology clinics in 3 healthcare systems
- 13,800 patients



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JAMA Network Open

Original Investigation | Geriatrics

An Intervention to Increase Advance Care Planning Among Older Adults With Advanced Cancer

A Randomized Clinical Trial

Angelo E. Volandes, MD, MPH; Yuchiao Chang, PhD; Joshua R. Lakin, MD; Michael K. Paasche-Orlow, MD; Charlotta Lindvall, MD, PhD; Seth N. Zupanc, BA; Diana Martins-Welch, MD; Maria T. Carney, MD; Edith A. Burns, MD; Jennifer Itty, MPH; Kaitlin Emmert-Tangredi, MSW; Narda J. Martin, MSN-ED, RN; Shreya Sanghani, MS; Jon Tilburt, MD; Kathryn I. Pollak, PhD; Aretha Delight Davis, MD, JD; Cynthia Garde, MBA; Michael J. Barry, MD; Areej El-Jawahri, MD; Lisa Quintiliani, PhD; Kate Sciacca, NP; Julie Goldman, MPH; James A. Tulsky, MD

Abstract

IMPORTANCE Many older adults with advanced cancer never communicate goals of care or treatment preferences to their clinicians, raising the risk that care received will not match their values. Scalable models of care may help surmount this barrier.

OBJECTIVE To test whether a combined patient and clinician intervention increased the rate of advance care planning (ACP) documentation in large health care systems.

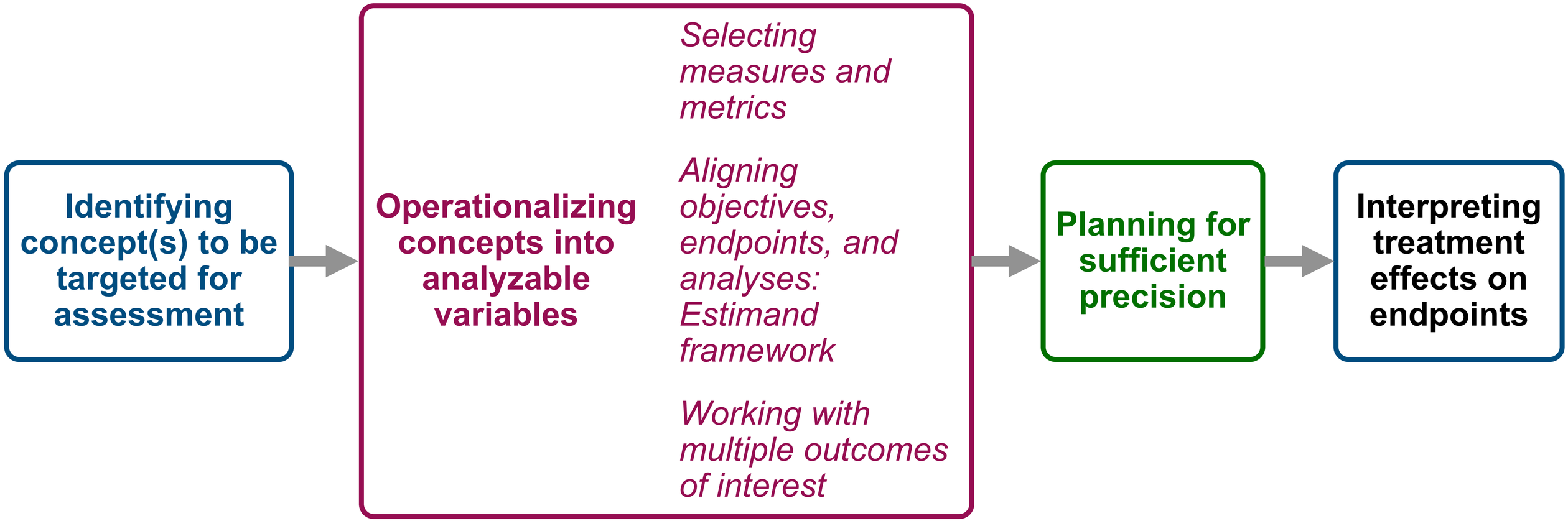
DESIGN, SETTING, AND PARTICIPANTS This stepped-wedge cluster randomized clinical trial using an open cohort design included patients aged 65 years or older with advanced cancer seen at

Key Points

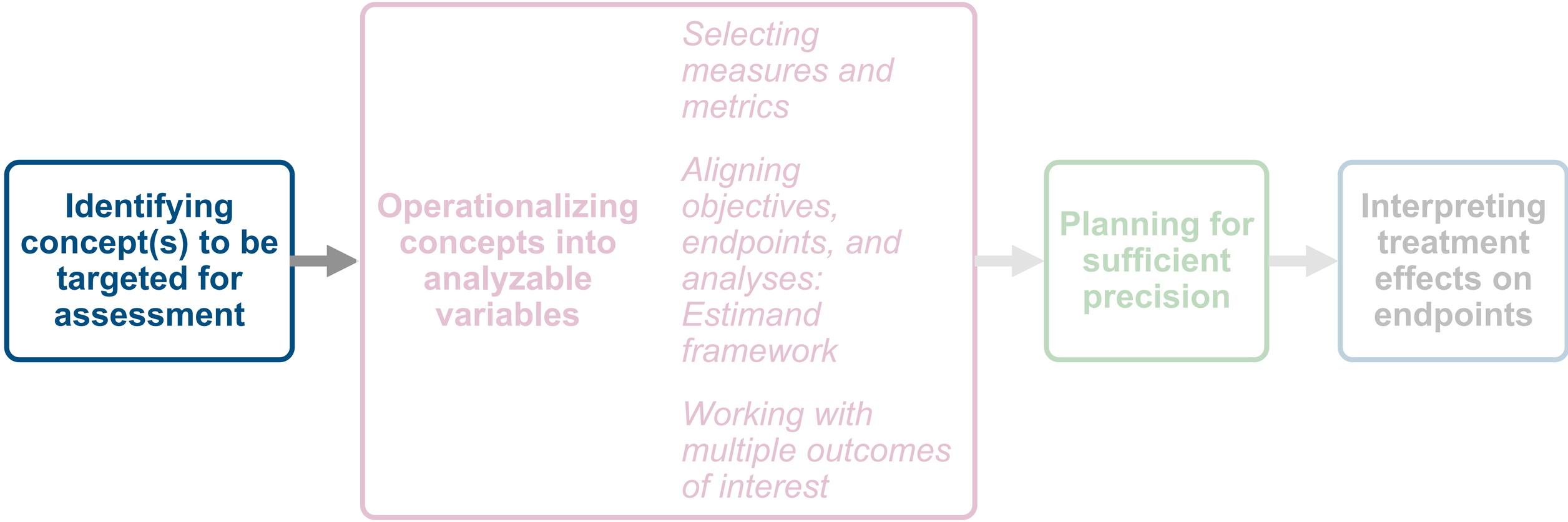
Question Can use of the combination of evidence-based patient video decision aids with clinician communication skills training in ambulatory oncology practices improve advance care planning (ACP) documentation among older patients (aged ≥65 years) with advanced cancer?

