Putting the ICH E9(R1) Guidance into Practice – A Multi-Disciplinary Collaboration

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Outline

- Background
  - Example – Clinical Trial Before and After Estimands
  - ICH E9(R1) Trial Planning Framework
  - Estimands
- Case study – Alzheimer Long-Term Prevention Trial
- Summary

Background

Example Clinical Trial – Before Estimands

- Major depressive disorder (MDD) monotherapy, placebo-controlled trial
- Primary endpoint: change from baseline to week X in a depression score
- Full Analysis Set: all randomized and dosed (called ITT)
- In trial conduct section: Subjects are discontinued from the double-blind (DB) phase and moved to a follow-up phase if they:
  - Discontinue the study treatment
  - Have severe non-compliance with the study drug
  - Start protocol prohibited medication
- In statistical section: Analysis based on MMRM using DB phase measurements, so on-treatment measurements for compliant subjects who take allowed medication only.

Example Clinical Trial – Points to Be Aware Of

Point 1:

- Analysis set called ITT; however, observations are not collected for some subjects up to the end of DB phase

Quote from the ICH E9(R1) Addendum:

defined to be as close as possible to including all randomised subjects. However, trials often include repeated measurements on the same subject. Elimination of some planned measurements on some subjects, perhaps because the measurement is considered irrelevant or difficult to interpret, can have similar consequences to excluding subjects altogether from the full analysis set, i.e. that the initial randomisation is not fully preserved. A consequence of this

Point 2:

- Implicit assumption of the MMRM analysis using only measurements prior to treatment discontinuation: If the subjects who discontinued study treatment would have continued the treatment as planned, they would have similar efficacy as the subjects who remained on treatment.

Example Clinical Trial – After Estimands

- Define Estimand = A precise description of the treatment effect reflecting the clinical question posed by the trial objective
- Include in the estimand definition the events previously mentioned under study conduct (named intercurrent events):
  - Treatment discontinuation
  - Severe non-compliance with the study drug
  - Initiation of protocol prohibited medication
- Define the strategy of handling each intercurrent event
- Select an analysis (estimator) that is aligned with the defined estimand

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

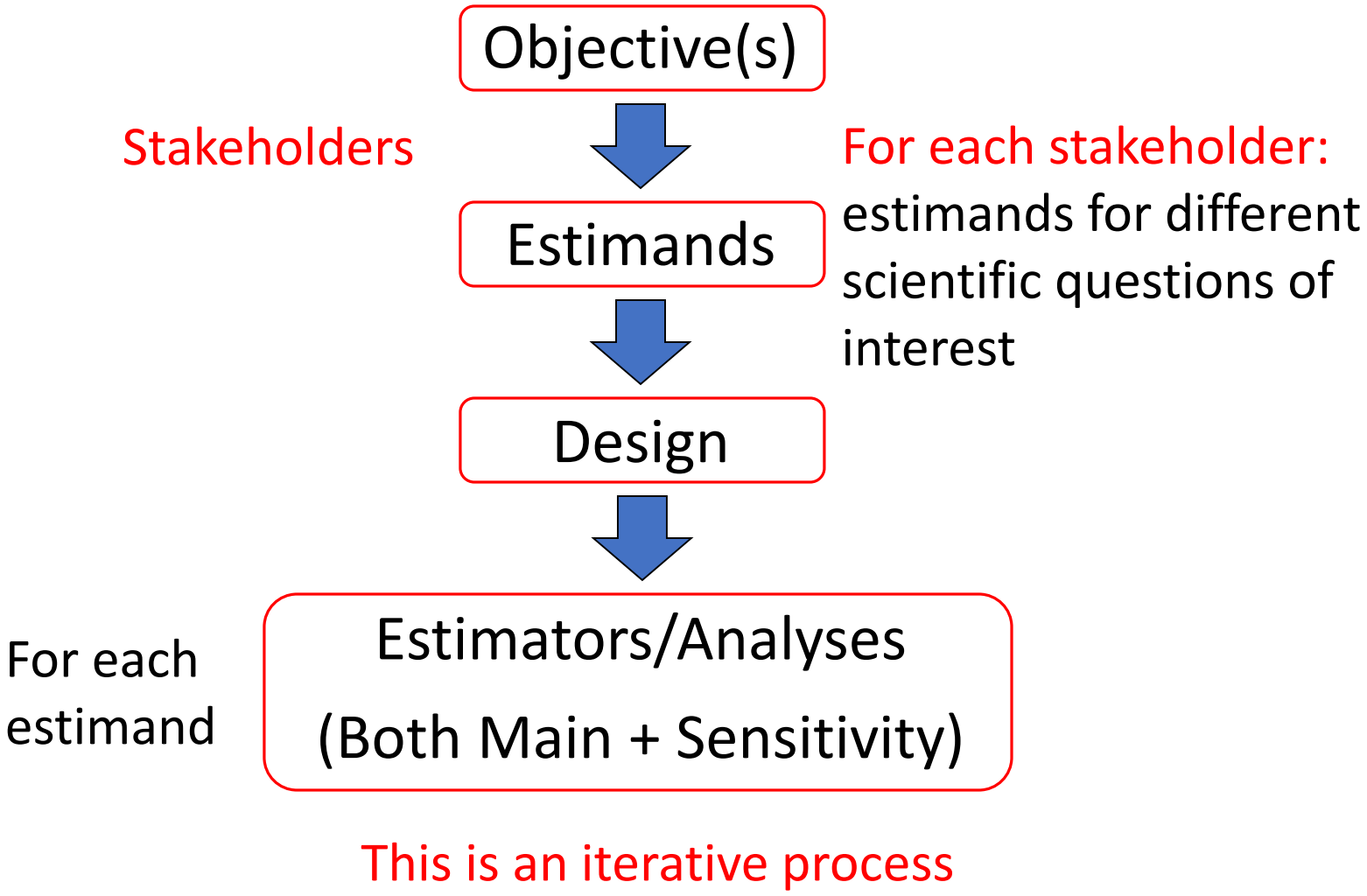
E9(R1)

