Measurement of Health-Related Quality of Life/Patient Reported Outcomes in Health Technology Assessments Submissions for Rare Skin Diseases

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HTA159

INTRODUCTION

BACKGROUND

- Rare diseases affecting the skin, or rare skin diseases (RSDs), are associated with psychological and psychosocial burden for the patient, including depressive symptoms, stress, and social isolation.[1] Moreover, recent research has linked these adverse psychological and psychosocial effects with exacerbation of skin disease.[2]
- Patients and payers assign significant weights to health-related quality of life and patient reported outcomes (HRQoL/PROs).
- While validated disease-specific tools are available for common skin diseases, validated tools may be less available for RSDs, resulting in inconsistencies in the methods assessing quality of life or difficulties in results interpretation.

OBJECTIVE

To investigate the of use of HRQoL/PROs tools in health technology assessment (HTA) submissions for RSDs, and how different HTA agencies evaluate and assess the appropriateness of HRQoL/PRO tools.

METHODS

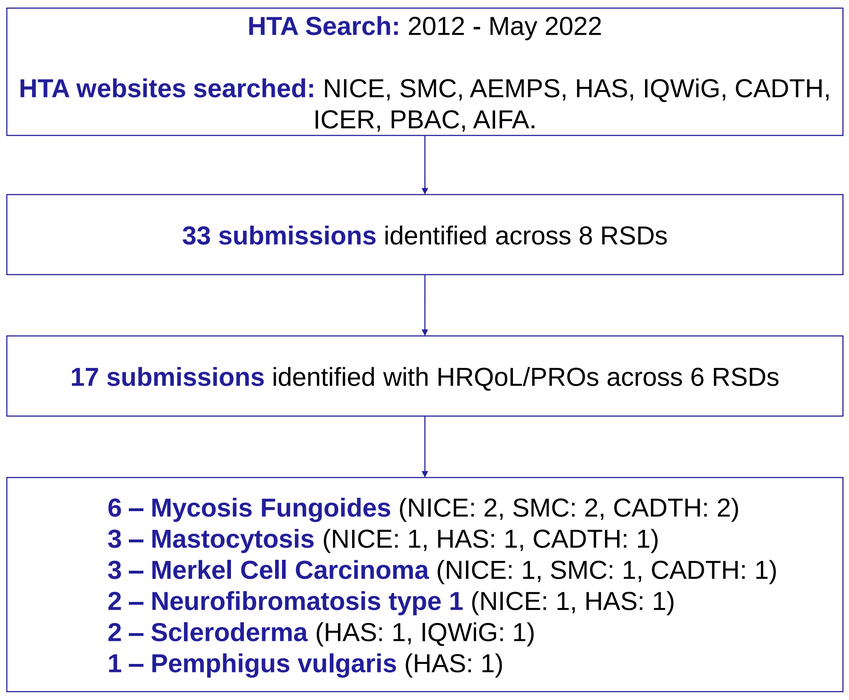
- A list of 271 rare diseases affecting the skin was compiled from the National Organization for Rare Disorders database and Genetic and Rare Diseases Information Center website. A total of 9 HTA websites were reviewed for submissions from the last 10 years (2012 to May 2022), which included HRQoL/PRO outcomes across these RSDs.
- HTA websites searched included: The National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Haute Autorité de Santé (HAS), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Clinical and Economic Review (ICER), Pharmaceutical Benefits Advisory Committee (PBAC), and Agenzia Italiana del Farmaco (AIFA).

