Use of Patient-Reported Outcomes as Key Drivers in Cost-Effectiveness Models: A Review of UK National Institute for Health and Care Excellence Health Technology Assessments

EE101

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BACKGROUND

- Patients are an important stakeholder group in health technology assessment (HTA), as it is essential that decision-makers understand the unique lived experiences of patients, their unmet needs, preferences, values, and priorities, and how a new technology may address them.[1,2]
- Patient-reported outcomes (PROs) are a type of clinical outcome assessment by which patients report their health status directly, without interpretation from clinicians or others.[3]
- For new health technologies, PROs have increasingly been recognized as an important component of clinical trials, regulatory approval processes, and reimbursement decision-making.[4-7]
- Including outcomes that matter to patients in cost-effectiveness models (CEMs) helps to further ensure that the patient perspective is included in the HTA process; however, the use of PROs in CEMs that are submitted as part of HTAs is not well understood.

OBJECTIVE

- Our objective was to review the use of PROs as key drivers in the CEMs submitted to the National Institute for Health and Care Excellence (NICE) in the United Kingdom.

METHODS

- HTAs conducted within the Technology Appraisal Program from January 2016 through August 2022 from the NICE website (www.nice.org.uk) were assessed.
  - HTAs were excluded based on titles and date information if they were terminated, were for oncology indications (as oncology indications routinely rely on non–patient-reported endpoints), wereincomplete (i.e., final guidance was not published), or were updated based on a review in our date window but originally published before January 2016 (as reviews typically provide little detail on the CEM).
- 3 reviewers independently assessed HTAs for eligibility based on detailed documentation, including the manufacturer's submission document. HTAs were included for full review if CEMs submitted by manufacturers contained a PRO as a key driver via the model structure (e.g., health state definition), treatment-effect parameters, treatment-stopping rules, or if utility estimates were informed by condition-specific utility measures administered in the key trials.
- 4 reviewers independently extracted information about the included HTAs.
  - For HTAs that met the inclusion criteria, several documents were reviewed, including the appraisal consultation committee papers, the appraisal consultation document, the final appraisal determination committee papers, the final appraisal determination, and the technology appraisal guidance.
  - For included HTAs, the following information was collected, where available, to characterize the use of PROs in the CEMs:
    - Whether the indication was for a PRO-dependent disease[7]
    - Whether the PRO was the primary endpoint in the clinical trial
    - Details of how the PRO was used in the CEM
    - Any justification provided for using the PRO in the CEM
    - Any critiques from the NICE evidence review group (ERG), assessment group (AG), or the appraisal committee (AC) on the use of the PRO in the CEM and any critiques related to whether the PRO has been validated
    - The final NICE recommendation

RESULTS

Overview of Included HTAs

- Of 428 HTAs reviewed, 26 (6.1%) met the eligibility criteria (Figure 1, Table 1).
- The included HTAs were largely conducted for interventions in PRO-dependent indications (e.g., migraine, rheumatoid arthritis), with the exception of 2 HTAs (7.7%) in heart failure (Table 1).
- For 18 of the included HTAs (69%), at least 1 of the key PRO drivers in the CEMs was a primary or co-primary endpoint in the clinical trials.

Use of PROs in CEMs

- When used, PROs were more likely to be incorporated in CEMs via treatment-effect parameters (n = 25, 96%), the model structure (n = 24, 92%), and treatment-stopping rules (n = 21, 81%) (Figure 2).
  - In 16 HTAs (62%), condition-specific PRO data collected in the trial were used to estimate utility parameters.
- Most of the HTAs used 1 or more of the following approaches in the CEMs for estimating long-term health and cost outcomes (Figure 2):
  - PRO-related extrapolations beyond the trial timeframe (n = 26, 100%)
  - Statistical analyses of PROs for modeling purposes (e.g., mapping, surrogacy analysis) beyond prespecified trial analyses (n = 24, 92%)
  - Relationships linking PROs to costs or resource utilization (n = 19, 73%)
- 19 HTAs (73%) provided justification for supporting the use of the PRO in the CEM in the committee papers, with the most commonly cited reason in both company submissions and the ERG reports being that the PRO was the best option for measuring aspects of the disease or correlates well with the patient's perception of the disease (Table 2).

NICE Critiques and Guidance

- In 19 HTAs (73%), the NICE ERG, AG, or AC criticized the use of the PRO in the CEM; the main concerns were related to how the PRO was operationalized in the CEM, the underlying data source selected, the statistical methods used, and the implementation of the PRO in clinical practice (Table 3).
- NICE recommended restricted use of most technologies (n = 22, 85%), and most had commercial arrangements (e.g., managed access agreements, patient access schemes).

