EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory experience with the Estimand framework

Lessons learnt and open questions

4th EFSPI Workshop on Regulatory Statistics

Presented by Lorenzo Guizzaro on 24 September 2019
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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.

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Content

- Experience so far
- Lessons learnt
- Open questions for future development

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The importance of asking the right question

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

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"The proportion of drop-outs expected is [], the strategy to handle missing data is []." "Follow-up will be censored…"	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.
The Estimand is described as follows. For the IEs [], the strategy chosen is [] because…	The strategy chosen for [] is [not] well justified [because].

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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.	Each case is different, difficult to give guidance applicable in all cases.

Example 1 - Presentation of the setting

- Degenerative disease where a disease-modifying agent is tested against placebo;

- There are symptomatic treatments available and some patients might start using them during the treatment.

Discussion of the estimand

Setting	**RCT**
Variable and summary measure	Average decline in performance at 1y
Proposal for handling initiation of symptomatic medication	Treatment-policy
Response to the proposal	Acceptable although hypothetical also of interest

Discussion of the estimand

Setting	RCT	Externally controlled single-arm trial
Variable and summary measure	Average decline in performance at 1y	Average decline in performance at 1y
Proposal for handling initiation of symptomatic medication	Treatment-policy	Treatment-policy
Response to the proposal	Acceptable although hypothetical also of interest	Not acceptable as different practices exist and might bias results

Special considerations for when the duration of the study is less than the duration of expected treatment in practice.

Example 2 - Presentation of the setting

- Chronic disease where we are interested to prevent very long-term complications;
- We have a surrogate endpoint that we can measure in a short trial;
- If a patient stops taking the treatment, the value of the surrogate endpoint does not revert to baseline (or the value it would have taken without treatment) immediately, but after a while.

