The Role of Noncomparative Evidence in Health Technology Assessment Decisions

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ABSTRACT

Background: Many health technology assessment (HTA) agencies express a preference for randomized controlled trial evidence when appraising health technologies; nevertheless, it is not always feasible or ethical to conduct such comparative trials. Objectives: To assess the role of noncomparative evidence in HTA decision making. Methods: The Web sites of the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, and the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]) in Germany were searched for single HTA reports (published between January 2010 and December 2015). The product, indication, outcome, and clinical evidence presented (comparative/noncomparative) were double-extracted, with any discrepancies reconciled. A noncomparative study was defined as any study not presenting results against another comparative treatment (including placebo or best supportive care), regardless of phase or setting, including dose-ranging studies. Results: A total of 549 appraisals were extracted. Noncomparative evidence was considered in 38% (45 of 118) of NICE submissions, 13% (34 of 262) of CADTH submissions, and 12% (20 of 169) of IQWiG submissions. Evidence submissions based exclusively on noncomparative evidence were presented in only 4% (5 of 118) of NICE appraisals, 6% (16 of 262) of CADTH appraisals, and 4% (6 of 169) of IQWiG appraisals. Most drugs appraised solely on the basis of noncomparative evidence were indicated for cancer or hepatitis C. Positive outcome rates (encompassing recommended/restricted/added-benefit decisions) for submissions presenting only noncomparative evidence were similar to overall recommendation rates for CADTH (69% vs. 68%, respectively), but were numerically lower for NICE (60% vs. 84%, respectively) and IQWiG (17% vs. 38%, respectively) (P > 0.05 for all). Conclusions: Noncomparative studies can be viewed as acceptable clinical evidence by HTA agencies when these study designs are justifiable and when treatment effect can be convincingly demonstrated, but their use is currently limited. Keywords: clinical effectiveness, decision making, evidence-based medicine, health technology assessment.

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Introduction

Health technology assessment (HTA) can be broadly defined as the evaluation of health care interventions in the context of their implications to the wider health system. HTA aims to systematically assess the clinical value (i.e., comparative health benefits) and the economic value (i.e., value for money) of interventions to inform decisions regarding their reimbursement and uptake [1].

To assess the clinical value of a new intervention, it is necessary to compare it against currently available interventions in terms of patient-relevant outcomes such as efficacy, safety, and health-related quality of life. To ensure accurate and objective comparisons between interventions, the best available clinical evidence must be used. Randomized controlled trials (RCTs) have historically been considered the gold standard in the hierarchy of clinical evidence, surpassed only by meta-analyses of RCTs, whereas nonrandomized studies and uncontrolled studies are considered weaker evidence (Fig. 1) [2]. Compared with non-RCTs, RCTs minimize the likelihood of confounding factors influencing the results and therefore produce a more robust and less biased estimation of treatment effect. For this reason, HTA agencies usually express a preference for RCT evidence to assess comparative effectiveness [3–5].

Nevertheless, there are situations in which it is not ethical, feasible, or practical to conduct an RCT [6,7]. For example, it may be unethical to offer a placebo or an intervention that is hypothesized to be less effective than the intervention under evaluation (e.g., in immediately life-threatening disorders). Alternatively, the disease may be so rare that it would be difficult to recruit enough participants to detect statistically significant differences between treatment arms (e.g., rare genetic disorders), or there simply may be no established treatment options to compare against (e.g., some advanced cancers). In such cases, noncomparative studies may provide the “best available”
In the clinical trial setting, noncomparative studies encompass a range of designs including dose-ranging studies, single-arm trials, case series, and case reports [8–11]. In the “real-world” setting (i.e., outside of the typical clinical trial setting), this may include registry studies, claims data, and some observational designs [12]. Although considered less robust than RCTs, noncomparative studies can—and do—inform health care decision making.

