



Implementation of the estimand framework: statistical perspectives

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The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the MHRA.

Regulatory requirements

- For regulatory approval a medicinal product should have therapeutic efficacy and a positive risk-benefit.
- In addition to statistically compelling evidence of efficacy, the magnitude of the benefit should outweigh the harmful treatment effects.

Examples of issues in CT in CNS

- Large drop-out rates
- Non-compliance: treatment discontinuation or switch, changing dosage
- High variable placebo response
- Large amount of missing data
- Heterogenous population

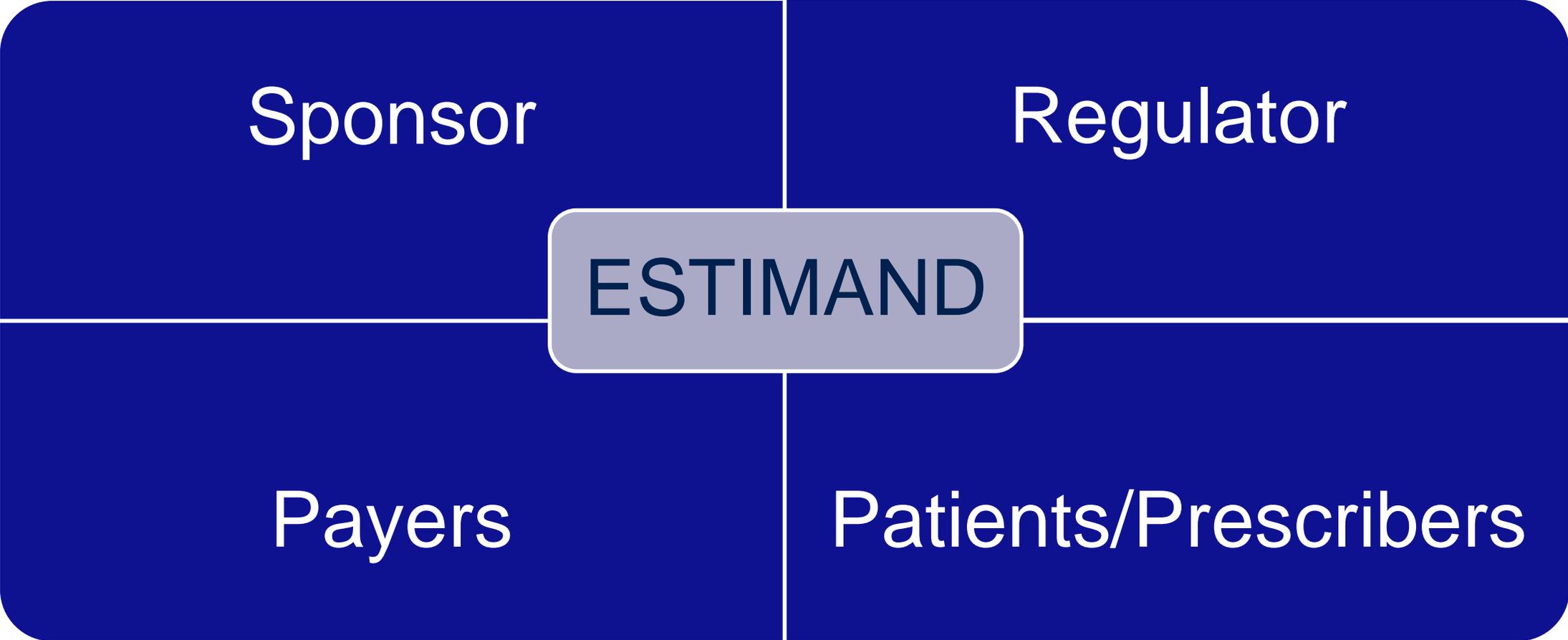
Choice of estimand: key players

Scientific question of interest

ESTIMAND

Consider the need of the stakeholder

Choice of estimand: key players



Guideline – Alzheimer's disease

Intercurrent events

“events that occur after randomisation and that would **affect** the interpretation of an **outcome** variable or **preclude** its observation” e.g.

- Discontinue treatment
- Initiation of new medication
- Death
- vascular or cardiac or metabolic events

Strategies

- Treatment policy (e.g. adherence to treatment)
- Hypothetical (e.g. medication changes)
- Composite (e.g. additional symptomatic treatment)
- Principal stratum (e.g. patients who can tolerate treatment for long time)

Intercurrent events: Strategies

Treatment Policy

Treatment policy for handling treatment adherence is acceptable. For the intercurrent event do not exist for all subjects e.g. if subject dies

Hypothetical

OK to use if ICE not related to treatment, e.g. COVID-19, use of rescue medication for ethical reasons

Composite

Dichotomisation of numerical outcome can lead to loss of information.

