EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory feedback and commentary on BPD clinical development

Considerations on methodology and relevance of endpoints

ISCTM 2020 Autumn Conference

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An agency of the European Union

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Borderline Personality Disorder

People with a diagnosis of Borderline Personality disorder suffer from significant burden[1], including from associated stigma[2].

Polypharmacy is common[3], with limited supporting evidence base.

The classification of personality traits and disorders is a field of active debate[4].

The psychometrics[5] and neurobiology[6] are complex and there is no guarantee of a "magic-bullet".

[1] Soeteman, D.I et al 2008. J of pers d, 22(3), 259-268.
[2] Sheehan L. et al 2016 Curr Psy Rep. Jan 1;18(1):11.
[3] Zanarini, M.C. et al 2004. JClinPsy65(1), 28–36.

[4] Hopwood, C.J. et al diagnosis. PDs and MH, 12,82.
[5] Richetin J. et al 2017 PLoS ONE. 12(10) e0186695.
[6] Ruocco A et al 2016. Harvard Rev Psy, 24, 311-329

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ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

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Intercurrent Events:

Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

CLINICAL TRIALS

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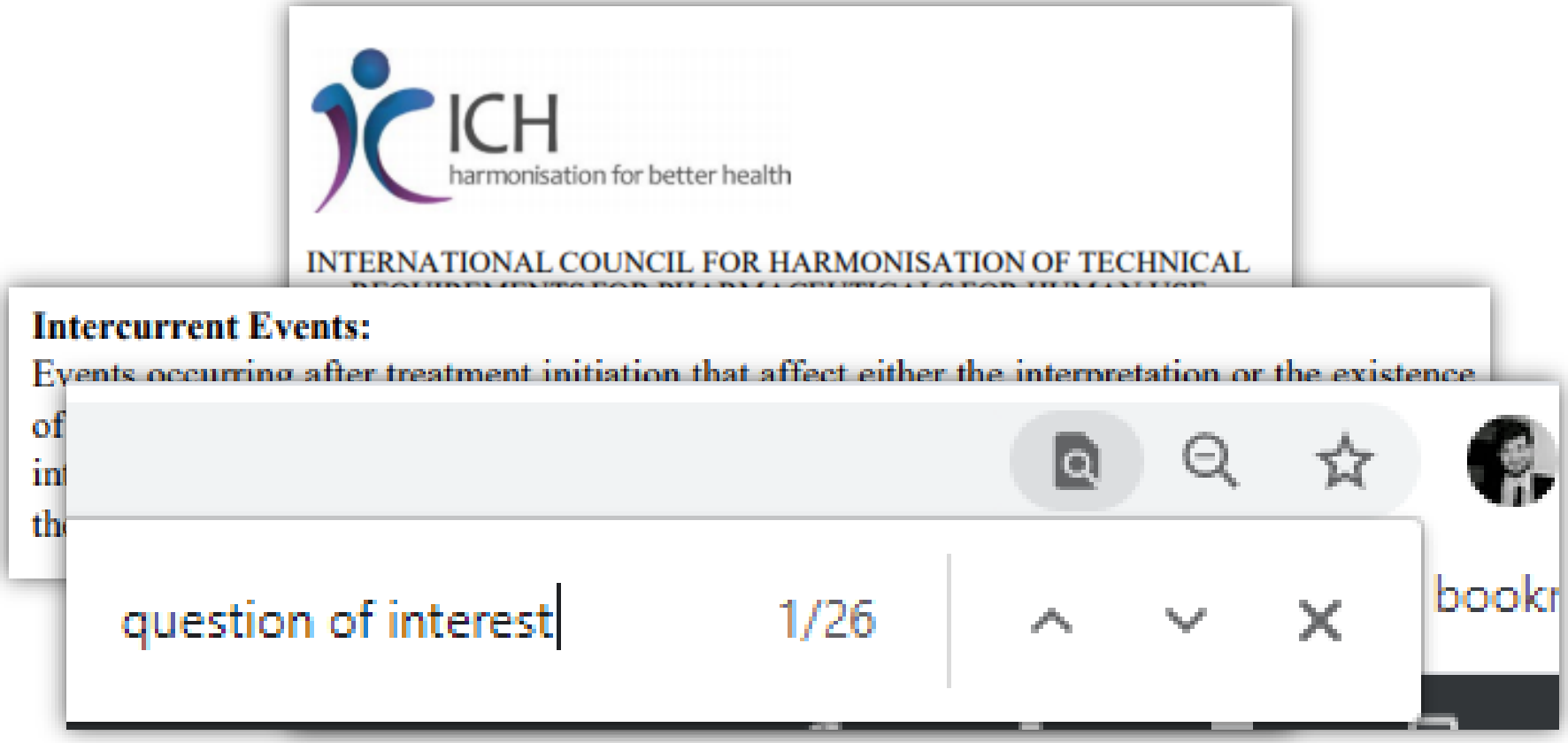

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How treatment discontinuation is incorporated in the question

Treatments are discontinued not only during trials, but also in practice.