Figure 1. Identifying Eligible HTAs

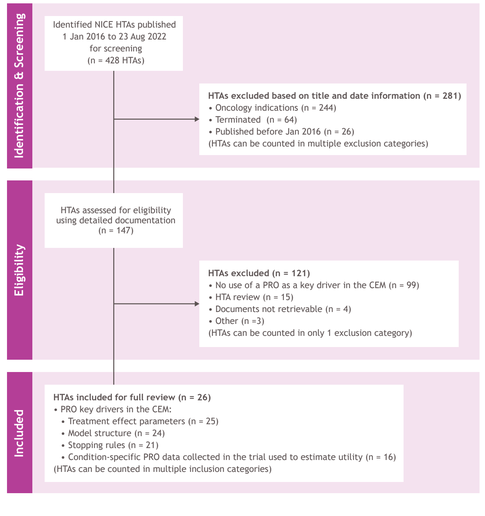


Table 1. Use of PROs in Individual HTAs (n = 26)

TA	Indication	Intervention	PRO(s) as key driver in CEM: Model structure	Treatment-effect parameters	Treatment-stopping rules	Utilities estimated from condition-specific PRO data from trials	PRO(s) used
Diseases of the musculoskeletal system and connective tissue, PRO-dependent indications[a] (n = 10, 38%)							
TA407	Ankylosing spondylitis	Secukinumab	✓	✓	✓	✓	BASDAI, BASFI
TA718		Ixekizumab	✓	✓	✓	✓	
TA719		Secukinumab	✓	✓	✓	✓	
TA415	Rheumatoid arthritis	Certolizumab pegol	✓	✓	✓	✓	DAS28,[b] EULAR (based on DAS28),[b] HAQ, HAQ-DI, self-assessment of pain
TA466		Baricitinib	✓	✓	✓	✓	EULAR (based on DAS28),[b] HAQ, HAQ-DI
TA480		Tofacitinib	✓	✓	✓	✓	DAS28,[b] EULAR (based on DAS28),[b] HAQ-DI
TA485		Sarilumab	✓	✓	✓	✓	ACR,[b] EULAR (based on ACR),[b] HAQ-DI
TA665		Upadacitinib	✓	✓	✓	✓	EULAR (based on ACR),[b] HAQ, HAQ-DI
TA676		Filgotinib	✓	✓	✓	✓	
TA744		Upadacitinib	✓	✓	✓	✓	
Diseases of the nervous system, PRO-dependent indications[a] (n = 6, 23%)							
TA659	Migraine	Galcanezumab	✓	✓	✓	✓	MHD, MSQ
TA682		Erenumab	✓	✓	✓	✓	MMD, MSQ
TA748	Myotonia in nondystrophic myotonic disorders	Mexiletine		✓		✓	INQoL
TA758	Narcolepsy	Solriamfetol	✓	✓			ESS
TA776	Obstructive sleep apnea	Pitolisant hydrochloride		✓		✓	ESS
TA777		Solriamfetol	✓	✓			ESS
Diseases of the respiratory system, PRO-dependent indications[a] (n = 3, 12%)							
TA479	Eosinophilic asthma	Reslizumab	✓	✓	✓		ACQ, exacerbation[b]
TA565		Benralizumab	✓	✓	✓		ACQ, exacerbation,[b] oral corticosteroid use[c]
TA751	Asthma	Dupilumab	✓	✓	✓		
Diseases of the skin and subcutaneous tissue, PRO-dependent indications[a] (n = 3, 12%)							
TA534	Atopic dermatitis	Dupilumab	✓	✓	✓		Composite of DLQI (PRO) and EASI (non-PRO)[b]
TA681		Baricitinib	✓	✓	✓		
TA814		Abrocitinib, tralokinumab, or upadacitinib	✓	✓	✓	✓	Composite of DLQI (PRO) and EASI (non-PRO),[b] DLQI alone
Diseases of other systems, PRO-dependent indications[a] (n = 2, 8%)							
TA610	Bladder pain syndrome	Pentosan polysulfate sodium	✓	✓	✓	✓	GRA, ICSI
TA743	Sickle cell disease	Crizanlizumab	✓		✓		ACS,[b] tolerance[b]
Diseases of other systems, non–PRO-dependent indications[a] (n = 2, 8%)							
TA773	Heart failure	Empagliflozin	✓	✓	✓		KCCQ-23 CSS
TA679	Chronic heart failure	Dapagliflozin	✓	✓			KCCQ-23 TSS

ACQ = Asthma Control Questionnaire; ACR = American College of Rheumatology; ACS = acute chest syndrome; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; DAS28 = Disease Activity Score-28; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ESS = Epworth Sleepiness Scale; EULAR = European League Against Rheumatism; GRA = Global Response Assessment; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire Disability Index; ICSI = Interstitial Cystitis Symptom Index; INQoL = Individualized Neuromuscular Quality of Life Questionnaire; KCCQ-23 CSS = Kansas City Cardiomyopathy 23-Item Questionnaire Clinical Summary Score; KCCQ-23 TSS = Kansas City Cardiomyopathy 23-item Questionnaire Total Symptom Score; MHD = migraine headache days; MMD = monthly migraine days; MSQ = Migraine-specific Quality-of-life Questionnaire; TA = technology appraisal.