Value affected by treatment

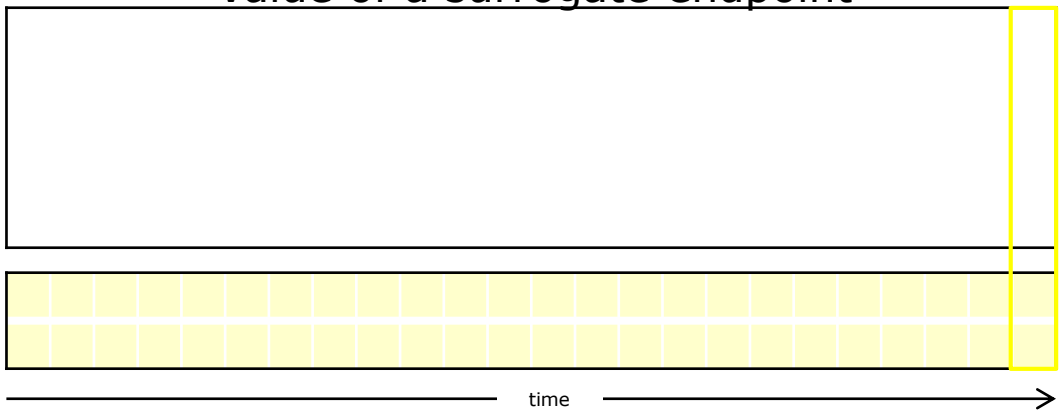
Value unaffected by treatment

Value of a surrogate endpoint

Value affected by treatment

Value unaffected by treatment

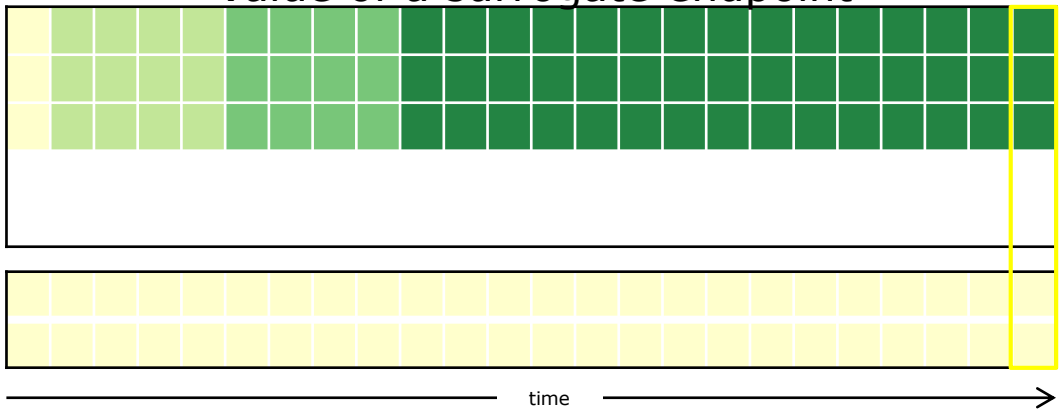
Value of a surrogate endpoint



Value affected by treatment

Value unaffected by treatment

Value of a surrogate endpoint



Value affected by treatment

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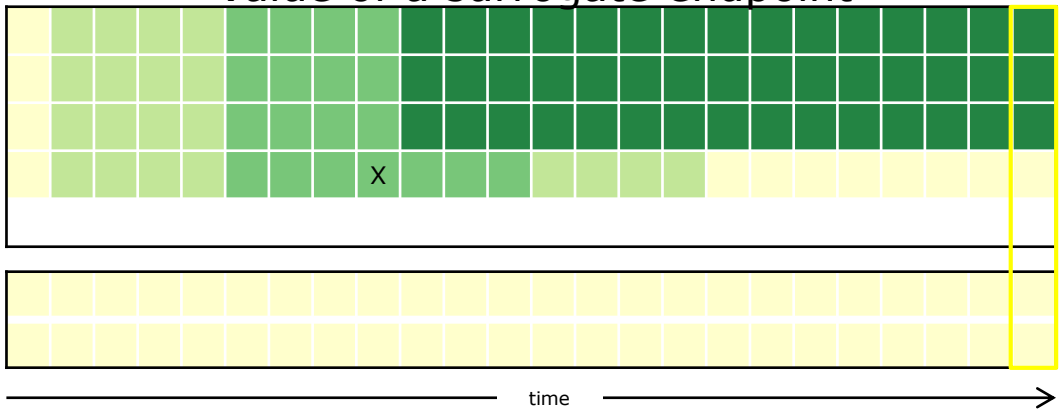

