Non randomised studies as evidence from the perspective of the Haute Autorité de Santé

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HAUTE AUTORITÉ DE SANTÉ

Need for comparative evidence for performing relevant HTA

- The main purpose of HTA in France is the appraisal of the clinical added value of a medicinal product which implies the need for comparative evidence

- Therefore, the increase in the use of non-randomised studies such as single-arm trials, while leading to an acceleration of clinical developments, is a challenge for performing relevant health technology assessment

=> It has led HAS to clarify its expectations regarding this tension in a published paper in the BMJ Evidence Based Medicine in February 2023 + the Doctrine of the appraisal committee was updated

EBM analysis

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Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health

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Key points

- RCT remains the gold-standard for estimating unbiased treatment effect

- Adaptations of the traditional RCT design which can lead to accelerated clinical developments while preserving randomisation should be encouraged whenever possible (some alternatives are proposed within the paper)

- In exceptional circumstances, lack of randomisation can be considered understandable but:

  - It is of the responsibility of the HTD to justify lack of randomisation and this justification will be appraised as acceptable or not by HAS on a case-by-case basis
  - To mitigate uncertainties as much as possible, the generation of comparative evidence in the form of a well-conducted external comparison is expected whenever possible

  => The expected methodological qualities of such external comparisons are clarified within the paper

Key points

Box 1 Methodological points of attention HAS should consider when assessing an external comparison between an uncontrolled trial and an external control

1. Justification of the lack of randomisation
   - A rationale appraised as acceptable by Haute Autorité de santé is provided.
2. Study design
   - Early planning during clinical development and before the conduct of the uncontrolled trial of the treatment of interest.
   - A priori definition of the clinical question, study population, intervention, comparator and outcomes in a protocol and statistical analysis plan.
   - An emulation of a target trial can enhance eliciting the appropriate clinical question (estimand) and designing the external comparison.
3. Search and selection of relevant sources of data
   - Well-performed systematic review identifying relevant prognostic variables, confounders and effect modifiers.
   - Well-performed systematic review (with eligibility criteria defined a priori) identifying relevant sources for external control.
4. Choice of the external control
   - The comparator and external source(s) of data has been chosen independently of the results of the uncontrolled trial, fit best the clinical question (does not arbitrarily favour the treatment of interest) and correspond to standard of care.
5. Analysis of the results
   - The study protocol, statistical analysis plan and report allow a transparent and appropriate assessment of the study.
   - A model for causal inference controlling an appropriate set of confounders and targeting the predefined estimand has been properly specified and estimated.
   - The model is preferably based on a method using individual patient data only such as propensity scores, g-computation or doubly robust estimation.
   - Underlying assumptions have been explored and seems to be met (such as positivity, sufficient overlap and sufficient balance for propensity scores).
   - If 'trimming' (ie, excluding patients in areas of the propensity score without overlap) have been performed, the resulting target population for which results can apply is described.
   - Residual confounding has been explored with analyses such as the use of negative and positive controls, consistency in results when using other external controls, or quantitative bias analysis and excludes a conclusion of no treatment effect.
   - Study characteristics of the uncontrolled trial and external control are sufficiently similar for excluding other sources of bias such as selection bias, attrition bias, measurement bias.
   - Safety can be properly documented for both groups.
6. Grading the clinical added value
   - The clinical added value of the treatment of interest is appraised considering the certainty of results, the relevance and magnitude of treatment effect and safety.