In the era of biomarker-based, “personalized” medicine and conditional regulatory approvals based on immature clinical data [13], there may be cases in which reimbursement decisions will need to be made on the basis of noncomparative studies such as phase 1 or phase 2 trials (e.g., dose-ranging or single-arm trials), with this trend anticipated to continue [14,15]. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have developed mechanisms to facilitate earlier patient access to promising medicines, such as breakthrough status (FDA), the accelerated approval pathway (FDA), and the adaptive pathways pilot (EMA). For example, the FDA approved ceritinib for non–small cell lung cancer and pembrolizumab for melanoma in 2014 under both the FDA breakthrough status and accelerated approval processes, supported by only phase 1 data [16,17]. Although these expedited regulatory pathways can ensure earlier market authorization, to achieve patient access, public reimbursement must also be achieved, which typically requires previous recommendation by an HTA body.

It will therefore be important to understand how HTA bodies react to noncomparative evidence, and whether a positive outcome is achievable with such data. This study aimed to address the following research questions to characterize the role of noncomparative evidence in HTA decision making, which may help inform future HTA submissions:

1. What are HTA agencies’ perceptions of noncomparative evidence, on the basis of recommendation and nonrecommendation rates, and what are the key differences in these rates between agencies?
2. Do recommendation rates for submissions presenting noncomparative evidence differ from rates for submissions presenting RCT evidence?
3. Are there any differences in recommendation rates/perceptions by parameters such as disease area and size of the patient population?

For this research, three HTA bodies were selected: the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, and the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]) in Germany. These agencies were chosen because they represent key jurisdictions that use varying criteria to inform decision making in different settings, and release publicly available and transparent appraisal documents for all interventions that are evaluated.

Methods

Data Sources

The Web sites of the three jurisdictions—NICE (https://www.nice.org.uk/), CADTH (https://www.cadth.ca/), and IQWiG (https://www.iqwig.de/)—were systematically searched for publicly available HTA appraisals published between January 2010 and December 2015. This date range was chosen because it allowed for a wide range of appraisals across the three agencies to be analyzed and it reflects recent decision-making trends; the evolution of HTA processes is such that decisions published before 2010 may be less relevant to today’s reimbursement landscape. The IQWiG and the CADTH pan-Canadian Oncology Drug Review (pCODR) did not publish their first decisions until 2011 and 2012, respectively; in addition, all three agencies revisit their methods every few years.

Appraisal Selection

The inclusion criteria encompassed all single technology appraisals for pharmaceutical interventions, irrespective of indication or outcome. Multiple technology appraisals, appraisals for vaccines and devices, requests for advice, and health economic dossiers were excluded.

Data Extraction

For each appraisal meeting, the inclusion criteria, indication, date issued, outcome, and clinical evidence presented were extracted. Appraisals were classified as recommended, restricted, or not recommended. Detailed definitions of these outcomes are described in Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.06.015.

The clinical evidence was defined as the data presented to support the clinical case, for efficacy, safety, quality of life, and economic outcomes, as categorized by the HTA agency. Data used to inform economic modeling were not included. The clinical evidence was first categorized into two categories, comparative study or noncomparative study, using the following definitions:

1. Comparative study: Any study against an active or placebo comparator:
   - Active-controlled RCT: randomized controlled study against a relevant active comparator (note that best supportive care was considered to fall under this category);
   - Placebo-controlled RCT: randomized controlled study against a placebo comparator (including vehicle-controlled studies, sham injections, and studies in which the active intervention + X was compared against placebo + X);
   - Other comparative study: study designs encompassing nonrandomized, controlled trials.
2. Noncomparative study: Any study that did not compare against an active comparator or placebo. This included, but was not limited to, single-arm trials, dose-ranging studies, registry studies, compassionate use programs, and uncontrolled extension studies.

Noncomparative studies were further classified into single-arm trials, single-arm extensions of comparative trials, dose-ranging studies, and other (see Appendix Table 2 in Supplemental Materials).
Materials found at http://dx.doi.org/10.1016/j.jval.2017.06.015). Categories were not mutually exclusive and more than one evidence type could be recorded per appraisal if multiple studies were presented. In addition, submissions were classified by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) category to determine whether any trends could be identified by disease area and by orphan versus nonorphan designation (using the EMA definition of an orphan disease, i.e., affecting ≤5 in 10,000 people in the European Union).

