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Translation of the estimand framework into regulatory guidance: what's next?

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Disclaimer

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

Some slides were developed by colleagues in the ICH E9(R1) Expert Working Group.

Acknowledgments

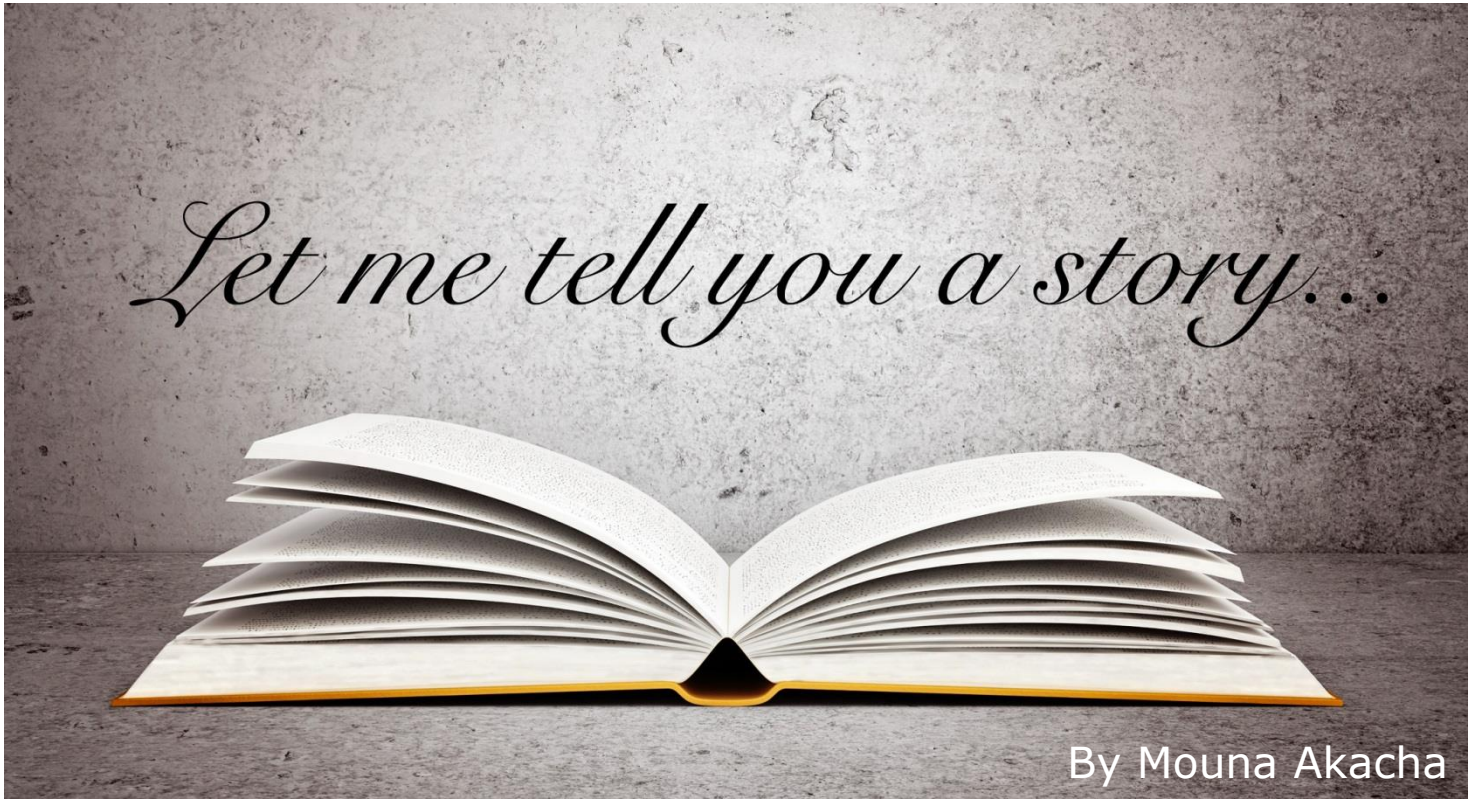
Inês Reis, Lorenzo Guizzaro, Mouna Akacha

Objective of the talk

- Reflect on implementation of the E9 Addendum on estimands and sensitivity analysis
  - Focus on the estimand part, less on sensitivity analysis (for now)
- What should regulators do to promote the estimand framework?
- How much can it be translated into regulatory recommendations at a disease level?