Value affected by treatment

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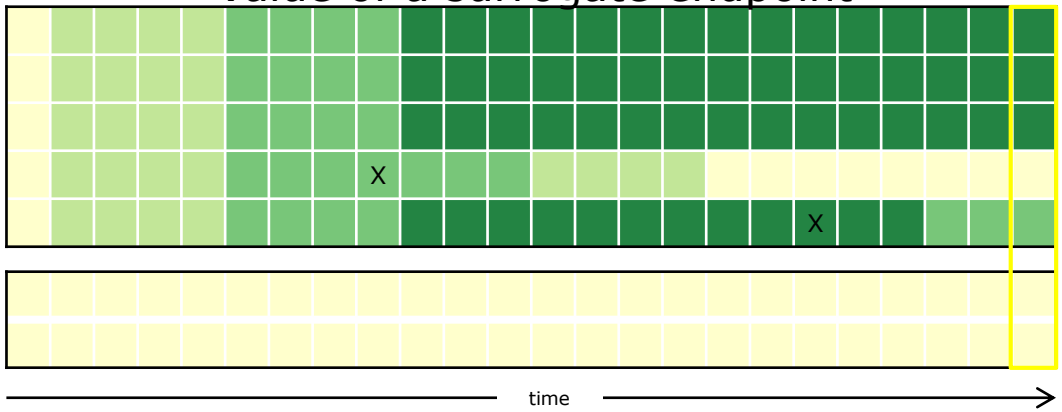