All appraisals were extracted independently by two separate authors, with any discrepancies resolved by a third author.

Data Analyses
The κ statistic [18] was used to evaluate inter-reviewer reliability. The Cohen κ was 0.75, reflecting good concordance between reviewers.

Descriptive statistics were presented as proportions for the submission and recommendation rates by study design. Odds ratios [18] were calculated to determine the odds of a positive submission outcome by evidence category. A two-tailed Fisher exact test was used to evaluate the effect of presenting noncomparative evidence on recommendation rates for each agency (recommended and restricted vs. not recommended), for submissions presenting noncomparative evidence versus those not presenting noncomparative evidence.

Results
A total of 549 appraisals were extracted on the basis of the inclusion criteria: 118 for NICE, 262 for CADTH, and 169 for IQWiG. Overall, NICE had the highest proportion of submissions with favorable outcomes (57% recommended, with a further 27% recommended with restrictions), followed by CADTH (10% recommended and 58% recommended with restrictions) and IQWiG (14% recommended and 24% restricted).

Noncomparative evidence was considered in 38% (45 of 118) of NICE submissions, 13% (34 of 262) of CADTH appraisals, and 12% (20 of 169) of IQWiG appraisals. Evidence submissions based exclusively on noncomparative evidence were presented in only 4% (5 of 118) of NICE appraisals, 6% (16 of 262) of CADTH appraisals, and 4% (6 of 169) of IQWiG appraisals (Table 1).

Numerically, the proportion of recommended, restricted, and not recommended submissions varied depending on the type of evidence presented for all agencies. Positive outcome rates (encompassing recommended, restricted, and added-benefit decisions) for submissions presenting only noncomparative evidence were similar to overall recommendation rates for CADTH (69% [11 of 16] vs. 68% [178 of 262], respectively), but were notably lower for NICE (60% [3 of 5] vs. 84% [99 of 118], respectively) and IQWiG (17% [1 of 6] vs. 38% [65 of 169], respectively).

Nevertheless, sample sizes were very small for submissions presenting noncomparative evidence alone, and the difference in proportions did not meet statistical significance for any agency (P > 0.05). Outcome rates for submissions including noncomparative evidence alongside an RCT were both numerically and statistically similar to the overall outcome rates for all agencies (Table 1).

Overall, the majority of the noncomparative evidence presented in the reviewed HTA submissions consisted of single-arm studies, followed by randomized dosing studies and single-arm extension studies (Fig. 2). For NICE and CADTH submissions, most of these studies were used to support efficacy and/or safety, with a smaller proportion supporting quality of life outcomes. For IQWiG, most of the noncomparative studies were not considered relevant for the assessment (Fig. 2).

In terms of disease area, most submissions presenting noncomparative evidence were treatments indicated for cancer or infection (specifi cally hepatitis C), with a substantial proportion also indicated for an orphan disease within these therapy areas (Fig. 3).

No meaningful time trends in the proportion of submissions presenting noncomparative evidence were observed (Fig. 4). The absolute number of submissions presenting noncomparative evidence was presented.

<table>
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<th>Table 1 – Overall recommendation rates and recommendations by study design.</th>
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<td>Submission outcome</td>
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<tr>
<td>Total submissions, N</td>
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<td>Recommended, n (%)</td>
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<td>Restricted, n (%)</td>
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<td>Not recommended, n (%)</td>
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<tr>
<td>All submissions including noncomparative evidence, N (%)</td>
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<td>Recommended, n (%)</td>
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<td>Restricted, n (%)</td>
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<td>Not recommended, n (%)</td>
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<tr>
<td>Odds of a positive* outcome, OR (95% CI)</td>
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<td>P value†</td>
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<td>Submissions with noncomparative evidence alone, N (%)</td>
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<td>Recommended, n (%)</td>
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<td>Restricted, n (%)</td>
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<td>Not recommended, n (%)</td>
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<tr>
<td>Odds of a positive* outcome, OR (95% CI)</td>
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<td>P value†</td>
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CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; HTA, health technology assessment; IQWiG, Institute for Quality and Ef ficiency in Health Care; NICE, National Institute for Health and Care Excellence; OR, odds ratio.

