



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# A regulator's perspective on estimands

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Lessons learnt and open questions

BBS/BES seminar: Causal Inference in Drug Development: Why, When, How?

Presented by Frank Pétavy on 21 August 2019  
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An agency of the European Union





## Disclaimer

The views expressed in this presentation are the personal opinion of the author and should not be understood as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties, or the views of the other representatives on the ICH E9(R1) expert working group.



## Scientific disclaimer

The knowledge and experience of the presenter with causal inference is limited. Reflections on estimands in this presentation are not directly related to causal inference thinking (or are they?).



# Acknowledgements

Lorenzo Guizzaro, physician and statistician, EMA

ICH E9(R1) expert working group members



## Outline

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- Experience so far
- Hypothetical strategies
- What next?



## How do European regulators know about estimands?

- **Trainings** in specific regulatory groups, at a therapeutic level (clinical assessors), between statistical assessors, either at EMA or at national agencies
- **Product assessment** (advice and evaluation)
  - The topic of estimands is often introduced in product assessment by statistical assessors, then discussed with clinical assessors
  - Some companies include estimands in their application dossier; although it is limited to larger organisations and to more elaborate proposals
  - Regularly discussed between statistical assessors
- Disease **guidelines**, when updated, do and will include estimand considerations
  - Work on hold in 2019 due to relocation of EMA to Amsterdam



## Experience so far

Estimands are routinely discussed in **Scientific Advice** and **Evaluation** procedures.

This increasingly sees productive exchanges between clinicians and statisticians;

## Lessons learnt



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The best discussion is achieved when a specific question is **framed correctly from the onset**.



## The importance of asking the right question

### Questions asked

“The **proportion of drop-outs** expected is [], the strategy to handle **missing data** is [].”  
“Follow-up will be censored...”

### Answer received

The issue should be reframed in the Estimand framework.  
Given the setting, at least [] should be considered as **intercurrent events**. The **strategy** seems to imply [] which is [not] recommended.

**Current emphasis is on estimation methods.  
But what exact question is meant about treatment effect?**



## The importance of asking the right question

Questions asked	Answer received
<p>“The <b>proportion of drop-outs</b> expected is [], the strategy to handle missing data is [].” “Follow-up will be censored...”</p>	<p>The issue should be reframed in the Estimand framework. Given the setting, at least [] should be considered as <b>intercurrent events</b>. The <b>strategy</b> seems to imply [] which is [not] recommended.</p>
<p>The Estimand is described as follows. For the <b>IE</b> of [], the <b>strategy</b> chosen is [] because...</p>	<p>The <b>strategy</b> chosen for the <b>IE</b> of [] is [not] well justified [because].</p>

# The importance of asking the right question

Questions asked	Answer received
<p>“The proportion of drop-outs expected is [], the strategy to handle missing data is []”</p> <p>“Follow-up will be censored...”</p>	<p>Now the question is (hopefully) clearer</p> <p>But...</p> <ul style="list-style-type: none"> <li>• Does the analysis method (estimator) align to the estimand?, or</li> <li>• Has the estimand been defined to correspond to the estimator?</li> </ul>
<p>The Estimator follows. For the IE of [], the strategy chosen is [] because...</p>	<p>The issue should be reframed in the Estimand framework. Given the setting, at least [], should be considered as intercurrent events. The strategy seems to imply []</p> <p>The IE of [] is [not] well justified [because].</p>



Experience so far	Lessons learnt
Estimands are routinely discussed in Scientific Advice and Evaluation procedures. This increasingly sees productive exchanges between clinicians and statisticians;	The exchanges between clinicians and statisticians often lead to see unanswered questions where further reflection and research are needed.
Often problems that are not posed in the Estimand framework are recognised at such by regulators;	The best discussion is achieved when a question is framed correctly from the onset.
Some guidance has been given in <b>disease-specific guidelines.</b>	



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Estimands are routinely discussed in Scientific Advice and Evaluation procedures. This increasingly sees productive exchanges between clinicians and statisticians;	The exchanges between clinicians and statisticians often lead to see unanswered questions where further reflection and research are needed.
Often problems that are not posed in the Estimand framework are recognised at such by regulators;	The best discussion is achieved when a question is framed correctly from the onset.
Some guidance has been given in disease-specific guidelines.	<b>Each case is different</b> , difficult to give overarching guidance.