Motivation

- Discussions at Scientific Advice and on Regulatory Guidelines at EMA in the past year
- This is only the beginning
- Stimulate feedback from stakeholders on Addendum **and** on how to implement it


Let me tell you a story...
By Mouna Akacha

Once upon a time, there was a scientist who wanted to...

- Compare a novel drug A to placebo in the treatment of a symptomatic disease
- He knows:
  - Clinical relevant endpoint is a score at week 24
  - Randomised clinical trials (RCT) are gold standard in drug development
- He ends up designing a parallel-group, placebo-controlled RCT

Throughout the study complications arise...

- Some patients cannot tolerate their randomised treatment and stop taking it
- Others feel that the treatment doesn’t work for them and they stop taking it as well
- Yet others have a worsening of their symptoms and take some rescue medication (according to the protocol)

Luckily our story is about a very charismatic scientist...

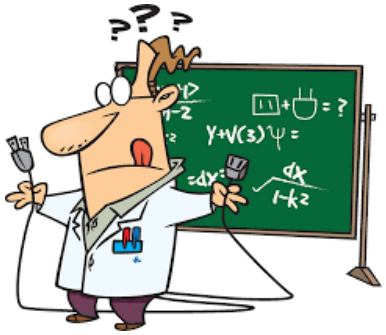
- He is able to convince all patients to stay in the trial
  - although they may no longer take their randomized treatment, possibly taking another treatment instead
- At trial end he has all symptom scores at week 24 to address his scientific question:
- "Is drug A better than placebo in reducing the symptoms of patients at week 24?"

To ensure that he will draw the right conclusions he consults the ICH E9...

- He performs an intention-to-treat (ITT) analysis as recommended in the ICH E9:
  - "Preservation of the initial randomization in analysis is important"
  - "... the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given."
- The ITT analysis results reveal that drug A is not better than placebo
- He is very puzzled as he saw an overwhelming effect in patients that were treated so he consults a statistician to check the analysis

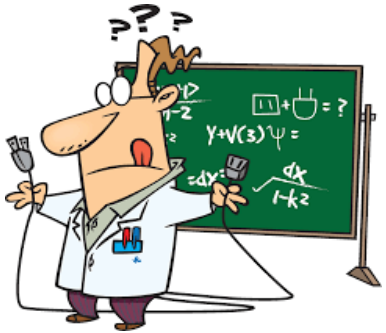
The statistician confirms that the ITT analysis is performed correctly...

- However, he also realizes that there are marked imbalances between both treatment arms in
  - intake of rescue medications
  - treatment discontinuations due to adverse events (AEs) or lack of efficacy
- He notices that the treatments have resulted in several outcomes:
  - Adverse events severe enough to cause treatment discontinuation
  - Unsatisfactory efficacy, resulting in treatment discontinuation or the use of rescue medications
  - Acceptable efficacy and tolerability such that patients adhere to the randomized treatment for 24 weeks



Looking back at the initial analysis he realizes that...

- The ITT approach does not capture these distinct outcomes and is thus difficult to interpret
- E.g. the ITT analysis does not distinguish between whether data are collected on rescue or not, and thus does not capture the 'lack of efficacy' aspect that leads to rescue intake
- He discusses with a colleague who tells him:



> Despite what you may have heard, randomized trials are not always free of confounding and selection bias. Randomized trials are expected to be free only from baseline confounding but not from post-randomization confounding and selection bias.
>
> Hernan et al. (2013)

Thinking more about the initial analysis he reminds himself that...

- The ITT approach targets the 'intention-to-treat' / 'treatment-policy' effect within the particular set-up of the trial
- And he wonders whether this effect is really of clinical interest

- He goes back to the scientist who:
  - Acknowledges issues with rescue medication, etc.
  - Still believes that it is a statistician's problem
  - Wonders what is really of clinical interest

What next?

- Description and explanation on the content of the Addendum
  - Trainings
  - Workshops, scientific meetings
  - Examples

- Implementation of the Addendum
  - Protocol writing
  - Impact on analysis methods
  - Relevance of estimands

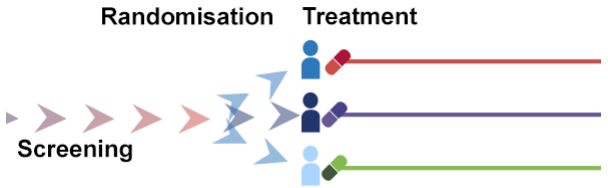
Two very relevant situations in the regulatory world