* Positive defined as recommended or recommended with restrictions vs. submissions not presenting noncomparative evidence.
† Two-tailed Fisher test, recommended + restricted vs. not recommended for submissions presenting noncomparative evidence vs. those not presenting noncomparative evidence.
evidence for all jurisdictions did tend to increase over time, but this reflected an increase in the number of appraisals overall. Similarly, recommendation rates for submissions including noncomparative evidence or presenting noncomparative evidence alone did not vary notably over time, compared with overall recommendation rates.

In terms of the critique given by different agencies, NICE and CADTH were critical of the lower quality of noncomparative evidence, highlighting the higher risk of bias, but were prepared to consider this evidence in the absence of more robust studies. IQWiG was generally not prepared to consider noncomparative studies, with ledipasvir/sofosbuvir for hepatitis C virus infection being the only drug given a favorable recommendation on the basis of noncomparative evidence alone in 2015 (and indeed the only submission in which noncomparative evidence was considered acceptable) [19].

Appendix Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.06.015 describes the drugs that were appraised solely on the basis of noncomparative evidence, including reasons for considering a clinical argument based on noncomparative evidence alone. These reasons could be broadly assigned to one of four main categories. In most of the

![Graph](image-url)

**Fig. 2** – (A) Type of noncomparative evidence and (B) role of that evidence. Note. Categories are not mutually exclusive (e.g., a study may provide both efficacy and safety evidence, and more than one type of study may be presented in each submission). “Other” for type of noncomparative evidence includes individual patient data, case series, and retrospective audits; no noncomparative “real-world” studies (e.g., registry studies) were identified. “Other” for role of evidence includes bioequivalence data. “Not considered” refers to submissions in which the agency explicitly stated that the evidence was not considered in their assessment. “Unclear” refers to submissions in which the agency did not explicitly state how the evidence was used for the assessment. CADTH, Canadian Agency for Drugs and Technologies in Health; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; QoL, quality of life.

![Graph](image-url)

**Fig. 3** – Submissions presenting noncomparative evidence, by disease area. Note. Orphan drugs and disease categories are not mutually exclusive (e.g., a drug may be categorized under both neoplasms and orphan drugs). CADTH, Canadian Agency for Drugs and Technologies in Health; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence.
submissions in which noncomparative evidence alone was considered acceptable (NICE, 5 of 5; CADTH, 16 of 16; and IQWiG, 1 of 6), a lack of effective treatment alternatives to compare against or unmet clinical need for new options was listed as one of the contributing factors (NICE, 5 of 5; CADTH, 15 of 16; and IQWiG, 0 of 1). The second most frequently listed reason was that the treatment under evaluation was licensed in a small patient population (and a comparative trial could therefore not be powered for statistical significance) (NICE, 2 of 5; CADTH, 6 of 16; and IQWiG, 0 of 1); thirdly, that the anticipated magnitude of treatment effect was sufficiently large that it would be unethical to conduct a comparative trial (NICE, 2 of 5; CADTH, 4 of 16; and IQWiG, 1 of 1). The fourth reason was that the disease was life-threatening and it would be unethical to compare against a

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**Table 2 – NICE, CADTH, and IQWiG guidance for the inclusion of noncomparative evidence within submissions.**