JAMA Network Open. 2025;8(5):e259150. doi:10.1001/jamanetworkopen.2025.9150

Key Endpoint Considerations in Pragmatic Clinical Trials

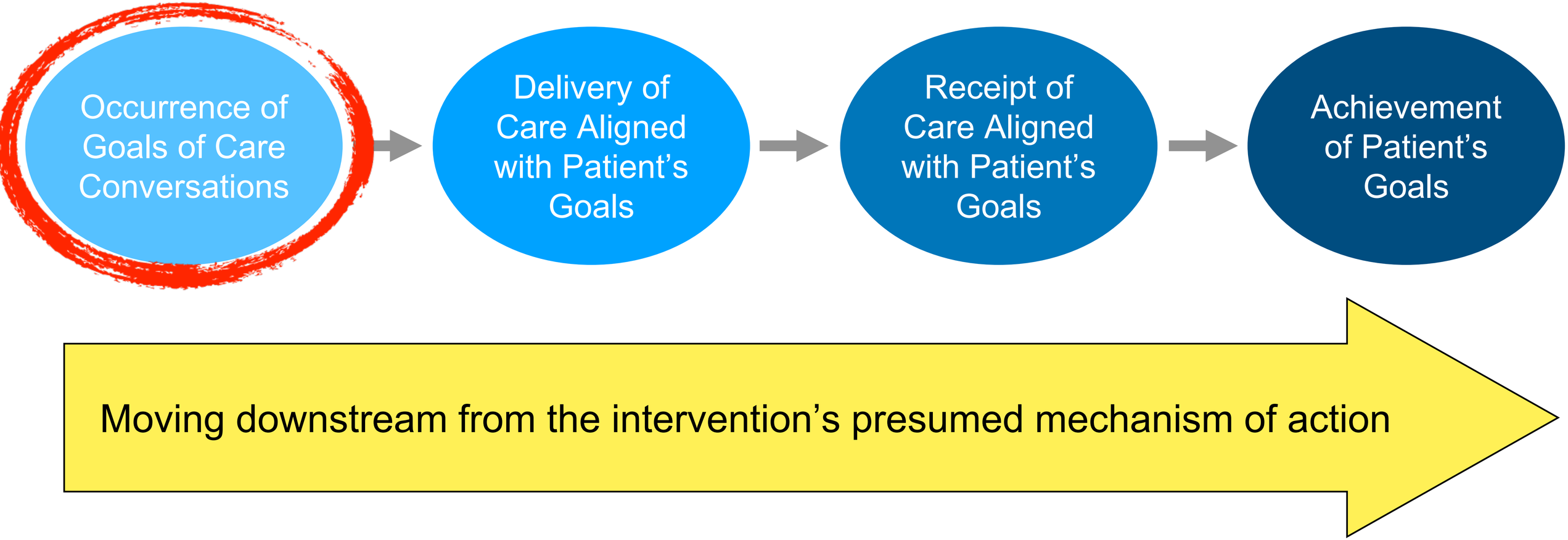


Key Endpoint Considerations in Pragmatic Clinical Trials

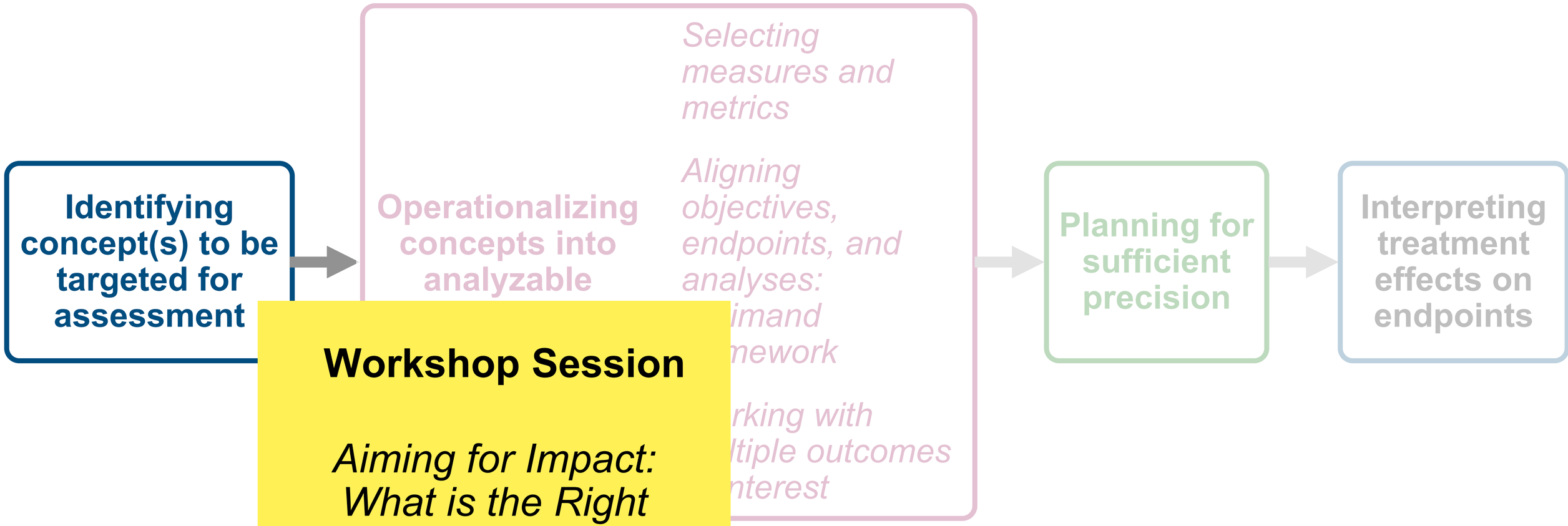


Identifying concept(s) to be targeted for assessment

ACP PEACE Example



Key Endpoint Considerations in Pragmatic Clinical Trials

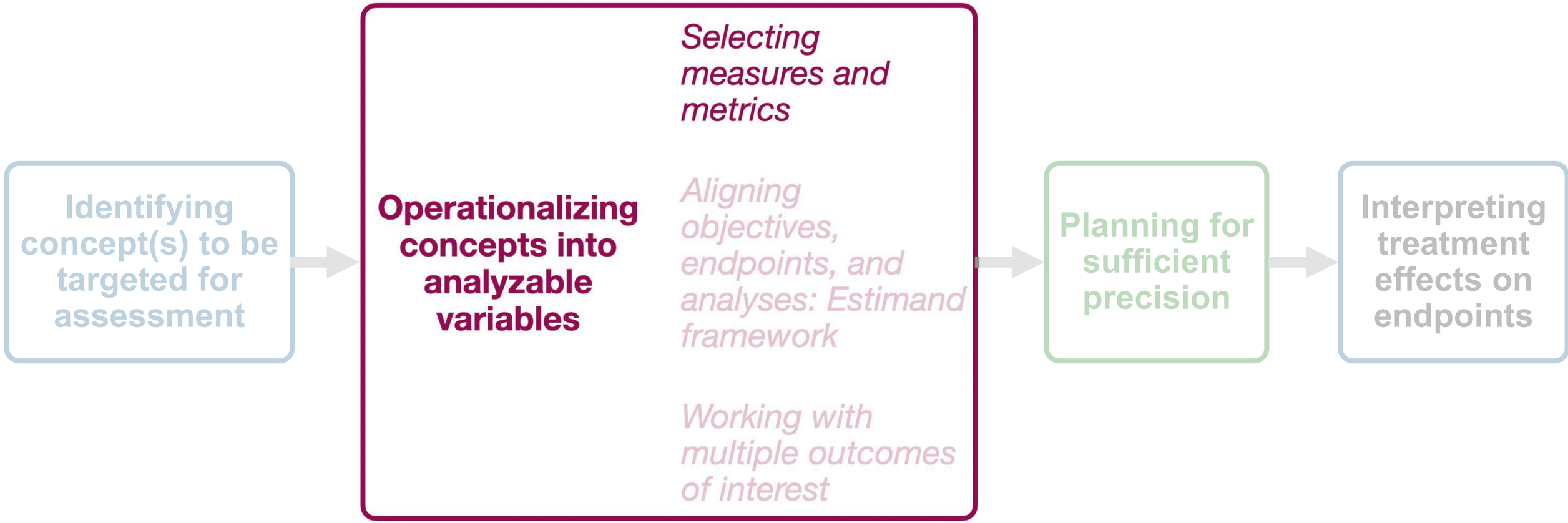


Workshop Session

Aiming for Impact: What is the Right Concept to Target?

Tues @11:35 AM

Key Endpoint Considerations in Pragmatic Clinical Trials



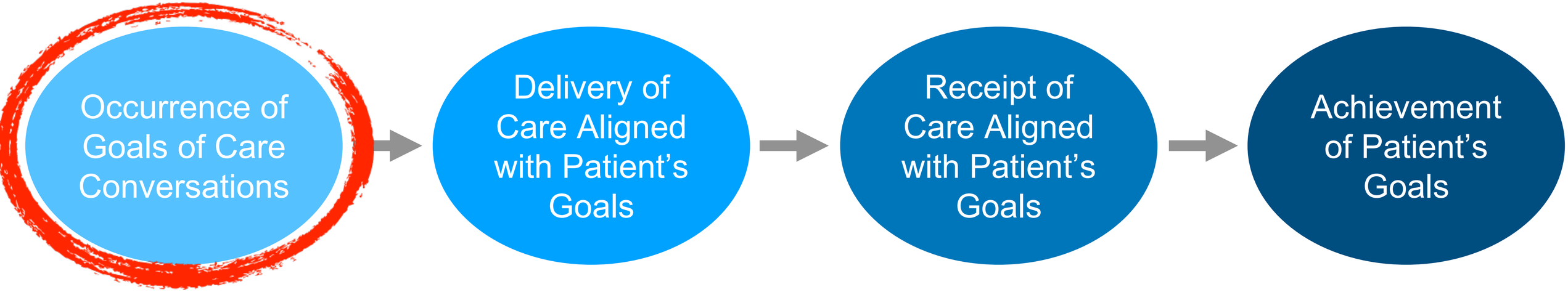
Operationalizing concepts into analyzable variables