# Hypothetical strategies

## EMA guidelines

- Hypothetical strategies are present in (some) EMA guidelines
- **Alzheimer's Disease Guideline, 2018:** “ (...) an appropriate target of estimation could be based on a hypothetical scenario in which the new concomitant medication or modifications in the dose of concomitant medications had not been introduced.”
- **EMA Diabetes Guideline, 2018:** “(...) the treatment effect can be estimated under the assumption that rescue medication, or use of other medications that will influence HbA1c values, was not introduced (hypothetical scenario).”
- What does this hypothetical scenario mean? Is it valid from a conceptual point of view and why? Some reflections in the following slides...





# Hypothetical strategies

## E9 Addendum

- Definition in the addendum: “A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.”
- It then goes onto say: “A wide variety of hypothetical scenarios can be envisaged.”
- We can envisage two types of hypothetical scenarios: there can be a question about a *hypothetically different clinical setting* or about a *hypothetically different outcome*.
  - (Credit to Tom Permutt)
- While the former can happen in real life, the latter is unlikely.



# Hypothetical strategies

## An imaginary example

- Gabriela does not tolerate a medicine prescribed to her; she may or may not stop taking it; more importantly taking additional medication would help her
- This additional medication may not be available for Gabriela (e.g. not marketed in her country or her doctor prefers not to prescribe it to her): this is a *hypothetically different scenario* and we would like to know what would happen to Gabriela in this case.
- Now we also want to know what would happen to Gabriela if she had tolerated the medicine. This *hypothetically different outcome* did not happen; it would also not happen if a patient like Gabriela takes the medicine in the same circumstances.
- Shall we conclude that the latter case should never be investigated in a clinical trial? After all it would never happen, neither to Gabriela nor to anyone else...