<table>
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<th>HTA agency</th>
<th>Guidance on the inclusion of noncomparative evidence</th>
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<td><strong>NICE</strong> [3]</td>
<td>The problems of confounding, lack of blinding, incomplete follow-up, and lack of a clear denominator and end point occur more commonly in nonrandomized studies and uncontrolled trials than in RCTs. Inferences will necessarily be more circumspect about relative treatment effects drawn from studies without randomization or control than those from RCTs. The potential biases of observational studies should be identified and ideally quantified and adjusted for. When possible, more than one independent source of such evidence should be examined to gain some insight into the validity of any conclusions. Evidence from sources other than RCTs is also often used for parameters such as the valuation of health effects over time into QALYs and for costs. Study quality can vary, and so systematic review methods, critical appraisal, and sensitivity analyses are as important for review of these data as they are for reviews of data on relative treatment effects from RCTs.</td>
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<td><strong>CADTH</strong> [4]</td>
<td>If no head-to-head trial(s) have been conducted vs. another available drug and the manufacturer is assuming different clinical benefit (efficacy or effectiveness or safety) of the submitted drug compared with other drugs in the class, an indirect comparison is required. The evidence to support these claims should be provided in detail. Reference to other studies that may provide information on clinical benefits other than efficacy and safety, or postmarketing data that provide information on longer term safety, should be supplied as required. For resubmissions, new efficacy data must be from an RCT. (If the new information is in support of improved safety, case-control or cohort studies will be accepted if RCTs are unavailable.)</td>
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<td><strong>IQWiG</strong> [5]</td>
<td>Conclusions for benefit assessments are usually inferred only from the results of direct comparative studies. An RCT represents the criterion standard in the assessment of drug and noninterventions. As a rule, the institute therefore considers RCTs in the benefit assessment of drugs and uses only nonrandomized intervention studies or observational studies in justified exceptional cases. Reasons for exception include nonfeasibility of an RCT (e.g., if the therapist and/or patient has a strong preference for a specific therapy alternative) or if other study types may also provide sufficient certainty of results for the research question posed. For diseases that would be fatal within a short period of time without intervention, several consistent case reports may provide sufficient certainty of results that a particular intervention prevents this otherwise inevitable course (dramatic effect). The institute disapproves of the use of nonadjusted indirect comparisons (i.e., the naive use of single-study arms).</td>
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Note. Guidance is copied or paraphrased from the respective method’s guide. CADTH, Canadian Agency for Drugs and Technologies in Health; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; RCT, randomized controlled trial.
placebo or a less effective comparator (NICE, 1 of 5; CADTH, 2 of 16; and IQWiG, 0 of 1). In many submissions, more than one of these reasons was listed.

Discussion

Overall, a minority of HTA submissions gained positive recommendations on the basis of noncomparative evidence alone: 11 for CADTH (4%), 3 for NICE (3%), and 1 for IQWiG (0.6%). Noncomparative evidence was nevertheless used as supporting evidence in 45 (38%) NICE submissions, 34 (13%) CADTH submissions, and 20 (12%) IQWiG submissions. NICE and CADTH were generally critical of the lower quality of noncomparative evidence, but recognized that there are situations in which noncomparative trial designs could be acceptable, in line with their method guidance (Table 2). IQWiG places strong emphasis on demonstrating additional therapeutic benefit from direct comparative trials versus the appropriate comparator and was highly critical of submissions presenting noncomparative evidence. This was reflected in a correspondingly lower recommendation rate for submissions based purely on noncomparative data than that seen for all submissions assessed. Nevertheless, although recommendation rates did vary between appraisals presenting comparative evidence and those presenting noncomparative evidence, sample sizes were small and no significant differences were observed.

Most of the submissions presenting noncomparative evidence were single-arm studies used to support safety and efficacy, with dose-ranging studies and extension studies also represented. The single-arm studies tended to reflect interventions in disease areas in which placebo-controlled trials were inappropriate given the life-threatening nature of the disease (e.g., cancers at late lines of therapy), interventions for diseases with a small patient population in which trials could not be powered to detect statistically significant differences between treatment arms (e.g., rare genetic disorders), and interventions for diseases where preliminary data suggested a magnitude of benefit that was sufficiently great and that comparative trials would not be ethical (e.g., hepatitis C). Other examples included terminal or rare conditions in which a high unmet need or lack of alternative treatment options to compare against would also make noncomparative evidence acceptable. Accordingly, most therapies that were recommended on the basis of noncomparative evidence were in oncology, orphan disease indications, or offered curative potential (specifically in hepatitis C infection).