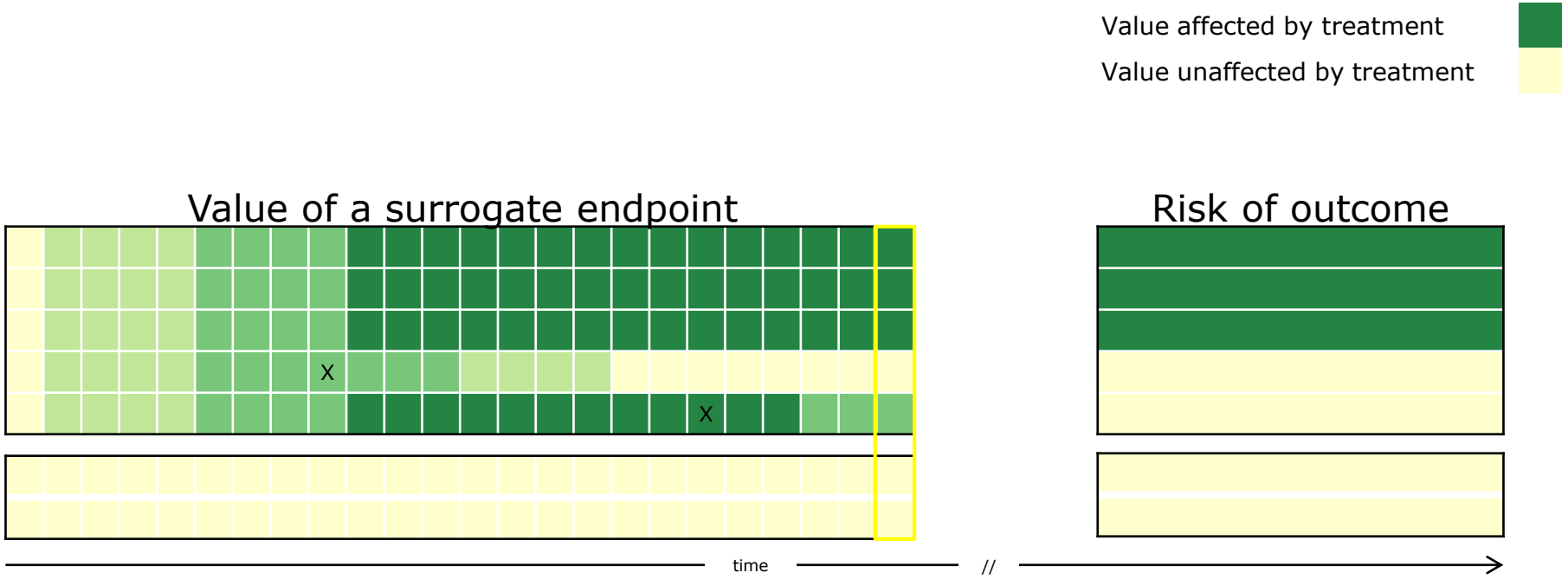
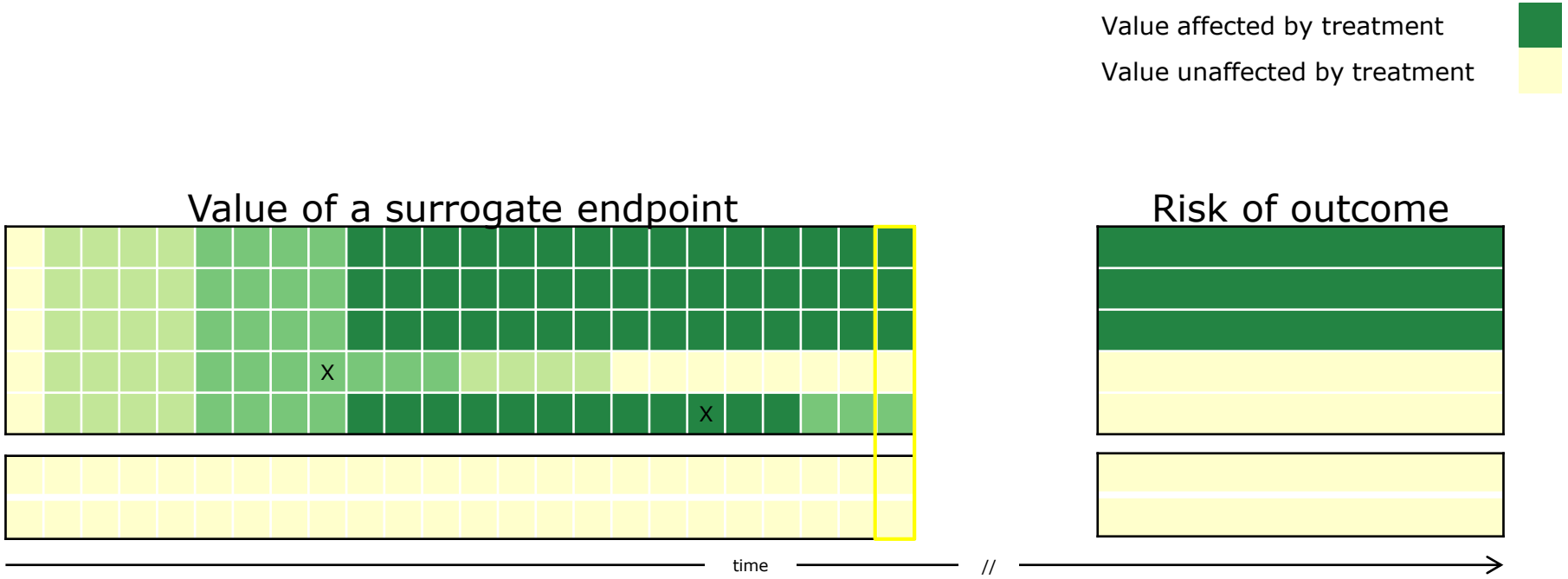



