Application of CPRD Data in NICE Submissions: Model Inputs for Functional Health States

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Objectives

To understand the suitability of data from the UK Clinical Practice Research Datalink to inform modelling inputs for functional health states in health technology assessment submissions, by examining case studies of recent NICE appraisals.

Background

- Electronic health records from Clinical Practice Research Datalink (CPRD), a representative sample of UK primary care practices, are the most common source of real-world data in submissions to the UK National Institute for Health and Care Excellence (NICE).[1]
- While generally considered a high-quality data source, there is a need to better understand the suitability of CPRD for specific use cases in economic modelling of conditions where patient subgroups and disease progression are best defined by functional outcomes (i.e. ability to perform daily activities).

Methods

- NICE single technology appraisals (TAs) published in the last 5 years (12/01/2018–12/06/2023, n=387) were reviewed, excluding oncology indications due to the additional availability of CPRD linkage with the disease-specific National Cancer Registration and Analysis Service (NCRAS) dataset.
- Committee papers from the resulting 143 appraisals were searched for case studies meeting the following criteria:
  - Model health states defined on the basis of functional outcomes
  - Reported use of CPRD (and linked secondary care data from the Health Episode Statistics [HES] database) and/or included discussion by the manufacturer or Evidence Assessment Group (EAG) of the suitability of CPRD to inform modelling inputs
- Three case studies were selected to exemplify different approaches,[2–4] and were supplemented by a feasibility assessment for a CPRD study to inform healthcare resource use (HCRU) inputs for an economic model in spinal muscular atrophy (SMA), as part of a Managed Access Agreement (MAA).[5]

Results

- An overview of the characteristics and key takeaways of each case study is presented in Table 1; the methodology and outcomes of the feasibility assessment in SMA are further outlined in Figure 1.
  - Rare genetic diseases represented the majority of indications in the case studies identified (n=3), while the final case study (TA773) was in a chronic cardiovascular indication.
  - Functional outcomes used to define health states included ambulatory and respiratory function (TA821, MAA ID1631), number of seizure-free days (TA873) and patient-reported outcomes (PROs; TA773).
  - The majority of case studies considered the use of CPRD to inform HCRU inputs (n=3/4), with one submission including discussion of inputs for clinical outcomes.
- Overall, no successful use of CPRD to obtain model inputs for functional health states (e.g. through an algorithm based on proxy variables) was identified; instead, use of CPRD was limited to sourcing overall population inputs, assuming no variation between health states.
  - Approaches to obtain health-state specific inputs required assumptions to be made about additional HCRU incurred upon disease progression.
  - Alternative means of data generation, where CPRD studies were not deemed feasible, included expert elicitation through Delphi methods.

Conclusions

While CPRD is generally considered to be an appropriate data source in NICE appraisals, it is not well suited to inform health states based on functional outcomes due to the limited nature of the clinical data recorded.

Submissions in rare indications may face particular challenges in the use of CPRD data, as structured diagnosis codes often lack the specificity and granularity required to identify clinically-meaningful patient subgroups.

To overcome the limitations of CPRD, manufacturers may have to assume no difference between functional health states, integrate other sources such as expert judgement or exclude this potentially valuable data source altogether.

