NOT READY FOR THE REAL WORLD? THE ROLE OF NON-RCT EVIDENCE IN HEALTH TECHNOLOGY ASSESSMENT

INTRODUCTION

The ‘evidence hierarchy’ of randomized controlled trial (RCT) over non-RCT evidence is well-established, and RCTs remain the ‘gold standard’ for regulatory and health technology assessment (HTA) submissions. However, RCTs are not always practical, feasible, or ethical.

To inform future submissions, we assessed acceptance based on non-RCT evidence across four HTA agencies, and explored agencies’ reactions to such study designs.

METHODS

All single HTA appraisals in 2015 from NICE (UK), CADTH (Canada), PBAC (Australia), and IQWiG (Germany) were included in the analysis, including resubmissions. Multiple technology appraisals, vaccines, and requests for advice were excluded.

The recommendation, reasoning behind the recommendation, and whether or not a non-RCT design trial (e.g. single-arm, uncontrolled, or observational) was presented as part of the clinical evidence package considered in the submission, were extracted.

RESULTS

• A total of 189 appraisals were extracted for 2015: 36 for NICE, 49 for CADTH, 59 for PBAC, and 45 for IQWiG.

• Non-RCT evidence was considered in:
  – 13 NICE appraisals (34%)
  – 5 CADTH appraisals (10%)
  – 15 PBAC appraisals (25%)
  – no IQWiG appraisals

• Overall, the majority of submissions where non-RCT evidence was considered were for infectious disease drugs [n=9] or oncologics [n=9].

• Only three treatments were given a positive recommendation solely on the basis of non-RCT evidence in 2015:
  – dacotavir for HCV GT3 infection (NICE, CADTH, PBAC)
  – ponatinib for CLL and Ph+ ALL (PBAC)
  – darunavir/cobicistat for HIV infection (CADTH).

• The remaining submissions included additional RCT evidence or were rejected due to high uncertainty about treatment effect.

• Non-RCT evidence did, however, contribute to a favorable outcome in some submissions, e.g. idelalisib for CLL and tolvaptan for PKD (NICE).

CONCLUSIONS

• NICE, CADTH, and PBAC will consider non-RCT studies such as real-world data and single-arm trials in certain circumstances, but are critical of the lower certainty of the evidence. IQWiG continues to prioritize RCTs.

• The contribution of non-RCT evidence to the HTA-decision-making process is currently limited; however, as adaptive pathways and personalized treatment strategies gain momentum, HTA bodies will need to become more flexible in their approach to assessing non-RCT evidence.

Figure 1: Appraisals published by HTA agencies in 2015 where non-RCT evidence was considered

Key: green = accepted submission; red = rejected submission

Case study 1: Dacotavir for HCV infection

• Accepted by CADTH, PBAC, and NICE with four uncontrolled studies

• Quality of evidence was criticized due to small sample sizes, open-label administration, and lack of a control group.

• However, the study design was considered acceptable and relatively consistent with trials for other new HCV treatments

• Patient and clinician presentations helped advocate for IFN-free regimens

Case study 2: Ponatinib for CLL and Ph+ ALL

• Accepted by PBAC on the basis of three single-arm, non-randomized studies, after an initial deferral

• Lack of a common comparator arm meant that no adjusted comparison could be made with dasatinib and nilotinib, and the studies compared were highly heterogeneous

• However, non-inferiority was considered demonstrated

• High unmet need considered

Case study 3: Tolvaptan for PKD

• Optimised by NICE based on one placebo-controlled RCT, one non-randomized extension study, and one real-world study

• Interim results from extension study helped support the case for long-term benefits of tolvaptan

• Real-world study included HRQoL data, which had not been collected in the placebo-controlled trial

Case study 4: Taliglucerase alfa for Gaucher Disease

• Rejected by CADTH with four uncontroll trials and an extension study

• Although the included studies indicated a clinical benefit, they were not robust or convincing enough for the evaluation of clinical benefits versus other ERTs

• Patient input and unmet needs could not overcome uncertainties in the clinical evidence package

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