While on treatment

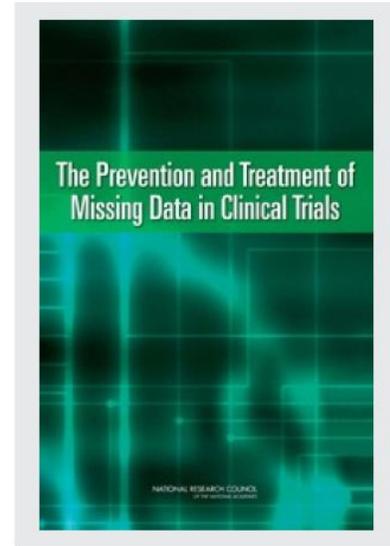
Not appropriate when ICE is indicative that treatment was no longer going to be of benefit.

Principal Stratum

Methodologically challenging . But can be considered valuable if defined a priori (e.g. effect in the population who would tolerate treatment)

Common statistical issues

- **Role of different analyses**
 - Main analysis
 - Sensitivity analyses
 - Supplementary analyses
- **Distinguishing missing data from intercurrent events**
- **Misalignment between analysis method and target estimand**
- **Misalignment between the analysis method and outcome scale type**



Example 1

The Company proposes to provide estimates of the effect of therapy **WOW** in the absence of **rescue medications (hypothetical estimand)**, using an **MMRM** model under the missing at random assumption (**MAR**) applied to the modified intention-to-treat (**mITT**) population (all randomised subjects who receive at least one dose of study treatment) and with all data subsequent to use of rescue medication deleted.

Analysis ignores the fact that use of rescue medication could be a consequence of lack of efficacy and hence MAR may be challenges.

Example 2

Estimate the effect of treatment **WOW** assuming all patients had continued on randomised treatment until week 26.

Estimand ignores the fact that some patients may not be able to tolerate treatment or need rescue therapy.

Estimand not of interest to regulators

Trial objectives : Need more details

Study **XX** is designed to assess the effect of experimental treatment **WOW** over control in patients suffering from **DD**

Study **XX** is designed to assess the effect of experimental **treatment WOW** over **control** in **patients suffering from DD** on **variable V defined/measured/assessedafter time T from randomisation** based on summary measure **S**, **regardless of whether the patient is still on treatment.**

Conclusion

- Regulators require **robust, unbiased**, and **unambiguously defined** estimates of treatment effect for decision making.
- **Reliable and validated** outcomes that are relevant to patients must be considered in decision making.
- We all need to improve how we **communicate** results to all stakeholders, in particular patients and prescribers.
- We need to learn from each other by **sharing real examples of estimands** from **case studies** across all therapeutic areas and stages of development for better implementation of the framework.

Let's discuss together!

We can offer

- Scientific advice
- Regulatory advice
- Broader scope meetings
- Innovation office meetings - innovationoffice@mhra.gov.uk
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456



Acknowledgement

Ines Reis (MHRA)

James Bell (EIWG)

Thank You



Regulatory aspects of the estimand framework - a medic's perspective

Dr Joel Raffel, Medical Assessor, MHRA



Medicines & Healthcare products Regulatory Agency

EPSPI Virtual Seminar 03/11/2020: The application of estimands from a neuroscience perspective

Speaker Introduction

- Medical Assessor, MHRA, 2018
- PhD – Imperial College London, 2014-2018
 - Outcome measures in multiple sclerosis
- Neurology Registrar, 2013

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Presentation outline

A medic's perspective...

