EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Delayed start design in neurodegenerative diseases

Dialogue on the design, its shortcomings, and on the interpretation of the results

2nd EFSPI Workshop on Regulatory Statistics

Presented by Lorenzo Guizzaro on 6 October 2017
Central Nervous System and Ophthalmology Office

Set-up

Student has been assigned the demonstration of disease-modification for an hypothetical Alzheimer product as extended essay for her MSc in Drug Development Science.

Grandpa is Student's grandfather, former biologist and epistemologist, now enjoying his golden years.

Disclaimer

The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

The starting material

Student has been given data from a hypothetical 2-years placebo-controlled double-blind trial.

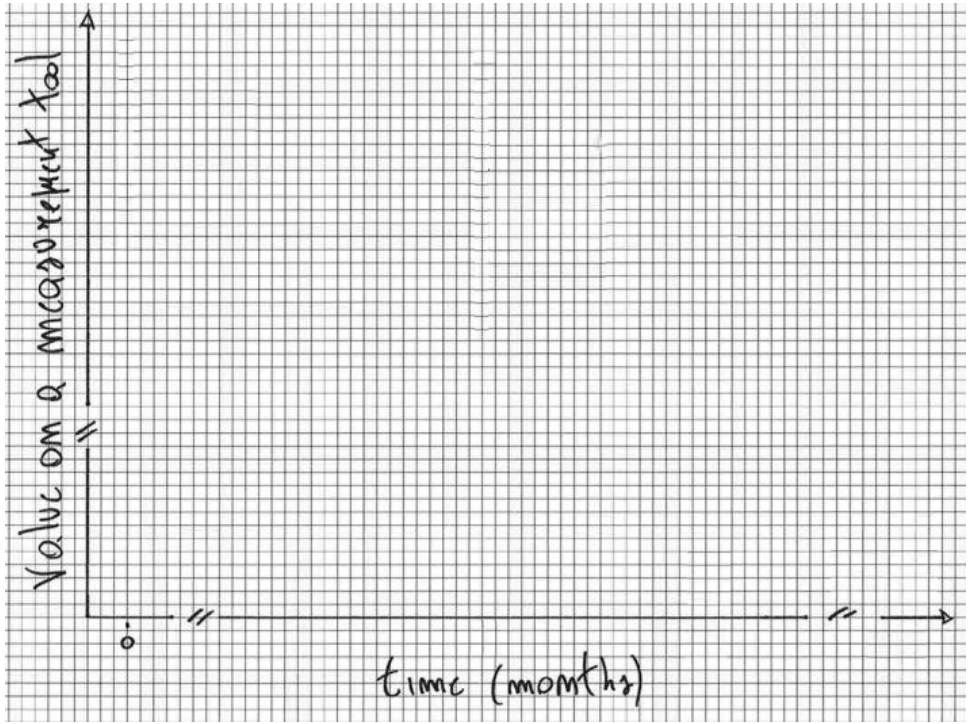
The target disease is Alzheimer's Disease, a disease that starts with the difficulty of learning new information and progressively brings to complete dementia.

The population is early AD: these patients very slowly progress to lose ability to perform in cognitive tasks (memory, attention, orientation and language) and in the activities of daily living.

The drug is designed to slow down progression, not to give a symptomatic boost.

Student is free to analyse/extend/expand the trial as she wishes.