TABLE 1

NICE technology appraisal case studies

	NICE TA Case Studies			Feasibility Assessment
	TA773 (2022)[2]	TA821 (2022)[3]	TA873 (2023)[4]	MAA ID1631[5]
Treament/ indication	**Empagliflozin in chronic HFrEF**	**Avalglucosidase alfa in Pompe disease**	**Cannabidiol in tuberous sclerosis complex**	**Risdiplam in SMA**
Modelled health states	Quartiles of the KCCQ-CSS, a **patient-reported outcome instrument**	Combination of **ambulatory and respiratory status** (wheelchair and ventilation dependency)	Categorical grouping of number of **seizure-free days** per week	Highest **motor function milestone** achieved (non-sitting, sitting, standing, walking) and **permanent ventilation**
Context for use of CPRD data	• Clinical outcome inputs were derived from analyses of patient-level data from the key **placebo-controlled randomised trial** for empaglifozin • Evidence from a CPRD study was used by the manufacturer to **characterise patients** in clinical practice and **validate the long-term predictions** of the model for standard of care, but did not inform any inputs	• Cost of disease management in the company submission was sourced from CPRD/HES, but was assumed to be **equal for all patients in the model** regardless of wheelchair and ventilation status, as results were only available for the total population • Additional health state costs were instead based **on assumed one-off and maintenance HCRU** upon progression	• Health state-specific HCRU inputs in the model were informed by the results of a **two-round Delphi panel** study involving 10 clinical experts • The results of the Delphi panel were **validated against a published CPRD study** of HCRU in the overall population of patients with tuberous sclerosis complex	• Criticism from previous NICE TAs indicated that **HCRU for SMA was underestimated in all available studies**,[5] the majority of which were drawn from patient and caregiver surveys and presented limitations such as recall bias, small sample sizes and limited consideration of costs outside of secondary care • The feasibility of sourcing resource use inputs from CPRD was therefore explored as an alternative (Figure 1)
Key comments on suitability of CPRD	• The EAG recommended that the manufacturer provide a version of the model that **captured the 'real-world' population**, in line with the CPRD study referenced • The manufacturer **pushed back against the suggestion**, with the justification that the lack of routine recording of KCCQ-CSS in CPRD/HES would require reducing the model's granularity	• The EAG raised concerns around the severity of patients with Pompe disease in the CPRD study conducted was comparable to that of other published studies referenced in the submission, but the assumption around health state-specific costs **was not discussed**	• The EAG requested that the manufacturer provide a **scenario analysis** using HCRU inputs from the published CPRD study • The manufacturer declined, stating concerns that the lack of stratification by seizure frequency would **fail to capture differences in resource use** and resulting benefit compared with previous TAs in rare epilepsies	• A CPRD study was deemed unfeasible due to **insufficient clinical information available** to determine motor function milestones/severity; various proxy measures and algorithms were discussed, but the additional complexity left the methodology open to critique (Figure 1) • Opinion from clinical experts also suggested **poor accuracy of diagnosis coding** of SMA types
Ultimate source of model inputs	• As above, unchanged in the final submission	• As above, unchanged in the final submission	• As above, unchanged in the final submission	• A **Delphi approach** will be used to elicit the required HCRU inputs from UK experts in SMA • In order to address previous critiques, the Delphi panel will aim to recruit across a range of specialities/settings, and will also include items from primary and home care

FIGURE 1

Feasibility assessment for a CPRD study of HCRU in SMA

1 — Aim: to determine whether HCRU inputs could be sourced from CPRD/HES according to the model health states (Table 1):

Methods

- The initial scoping assessment confirmed availability of **key categories of HCRU** and SMA diagnosis codes
- Absence of data on motor function, however, meant that an **algorithm would be needed** to stratify patients by model health states
- Input on potential approaches was sought from **experts in SMA and epidemiology**

2 — Two potential approaches were explored based on data available in the CPRD/HES:

Natural History: We explored the possibility to assign likely motor function based on the **natural history of SMA**, accounting for SMA type, age and treatment with DMTs

HCRU Proxies: In addition, we examined whether **certain HCRU items** (e.g. equipment such as mobility aids, tests and procedures, visits to specialists), **alone or in combination**, could be indicative of motor function

3 — Key challenges were identified, and a CPRD study was deemed to be unfeasible

Natural History: Experts agreed this would be insufficient, due to the **heterogeneous natural history of SMA**. In addition, only treatments in the primary care setting are explicitly recorded, which would **not capture DMTs**

HCRU Proxies: Experts indicated use of HCRU items would vary in each group, but no items could be **uniquely linked to specific groups**; concerns also included the potential for **recursive analysis**

Abbreviations: CPRD: Clinical Practice Research Datalink; **DMT:** disease modifying treatment; **EAG:** Evidence Assessment Group; **HCRU:** healthcare resource use; **HES:** Health Episode Statistics; **HFrEF:** heart failure with reduced ejection fraction; **KCCQ-CSS:** Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; **MAA:** Managed Access Agreement; **NICE:** National Institute for Health and Care Excellence; **SMA:** spinal muscular atrophy; **TA:** technology assessment.

References: [1]Leahy TP *et al.* BMC Health Services Research 2020;20:1–9; [2]NICE. TA773. Available at: www.nice.org.uk/guidance/ta773 [Last accessed: 27.09.23]; [3]NICE. TA821. Available at: www.nice.org.uk/guidance/ta821 [Last accessed: 27.09.23]; [4]NICE. TA873. Available at: www.nice.org.uk/guidance/ta873 [Last accessed: 27.09.23]; [5]NICE. MAA ID1631. Available at: www.nice.org.uk/guidance/ta755/resources/managed-access-agreement-pdf-10897406893 [Last accessed: 27.09.23].

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