Value affected by treatment
Value unaffected by treatment
Value of a surrogate endpoint
Risk of outcome
X
X
time
//



For the last patient, the variable should take the value that it would have taken under no influence by the treatment (a version of the composite strategy?)

Example 3 - Presentation of the setting

- An investigational drug supposed to slow-down disease progression in Alzheimer's Disease

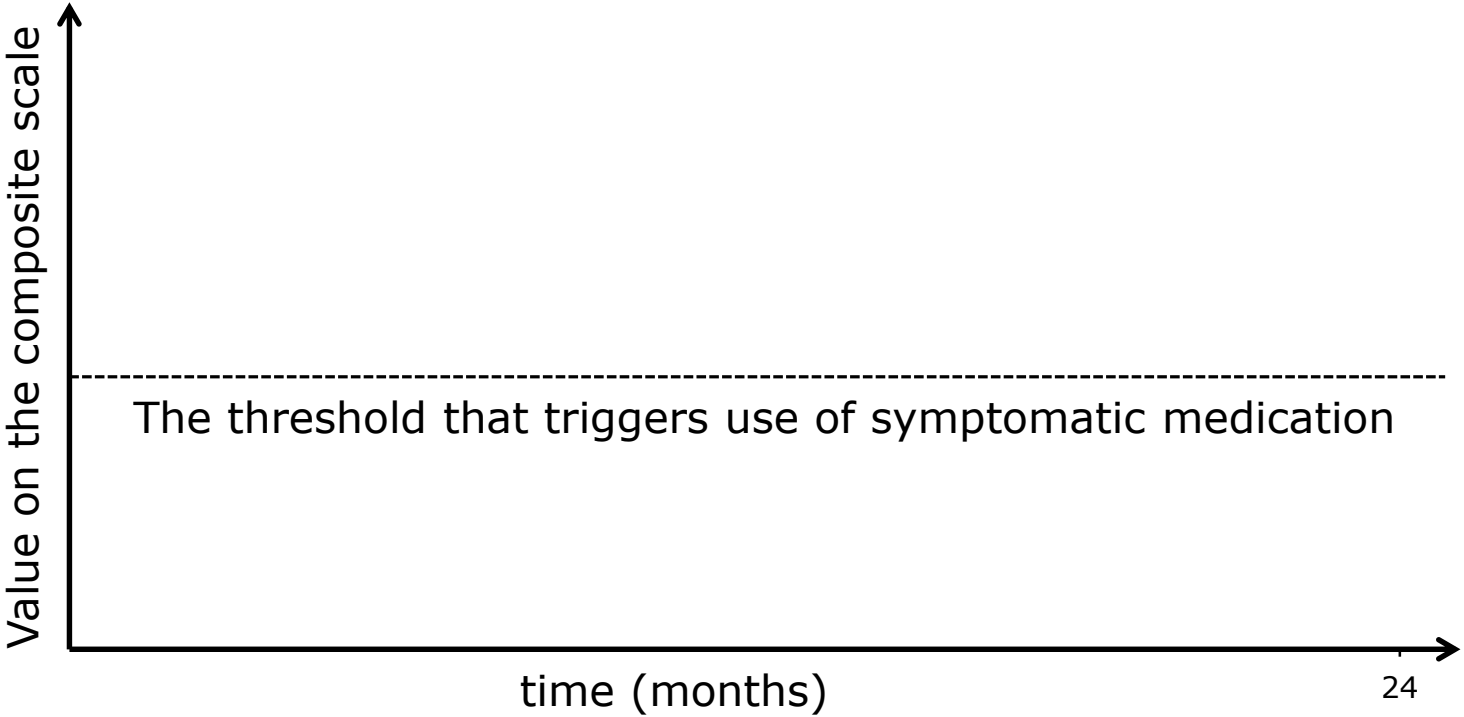
- Patients recruited in the Prodromal (i.e. pre-dementia) stage, some expected to progress within the duration of the trial