The starting material



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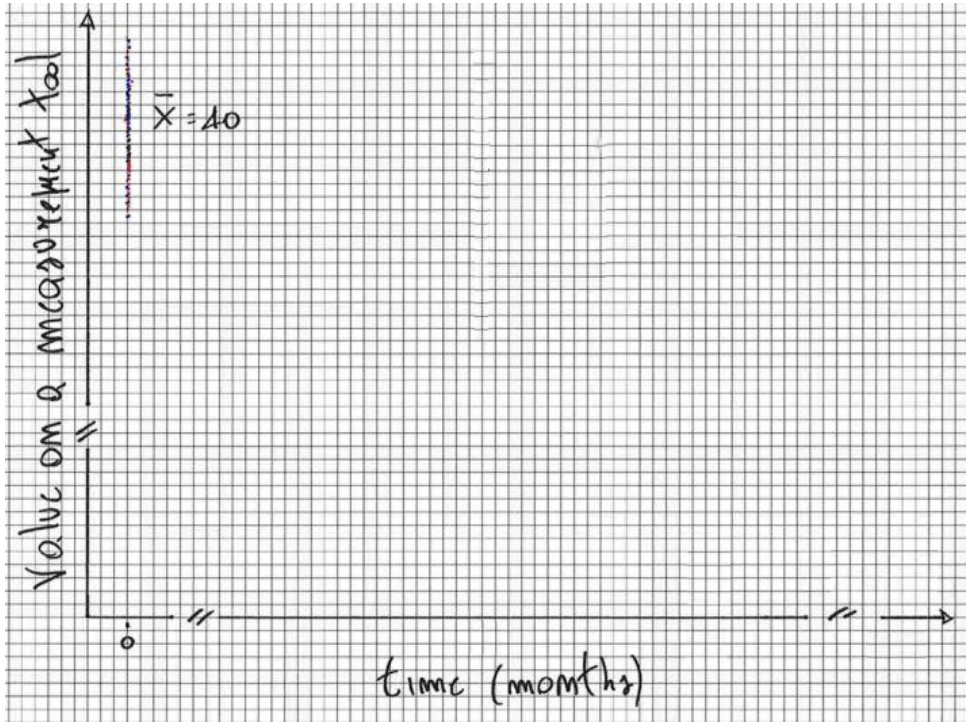

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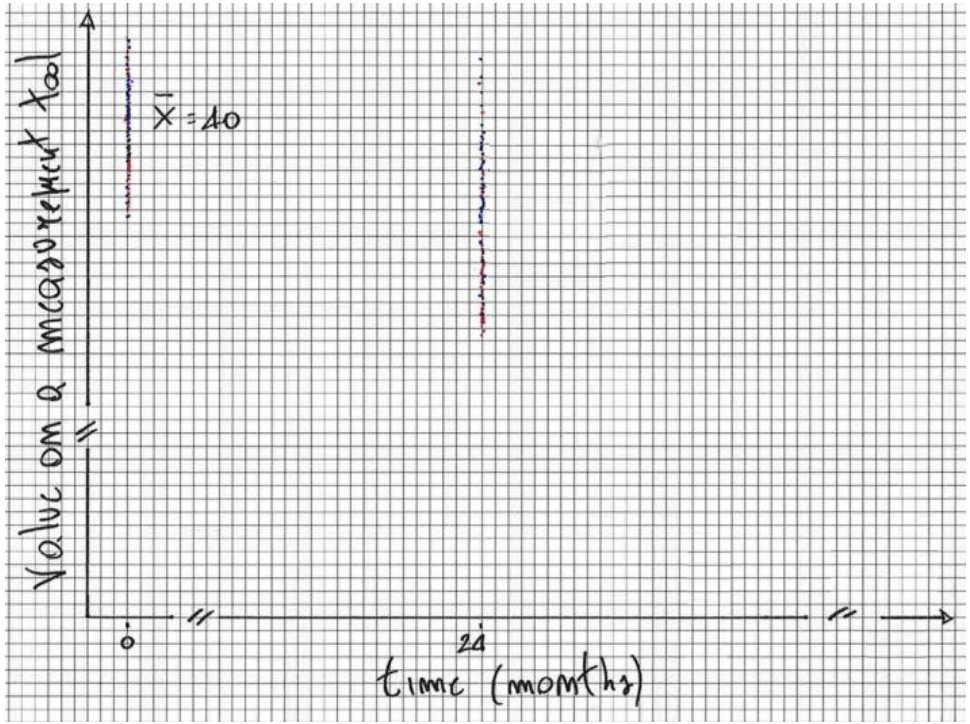