Final version

Adopted on 20 November 2019

https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

ICH E9(R1) - Trial Planning Framework



Slide from ICH E9 (R1) EWG

A. Treatment

Treatment conditions of interest

B. Population

Patients targeted by the scientific question

C. Variable (or endpoint)

that is required to address the scientific question (to be obtained for each patient)

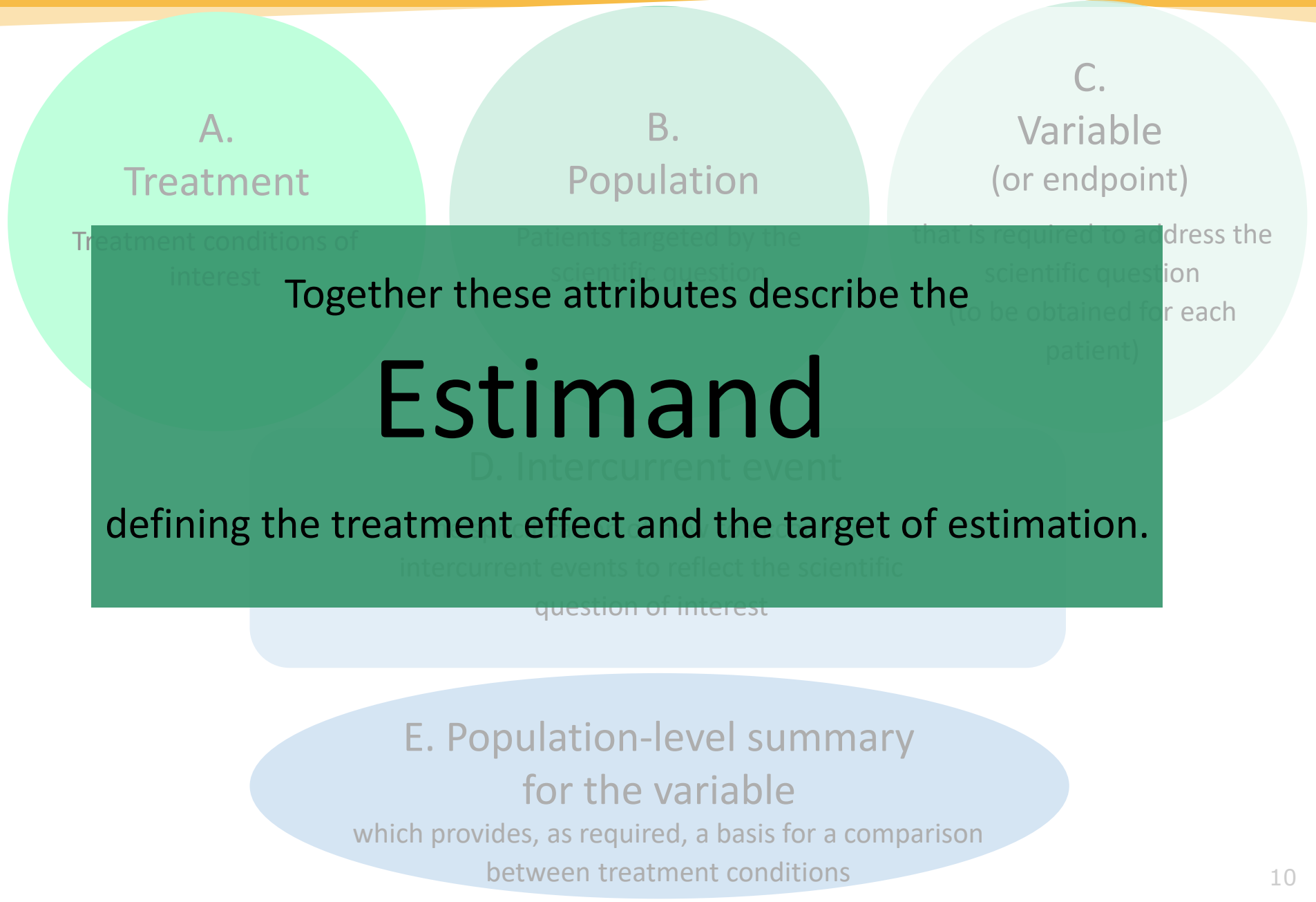
D. Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest