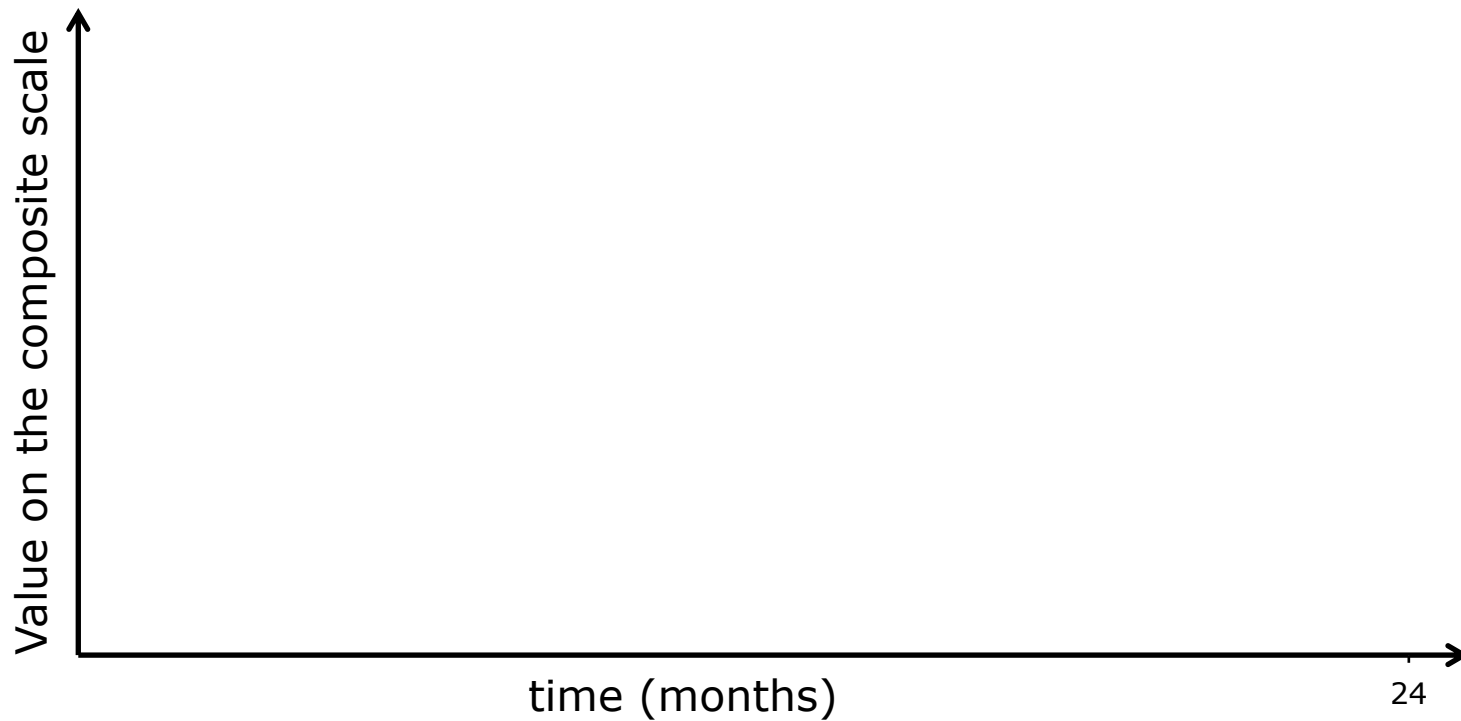
# Hypothetical strategies

## Guideline on Alzheimer's Disease

- Handling of “use of symptomatic medication” in prodromal AD trials investigating disease-modifying products
- An investigational drug is supposed to slow down disease progression
- Patients are recruited in the prodromal (i.e. pre-dementia) stage
  - Some are expected to progress within the duration of the trial
- Variable is change from baseline to 24 months on a composite scale
- All other available medicines are symptomatic
  - None is approved in the EU for prodromal AD, though it happens that patients receive some of them in that disease stage, or upon progression to dementia, which can happen during the trial