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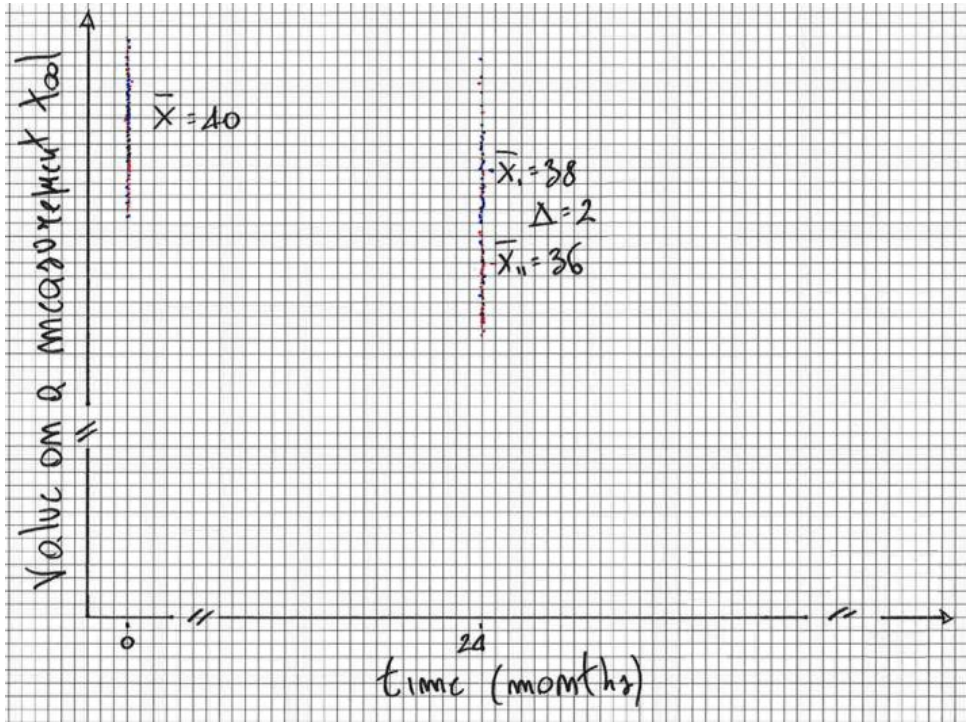

The strategy to demonstrate disease modification

Student How should I demonstrate that the treatment is not symptomatic but disease modifying?

Grandpa How do you define disease modification?

The strategy to demonstrate disease modification

A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes.

[…]

Since a disease modifying effect correlated with a persistent delay in the underlying neuropathological process is difficult to prove without adequately validated and qualified biomarkers as outcome parameters, a slowing or delay of clinical decline (cognitive and functional) as demonstrated by innovative trial designs may be acceptable as an alternative development goal. (EMA, 2016)

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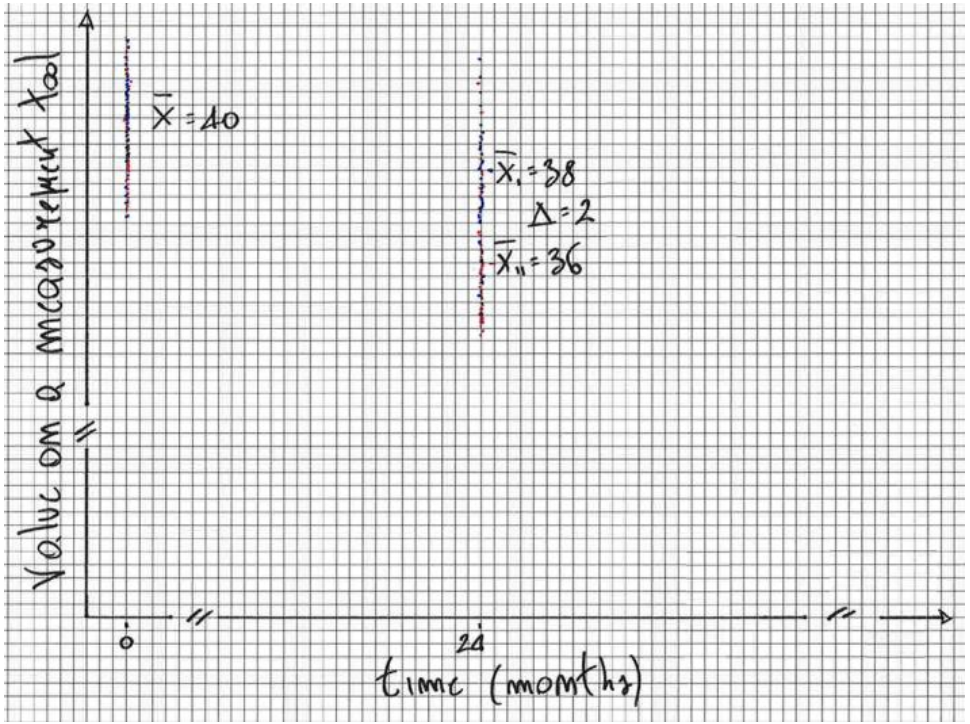
The strategy to demonstrate disease modification

Grandpa The idea of persistence appears to be consistent with the continued existence of the difference created between the two groups of patients in the trial you have shown me if the patients are then kept in the trial and all assigned to the same thing.

That "same thing" being the drug ("delayed-start") or placebo ("randomised withdrawal").