Doctors will not know at the moment of prescribing, hence the primary information should not be “the effect if nobody discontinued treatment” or “the effect in patients who do not discontinue treatment”.

In the primary estimand, it is generally required that the “treatment-policy strategy” is adopted for the intercurrent event of “treatment discontinuation”.

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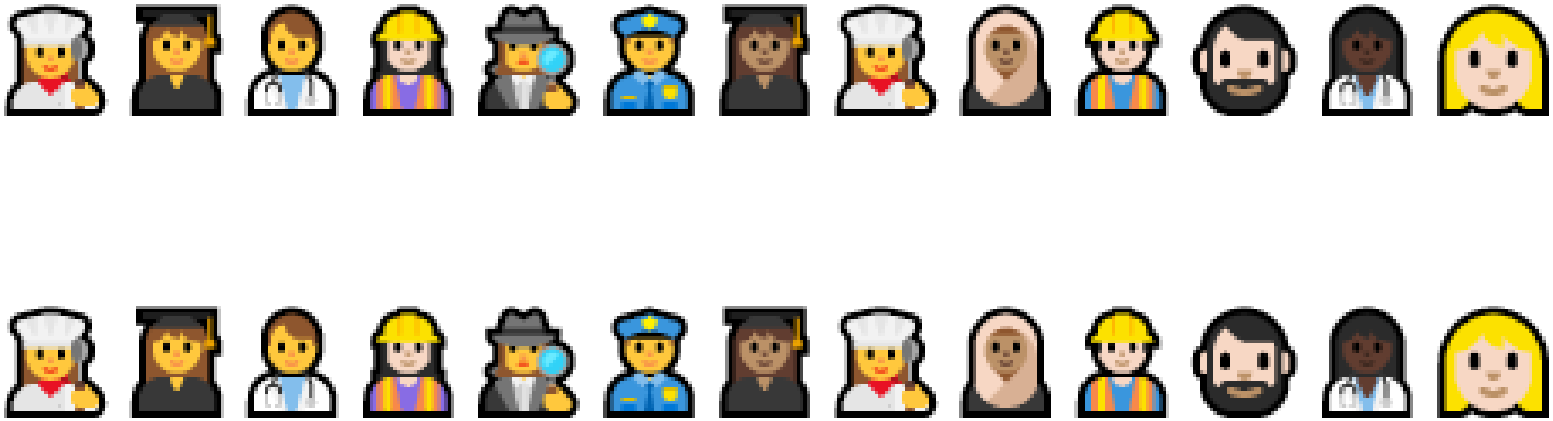
Excluding randomized patients from the analysis



