Factors to be Considered to Ensure Acceptability of Historically Controlled Studies by HTA Bodies

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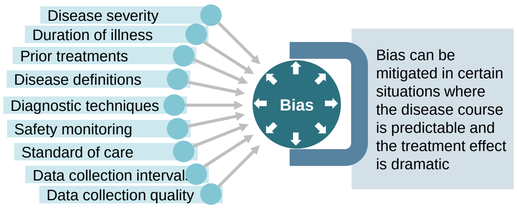
CONTEXT

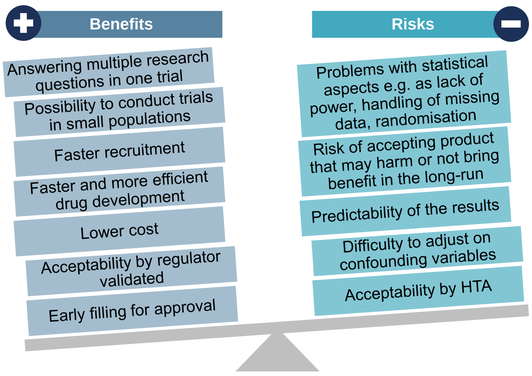
- To assess the added clinical value of a new intervention, it is necessary to compare it against currently available interventions with the use of best available clinical evidence.
- Randomized controlled trials (RCTs) have historically been considered as the gold standard in the hierarchy of evidence. RCTs allow minimizing the likelihood of confounding factors and give a more reliable and less biased estimation of treatment effect compared to uncontrolled trials.
- However, there are some clinical settings where such comparative studies are not always ethical, feasible or practical. For example, in life-threatening disorders, it may be unethical to offer a placebo or intervention that is expected to be less effective than the intervention being assessed. Moreover, in the case of rare disorders, it can be difficult to recruit a sufficient number of participants to detect statistically significant differences between treatments.
- In some circumstances, especially when preliminary evidence demonstrates potential dramatic efficacy in well-defined small populations with high unmet needs, single-arm trials (SATs) may be accepted by regulatory agencies.
  - Between January 1999 and May 2014, 21% approved indications in FDA and 11% in EMA were based on uncontrolled trials [1].
- With the fast development of innovative therapies and the curative potential of some drugs, SATs are widely discussed by decision-makers. What constitutes dramatic efficacy and high unmet medical need is debated with limited guidance for drug development and optimal management of remaining uncertainties.
- Natural history studies may play a key role in clinical development programs of future pipeline based on SATs, as an external control approach. Draft guidance on natural history studies for drug development in rare diseases was recently launched by the US. This guidance recognises the potential use of an external control approach in certain situations where the disease course is predictable and the treatment effect is dramatic to mitigate selection bias. [2] (Figure 1)

Figure 1. Bias factors when using external cohort which can affect outcomes [2]



- SATs are associated with many risks, but they also have undeniable benefits. (Fig.2)

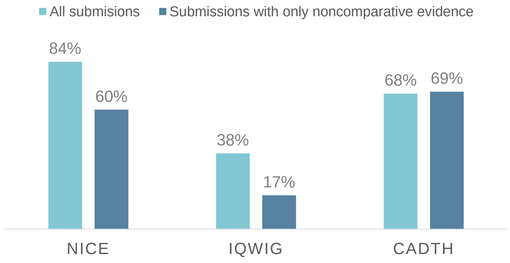
Figure 2. Risk-benefit analysis of SATs



DISCUSSION

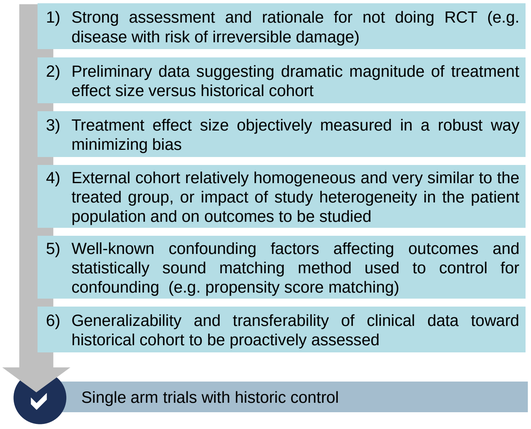
- High uncertainty inherent to SATs is challenging from the HTA perspective. Even if European HTA bodies generally accept different types of evidence for the assessment process, RCTs are usually the most preferred source for clinical data [3]
  - The analysis of 549 HTA appraisals has shown, that in England and Germany the rate of positive decisions was lower for submissions containing only non-comparative evidence compared to the overall number of submissions. The rate was similar in Canada [4]. (Fig. 3)

Figure 3. Rate of positive HTA decisions by type of submitted evidence [4]



- HTA bodies have limited guidance regarding SATs.
  - 2015 EUnetHTA guidelines stated that „the inclusion of non-randomised studies in an HTA report requires large efforts but often fails to increase the validity of the report's conclusion". Therefore, the decision on the inclusion of non-RCTs should be made only after careful consideration of all advantages and disadvantages [5].
  - IQWIG in HTA guidelines considers acceptance of non-RCTs in the benefit assessment of drugs only in justified exceptional cases. Reasons for exception include [6]:
    - non-feasibility of an RCT (e.g., if the therapist and/or patient has a strong preference for a specific therapy alternative), or
    - life-threatening disease course, where the particular intervention prevents this otherwise inevitable course (dramatic effect).
  - However, in the available HTA guidelines, no statements have been made according to SATs with an external cohort approach.
- The use of SATs and the external control approach should be enough justified to be accepted by HTA bodies as presented in Figure 4.

Figure 4. Factors ensuring acceptability of submissions using SATs with external control by HTA bodies



- High uncertainty inherent to SATs are challenging drug reimbursement and pricing decisions and may compromise patient access. Case-by-case early dialogues with regulatory bodies and HTA bodies are currently key to ensure SATs is well justified and external control approach is robust enough to allow for comparison of an added benefit.

CONCLUSIONS

- There is a need for continuous multi-stakeholder dialogues to define SATs-related evidence requirements and specific conditions for use to satisfy regulatory agencies and HTA bodies/payers, optimally through operationalized guidelines supporting the used of SATs and natural history data as an external control approach.

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