The strategy to demonstrate disease modification



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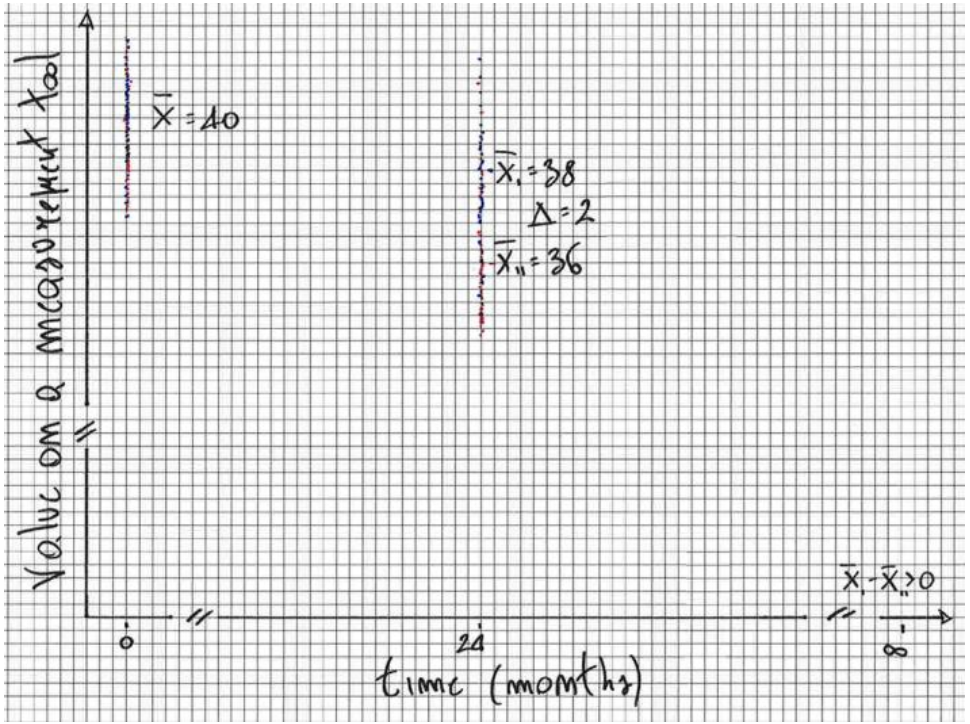

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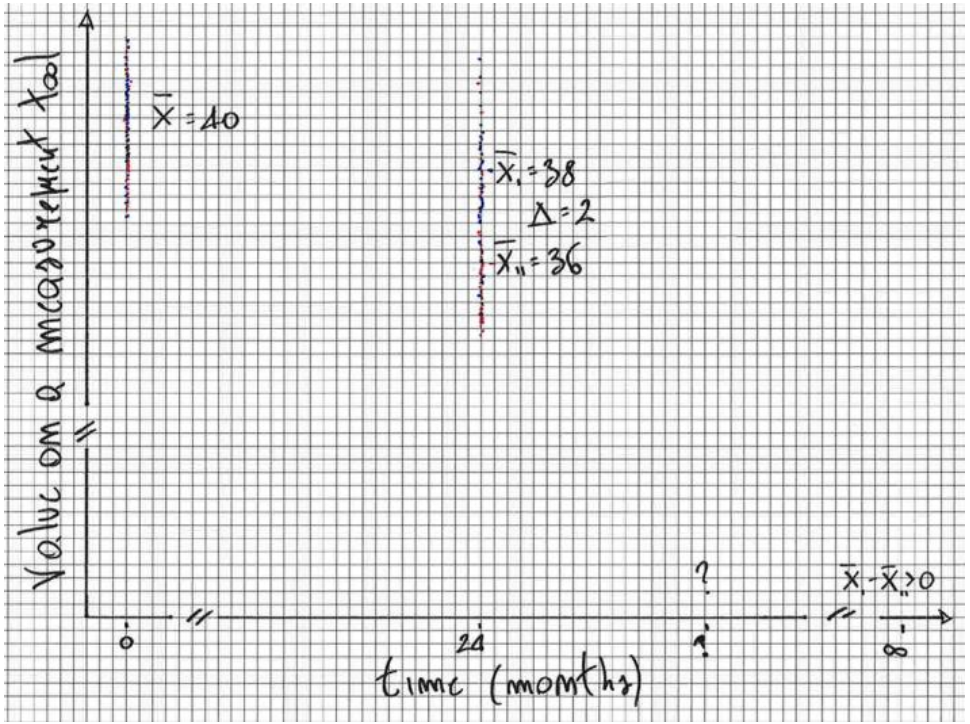


The strategy to demonstrate disease modification

Grandpa You'll need to show three things:

(i) That there is a difference at the end of the double blind period between subjects assigned to active treatment and to placebo

(ii) That the difference persists (i.e. still exists) at the end of the extension phase

(iii) (since the extension phase is necessarily shorter than patients' life expectancy) that the difference is not shrinking too much/too quickly (no obvious cut-off)

Any easier with the biomarkers?