Product advice and evaluation

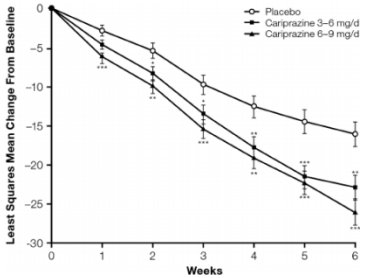
Guidelines for drug development

Guidelines for drug development

- Section on confirmatory clinical trials …
  - Design: choice of control, duration, etc.
  - Endpoints



- … and Statistical section
  - Focus on estimation
  - Missing data - and implicitly intercurrent events!
  - (Many) sensitivity analyses



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One Guideline example:

Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias

Draft

11. Statistical considerations

As for any trial it is of critical importance to clearly specify the scientific question of interest that the trial seeks to address. This should consider, explicitly, post-randomisation events such as patient withdrawals from randomised treatment or from protocolled follow-up, and use of alternative therapeutic interventions. The handling of missing data, particularly resulting from early withdrawals, is of particular concern in Alzheimer's disease trials, as the proportion of patients with missing data is

In the statistical section?

Where should **estimands** be best addressed?

…or earlier, in the clinical trial section?

Options? How much detail?

1 Describe relevant estimands

- Lists recommended estimands
- Says how to handle intercurrent events
- Impact on design, data collection and study conduct

2 High level description

- Leaves flexibility for choice of estimands
- Lists points to consider, e.g. intercurrent events affecting estimand
- Risk of inconsistency in advice and evaluation

3 Status Quo

- Left to statisticians to pick up the pieces if things go wrong

Options? In which part of the guideline?

1 In the clinical section only

- Estimands should be considered early on in the clinical trial planning
- Estimation considerations still developed in the statistical section

2 In the statistical section

- As a transition until clinicians take ownership of estimand concept and terminology
- Risk of misalignment between clinical trial and statistical section

3 Status Quo

- Nowhere
- Left to Scientific Advice and other interactions

Are we too optimistic?

1 Describe relevant estimands

- Lists recommended estimands
- Says how to handle intercurrent events
- Impact on design, data collection and study conduct

How much can or should estimands be delineated?

- Is it possible to state a preferred estimand in a clinical setting?

- Fall back position: only provide tools to discuss the most suitable estimand
- Pros and cons of each strategy, and for each intercurrent event

Going back to the example: Alzheimer's Disease

- What are potential intercurrent events?
  - Adherence to randomised treatment
  - Additional medication
  - Death

- But are they always relevant?
- Different settings : Mild Cognitive Impairment versus advanced stages of dementia
- Different treatment positioning
  - Disease-modifying or symptomatic treatment
  - With or without add-on medication

Going back to the example: Alzheimer's Disease

- Which preferred strategy?
  - Treatment policy
  - Hypothetical
  - Other?

- Data collection
  - Importance depends on the target of estimation
  - More data to collect?

Draft ICH E9(R1) Addendum – open for comments!

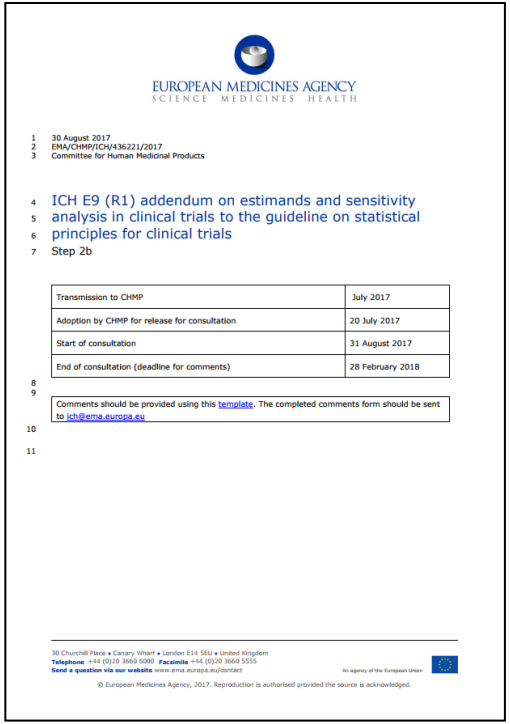
Draft **ICH E9 (R1) Addendum** – Step 2b has been published in the EMA website

Comments can be sent to

ich@ema.europa.eu

until 28 February 2018,

using the template provided



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30 August 2017
EMA/CHMP/ICH/436221/2017
Committee for Human Medicinal Products

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

Step 2b

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018

Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

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Thank you for your attention

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