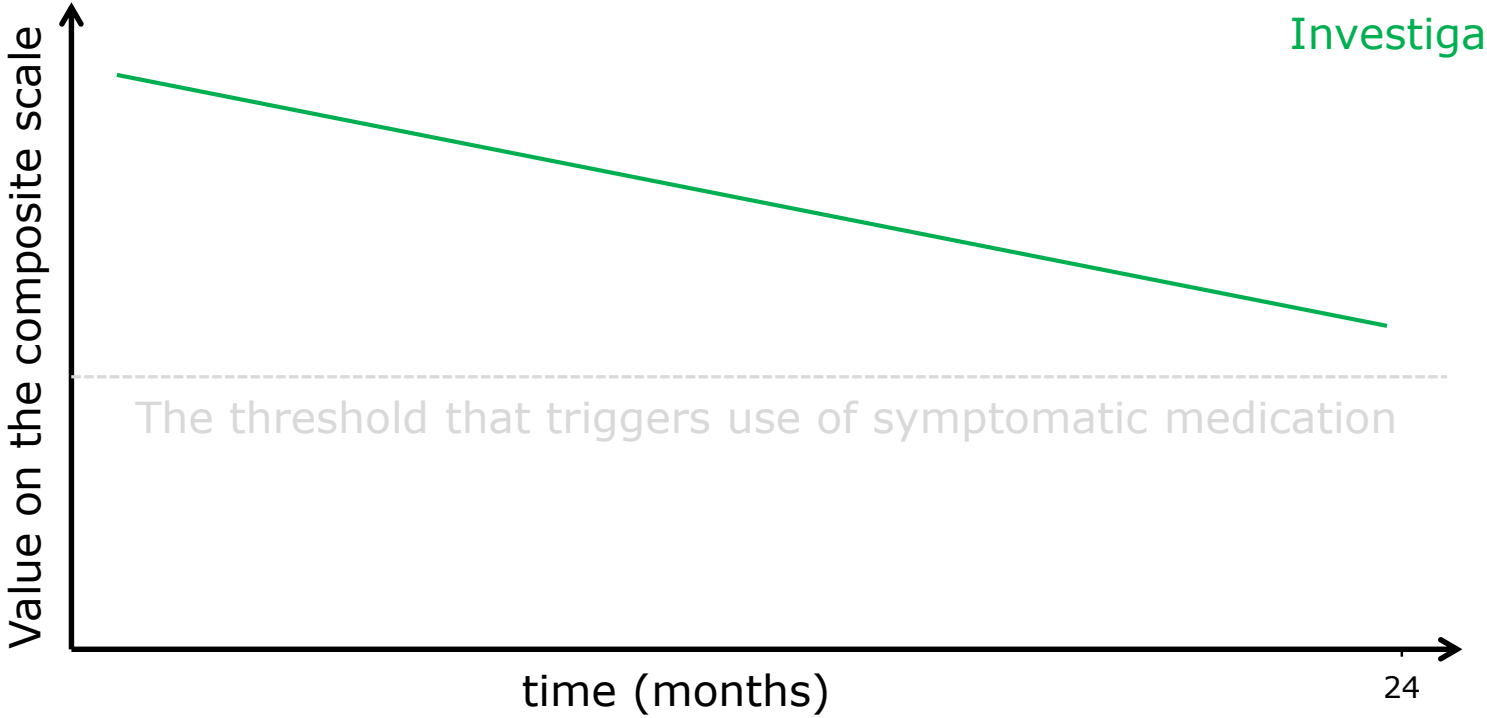
- All drugs available are symptomatic, none is approved in the EU for prodromal AD (but it happens that patients receive some of them in that stage)