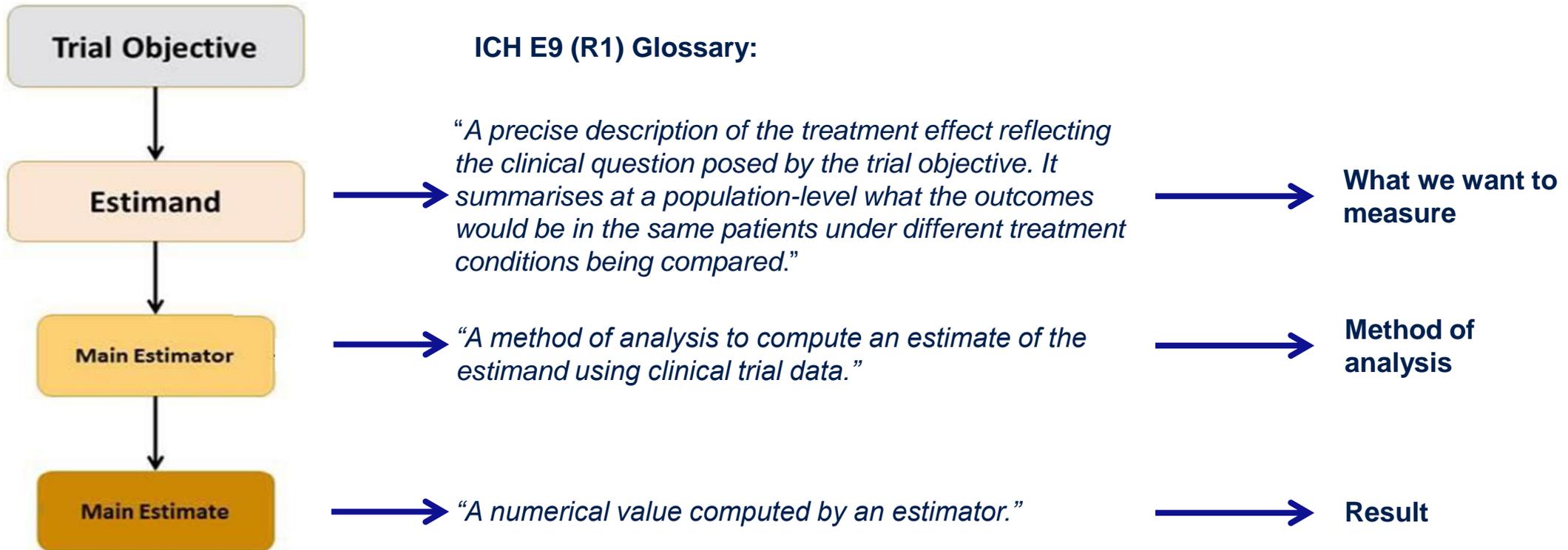
- General thoughts on the estimand framework
- Examples from neurological disease

General thoughts

Survey of five medical assessors:

1. *“I tried to read the guideline, but found the vocabulary **confusing**. I will probably **rely on a statistician** when I need it!”*
2. *“I don’t really fully understand **where it fits in**... Is it an alternative to PICO?”*
3. *“I haven’t used it in my assessments yet – some of it seems unnecessarily complicated, and **describes what we have been doing for decades**.”*
4. *I’ve seen an estimand-based analysis and didn’t really trust it - I think it is often safer to **just use ITT analysis**.”*
5. *“Once you understand it, it’s very useful..... it can improve the relevance of clinical trial data to real-world efficacy/safety, and can help standardise how we assess.”*

1. “I tried to read the guideline, but found the vocabulary **confusing**. I will probably **rely on a statistician** when I need it!”



“Intercurrent events”