RESULTS

Identification of HTA submissions

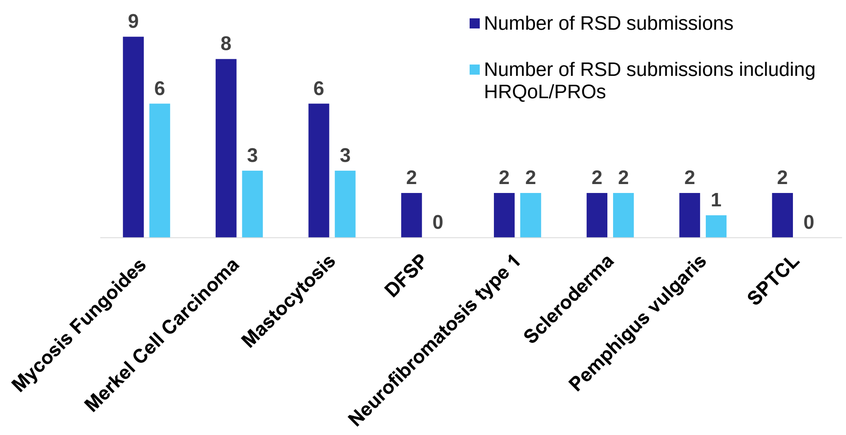
- A total of 33 HTA submissions across 5 different agencies (NICE: 10, HAS: 8, SMC: 6, CADTH: 5, IQWiG: 4) were identified (**Figure 1**).
- The 3 most frequently identified RSD indications among all HTA submissions identified were mycosis fungoides: 9, Merkel cell carcinoma: 8, and mastocytosis: 6 (**Figure 2**).

Figure 1. Identification of HTA submissions from selected agencies



- Among the 33 identified submissions, HRQoL/PRO tools were referenced in 17 submissions (52%) across 6 RSD indications (mycosis fungoides: 6, Merkel Cell Carcinoma: 3, mastocytosis: 3, neurofibromatosis type 1: 2, scleroderma: 2, pemphigus vulgaris: 2) (**Figure 2**).
- The final list of submissions selected for analysis came from 5 agencies: NICE (5), SMC (3), HAS (4), IQWiG (1), CADTH (4).

Figure 2. RSD submissions identified, and RSD submissions identified including HRQoL/PROs



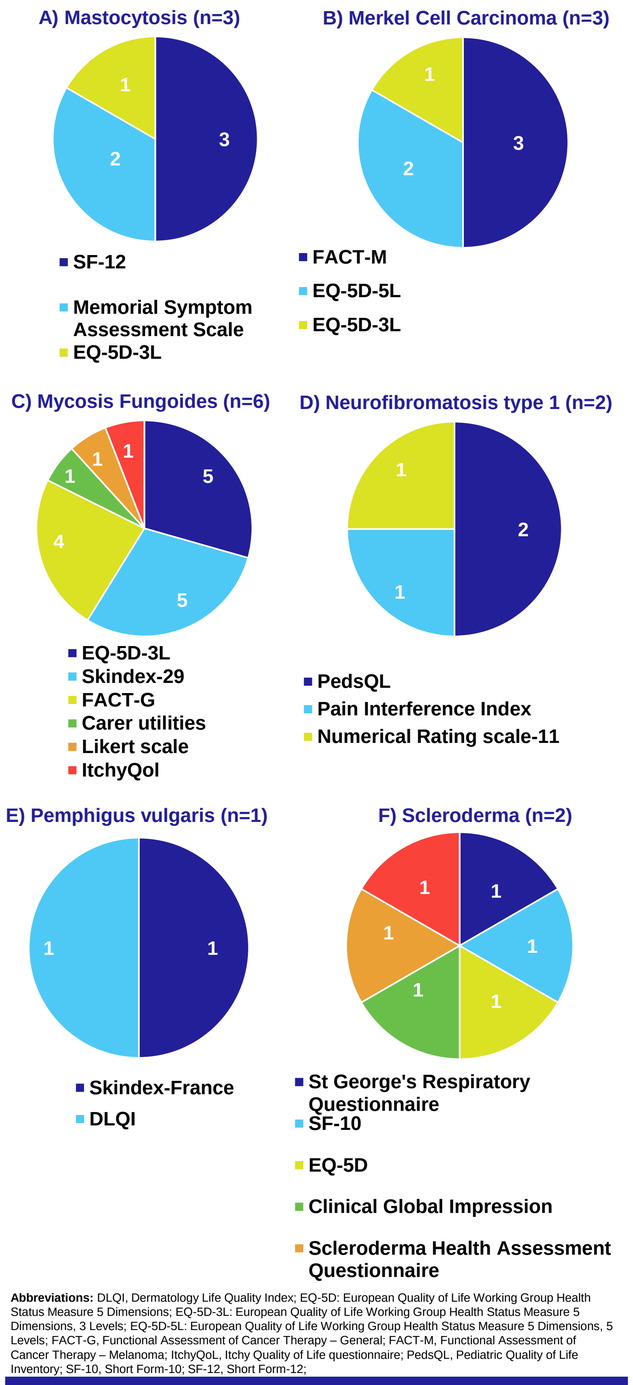
Abbreviations: DFSP, dermatofibrosarcoma protuberans; SPTCL, subcutaneous panniculitis-like T-cell lymphoma