A few simplifying assumptions

- Within each arm, all patients will have the same decline;
- All patients will start a symptomatic medication as soon as they reach a certain threshold;
- The symptomatic treatment would provide a small symptomatic improvement to everyone.


Value on the composite scale
time (months)
24


Value on the composite scale
The threshold that triggers use of symptomatic medication
time (months)
24


Investigational
The threshold that triggers use of symptomatic medication
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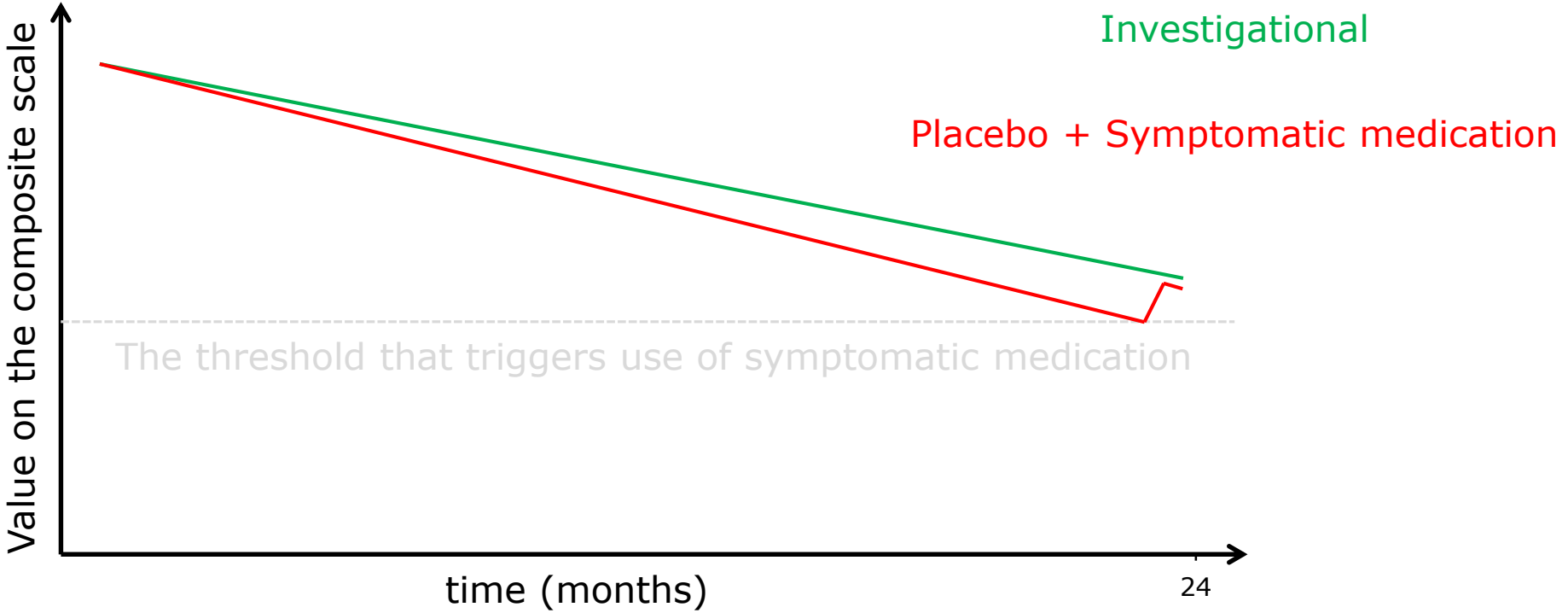
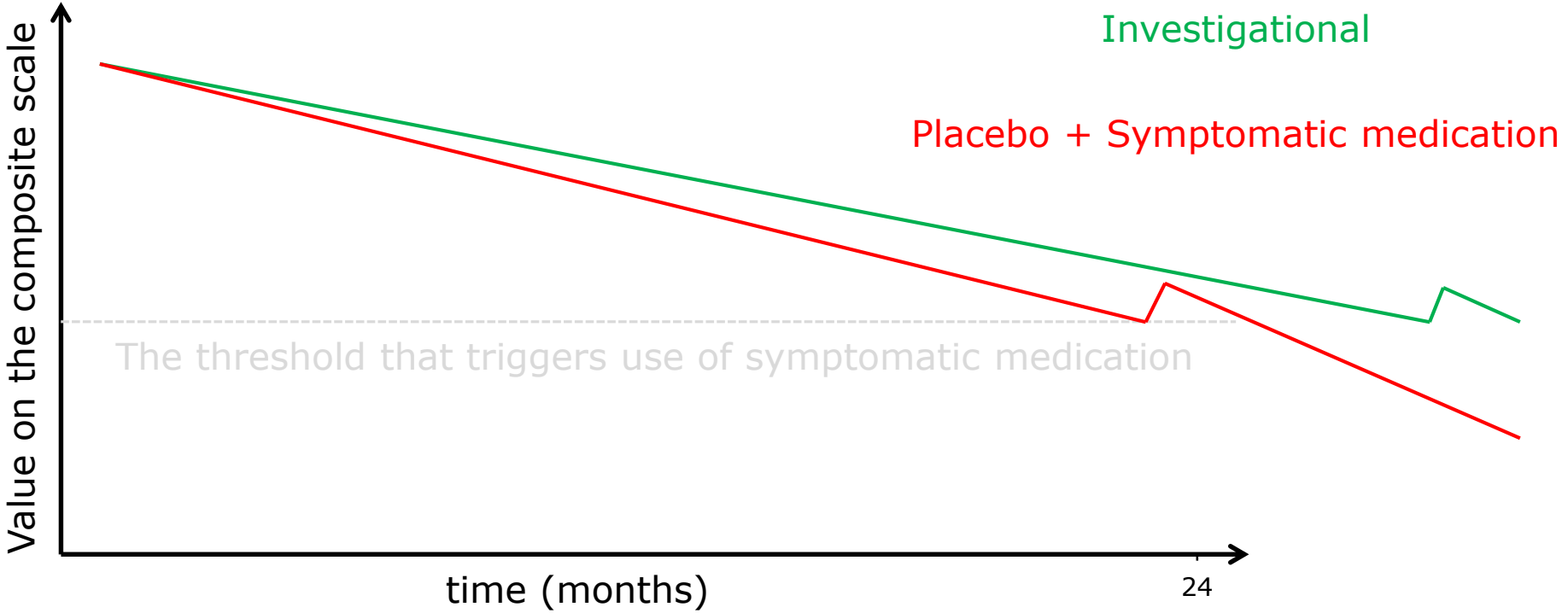

Investigational
Placebo + Symptomatic medication
The threshold that triggers use of symptomatic medication
Value on the composite scale
time (months)
24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Value on the composite scale
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The instances where the timeframe of interest for the treatment effect does not correspond with the trial duration may require a special reflection when choosing the strategy for handling intercurrent events.

Should the time dimension of the variable of the estimand always correspond to the duration of the trial?

Any questions?

Further information

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