The use of patient and carer perspectives and real-world evidence in orphan disease health technology assessment submissions

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Introduction and objectives

Health technology assessments (HTAs) represent a critically important process, which ensures that effective and safe drugs reach the patients who need them.

Generating robust evidence for HTA submissions in the orphan disease space is a particular challenge, as limited patient numbers can preclude the use of randomised controlled trials (RCTs) and necessitate the use of real-world evidence (RWE). Nevertheless, reaching these patients and incorporating their views into the HTA submission process remains critically important to ensure effective representation and provide important evidence on the burden of disease and lived experiences.

The aim of this study was to assess the use of RWE and the contribution of the patient/carer voice in orphan disease HTA submissions in the UK (through the National Institute for Health and Care Excellence [NICE]) and Canada (through Canada's Drug Agency [CDA-AMC]), and to compare trends in RWE and the patient/carer voice in NICE and CDA-AMC.

Methods

The NICE database was searched from 18th April 2022 to 18th April 2024 to identify orphan disease technology appraisal submissions (defined as diseases with Orphanet identifiers); matched submissions were manually identified on the CDA-AMC website. Year 1 of the analysis was designated as 18th April 2022 to 17th April 2023, and Year 2 as 18th April 2023 to 17th April 2024. Data were extracted into Excel® by one reviewer and checked by a second reviewer to reduce error and bias. Pre-defined outcomes of interest included: the use of RWE and of patient/carer inputs. A thematic longitudinal analysis was performed.

Results

A total of 36 orphan disease drug submissions were identified (58 across NICE and CDA-AMC: 36 from NICE [11 in Year 1, 25 in Year 2] and 22 from CDA-AMC [7 in Year 1, 15 in Year 2]) (Table 1). Out of the 58 total submissions, 41 (70.7%) were recommended, 7 (12.1%) were not recommended, and 10 (17.2%) were recommended with conditions.

Table 1: List of included health technology assessments

Year	#	Drug (Brand)	Company	Submission to
1	1	Cannabidiol (Epidyolex®) for TSC	GW Pharma	NICE
1	2	Vutrisiran (Amvuttra®) for hereditary ATTR	Alnylam	NICE
1	3	Zanubrutinib (Brukinsa®) for WM	BeiGene	NICE, CDA-AMC
1	4	Azacitidine (Onureg®) for AML	Celgene (BMS)	NICE, CDA-AMC
1	5	Avacopan (Tavneos®) for GPMP	Vifor/Otsuka	NICE, CDA-AMC
1	6	Avalglucosidase alfa (Nexviadyme®) for PD	Sanofi Genzyme/Aventis	NICE, CDA-AMC
1	7	Asciminib (Scemblix®) for CML	Novartis	NICE, CDA-AMC
1	8	Fenfluramine (Fintepla®) for DS	Zogenix (UCB)	NICE
1	9	Teduglutide (Revestive®) for SBS	Shire (Takeda)	NICE, CDA-AMC
1	10	Ibrutinib (Imbruvica®) for WM	Janssen	NICE
1	11	Venetoclax (Venclyxto®) for AML	AbbVie	NICE, CDA-AMC
2	12	Cabozantinib (Cabometyx®) (with nivolumab) for advanced RCC	Ipsen	NICE, CDA-AMC
2	13	Olaparib (Lynparza®) for BRCAm advanced EOC, FTC, or PPC	AstraZeneca	NICE
2	14	Daratumumab (Darzalex SC®) (with CyBorD) for AL amyloidosis	Janssen-Cilag	NICE, CDA-AMC
2	15	Momelotinib (Ojjaara®) for myelofibrosis-related splenomegaly or symptoms	GSK	NICE
2	16	Epcoritamab (Epkinly®) for rrDLBCL	AbbVie	NICE, CDA-AMC
2	17	Belumosudil (Rezurock®) for cGVHD	Sanofi-Aventis	NICE, CDA-AMC
2	18	Loncastuximab tesirine (Zynlonta®) for rrDLBCL and high-grade BCL	Swedish Orphan Biovitrum	NICE
2	19	Ivosidenib (Tibsovo®) for IDH1 R132m advanced cholangiocarcinoma	Servier Laboratories	NICE
2	20	Olaparib (Lynparza®) (with bevacizumab) for advanced high-grade EOC, FTC, or PPC	AstraZeneca	NICE
2	21	Durvalumab (Imfinzi®) (with gemcitabine and cisplatin) for locally advanced, unresectable, or metastatic biliary tract cancer	AstraZeneca	NICE, CDA-AMC
2	22	Targeted-release budesonide (Kinpeygo®) for primary IgA nephropathy	STADA/Britannia Pharmaceuticals	NICE
2	23	Risdiplam (Evrysdi®) for SMA	Roche	NICE, CDA-AMC
2	24	Daratumumab (Darzalex®) (with Rd) for MM	Janssen	NICE, CDA-AMC
2	25	Ruxolitinib (Jakavi®) for PV	Novartis	NICE, CDA-AMC
2	26	Glofitamab (Columvi®) for rrDLBCL	Roche	NICE, CDA-AMC
2	27	Pegunigalsidase alfa (Elfabrio®) for FD	Chiesi	NICE
2	28	Cipaglucosidase alfa (Pombiliti®) (with miglustat) for late-onset PD	Amicus Therapeutics	NICE
2	29	Olaparib (Lynparza®) for high-grade EOC, FTC, or PPC	AstraZeneca	NICE, CDA-AMC
2	30	Axicabtagene ciloleucel (Yescarta®) for rrFL	Kite/Gilead	NICE, CDA-AMC
2	31	Axicabtagene ciloleucel (Yescarta®) for rrDLBCL	Kite/Gilead	NICE, CDA-AMC
2	32	Bulevirtide (Hepcludex®) for chronic hepatitis D	Gilead	NICE
2	33	Daratumumab (Darzalex®) (with lenalidomide and dexamethasone or bortezomib and dexamethasone) for MM	Janssen	NICE, CDA-AMC
2	34	Mosunetuzumab (Lunsumio®) for rrFL	Roche	NICE
2	35	Ripretinib (Qinlock®) for advanced GIST	Deciphera Pharmaceuticals/ Medison Pharma Canada	NICE, CDA-AMC
2	36	Tafasitamab (Minjuvi®) (with lenalidomide) for rrDLBCL	Incyte	NICE, CDA-AMC

