EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

HTA362

BEING SPECIFIC ABOUT ANALYSIS PRE-SPECIFICATION

challenges and opportunities in the context of EU HTA

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Pre-specification is well understood in regulatory setting, where details of statistical analyses are finalized in SAP before breaking the blind. This is not yet mandated for HTA.

EUnetHTA METHODS GUIDELINES

> *...it is required that all confounders and effect modifiers relevant for adjustment are measured and that the model and covariate selection strategies for adjustment are prespecified and based upon transparent criteria*[1]

> *This means that a particular research question (the PICO) is prespecified for a given assessment*[1]

Recent informal survey among HTA ESIG members suggests[2]:

a) Different interpretations of pre-specification across companies
b) Pre-specification outside of the CSR SAP is not uncommon
c) Limited experience with how authorities perceive evidentiary value

Where, when and ***how*** to pre-specifiy?

Is EU HTA JCA a good opportunity to become specific about 'pre-specification for HTA'?

Can we learn from existing pre-specification/ pre-analysis plan concepts in the pharma sector e.g. CSR, economic research?

SOME DRIVERS OF PERCEIVED EVIDENTIARY VALUE OF 'PRE-SPECIFICATION FOR HTA'

1. **Credible pre-registration of analyses** → Document final SAP versions in auditable quality management system
2. **High end-to-end transparency** → To claim benefit of pre-specification, design with purpose and summarize results of ***all*** pre-planned analyses
3. **Limited # of analyses per 'concept'** → Only specify the most important analyses, as a large number of related ones dilutes strength of findings
4. **Limited degrees of freedom per analysis** → Be as detailed as possible, to limit opportunities for post-hoc cherry picking

DO YOU AGREE?

Provide ***your*** ranking by scanning the QR code!

WHAT *COULD* ONE VERSION OF 'PRE-SPECIFICATION FOR HTA' LOOK LIKE?

Pre-registration and finalization prior to unblinding of the trial

Documentation of pre-registration with **audit trail and versioning**

Change log as an integrated part, describing changes and the reasons vs original version

Regulatory CSR SAP

A document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol [*ICH E9*[3]]

HTA SAP

A separate document that contains a description of the principal features of the statistical analysis needed for HTA bodies and payers

CSR

- Reporting results of **all** protocol and CSR SAP pre-planned analyses
- Additional work distinguished in CSR from work not pre-planned in protocol/CSR SAP
- Aim: **communicate overall study results** to regulatory agencies

HTA ANALYSIS REPORT

- Stand-alone document (independent of CSR) reporting results of HTA pre-specified analyses
- Additional work distinguished in the report from work not pre-planned in HTA SAP
- Aim: **increase evidentiary value towards HTA bodies and payers**, by transparently declaring selected statistical analyses 'pre-specified'

Pre-specification of statistical analyses will be key for EU HTA - which is fast approaching. Therefore, there is an imminent need for dialogue and collaboration about how and when to do this in a pragmatic and workable way!

CSR: Clinical Study Report; ESIG: European Special Interest Group; JCA: Joint Clinical Assessment; HTA: Health Technology Assessment; SAP: Statistical Analysis Plan; PICO: Population, Intervention, Comparator, Outcome

[1]https://www.eunethta.eu/jointhtawork/

[2] We acknowledge Katrin Kupas (BMS) for conducting the survey

[3]https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials-scientific-guideline

Join us

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