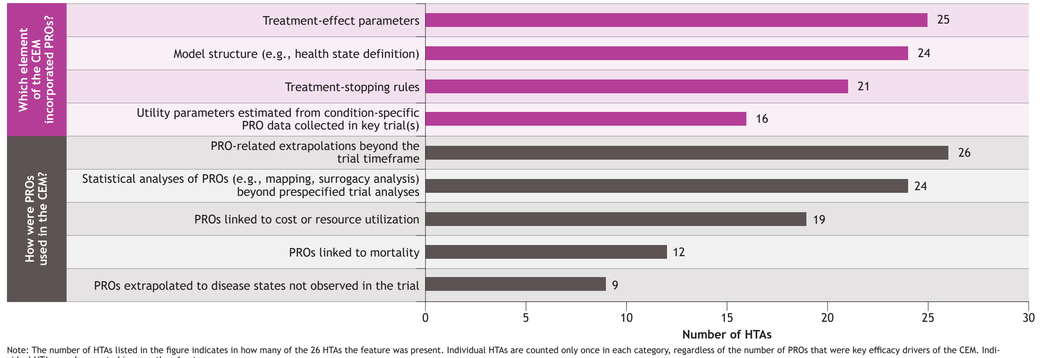
[a] PRO-dependent indications were determined according to the definition of Gnanasakthy et al.,[7] who reported a list of PRO-dependent diseases and defined PRO-dependent diseases as those that typically rely on PRO assessments to inform the primary or secondary trial endpoints for the evaluation of treatment benefit by regulators.

[b] Partial PRO, which is made up of PRO and non-PRO components.

[c] Corticosteroids were indicated to help control asthma-related symptoms.

Note: All HTA documents were accessed via the NICE website (www.nice.org.uk) from October 2022 through March 2023.

Figure 2. Characteristics of the Use of PROs (n = 26)



Note: The number of HTAs listed in the figure indicates in how many of the 26 HTAs the feature was present. Individual HTAs are counted only once in each category, regardless of the number of PROs that were key efficacy drivers of the CEM. Individual HTAs may be counted in more than 1 category.

Table 2. Reasons Supporting the Use of the PRO in the CEM (n = 19 HTAs)

Reason	Number of unique HTAs	Number of HTAs with the reason cited in the company submission	Number of HTAs with the reason cited in the ERG report
The PRO is the best option for measuring aspects of the disease or correlates well with patient's perception of the disease	12	10	3
The PRO allows the CEM to estimate key outcomes (e.g., costs, QALYs)	9	6	3
The PRO is used in clinical practice or referenced in clinical guidelines	8	7	2
The PRO is established, reliable, or robust	7	5	3
The PRO was used in previous NICE HTAs	6	5	1
The PRO is validated	5	3	2
Other	6	4	2

QALY = quality-adjusted life-year.

Table 3. Critiques From the NICE ERG, AG, or AC on the Use of the PRO in the CEM (n = 19 HTAs)

Main categories	Examples
Concerns with how the PRO was operationalized in the CEM (n = 16, 62%)	Alignment with how PRO is used in clinical practice is needed, assumptions made in CEM are not substantiated with data, methods used are not consistent with past NICE HTAs, lack of proper data used to support how the PRO was incorporated into the CEM
Concerns about the underlying data source (n = 11, 42%)	Inadequate sample size, data collected on different patients from patients used in CEM, concerns that the data do not adequately represent the patients of interest, alternative data source is preferred
Concerns with the statistical methods used when incorporating the PRO in the CEM (n = 10, 38%)	Inadequate details of the statistical analysis provided, alternative statistical methods better suited for data, more robust statistical methods needed, additional data needed to make decision about appropriate statistical methods
Concerns about the implementation of the PRO in practice (n = 8, 31%)	The PRO is used to determine whether patients are eligible for therapy and there are concerns that the PRO is too complex for patients to fill out or additional accommodations are needed for patients when implementing PRO in clinical practice

CONCLUSIONS

- This review elucidates how PROs have been incorporated as key drivers in manufacturers' CEMs submitted to NICE and provides insights on NICE's critiques of their use in 26 HTAs from January 2016 through August 2022.
  - Several recent NICE HTAs have used PROs as key drivers in CEMs. Most of these HTAs were for PRO-dependent diseases, and PROs were most commonly included in the CEMs if they were the best option for measuring aspects of the disease or correlate well with the patient's perception of the disease.
  - When used, PROs were more likely to be incorporated in CEMs via 1 or more of the treatment-effect parameters, model structure, and treatment-stopping rules.
  - Overall, NICE was receptive of the use of PROs as key drivers in CEMs, provided that the PROs were properly operationalized, suitable data sources were used in the CEMs, and robust statistical methods were used.
- These insights provide guidance for future researchers and decision-makers seeking to ensure that the patient voice is incorporated into the HTA process.

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