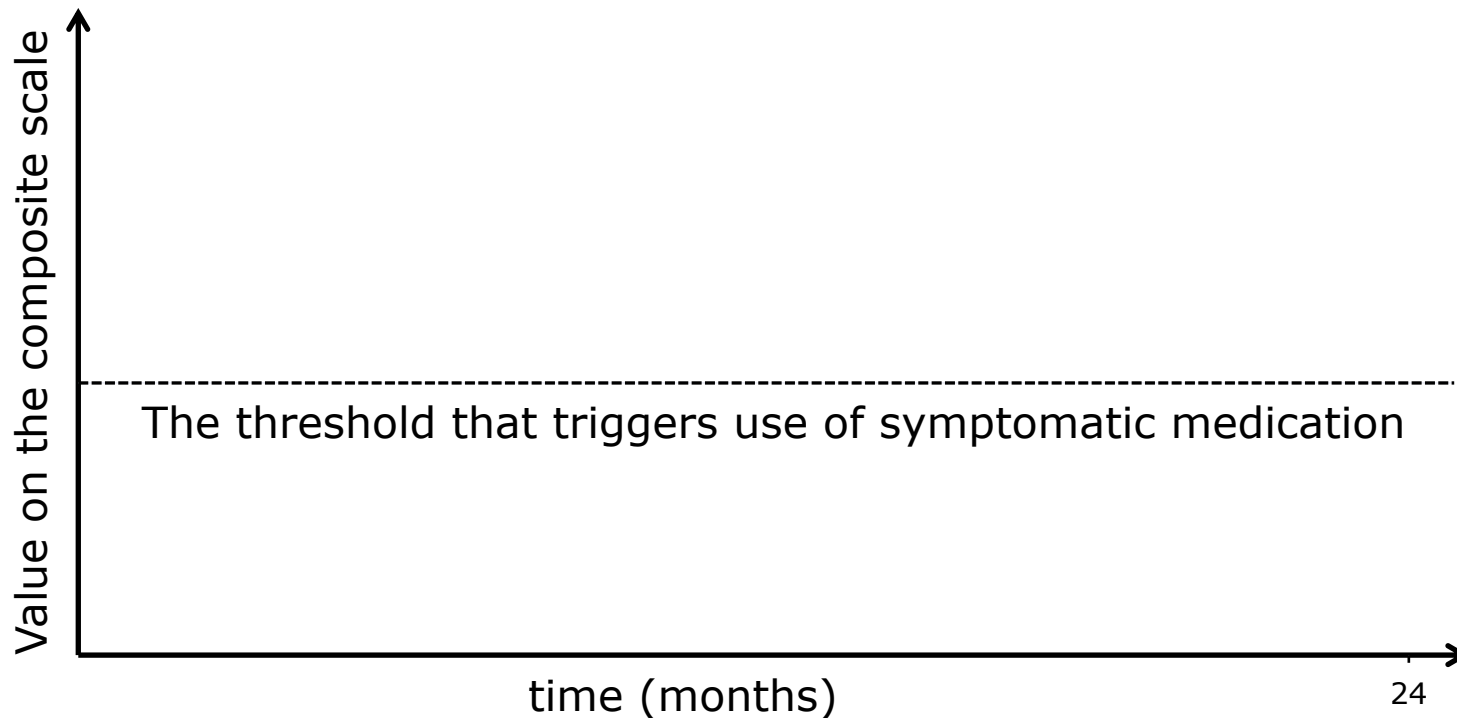


## How to deal with symptomatic treatment?



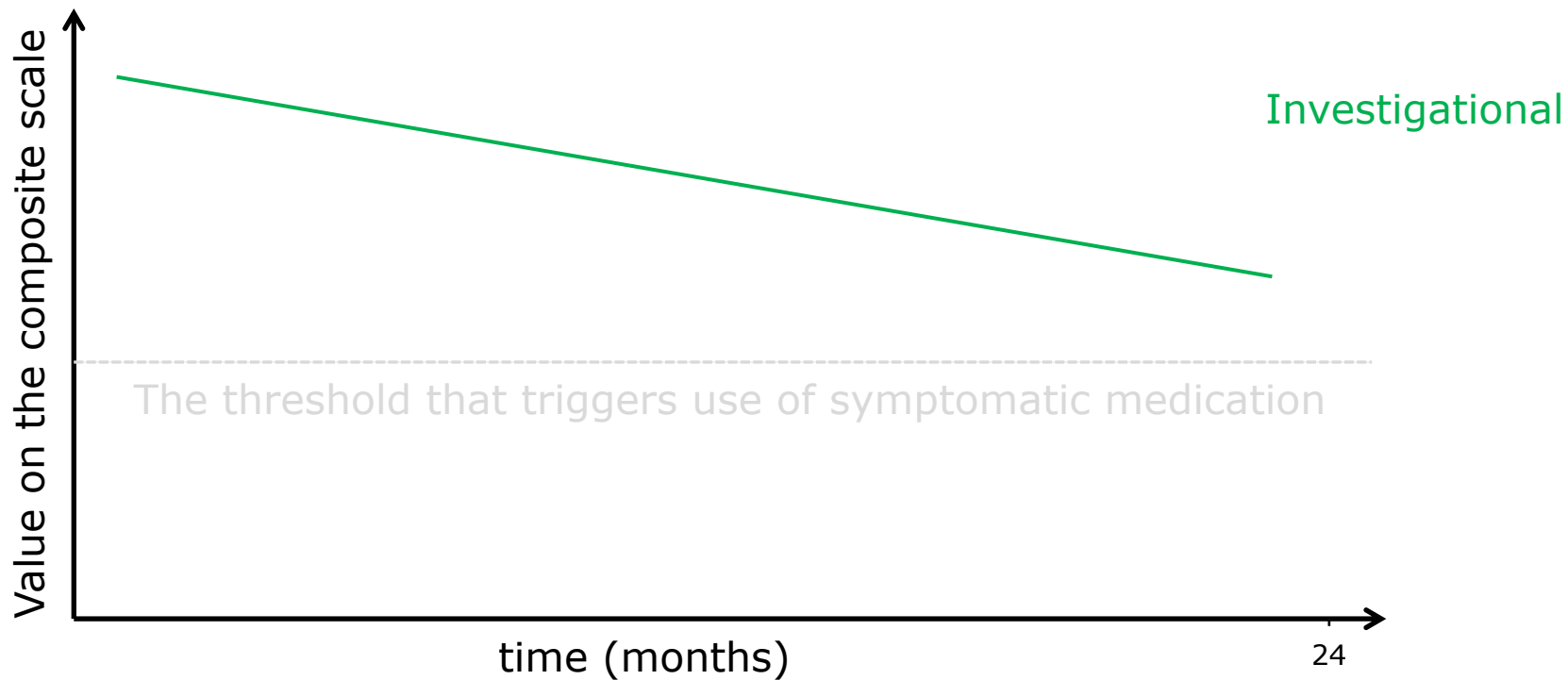


## How to deal with symptomatic treatment? (cc'd)



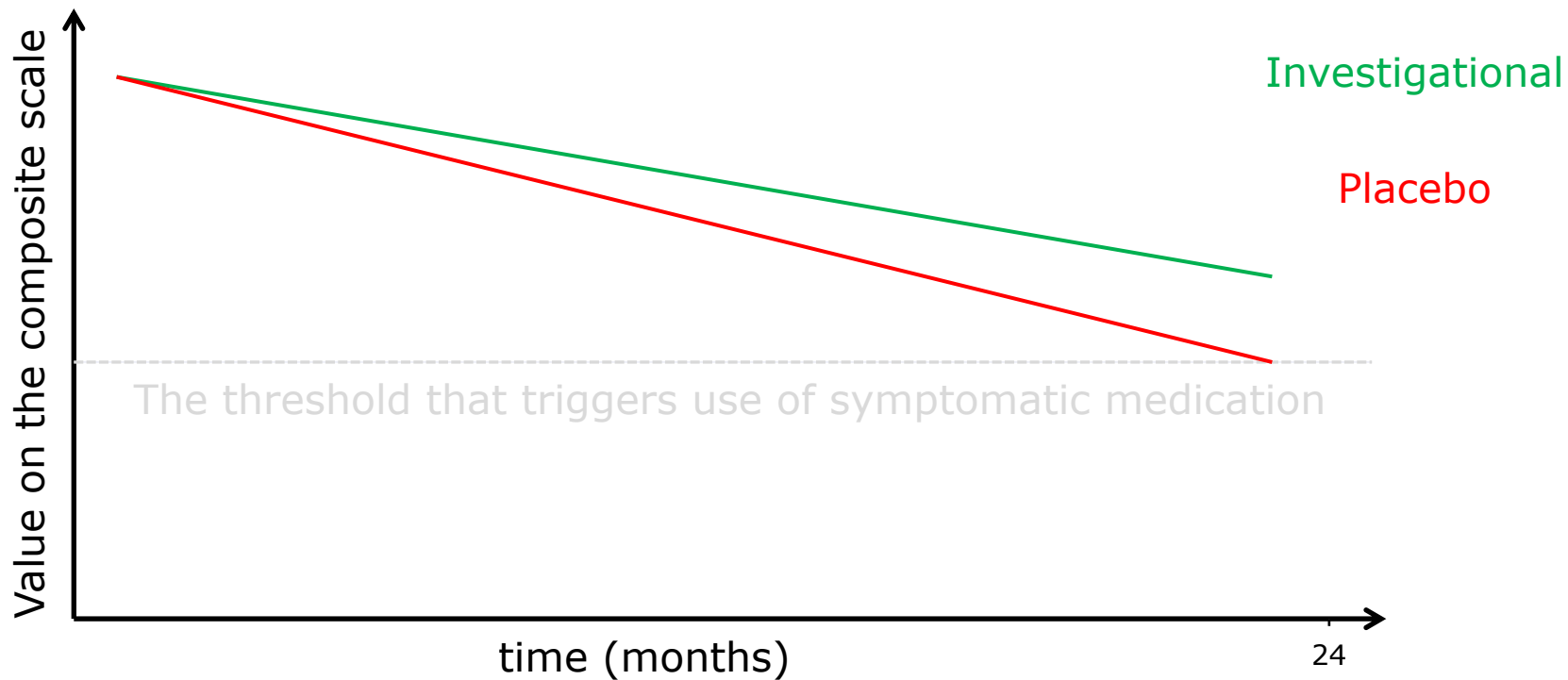


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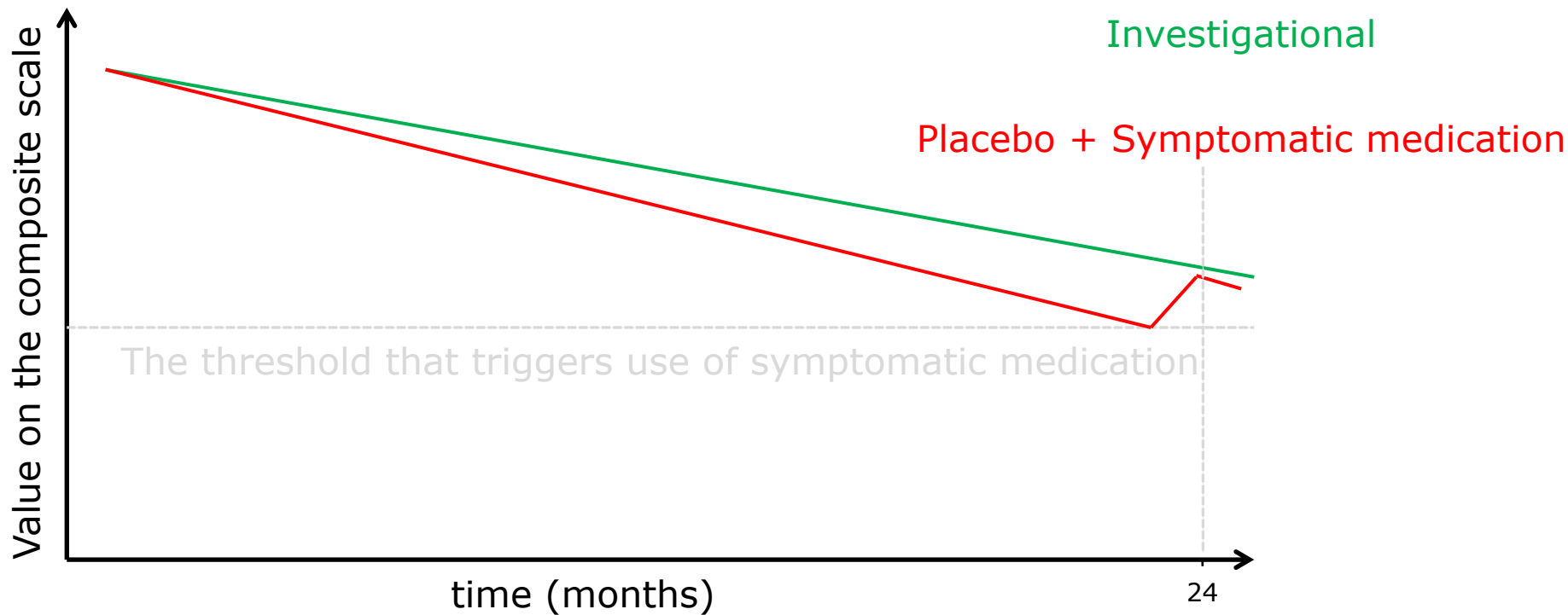


## How to deal with symptomatic treatment? (cc'd)





## How to deal with symptomatic treatment? (cc'd)







## Reflections

- Patients will always take symptomatic treatments **if available** and we are **not interested** in the effect if the symptomatic treatment is not available.
  - Consequently **this hypothetical strategy** for the intercurrent event of symptomatic treatment should not be of interest.
- But are we interested in the effect of the investigational treatment **ONLY** at 24 months (time point for the outcome in this trial), or in a **long-term effect**?
  - In the long run the effect of additional symptomatic treatments will be **negligible** as compared to the effect of the disease-modifying agent.