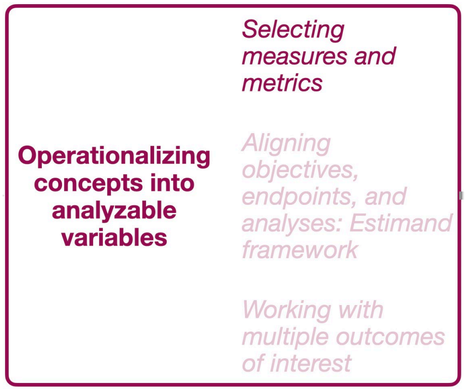
Selecting measures and metrics

Aligning objectives, endpoints, and analyses: Estimand framework

Working with multiple outcomes of interest

ACP PEACE Example





ACP PEACE Example

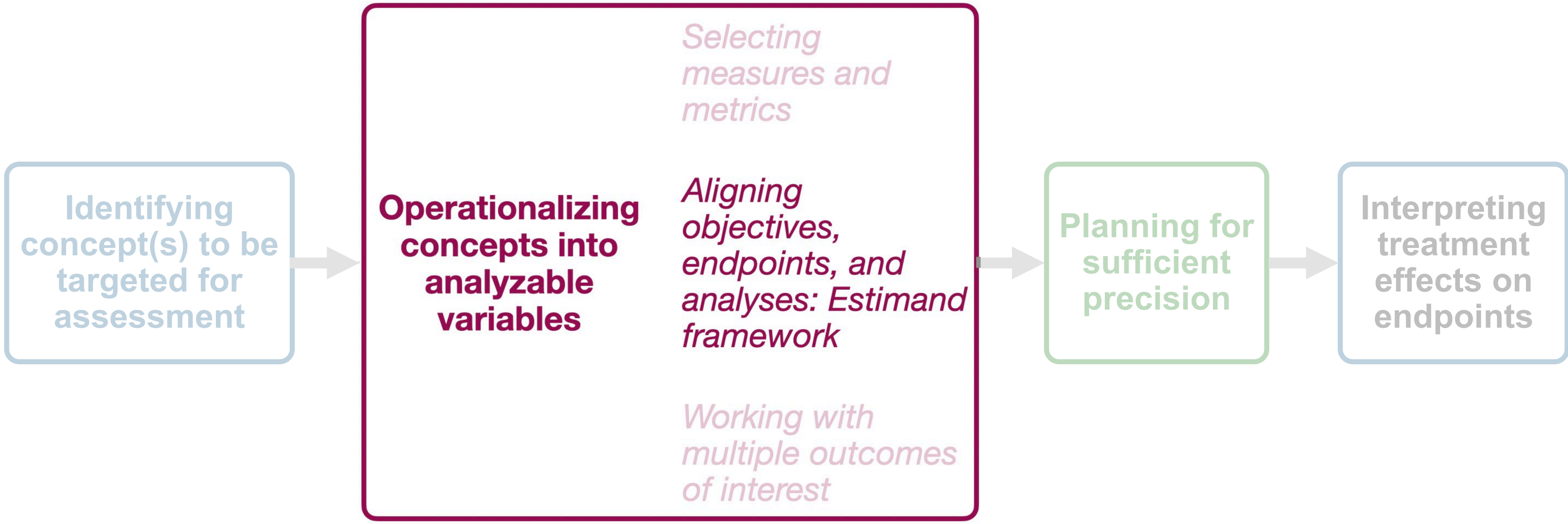
Occurrence of Goals of Care Conversations

Advanced Care Planning (ACP) documentation in free-text clinical notes in the electronic health record (EHR)* — Binary (Y/N)

- Goals of care, **or**
- Limitation of life-sustaining treatment, **or**
- Palliative care, **or**
- Hospice

*Natural language processing-assisted human adjudication of communication documentation

Key Endpoint Considerations in Pragmatic Clinical Trials



Operationalizing concepts into analyzable variables

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ACP PEACE

Example

ACP PEACE designed prior to full adoption of estimand framework and extension to cluster-randomized trials not released until March 2026

RESEARCH METHODS AND REPORTING

OPEN ACCESS

Check for updates

CRT-Estimands Framework: consensus based extension of the ICH E9(R1) addendum for cluster randomised trials

Brennan C Kahan,[1] Frank Bretz,[2,3] Andrew Copas,[1] Michael O Harhay,[1,4] Gary S Collins,[5] Melanie Bahti,[6] Dongquan Bi,[1] Marion K Campbell,[7] Katherine R Courtright,[4,6] Timothy Feeney,[8,9] Andrew B Forbes,[10] Amit X Garg,[11] Scott D Halpern,[4,6] Patrick J Heagerty,[12] Karla Hemming,[13] Sally Hopewell,[14] James P Hughes,[12] David M Murray,[15] Joseph S Ross,[16,17] Derek Stewart,[18] Monica Taljaard,[19,20] Obioha C Ukoumunne,[21] Catherine L Auriemma,[6] Fan Li[22]

For numbered affiliations see end of the article

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Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/bmj-2025-089050

Accepted: 06 March 2026

In order to assess the relevance of trial results or the appropriate trials methods, interest holders (eg, clinicians, patients, and policy makers) need a clear description of the trial's research question. To improve clarity and consistency in clinical trials, the International Conference on Harmonisation (ICH) released the ICH E9(R1) addendum, which set out a framework for defining estimands in cluster randomised trials, with the objective of improving the clarity of the estimands, and consequently, the research questions, in these trials. This article presents the CRT-Estimands Framework with explanations and examples of how it can be implemented. Adopting the framework will improve the clarity of estimands in cluster randomised trials and facilitate

Operationalizing concepts into analyzable variables

Selecting measures and metrics

Aligning objectives, endpoints, and analyses: Estimand framework

Working with multiple outcomes of interest

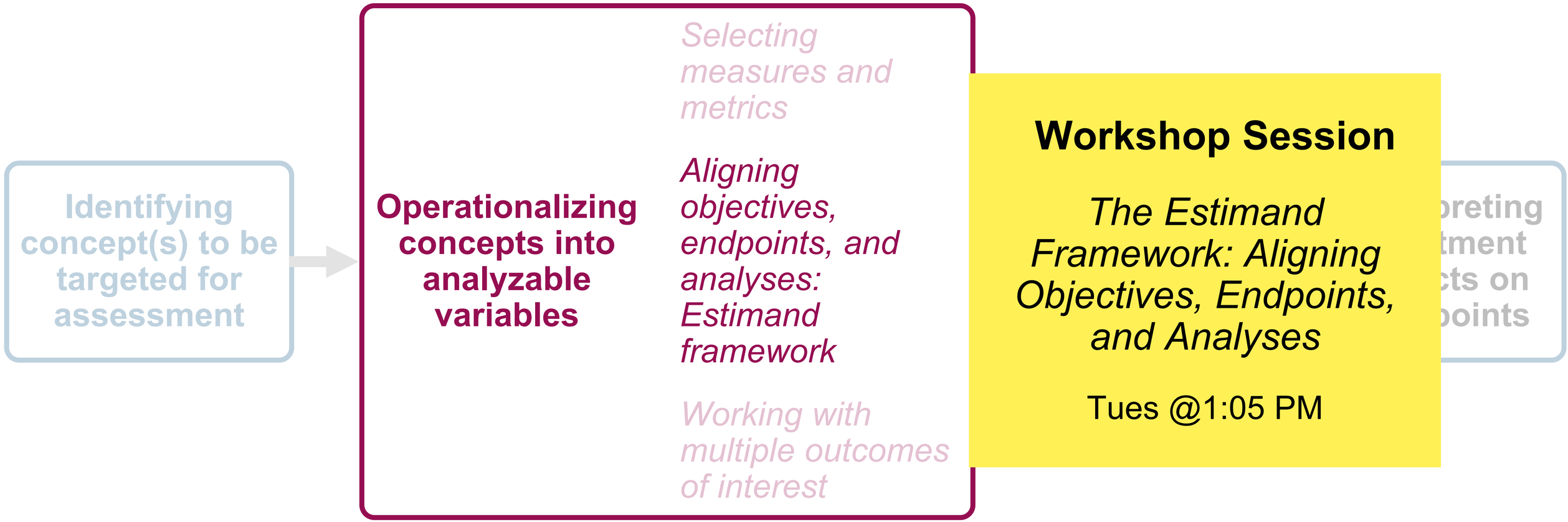
ACP PEACE Example

Noncompliance and nonadherence → Affect the interpretation or existence of outcome measurement = *"Intercurrent Events"*

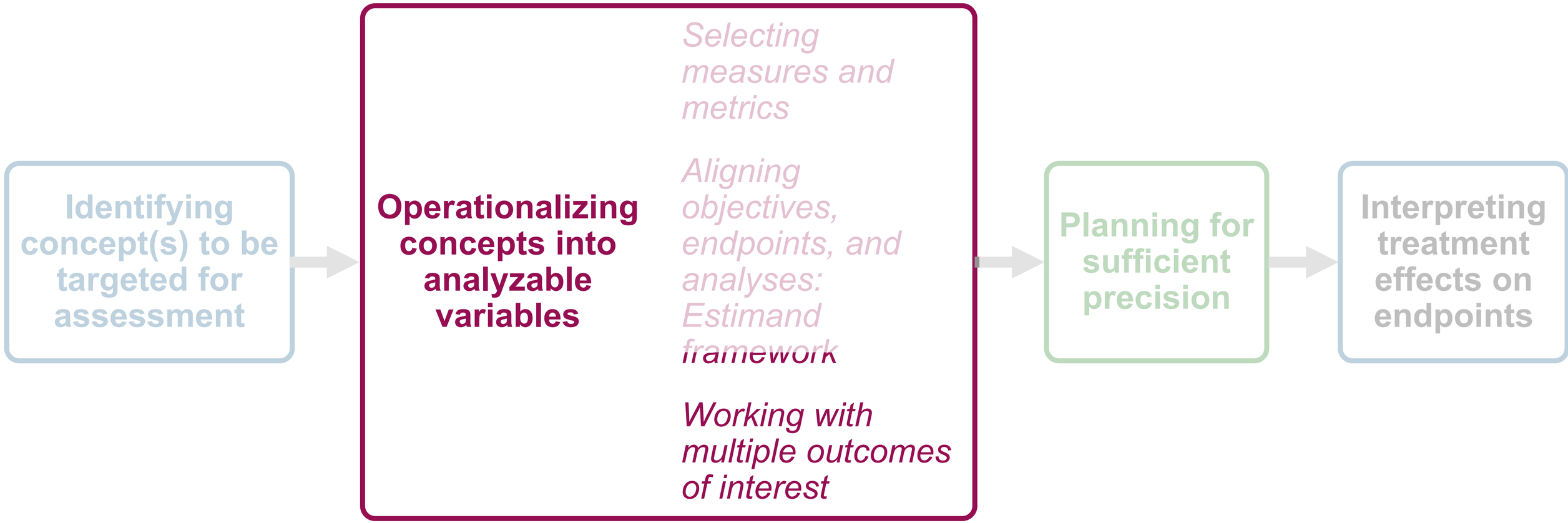
ACP PEACE used an intent-to-treat approach

In estimand framework parlance, known as a "Treatment Policy" strategy for handling this particular type of intercurrent event