Student *packing her stuff* Ok. And I guess for the biomarkers I just show any difference at any point on any one of the biomarkers?

Grandpa Well…

Student No?

Any easier with the biomarkers?

In principle, any modification in the function of the brain (even from a symptomatic treatment) must be reflected in something that is “visible” in some biomarker.

Any easier with the biomarkers?

In principle, any modification in the function of the brain (even from a symptomatic treatment) must be reflected in something that is “visible” in some biomarker.

With the currently available knowledge, it’s hard to conclude on disease modification with a difference in any given biomarker at any given time.

Hence, similar considerations to those made for a cognitive/functional score should apply.

Nothing can go wrong. Or can it?

Student Ok then…

Grandpa Don’t you want anything to write in the limitations section?

Student Is that a good thing?

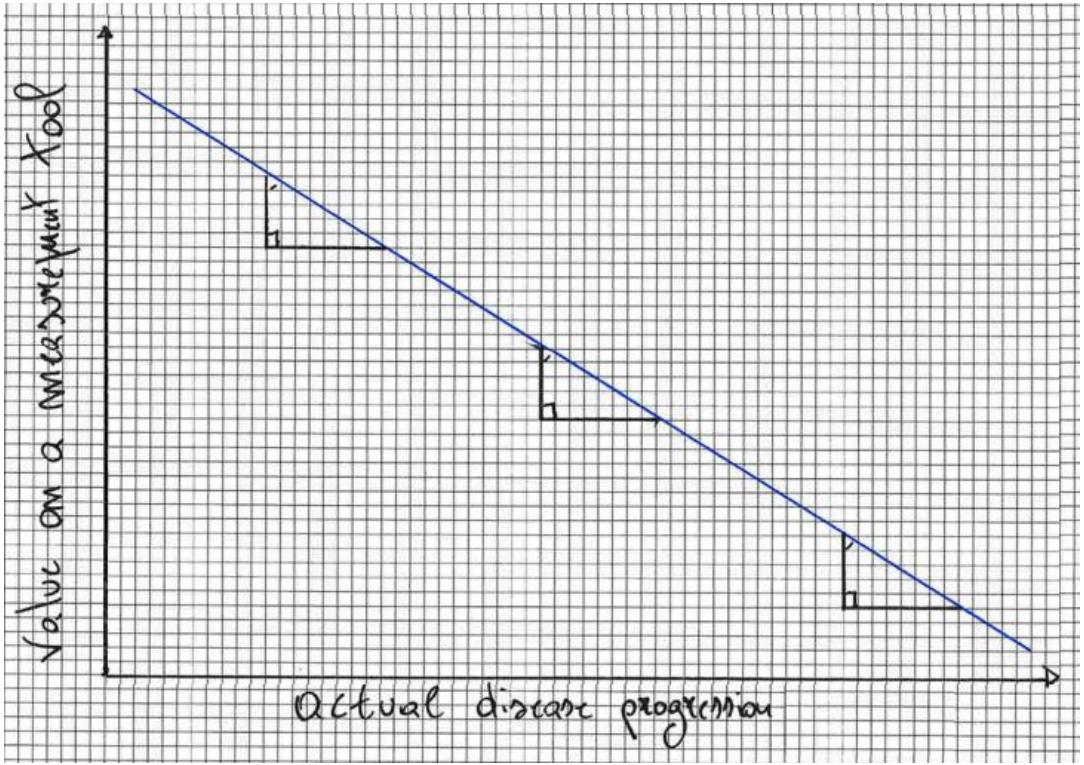
Grandpa What is it that – not being the effect of a disease-modifying medicine – would still give a positive result to all the points described?

A self-sustaining difference

- Some performances can be also a “training”. For example, being more involved in social interactions can be the effect of a symptomatic treatment, but it will also itself stimulate the maintenance of a certain degree of functioning.