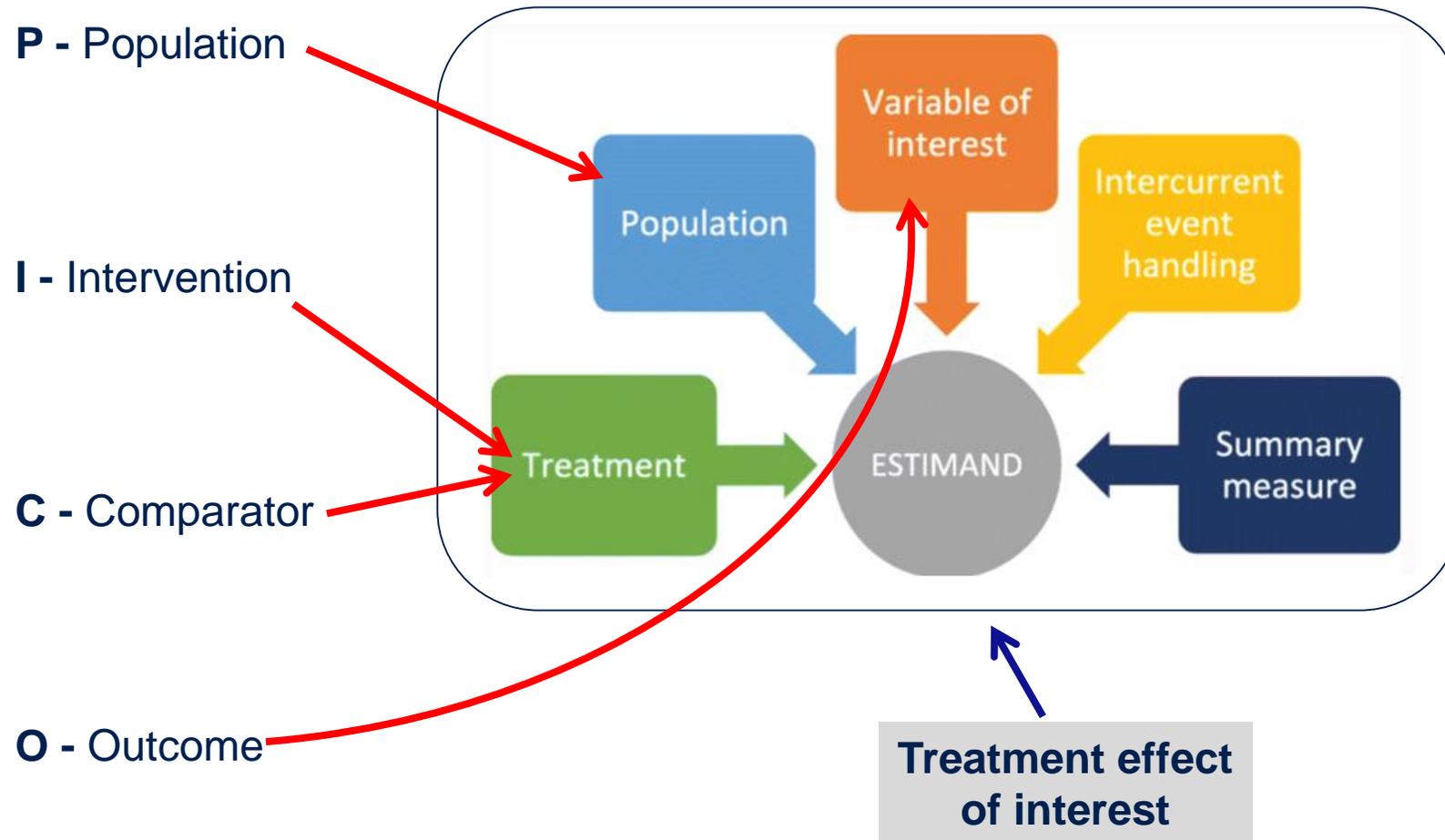
“Principal stratification strategy”

“While on treatment strategy”

“Population-level summary”

“Target of estimation”

2. "I don't fully understand **where it fits in...** is it an alternative to PICO?"



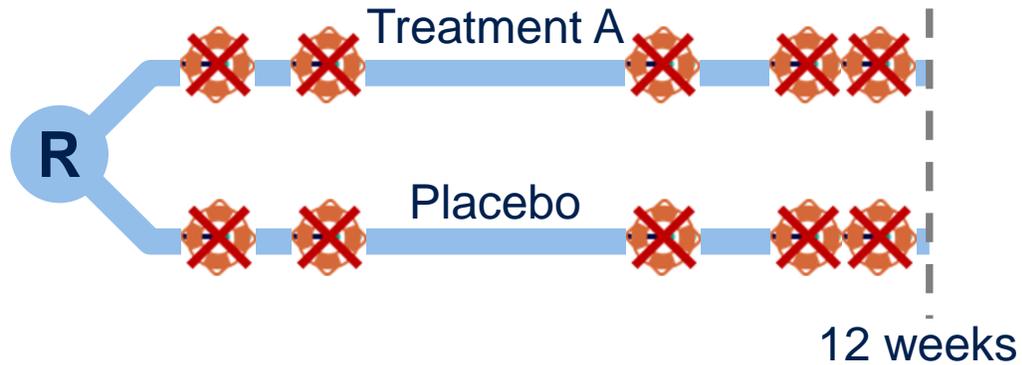
3. *“I haven’t used it in my assessments yet – some of it seems unnecessarily complicated, and **describes what we have been doing for decades.**”*

Review > [Trials. 2020 Jul 23;21\(1\):671. doi: 10.1186/s13063-020-04546-1.](#)

A narrative review of estimands in drug development and regulatory evaluation: old wine in new barrels?

M Mitroiu ^{1 2}, K Oude Rengerink ^{3 4}, S Teerenstra ^{3 5}, F Pétavy ⁶, K C B Roes ^{3 5}