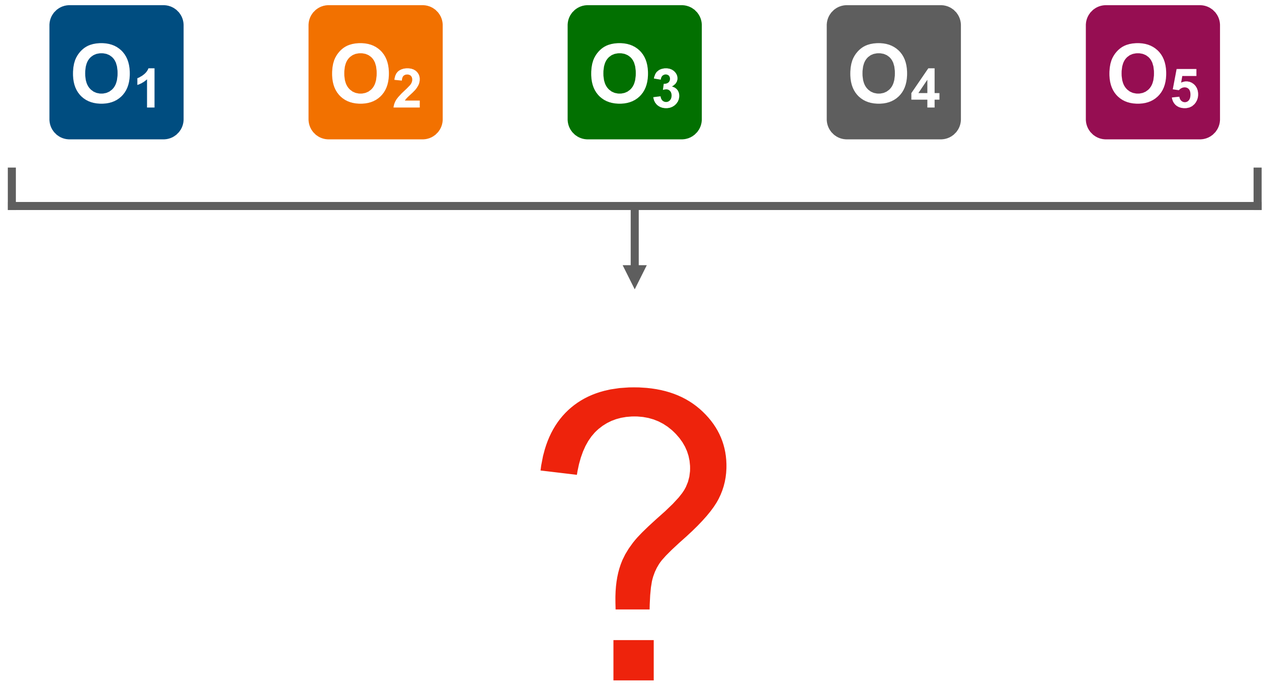
Key Endpoint Considerations in Pragmatic Clinical Trials



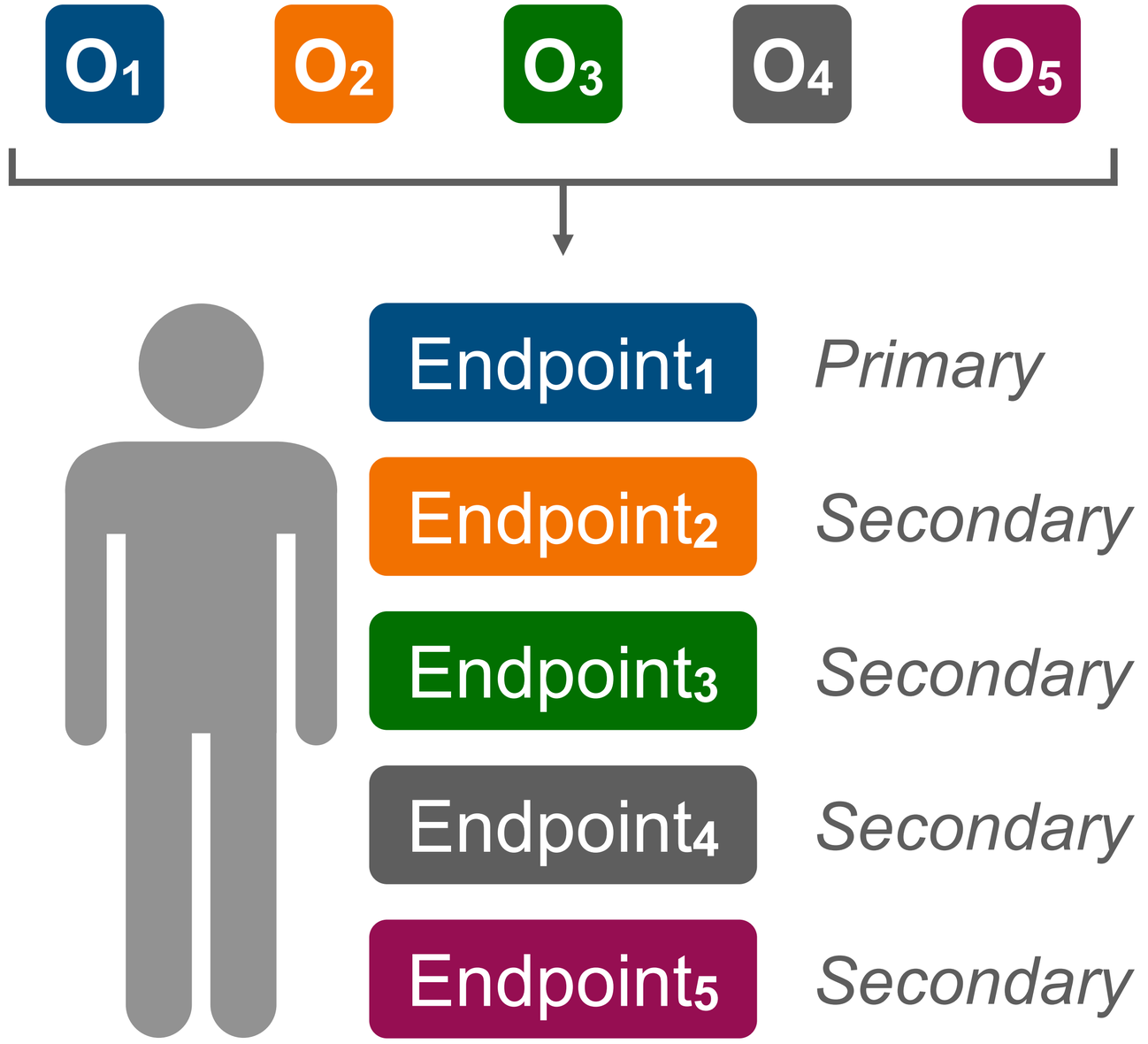
Key Endpoint Considerations in Pragmatic Clinical Trials



