# Can you have a common approach to the statistical analysis plan when conducting real-world evidence studies to meet multi-HTA requirements?

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## BACKGROUND

- Real-world evidence (RWE) studies are often used to augment the evidence package for health technology assessment (HTA) submissions. However, RWE studies are associated with potential biases that need to be address to ensure the validity of results.
- The UK's National Institute for Health and Care Excellence (NICE) and the French Haute Autorité de Santé (HAS) have formalised their requirements for RWE studies supporting HTA.
- A number of methodological details are provided in the NICE and HAS RWE guidelines, including methods minimising bias at the study design and analysis stages, and identification of confounders.

## OBJECTIVES

1. **To review** the statistical methods provided by NICE and HAS in the guidelines
2. **To assess** whether a common statistical analysis plan (SAP) would be feasible for both HTA bodies

**Table 2. Overview of the methods considered for addressing risk of bias from NICE and HAS**

| Method | NICE | HAS |
|---|---|---|
| Stratification | | |
| Matching | | |
| Multivariate regression | | |
| Propensity score matching | | |
| Structural marginal model with inverse-probability of treatment weighing (including G-methods) | | |
| Instrumental variables | | |
| Double difference methods | | |
| Regression discontinuity designs | | |
| Instrument based methods or quasi – experimental design | | |
| Negative controls | | |
| Informed by external data on confounder-outcome relationship | | |
| Marginal structural models with weighting or other G-methods | | |
| Complete record analysis | | |
| Advanced methods<br>i) Imputation<br>ii) inverse probability weighting<br>iii) maximum likelihood estimation | | |
| Sensitivity or bias analysis | | |
| Calibration and advanced methods | | |
| Consecutive inclusion of patients | | |
| Sensitivity analysis | | |
| Target trial approach | | |

Covered in detail | Some information is provided | More detail is required

## METHODS

Two recent RWE guidelines were reviewed (Table 1):

- The NICE RWE Framework published in June 2022, and aimed to provide guidance to those using RWE to inform decision making.
- The HAS RWE Methodological Guideline published in June 2021, and aimed to support the implementation of RWE studies that are being evaluated by the committee.

The guidelines were compared in terms of methodological details provided, focusing on the statistical methods for addressing confounding bias, information bias, and selection bias.

**Table 1. Details of RWE guidelines reviewed**

| Country/HTA body | RWE guideline | Publication date |
|---|---|---|
| NICE | NICE real-world evidence framework | June 2022 |
| HAS | Real-world studies for the assessment of medicinal products and medical devices | June 2021 |

## RESULTS

- Both guidelines include methods for addressing confounding bias, information bias is covered in more detail in the NICE guideline compared to HAS, and selection bias is addressed by both (Table 2).
- Both guidelines propose methods for observed confounding, including 'G-methods', instrumental methods, and propensity score matching.
- NICE addresses also residual confounding bias, using negative controls.
- For addressing information bias, both guidelines propose sensitivity analysis, but NICE provides more guidance for imputation techniques compared to HAS.
- For selection bias, HAS suggest consecutive inclusion of patients and sensitivity analysis, whereas NICE highlights the importance of the 'target trial approach', which applies the study design principles of an RCT to RWE studies.

## CONCLUSION

- A common SAP might be feasible as there is some alignment in the analytical methods recommended by NICE and HAS in terms of approaches to address bias, potentially allowing for an RWE study to be transferable between the two.
- Some methods reported by NICE are not reported by HAS and vice versa, and neither NICE nor HAS are prescriptive for all typical SAP requirements.
- Uncertainty therefore remains whether the methods requested for one would be acceptable to the other.
- As the need for RWE to fill important HTA evidence gaps increases, so does the need for prescriptive, transparent guidelines and alignment across HTA bodies to maximise the acceptability and utility of RWE studies.

1. National Institute for Health and Care Excellence (NICE). NICE real-world evidence framework. 23 June 2022
2. Haute Autorité de Santé (HAS) . Real-world studies for the assessment of medicinal products and medical devices. 10 June 2021
3. NICE. NICE DSU Technical support document 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal: Methods for comparative individual patient data. 2015