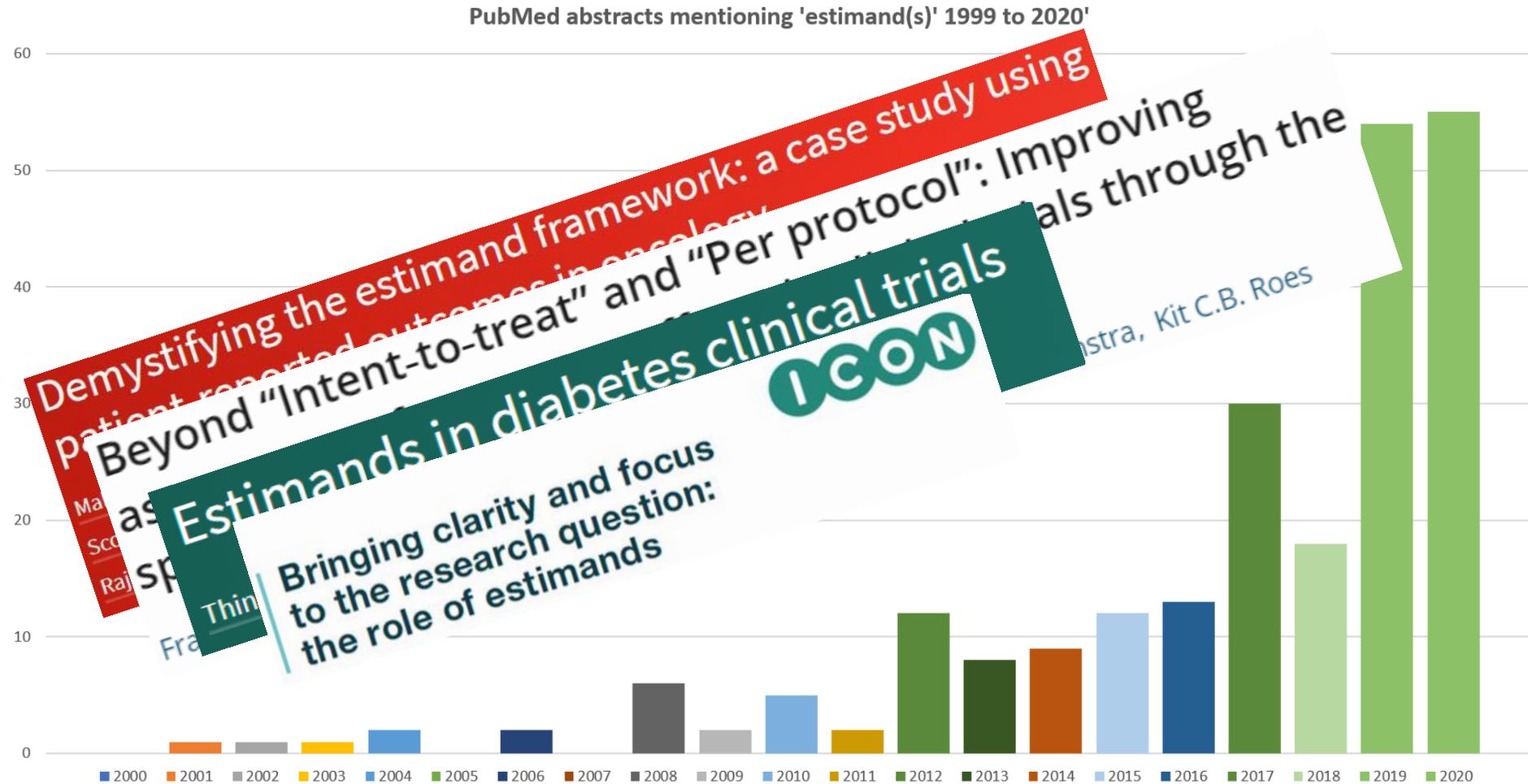
4. *I've seen an estimand analysis and didn't really trust it - I think it is often safer to just use ITT analysis.*"



ITT analysis:

- **statistically significant difference** in outcome at 12 weeks.
- **Clinical relevance of difference** questionable.

5. "Once you understand it, it's very useful.... it can improve the relevance of clinical trial data to real-world efficacy/safety, and can help standardise how we assess."



Examples

1. Huntington's disease
2. Migraine
3. Neuropathic pain
4. Multiple sclerosis
5. Alzheimer's disease

MY OWN PERSONAL VIEWS. UNINFORMED. NOT AN ASSESSMENT.

Huntington's disease

• Withdraw from Treatment

- Due to Treatment and/or Disease Progression Related reasons (TDPR) -> **Treatment Policy**
 - the actual observed “off-treatment” values will be analyzed.



- Due to Non-Treatment or Disease Progression Related reasons (NTDPR) **hypothetical strategy**
 - Discard the actual observed “off-treatment” values and imputed by hypothetical values as if patients had continued receiving the study treatment.



ICH E9 R1:

"A very different hypothetical scenario might postulate that intercurrent events would not occur, or that different intercurrent events would occur. For example, for a subject that will suffer an adverse event and discontinue treatment, it might be considered whether the same subject would not have the adverse event or could continue treatment in spite of the adverse event. The clinical and regulatory interest of such hypotheticals is limited and would usually depend on a clear understanding of why and how the intercurrent event or its consequences would be expected to be different in clinical practice than in the clinical trial."