E. Population-level summary for the variable

which provides, as required, a basis for a comparison between treatment conditions

Slide from ICH E9 (R1) EWG



Together these attributes describe the

Estimand

defining the treatment effect and the target of estimation.

Trial Objective and Different Questions of Interest

- General or very specific?
- A trial objective could be general and could encompass different questions of interest, one to be chosen as primary.
- For each stakeholder, useful to:
  - define the question of interest for each estimand
  - think how that estimand is useful for the targeted stakeholder

Five ICH E9(R1) Identified Strategies of Addressing Intercurrent Events

- Treatment Policy – to be used in case study
- Hypothetical – a hypothetical scenario is envisaged around the intercurrent event; examples:
  - if subjects had not discontinue study treatment
  - if subjects had discontinued study treatment instead of switching to an alternative treatment
- Composite – captured in the variable (e.g. binary responder variable)
- Principal Stratum – captured in the population (e.g. stratum of subjects who would tolerate the experimental treatment)
- While on treatment / Prior to the Intercurrent Event – captured in the variable (e.g. area under curve based on the measurements collected while on treatment)

Estimand Framework – Steps For Implementation

- Define the stakeholder question of interest linked to the trial objective
  - Important: understand clinical questions that translate into using different strategies for intercurrent events
- Define all components of an estimand
- Consider the trial design and any key implementation elements needed to address that estimand
  - Important: multi-disciplinary collaboration
- Define data to be included vs missing/censored under this estimand
- Define the estimators (analyses) for this estimand, specifying the model and missing data assumptions for each estimator:
  - Main estimator
  - Sensitivity estimator(s) – describe what assumptions of the main estimator are changed

Case Study –
Apply Estimand Framework

Case Study Set-up

- Disease area – Alzheimer's Disease
- Phase 3 long-term prevention trial in asymptomatic subjects who are at risk for developing Alzheimer's Dementia
- Trial Objective: To determine superiority of drug vs placebo in slowing cognitive decline.
- Main stakeholder: regulatory agency

Intercurrent Events for Case Study

Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

- Treatment Discontinuation
- Initiation of Alzheimer's Disease Therapies (ADT)

Intercurrent Events for Case Study

Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

- Treatment Discontinuation – consider first as single intercurrent event
- Initiation of Alzheimer's Disease Therapies (ADT)

Estimand Question of Interest

Stakeholder = regulatory agency

- What is the effect of assigning subjects for the pre-specified duration to drug versus placebo?

The intercurrent event of Treatment Discontinuation would be addressed by the Treatment Policy Strategy: All observed values of the variable are of interest, regardless of whether or not the subject had discontinued the treatment.