Green indicates recommended; **orange** indicates mixed recommendations; **red** indicates not recommended.

The use of real-world data in the orphan disease space

The pivotal study design used in the HTA submissions was either an RCT (29/58; 50.0%), a mix of RCT and non-randomised interventional study (10/58; 17.2%), a non-randomised interventional study (9/58; 15.5%), a mix of an RCT plus RWE (7/58; 12.1%), a mix of a single-arm study plus RWE (2/58; 3.5%), or exclusively RWE (1/58; 1.7%) (Figure 1).

Figure 1: Pivotal source of study evidence for submission

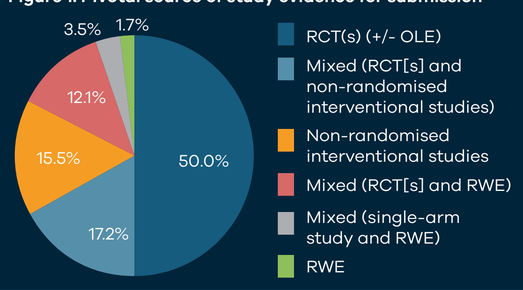


Figure 2: Key sources of patient/carer contributions to HTA assessments in NICE (UK) or CDA-AMC (Canada)

NICE

- Action Kidney Cancer
- AMMF – the Cholangiocarcinoma Charity
- Anthony Nolan
- Association for Glycogen Storage Disease UK
- Blood Cancer UK
- British Liver Trust
- Cholangiocarcinoma - UK
- GIST Cancer UK
- Kidney Cancer UK
- Kidney Research UK
- Leukaemia Care
- Lymphoma Action
- MPN Voice
- Muscular Dystrophy UK (MDUK)
- Myeloma UK
- Ovacome
- Ovarian Cancer Action
- Pompe Support Network
- Sarcome UK
- SMA Reach UK
- Society for Mucopolysaccharide and Related Diseases (MPS Society)
- Spinal Muscular Atrophy UK (SMA UK)
- Target Ovarian Cancer
- TreatSMA
- UK Kidney Association
- Vasculitis UK

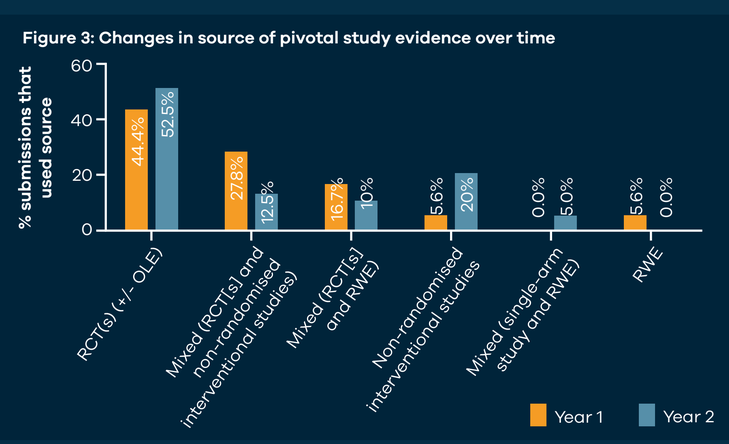
CDA-AMC (Canada)