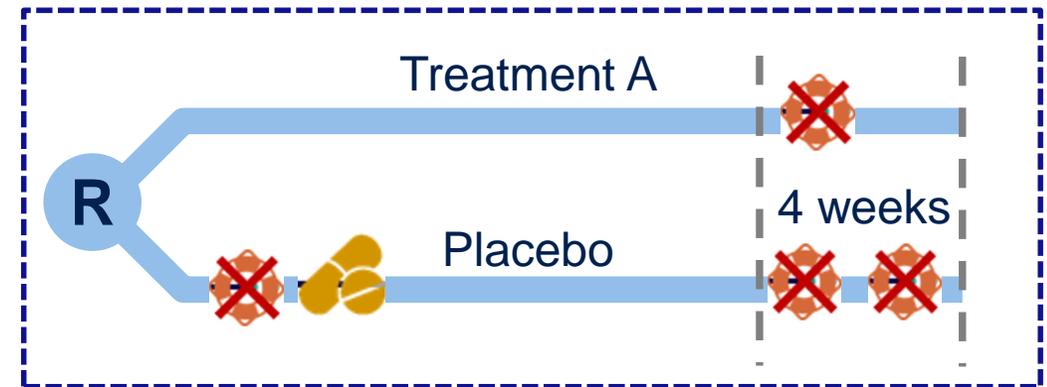
Taken from slides presented by Carrie Li, Giuseppe Palermo, Roche

Proposed estimands for ICE in migraine prevention

Intercurrent event	Estimand strategy	Comments
Use of “rescue” medication (e.g. Triptans)	Composite strategy on assessment level, define “failure” for respective study day, i.e. count a migraine day irrespective of occurrence of a migraine attack	Failure on a study day basis
Use of prohibited medications for migraine	Composite strategy, i.e. define patient as a treatment failure for responder analysis	Failure on a patient level basis or failure on a study day basis used in counting of migraine days.

Proposed composite strategy:

Estimand: The effect of treatment on the chance of seeing a 50% reduction in days with migraine or use of rescue medication, without use of prohibited preventive migraine medication, while remaining in the study



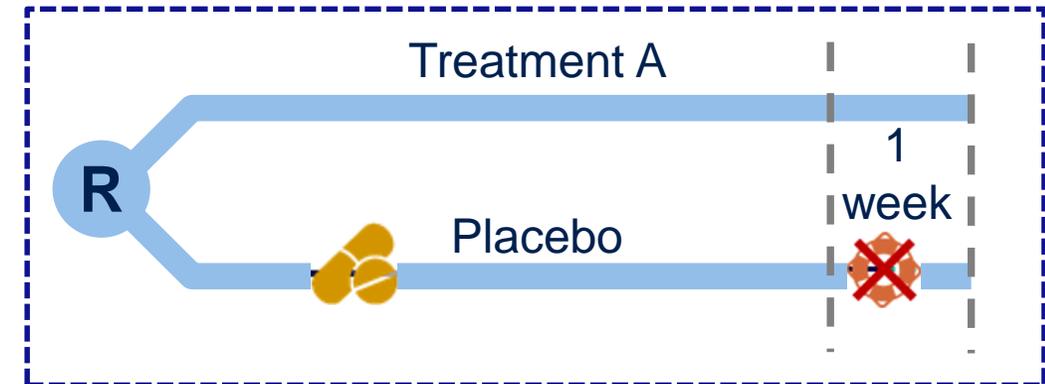
Proposal taken from slides presented by Mette Krog Josiassen, Lundbeck, and Peter Quarg, Novartis Pharma AG

Proposed estimands for ICE in chronic neuropathic pain

Intercurrent event	Estimand strategy	Comments
Use of short term acute “rescue” medication (e.g. Paracetamol)	Hypothetical strategy by collecting the value prior to intake as representative for that day (what if no rescue would have been taken)	Handling on a study day basis
Use of prohibited medications for neuropathic pain	Composite strategy, i.e. define patient as a treatment failure for responder analysis	Failure on a patient level basis

Proposed composite strategy:

Estimand: The effect of treatment on the chance of seeing a 50% improvement in average weekly pain levels without starting prohibited pain medication. Patients are required to enter pain levels prior to intake of short acting pain medication on a study day.