Addendum (Section A.3.4):

- Characterising beneficial effects using estimands based on the treatment policy strategy might also be more generally acceptable to support regulatory decision making, specifically in settings where estimands based on alternative strategies might be considered of greater clinical interest, but main and sensitivity estimators cannot be identified that are agreed to support a reliable estimate or robust inference.
- An estimand based on the treatment policy strategy might offer the possibility to obtain a reliable estimate of a treatment effect that is still relevant. In this situation, it is recommended to also include those estimands that are considered to be of greater clinical relevance and to present the resulting estimates along with a discussion of the limitations, in terms of trial design or statistical analysis, for that specific approach.

Define Estimand – 5 Attributes

- Treatment: Drug vs placebo (specify dosing, frequency, any allowed concomitant medications that could have an impact on cognition)
- Population: asymptomatic subjects who are at risk for developing Alzheimer's Dementia
- Variable: Change from baseline to Month 54 (Year 4.5) in the cognitive endpoint
- Intercurrent events and their corresponding strategies:
  - Treatment Discontinuation [Treatment Policy Strategy]: All observed values of the variable are of interest, regardless of whether or not the subject had discontinued the treatment.
- Summary measure: Difference in means of the variable

Trial Design and Key Implementation Elements

- Design: parallel, double-blind, 1:1 randomization into:
  - drug
  - placebo
- Key implementation elements:
  - Keep the subjects who discontinue treatment in the double-blind phase, following the same schedule as the subjects who remain on treatment
  - Collect timing and reason of treatment discontinuation
  - Need: multi-disciplinary collaboration to create trial protocol

Data Included Under Estimand vs Missing

- Data included for analysis under the defined Estimand:
  - Variable values collected from baseline to Month 54 for all randomized subjects, including the values collected after treatment discontinuation
- Data missing:
  - Intermediate missing due to Intermediate events such as missed visits, missed data collections.
  - After study withdrawal

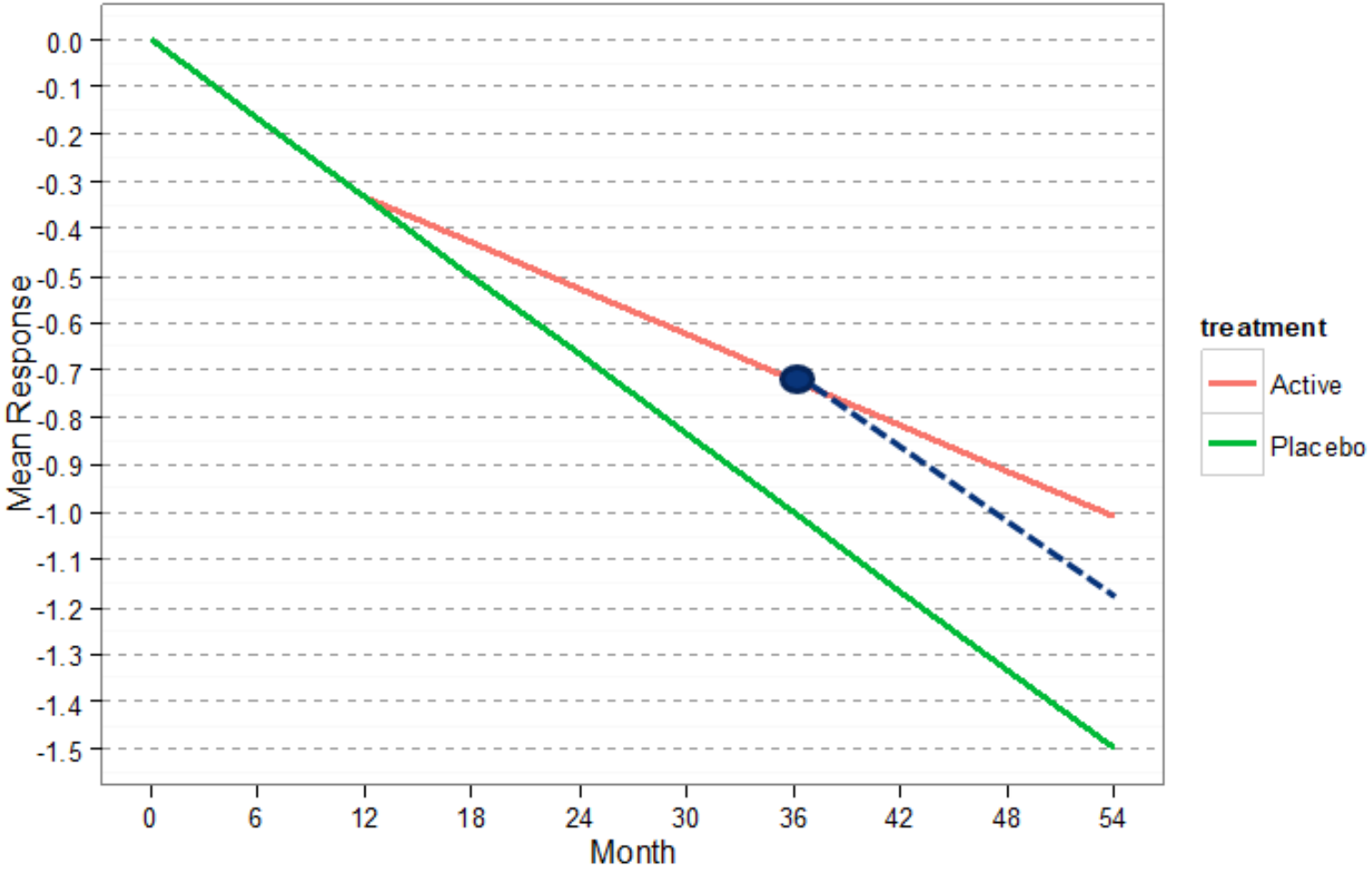
Estimators and Their Assumptions
Main Estimator