Multiple outcome variables associated with a disease

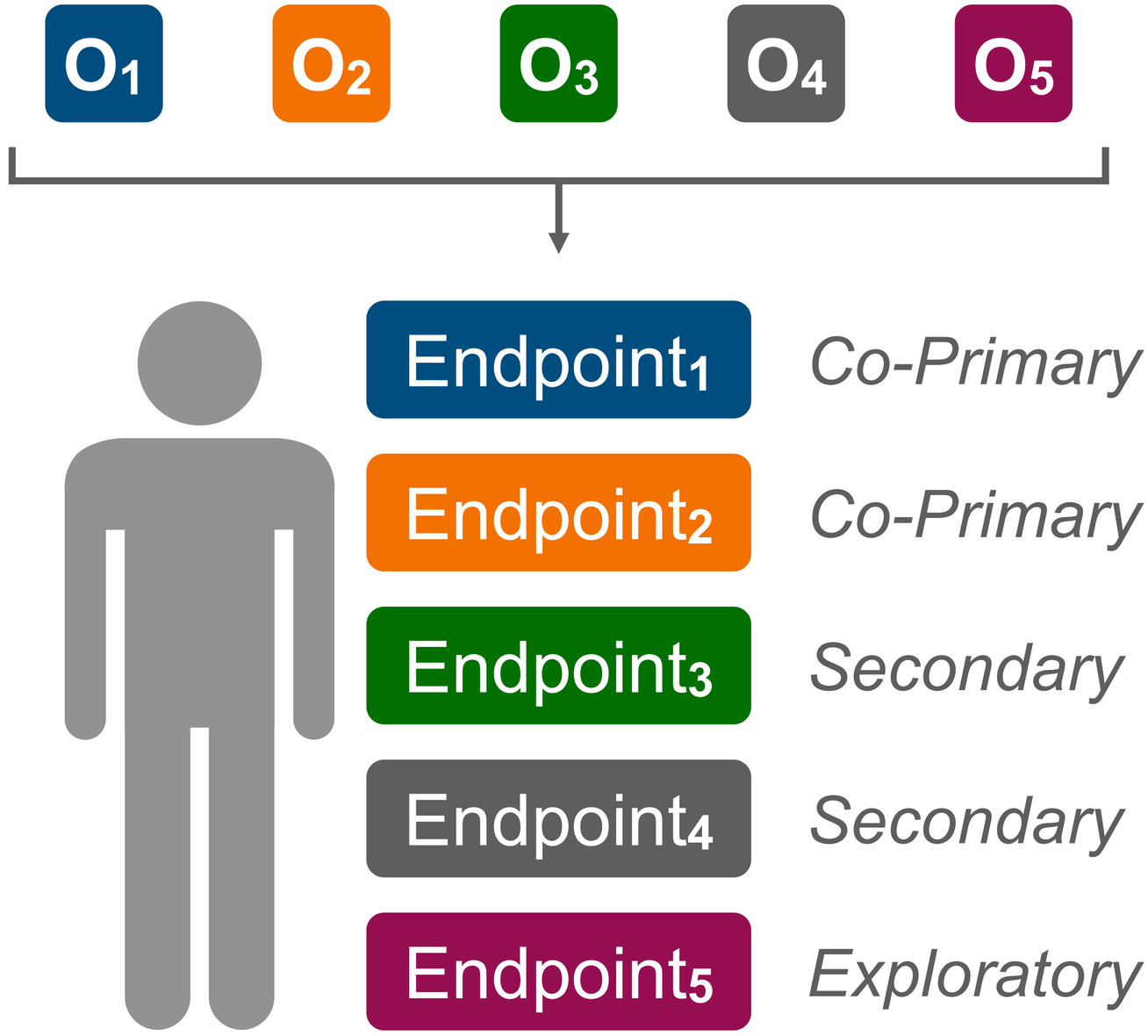


Multiple outcome variables associated with a disease



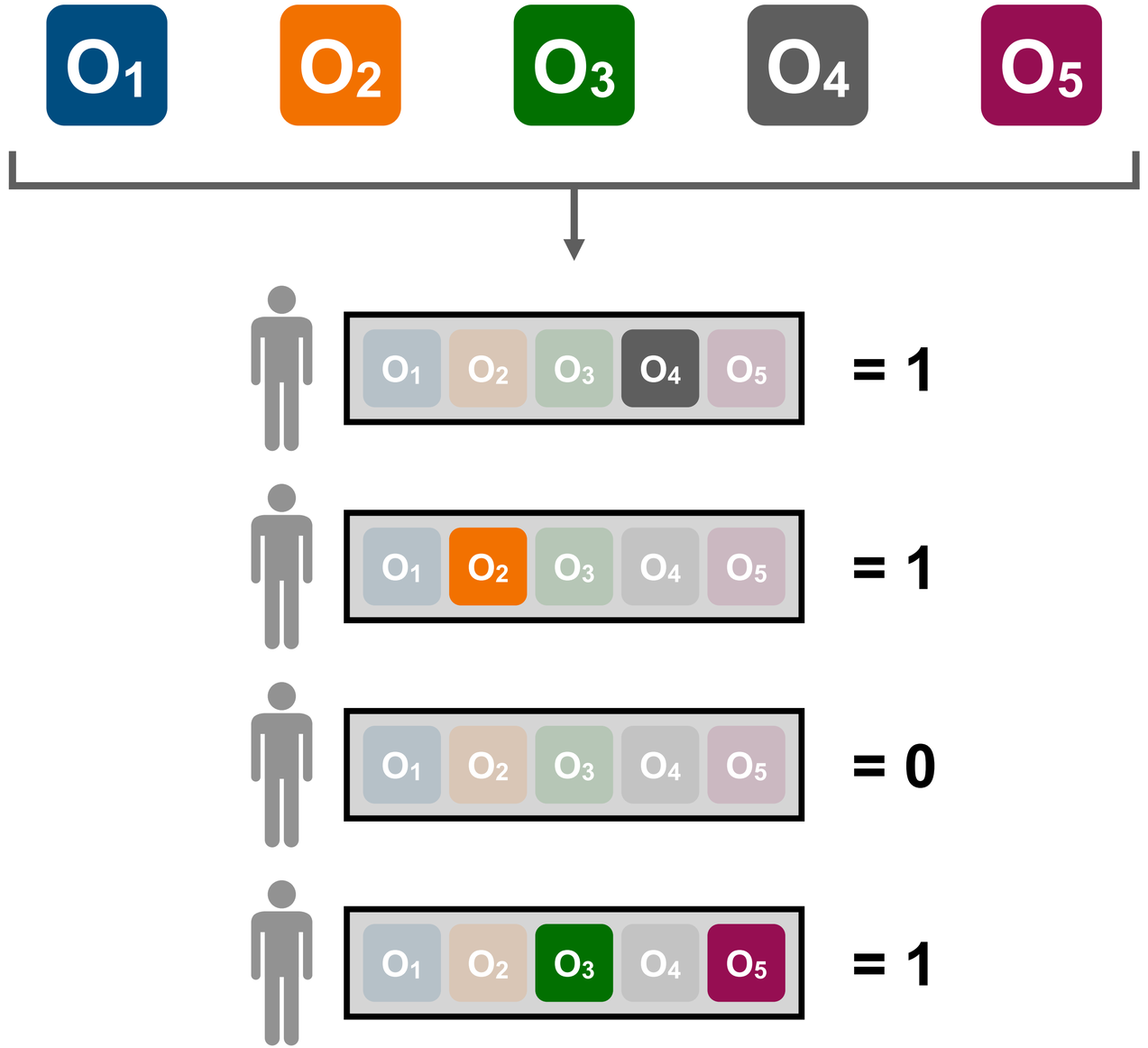
Treat outcome variables as separate endpoints

Multiple outcome variables associated with a disease



Treat outcome variables as separate endpoints

Multiple outcome variables associated with a disease



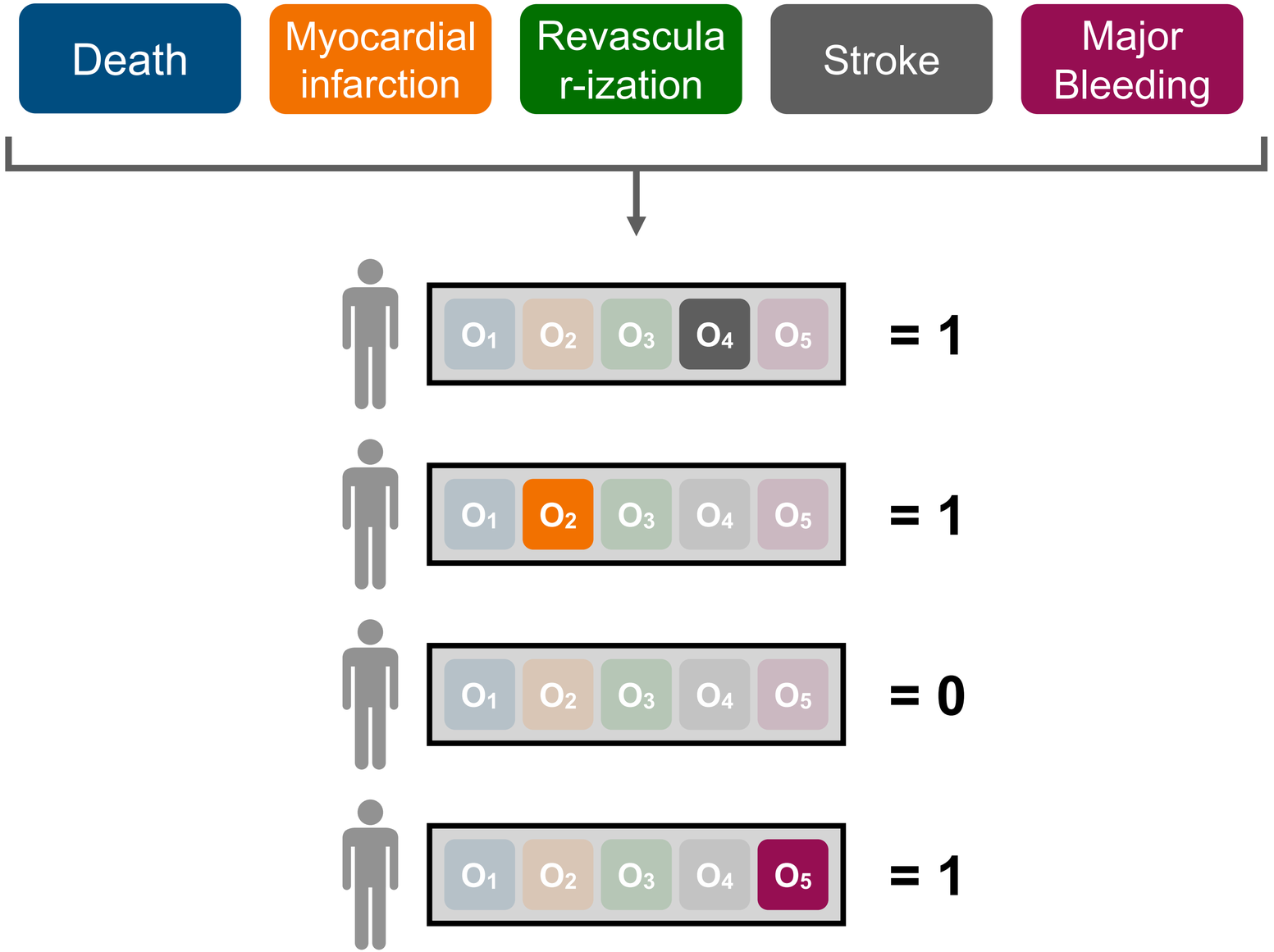
Form a composite endpoint

"[Defined] as the occurrence or realization in a subject of any one of the specified components"

FDA Multiple Endpoints in Clinical Trials, October, 2022, p. 10

Example

Major adverse cardiac and cerebrovascular events (MACCE)