Proposal taken from slides presented by Mette Krog Josiassen, Lundbeck, and Peter Quarg, Novartis Pharma AG

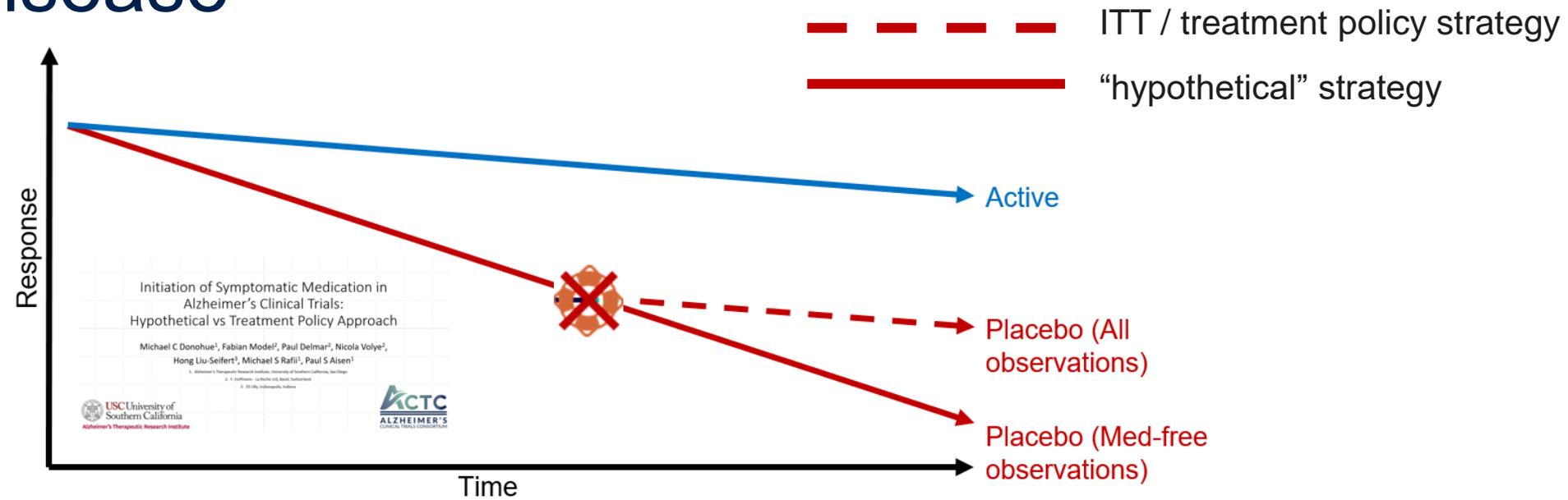
Proposed estimands for ICEs in progressive MS

Intercurrent event	Estimand strategy	Comments
Treatment withdrawal for lack of efficacy	Composite variable or treatment policy strategy	Impute an event or use future information. Keep patients on study
Treatment withdrawal, not efficacy related	Treatment policy strategy	Use future information. Keep patients on study
Start of other DMT therapy due to lack of efficacy	Treatment policy strategy (until highly effective DMT would be available)	Since start of other DMT therapy also means treatment withdrawal
Start of other DMT therapy, not efficacy related	Treatment policy strategy (until highly effective DMT would be available)	Since start of other DMT therapy also means treatment withdrawal
Death	Composite variable strategy or ignore	Imputation of event. Since number of deaths usually balanced and low in size, simple censoring likely not changing anything (“ignore”)
Relapse event	<ul style="list-style-type: none"> - Hypothetical strategy to estimate effect on progression independent of relapses - Principle stratum strategy to estimand treatment effect in non-relapsing patients 	<i>Progression defined as a worsening of 1 point or 0.5 points on the EDSS scale, required to be confirmed by a second assessment 3 months later</i>