- Having a certain level of performance could avoid or reduce the emergence of deleterious compensatory mechanisms. In this scenario a disease-modifying effect would be a corollary to any symptomatic effect.

The structure of the outcome measurement tools



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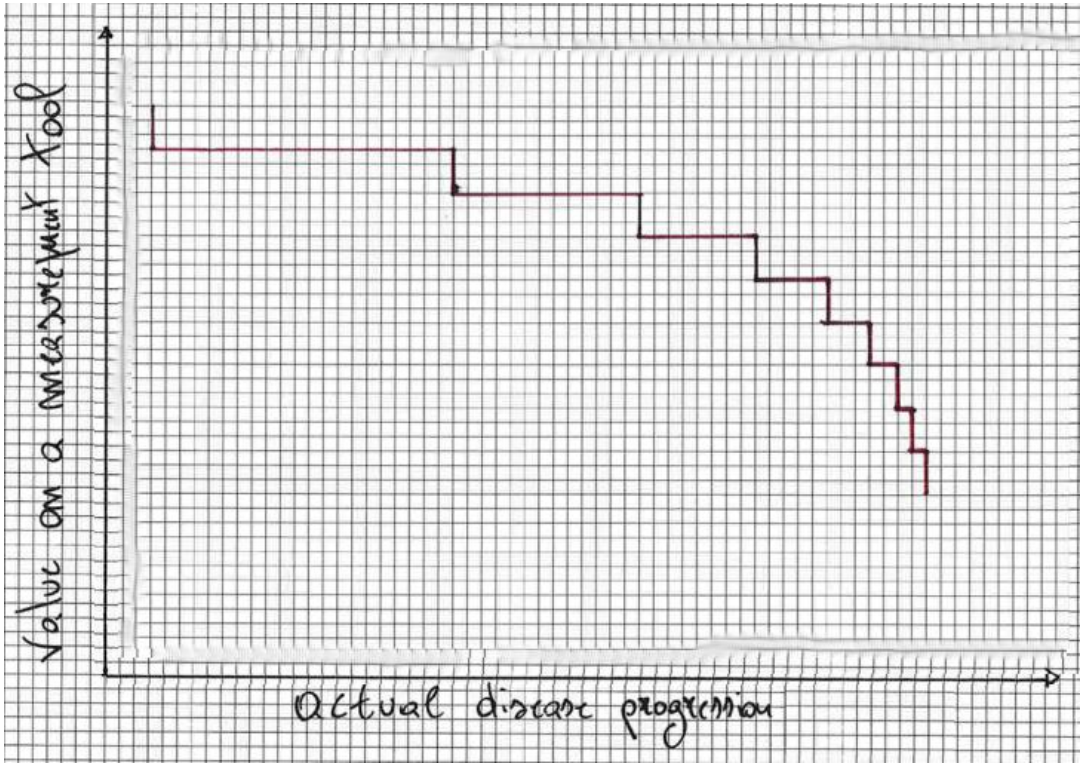

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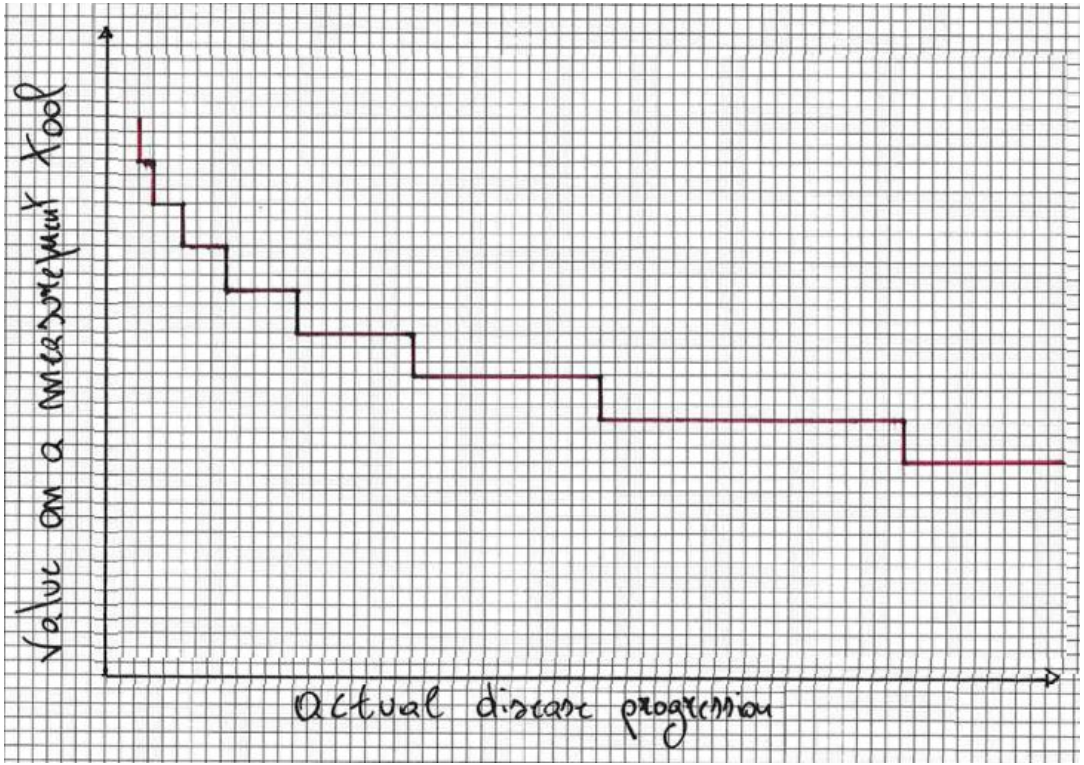