No notable time trends were observed with respect to the role of noncomparative evidence in HTA decision making. Nevertheless, in an era of increasingly targeted medicine and in which conditional approvals are becoming more common, it is likely that noncomparative evidence will begin to play a greater role in HTA. Payors will therefore need to adapt if they are to permit patient access to innovative new drugs, and they are already considering how to do this. For example, although IQWiG considered very few noncomparative studies to be relevant for the benefit assessment, the 2015 IQWiG-Herbst Symposium (an annual conference that explores current and controversial topics in health care) focused on the role of real-world data (including noncomparative data) in benefit assessment [20]. The first positive recommendation by IQWiG in 2015 on the basis of noncomparative evidence alone (sofosbuvir/ledipasvir) could also be considered an indicative milestone.

Nevertheless, challenges remain, and HTA agencies remain critical of noncomparative evidence. The use of such evidence introduces an element of uncertainty in estimating treatment effect; granting access to innovative medicines without a robust supporting evidence base could be exposing patients to inefficacious or even harmful medicines. For example, fewer than half of oncology medicines are successful at phase 3 [21], yet a considerable number have been approved on the basis of phase 2 or even phase 1 single-arm data. Furthermore, many drugs have received accelerated market authorization conditional on subsequent follow-up data being made available, yet these continue to be available to patients despite the manufacturer not fulfilling this requirement [22].

Despite limitations associated with RCTs such as uncertain generalizability to clinical practice and limited duration [23], they remain the most objective tool for quantifying treatment effect. It is therefore unlikely that the RCT will be replaced by a standard noncomparative study design as the gold standard in the foreseeable future. Instead, opportunities exist to better define the role of noncomparative evidence: acceptable when RCT designs are not practical, feasible, or ethical, and useful to strengthen and validate RCT data in the context of the real world and long-term evaluation.

A key limitation of this analysis was the extraction of information from publicly available summary reports, rather than from manufacturers’ submissions (which are generally not publicly available). The summary reports may have left out additional supporting evidence included in the manufacturer’s submission or information on the role or type of evidence. Nevertheless, it is likely that any noncomparative study that played a role in the decision-making process would have been described in the appraisal summary document. It should also be noted that this study focused on the role of noncomparative evidence to support the clinical value proposition, but that such evidence can also play a role in supporting an economic value proposition (e.g., the use of single-arm extension data to validate long-term cost-effectiveness model survival predictions).

To our knowledge, this is the first published study to explicitly and systematically assess the role of noncomparative evidence in HTA, and it may be useful to inform future evidence generation strategies for medicines. The study reflects the priorities of three internationally recognized and often-referenced jurisdictions; nevertheless, different HTA bodies have varying criteria, and individualized strategies are needed when determining a submission strategy. Further research could expand the scope of this study to include additional HTA agencies.

Conclusions

The role of noncomparative evidence in decision making by HTA bodies is currently small, but may be accepted in cases in which:

1. there is a high unmet need for treatment or there are no established alternative treatment options to compare against (e.g., rare genetic disorders and rare cancers);
2. the disease is rare and it is not possible to design a trial with sufficient power to detect statistically significant differences between treatment arms (e.g., ultra-orphan indications);
3. preliminary clinical data suggest a clinical effect that is sufficiently large in magnitude that a direct comparative trial to a treatment alternative would not be considered ethical (e.g., hepatitis C);
4. the illness is severe and life-threatening with no efficacious treatment alternatives and randomizing patients to a placebo or investigator’s choice arm would not be considered ethical (e.g., very advanced cancers).

In the aforementioned categories, noncomparative evidence may be viewed as acceptable clinical evidence by some HTA bodies as long as the study design is justifiable and meets the
jurisdiction’s reference case, and when treatment benefit can be convincingly demonstrated. In future, the increasing trend toward personalized medicine and conditional regulatory approvals may necessitate a greater role of noncomparative evidence in HTA decision making.

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Supplemental Materials
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REFERENCES