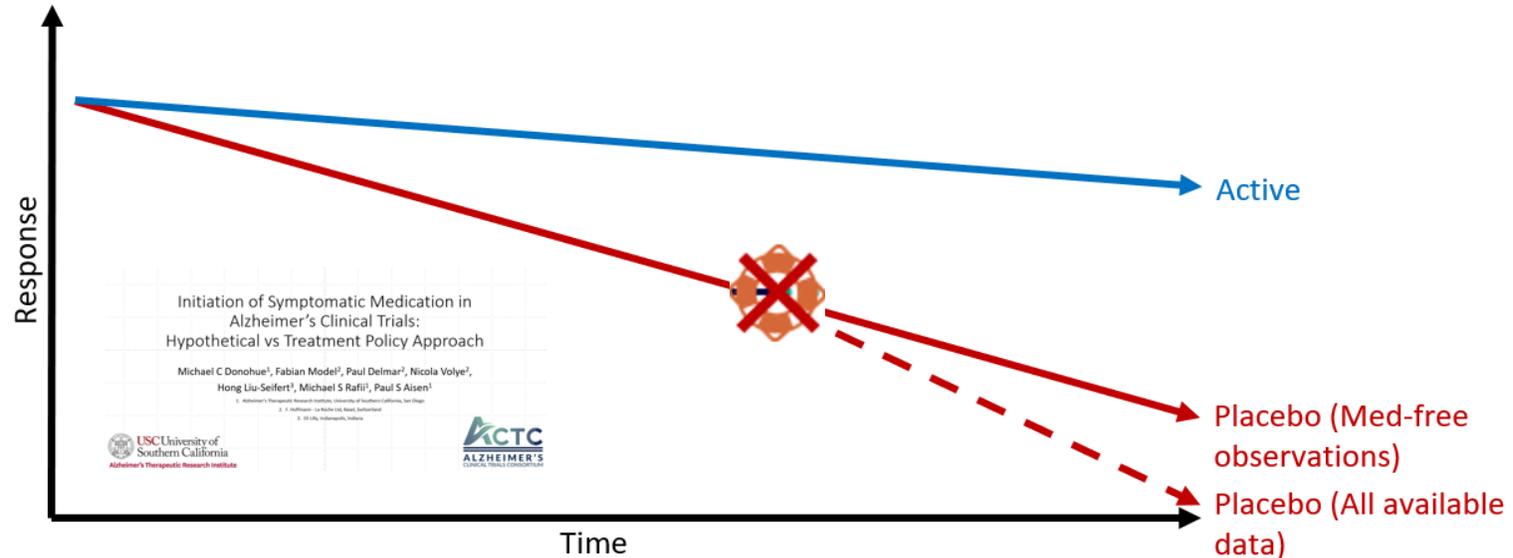
Proposal taken from slides presented by Hans Ulrich Burger, Nikos Sfikas and Fabian Model. Roche and Novartis, Basel

Alzheimer's disease

We might assume:



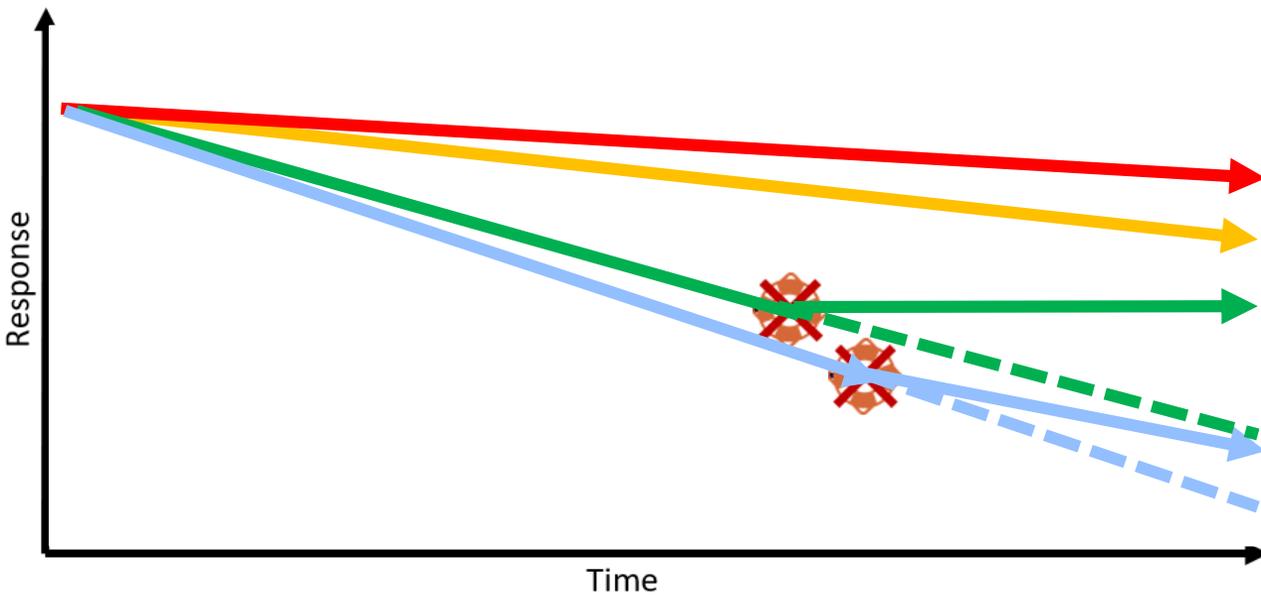
What was observed:



Taken from slides presented by Paul Delmar, Roche

Possible Estimands:

- Treatment policy: what is the treatment effect, regardless of whether symptomatic medications are taken
- Hypothetical policy: what is the treatment effect in the hypothetical scenario where symptomatic medications are not taken



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