Unblinding

- The delayed-start period is hardly double-blind, and (more?) importantly also the initial assignment can be revealed by effects of the medicine.

Handling of intercurrent events

Student *putting her jacket on* Thanks – I'm going for drinks now!

Grandpa Aren't you forgetting something?

Student Didn't I say "thanks"?

Handling of intercurrent events

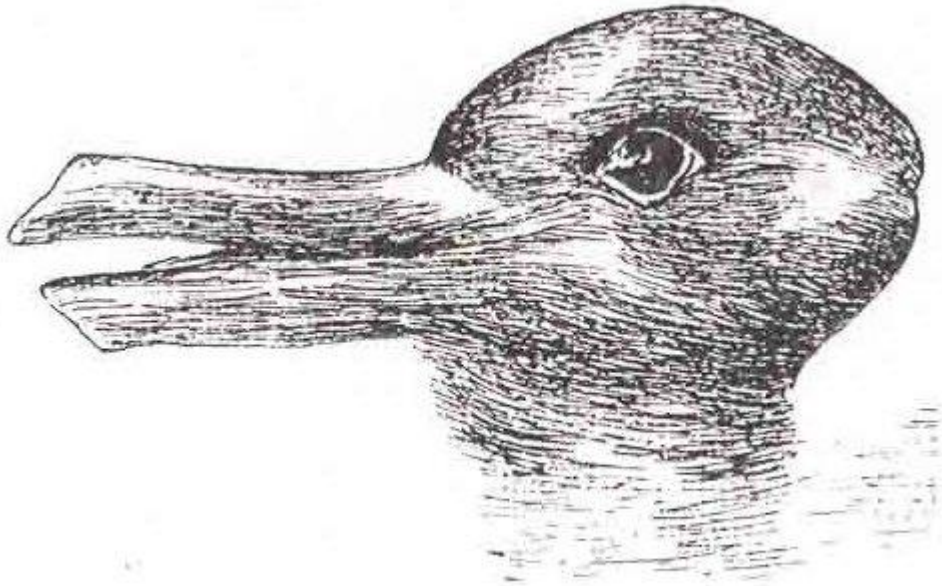
Grandpa As the demonstration of an effect being disease-modifying and not purely symptomatic relates to a theoretical property of the medicine rather than to one treatment policy over another, wouldn't "had all patients adhered to the assigned treatment" be - for the delayed-start period - a sensible target of estimation?