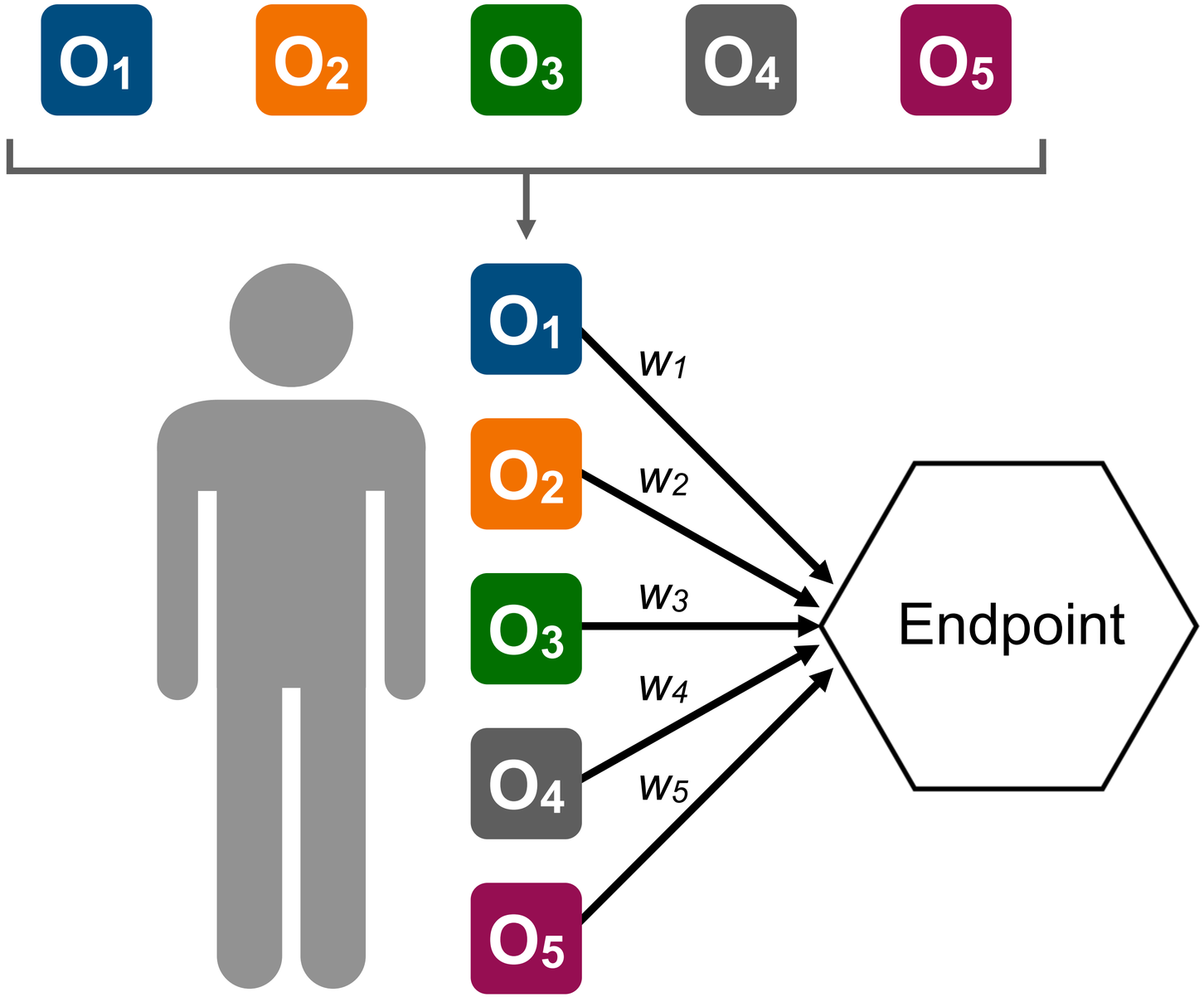


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FDA Multiple Endpoints in Clinical Trials, October, 2022, p. 10

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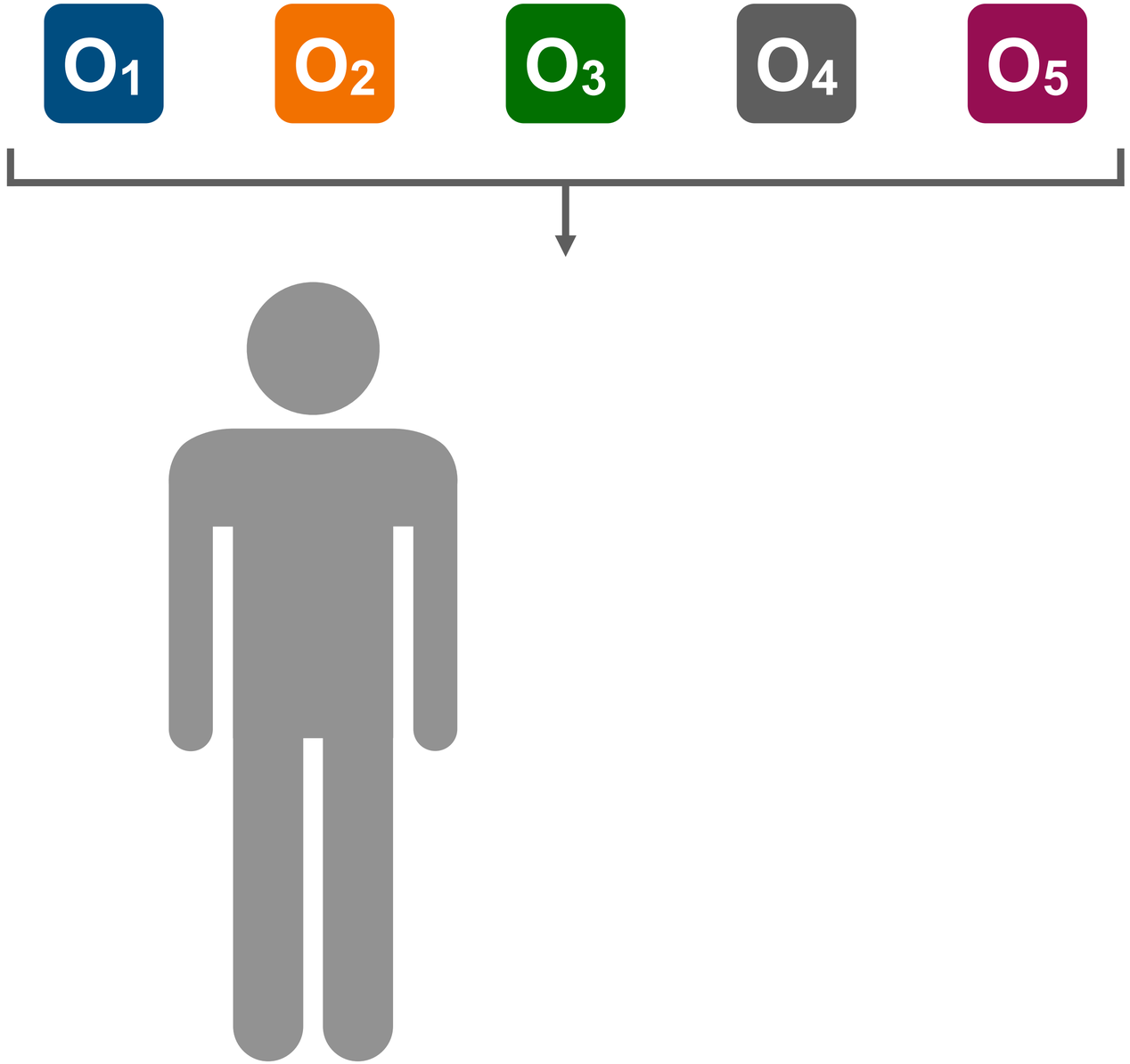


Form a multi-component endpoint

"[A] within-subject combination of two or more components"

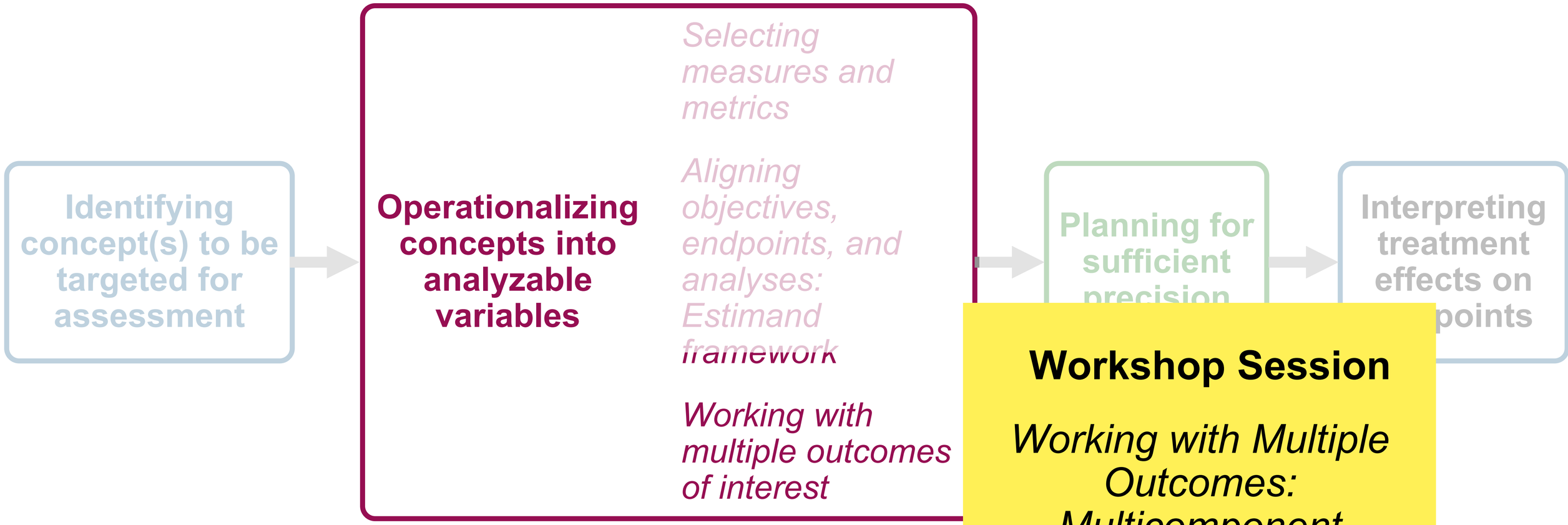
FDA Multiple Endpoints in Clinical Trials, October, 2022, p. 11