- Missing Data assumptions:
  - For intermediate missing: measurements assumed similar to those from the other subjects from same treatment group, who did not experience intermediate missing
  - After study withdrawal: measurements assumed similar to those in the placebo group
- Main Estimator:
  1. Impute intermediate missing based on MCMC
  2. Impute monotone missing based on a control-based multiple imputation method
  3. Analysis based on ANCOVA using treatment and certain baseline variables
  4. Combine results based on Rubin's rules

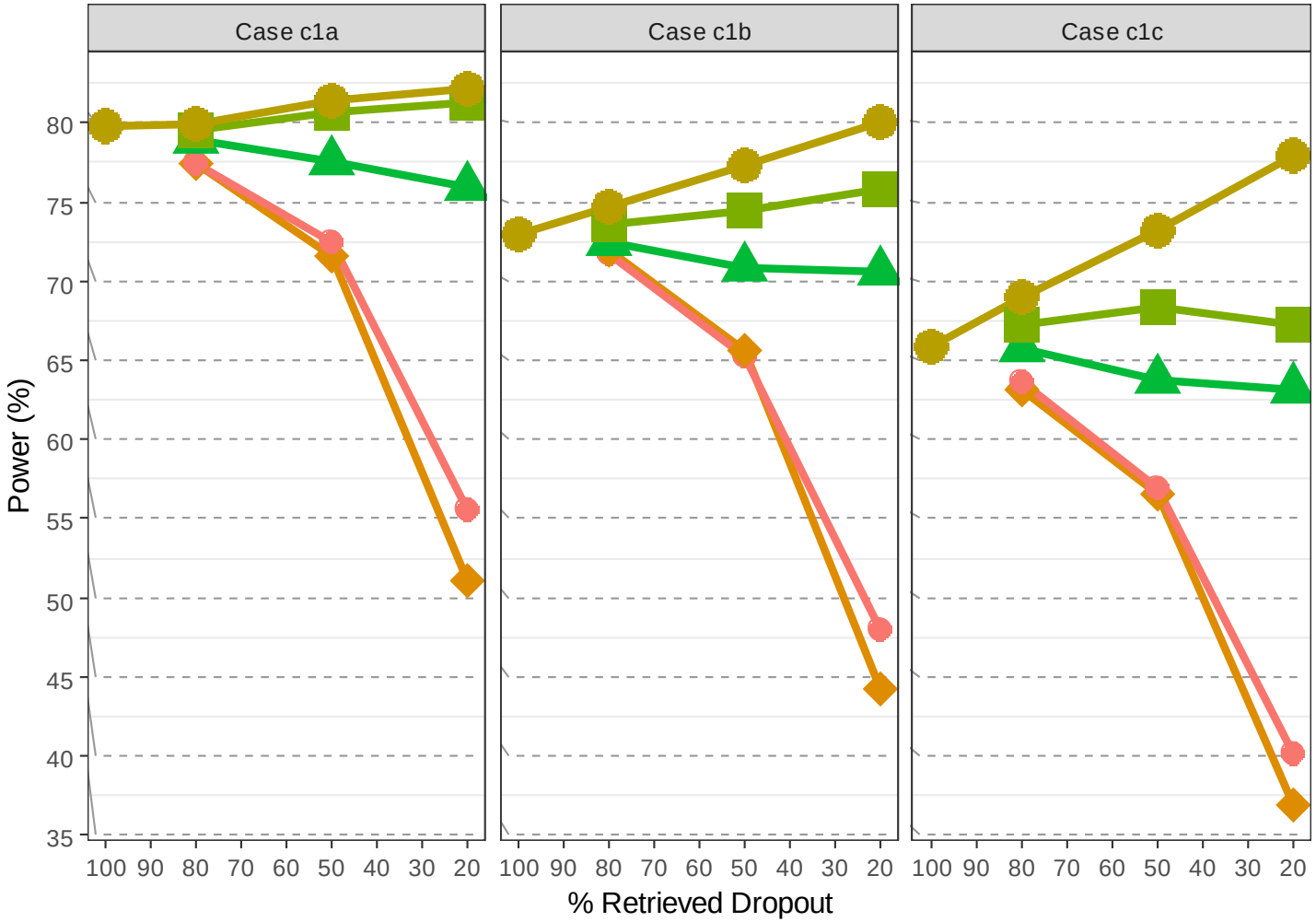
Estimators and Their Assumptions
Sensitivity Estimator