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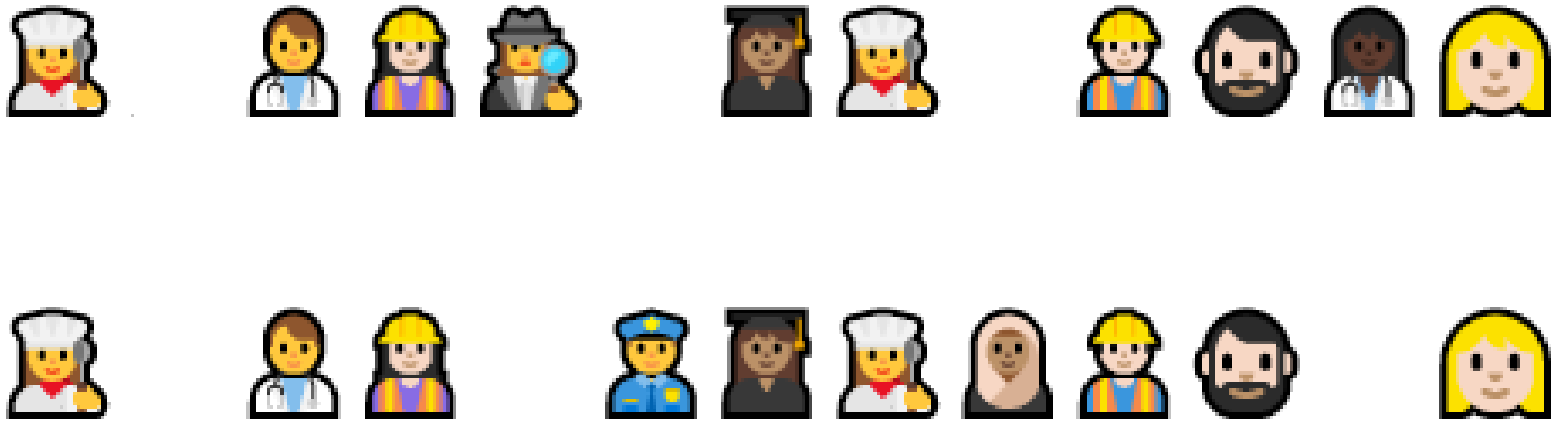
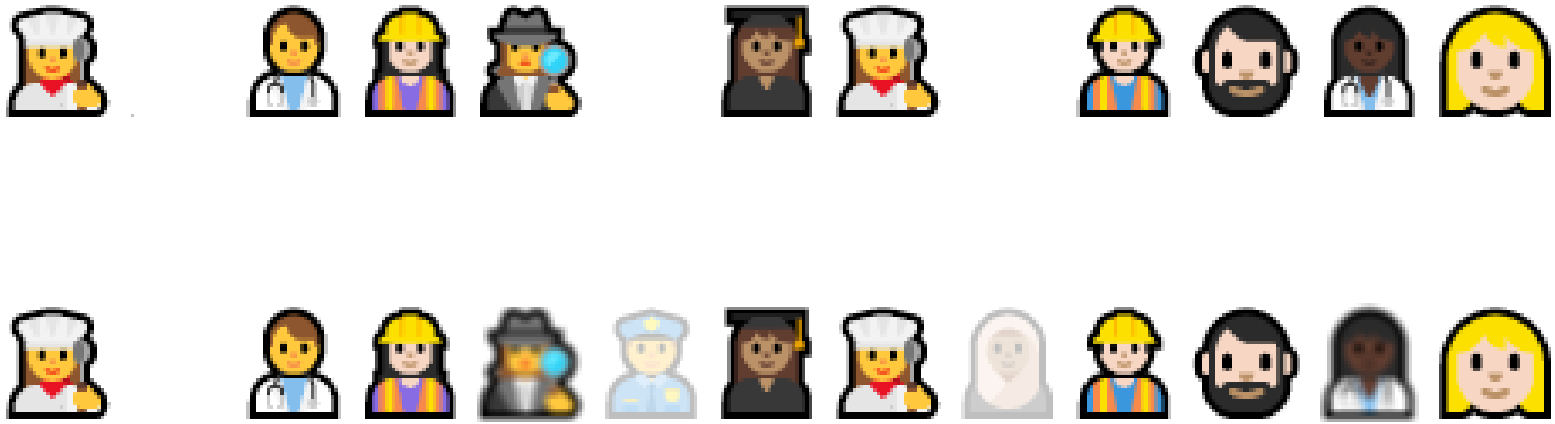
Excluding randomized patients from the analysis



The Principal Stratum Strategy: a possible secondary question



Handling of missing data

To achieve an estimator in line with the treatment-policy strategy, adequate covariates must be accounted for (e.g. in the imputation model, as auxiliary variables, for computing the weights).

In addition, given the clinical context, considerable weight should be put on sensitivity analyses exploring a MNAR mechanism.

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The clinical question and the "real world"

Also the way the population is selected at baseline and what additional care is (not) allowed shapes the question that the study answers in relation with the real world practice. This applies for example to:

- Applying very selective eligibility criteria;
- Restricting the access to additional care, such as psychotherapy[1].

[1] Hörz, S et al, 2010. Psych. Serv., 61(6), pp.612-616..

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Requirements for confirmatory trials and adaptations

Confirmatory trials need to provide robust evidence of safety and efficacy.

This does not mean that they must be run and analyzed “as always”, in fact regulators themselves promote innovation on the topic (see the Estimands framework).

Adaptive features (most often: sample-size re-estimation) are routinely discussed in the context of Advice to developers. Early engagement is encouraged. Requirements – for example - in terms of type I error control are nonetheless stringent.

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Different questions at different stages of development

For early decision making on further development of a candidate medicine, outcome measurement tools that demonstrate that "something related to the disease" (including as recorded by sensors) is affected might be sufficient if well validated.

For later phase clinical development, it is important that a clinically meaningful effect is demonstrated and quantified.

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More will be asked for tools to be used in confirmatory trials

Questions likely to be asked might include:

- What is the quantity the tool measuring? Is it the same thing at the beginning and at the end of a trial?
- What is the theory underlying to the development of the tool?
- Was the tool measured with knowledge of a specific candidate medicine? Which datasets were used to develop and test the tool?

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What is the matter with you?

~~What is the matter with you?~~

What matters to you?[1]

[1] Berwick, D.M., 2016. JAMA, 315(13), 1329-1330.

Any questions?

Further information

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