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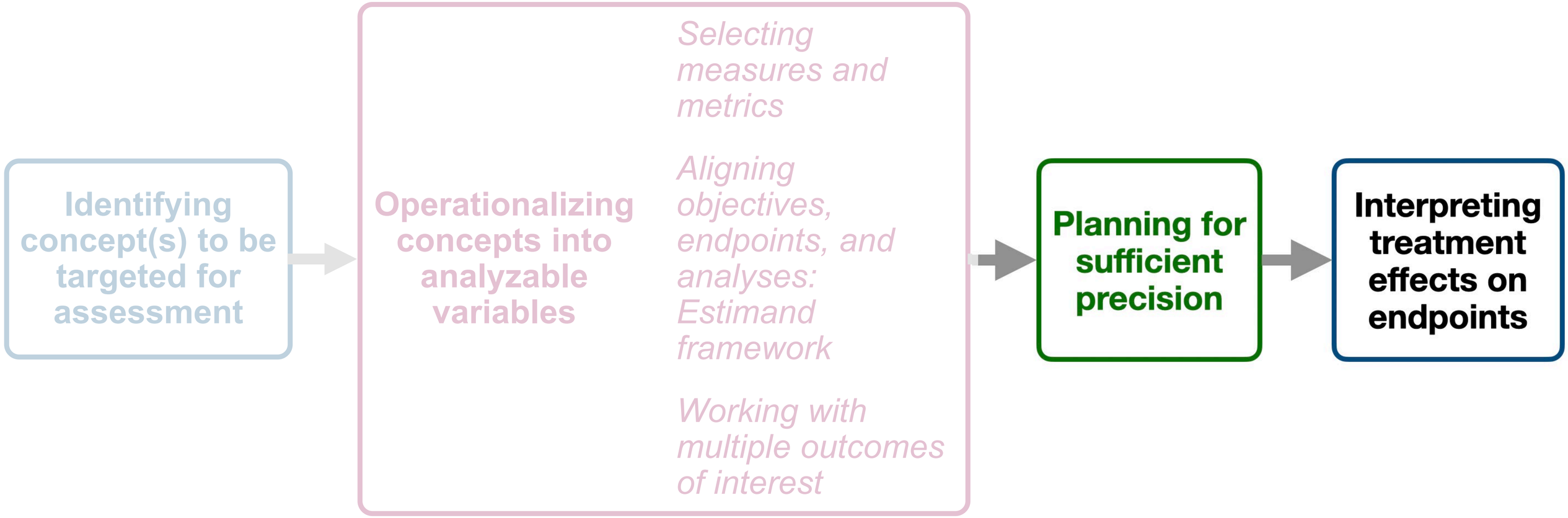


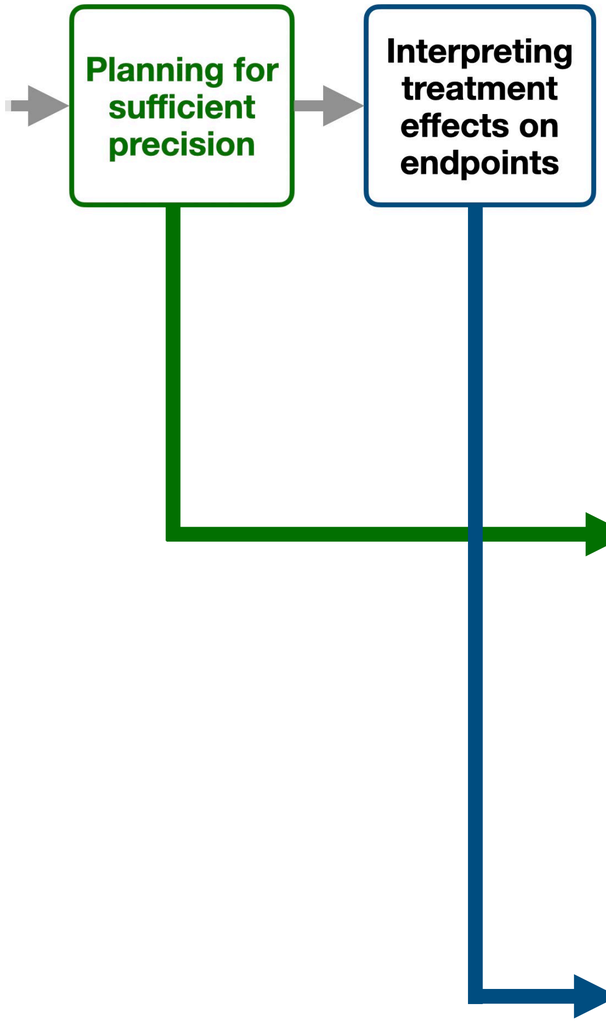
Other options (e.g., hierarchical composite endpoints)

Key Endpoint Considerations in Pragmatic Clinical Trials



Key Endpoint Considerations in Pragmatic Clinical Trials





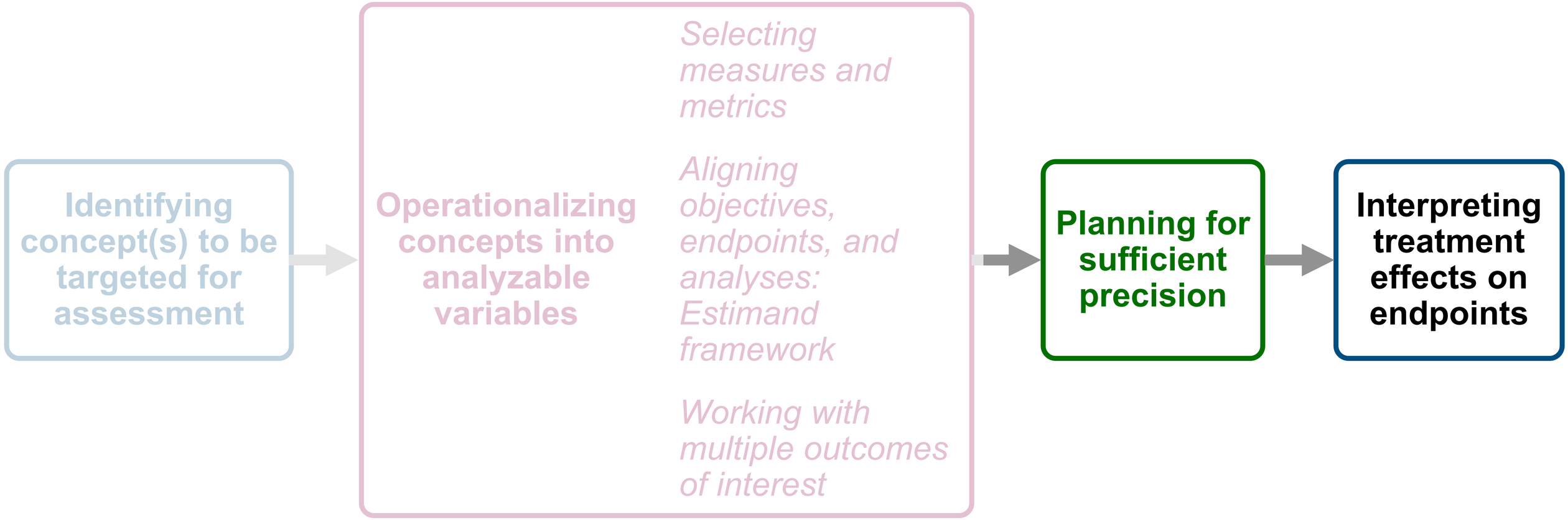
ACP PEACE Example

"The study had greater than 90% power to detect a 10% absolute increase of ACP documentation rate (the primary outcome) with a 2-sided significance level of α = .05."

"Although the absolute effect was modest (adjusted estimated rate effect of 7%), when considered across a population, the increase in documentation is both clinically and statistically meaningful."