The clinical relevance of the results

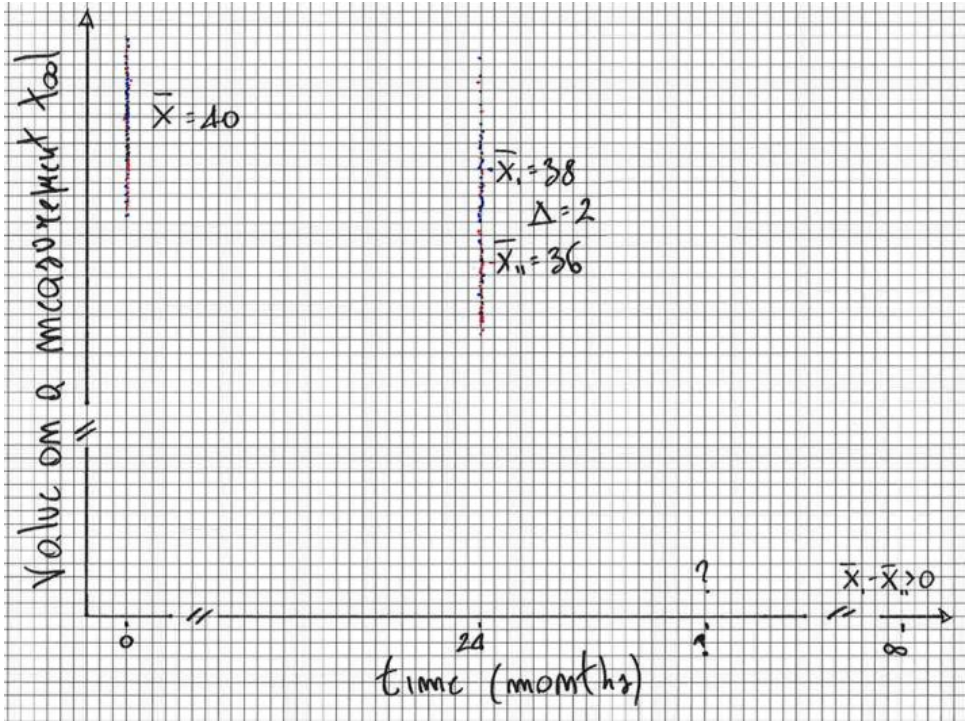
Student I had some feedback from my supervisor! Quite happy – only says we might need to defend the clinical relevance of the magnitude of change. Not easy because they gave me a slow-progressing population and my treatment does not give any symptomatic "boost" but only slows down progression.

Grandpa Have you ever heard of gestalt shift?

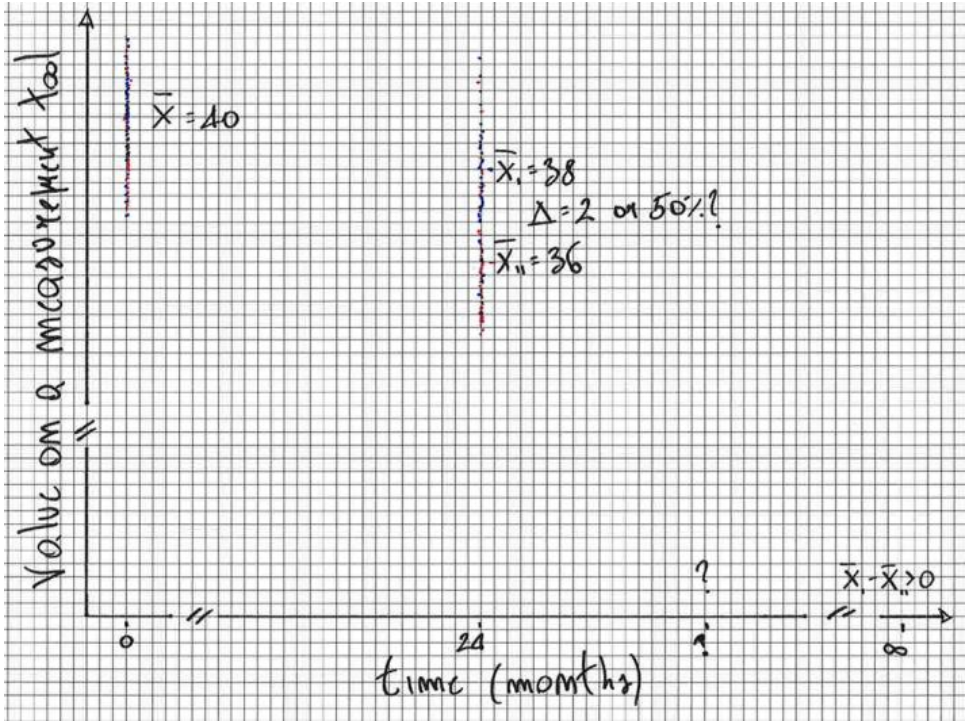
A gestalt shift



A gestalt shift



A gestalt shift



Take home messages

- A delayed-start design might be appropriate to characterise the properties of a treatment for neurodegenerative diseases

- Alternative interpretation of the data should be discussed and excluded

- Proving disease modification might impact the interpretation of data

Any questions?

Further information

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