- Missing Data assumptions:
  - For intermediate missing: measurements assumed similar to those from the other subjects from same treatment group, who did not experience intermediate missing
  - After study withdrawal : measurements assumed similar to those observed in the subjects from the same treatment group, who discontinue the treatment but have off-treatment data (retrieved dropout subjects)
- Main Estimator:
  1. Impute intermediate missing based on MCMC
  2. Impute monotone missing based on a multiple imputation method based on retrieved dropouts
  3. Analysis based on ANCOVA using treatment and certain baseline variables
  4. Combine results based on Rubin's rules

Impact on Sample Size
Example of Scenario for Off-Treatment Response



Estimated Power



Case	%TrtDC Pbo	%TrtDC Drug
c1a	31.3%	30.1%
c1b	31.3%	36.1%
c1c	31.3%	42.1%

Estimator	Description
cir	Copy Increment from Reference Multiple Imputation (MI)
mar_dc	MI regression based on the Missing at Random assumption, with treatment discontinuation in the imputation model
mmrm	Mixed Model for Repeated Measures
rd_subset	MI based on retrieved dropouts (subjects who discontinue treatment and have off-treatment retrieved measurements)
rd_trt	Other type of MI based on retrieved dropouts

Elena Polverejan & Vladimir Dragalin (2019) Aligning Treatment Policy Estimands and Estimators—A Simulation Study in Alzheimer's Disease, Statistics in Biopharmaceutical Research, DOI: 10.1080/19466315.2019.1689845

Estimand – Two Intercurrent Events

Same components as the previously defined estimand, except:

Intercurrent events and their corresponding strategies:

- Treatment Discontinuation [Treatment Policy Strategy]: All observed values of the variable are of interest, regardless of whether or not the subject had discontinued the treatment.
- Initiation of ADT: example of strategies
  - [Treatment Policy Strategy]: All observed values of the variable are of interest, regardless of whether or not the subject had initiated ADT.
  - [Hypothetical Strategy]: as if subjects were not provided ADT at the start of their Alzheimer cognitive impairment symptoms

Missing Data Assumptions: Assume that subjects who initiate ADT would be having instead, after ADT initiation, worse efficacy than the subjects from the same treatment group who don’t initiate ADT.

Multi-Disciplinary Collaboration

Involved functions:

- Clinical
- Regulatory
- Commercial
- Statistical
- Medical writing
- Data manager
- Trial monitor

Summary and Next Steps

- Implementation of the estimand framework complex:
  - Multiple stakeholders
  - Multiple questions of interest – need “translation” of questions into strategies
  - Multiple intercurrent events
    - handled by different strategies, reflected in different estimand components
- Multidisciplinary collaboration essential
- Statisticians:
  - Understand the types of estimators available for various strategies for intercurrent events and impact on sample size, power and other trial characteristics
- Next steps: Broaden the experience of defining estimands and estimators for different therapeutic areas, including for CNS clinical trials