- Canadian Cancer Survivor Network
- Canadian Liver Foundation
- Canadian Myeloproliferative Neoplasm (MPN) Network
- Canadian Organization for Rare Disorders
- CanCertainty Coalition
- Cell Therapy Transplant Canada (CTTC)
- Cholangiocarcinoma Foundation
- Colorectal Cancer Resource and Action Network (CCRAN)
- Cure SMA Canada (CSMAC)
- Gastrointestinal Society
- GIST Sarcoma Life Raft Group Canada (LRGC)
- Kidney Cancer Canada
- Leukemia & Lymphoma Society of Canada
- Lymphoma Canada
- Muscular Dystrophy Canada (MDC)
- Myeloma Canada
- Ovarian Cancer Canada
- Regroupement québécois des maladies orphelines (RQMO)

Results continued

The use of different pivotal study design sources changed over time, (8/18 [44.4%] informed by RCTs in Year 1, 21/40 [52.5%] in Year 2; 5/18 [27.8%] informed by a mix of RCT and non-randomised interventional study in Year 1, 5/40 [12.5%] in Year 2; 3/18 [16.7%] informed by a mix of RCT and RWE in Year 1, 4/40 [10%] in Year 2; 1/18 [5.6%] informed by a non-randomised interventional study in Year 1, 8/40 [20%] in Year 2; 1/18 [5.6%] informed by RWE alone in Year 1, none in Year 2; 0/18 [0.0%] informed by a mix of single-arm studies and RWE in Year 1, 2/40 [5.0%] in Year 2) with more submissions using RCTs as the key submission source in Year 2 versus Year 1 (Figure 3).

Figure 3: Changes in source of pivotal study evidence over time



The voice of patients and carers

Patient and carer contributions (defined as either the inclusion of patient experts in the committee meetings or the receipt of formal patient group submissions) were provided for all HTA submissions to both NICE and CDA-AMC. These contributions appeared to be exclusively championed by a range of charities (Figure 2), who collated evidence from their own sources (including data sources such as patient surveys, telephone or video interviews, face-to-face interviews, online forums, and formal studies) and nominated patient experts to provide individual submissions.

Out of 36 NICE submissions, only one did not have a patient expert attending the committee meetings (vutrisiran for treating hereditary transthyretin-related amyloidosis) and only one did not have a patient group submission (bulevirtide for treating chronic hepatitis D). In one NICE submission (cabozantinib with nivolumab for untreated advanced renal cell carcinoma), patient experts fed back on the submission process, indicating that the committee meetings were too technical for them to meaningfully engage. Out of 22 CDA-AMC submissions, all (100%) had a patient group submission but no patient experts appeared to be invited to attend any of the committee meetings.

Conclusion

This study highlights an increase in rare disease HTA submissions, with submissions almost doubling from Year 1 to Year 2. Pivotal study evidence appears to be increasingly informed by RCTs or non-randomised interventional studies despite the difficulties around small patient numbers. Patient experts provided input either through attending committee meetings or patient group submissions. Charities and self-assembled patient groups played a critical role in providing key supportive evidence around patient burden and lived experiences of patients, families, and carers in different orphan disease settings, which often had a key influence on the final recommendation. Further work is needed to ensure that patients can meaningfully contribute to the HTA process in line with guidance on the importance of patient–public involvement in research (1, 2).

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Abbreviations

AL, amyloid light-chain amyloidosis
AML, acute myeloid leukaemia
AMMF, Alan Morement Memorial Fund
ATTR, hereditary transthyretin amyloidosis
BCL, B-cell lymphoma
BMS, Bristol-Myers Squibb
CCRAN, Colorectal Cancer Resource & Action Network
CDA-AMC, Canada's Drug Agency
cGVHD, chronic graft-versus-host disease
CML, chronic myeloid leukaemia
CSMAC, Cure Spinal Muscular Atrophy Canada
CTTC, Cell Therapy Transplant Canada
CyBorD, cyclophosphamide–bortezomib–dexamethasone
DS, Dravet syndrome
EOC, epithelial ovarian cancer
FD, Fabry disease
FTC, fallopian tube cancer
GIST, gastrointestinal stromal tumour
GPMP, granulomatosis with polyangiitis/microscopic polyangiitis
GSK, GlaxoSmithKline
HTA, health technology assessment
IgA, immunoglobulin A
LRGC, Life Raft Group Canada
M, mutation
MDC, Muscular Dystrophy Canada
MDUK, Muscular Dystrophy UK
MM, multiple myeloma
MPN, myeloproliferative neoplasm
MPS, mucopolysaccharide
NICE, National Institute for Health and Care Excellence
OLE, open-label extension
PD, Pompe disease
PPC, primary peritoneal cancer
PV, polycythaemia vera
RCC, renal cell carcinoma
RCT, randomised controlled trial
Rd, lenalidomide and dexamethasone
RQMO, Regroupement québécois des maladies orphelines
rrDLBCL, relapsed, refractory diffuse large B-cell lymphoma
rrFL, relapsed/refractory follicular lymphoma
RWE, real-world evidence
SBS, short bowel syndrome
SMA, spinal muscular atrophy
TSC, tuberous sclerosis complex
WM, Waldenstrom's macroglobulinaemia