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Key Endpoint Considerations in Pragmatic Clinical Trials



Tension in Constructing and Interpreting Endpoints

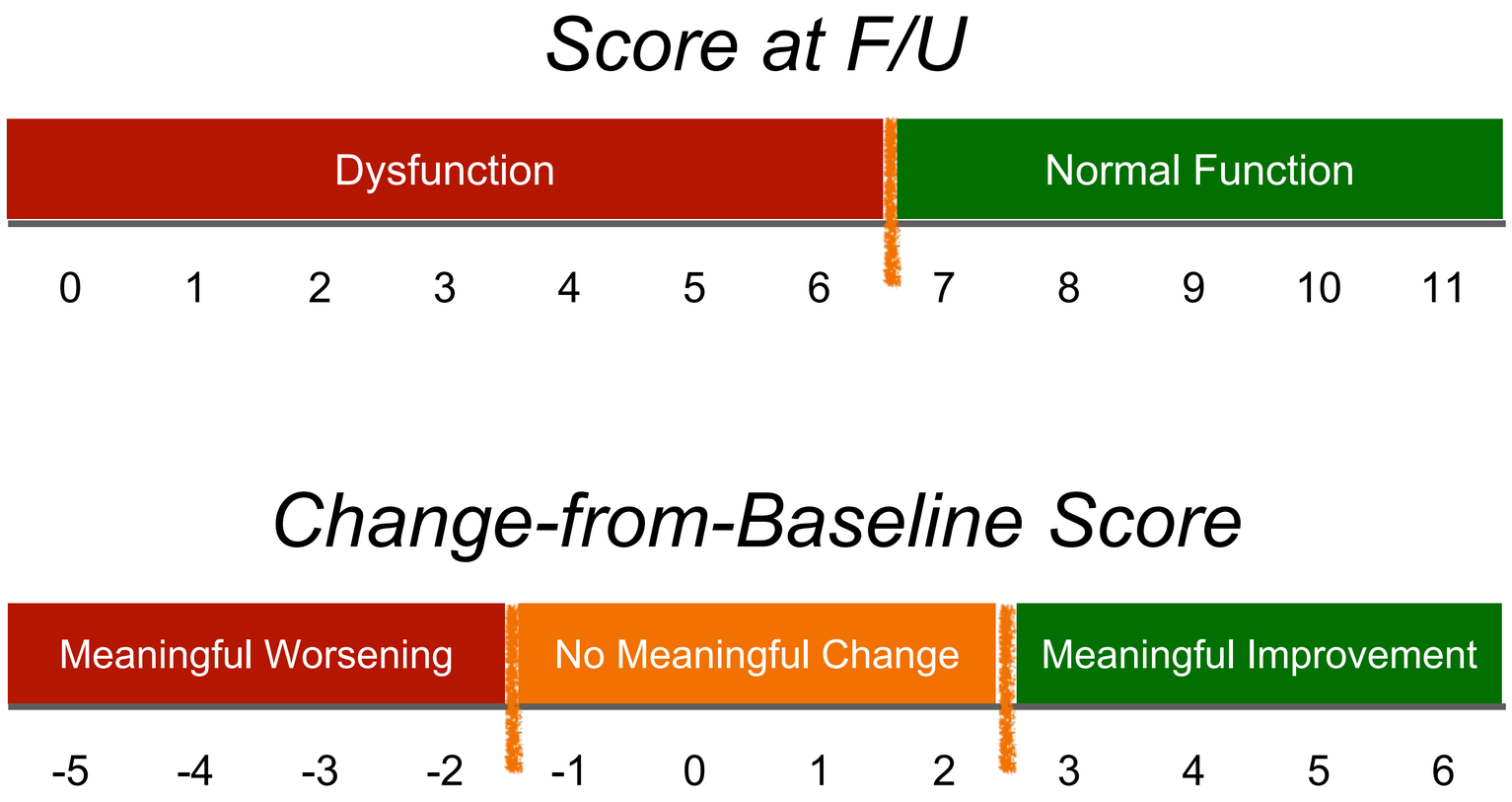
Biostatisticians typically favor an endpoint that uses all the information collected to provide the most power to detect whether the intervention did something

(e.g., continuous scale score from a pain measure)

Clinicians typically favor endpoints that seem to have immediate clinical interpretation

(e.g., scale score categorized into clinically relevant categories)

Categorization of Scores to Improve Interpretability



Tension in Constructing and Interpreting Endpoints

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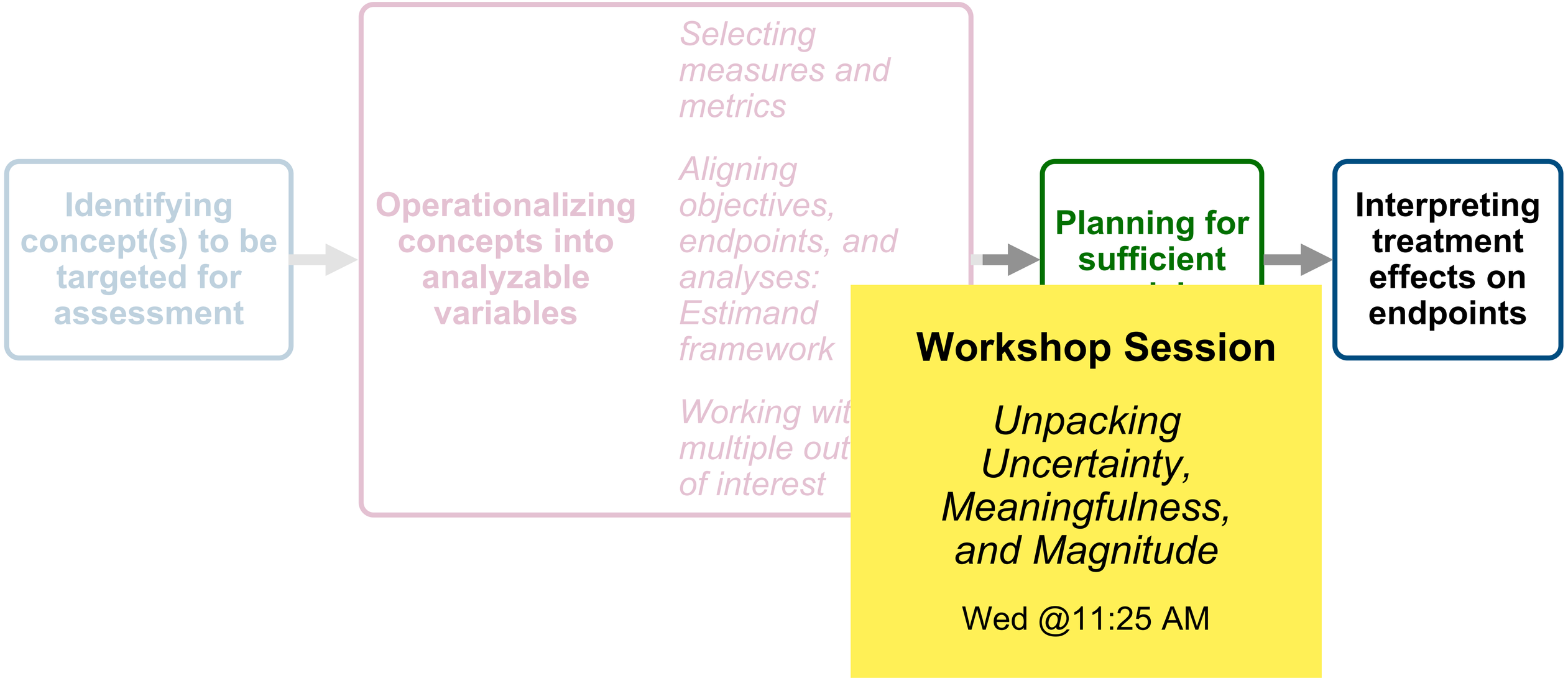
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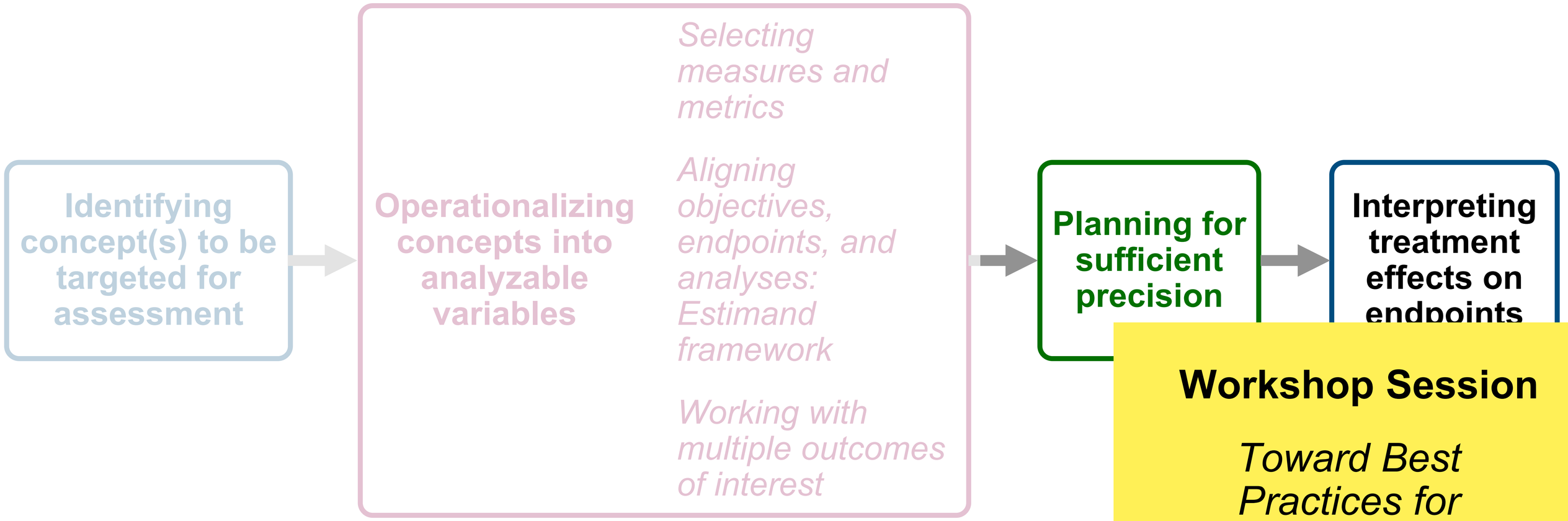
Resolution

- Test for treatment effect using a statistical model of the most granular endpoint (e.g., continuous score)
- Interpret treatment effects using the statistical model to show implications of the treatment effect (e.g., what proportion expected to exceed some value of endpoint)

Key Endpoint Considerations in Pragmatic Clinical Trials



Key Endpoint Considerations in Pragmatic Clinical Trials



Workshop Session

Toward Best Practices for Interpretation of Endpoints

Wed @1:10 PM

Key Endpoint Considerations in Pragmatic Clinical Trials