  - The time from diagnosis to death can exceed 10 years, and this is the whole period of interest.
- If we could study patients for longer we would disregard the effect of symptomatic treatments (**treatment policy strategy**)



## What next for estimands?

- **Implementation** time
  - More training
  - Initial reflection on early examples (feedback loop)
  - What more to investigate? (e.g. alignment with estimation, a formal link with causality)
- **Interaction** between stakeholders
  - It is and will continue happening at a product or guideline level
  - Would a general discussion be helpful? In what shape? What should be discussed?



# Any questions?

## Further information

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# Back-up



## Other reactions on aspects related to estimands

- The (wrong) idea of an homogeneous estimand (e.g. TP for all IEs)
- What to do with per protocol analysis: is it a principal stratum question or something we don't need anyway?
- Trimmed means (composite strategy for continuous outcomes): discussed once in an NI setting, a complex setting with different constraints ('conservativeness', i.e. sensitivity to 'data quality' changes going the other way from a regulatory decision-making perspective), so not the best example. Regardless of this example, regulators are always cautious with new methods, by definition. Hopefully we can receive more examples on trimmed means.
- Data collection needs to be improved: reasons for treatment discontinuation either not clear or not detailed enough



## An example with many intercurrent events

- Prophylaxis of (negative) episodes in patients with disease A
- Randomised parallel-group comparison of prophylaxis with medicinal product P to no prophylaxis, with a main trial phase over a few months
- Translation of the statistical analysis to make IE and strategies explicit:
  1. Short periods of non-compliance are ignored
  2. Periods when the treatment is purposefully interrupted for medical reasons are excluded
  3. Observation is stopped after treatment switching
  4. Observation is stopped after treatment discontinuation
  5. Patients who develop neutralising antibodies to the medicinal product are excluded