- Across the 6 RSD indications, the number of submissions within each indication ranged from 1 (pemphigus vulgaris) to 6 (mycosis fungoides) (**Table 1**).
- Avelumab, selumetinib, rituximab, and midostaurin were the only submissions in Merkel cell carcinoma, neurofibromatosis type 1, pemphigus vulgaris, and mastocytosis, respectively (**Table 1**).

HRQoL/PRO tools across RSD submissions

- A total of 20 different HRQoL/PRO tools were identified across the RSD submissions (**Table 1**).
- The most frequently used tools were EQ-5D-5L (n=7), skindex-29 (n=5), and FACT-G (n=4) (**Table 1**).
- Inconsistencies in the use of HRQOL/PRO tools were noted. For example, across the 2 scleroderma submissions identified, 6 different tools were used to assess HRQoL/PROs, with no overlap in tools used between the 2 submissions (**Figure 8**, **Table 1**).
- The Scleroderma Health Assessment Questionnaire was the only disease-specific tool identified; however, FACT-M was considered appropriate to assess HRQoL in individuals with Merkel cell carcinoma by CADTH (**Table 1**).

Figure 3. HRQoL/PRO tools across RSD submissions



Abbreviations: DLQI, Dermatology Life Quality Index; EQ-5D: European Quality of Life Working Group Health Status Measure 5 Dimensions; EQ-5D-3L: European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels; EQ-5D-5L: European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-M, Functional Assessment of Cancer Therapy – Melanoma; ItchyQoL, Itchy Quality of Life questionnaire; PedsQL, Pediatric Quality of Life Inventory; SF-10, Short Form-10; SF-12, Short Form-12;

Table 1. Summary of HRQoL/PRO tools across submissions in RSDs

HTA	Indication	Intervention	HRQoL/PRO Tool Used	Comments on HRQoL/PRO
NICE 2021	Mastocytosis	Midostaurin	Memorial Symptom Assessment Scale (MSAS), SF-12 (SF-12 was mapped to the EQ-5D-3L)	Utility values used in the model had been derived from the single-arm D2201 trial, not from people having current clinical management.
NICE 2018	Merkel Cell Carcinoma	Avelumab	EQ-5D-5L, FACT-M, EQ-5D-3L	The committee concluded that it could accept the company's utility values but acknowledged that these were very high.
NICE 2019	Mycosis fungoides	Brentuximab Vedotin	Skindex-29, EQ-5D-3L	Neither Skindex-29 score or EQ-5D-3L fully capture both the skin related and physiological symptoms.
NICE 2021	Mycosis fungoides	Mogamulizumab	Carer utilities	There may be an effect on carers' health-related quality of life, but this cannot be robustly modelled.
NICE 2022	Neurofibromatosis type 1	Selumetinib	PedsQL	Direct utility values from the trial were not used in the modelling or to validate the utility values derived from the time trade off study.
SMC 2018	Merkel Cell Carcinoma	Avelumab	FACT-M, EQ-5D-5L	There is no robust evidence that avelumab improves quality of life.
SMC 2021	Mycosis fungoides	Mogamulizumab	Skindex-29, FACT-G, EQ-5D-3L, Likert scale & the ItchyQoL	Criterion for a substantial improvement in quality of life was met.
SMC 2020	Mycosis fungoides	Brentuximab Vedotin	Skindex-29, FACT-G, EQ-5D-3L	No comments on HRQoL/PROs.
HAS 2018	Mastocytosis	Midostaurin	SF-12	The impact on quality of life compared to the current management strategy cannot be determined.
HAS 2022	Neurofibromatosis type 1	Selumetinib	PedsQL, Numerical Rating Scale-11, PII	No robust conclusion can be drawn.
HAS 2020	Pemphigus vulgaris	Rituximab	Skindex-France, DLQI	QoL results cannot be accepted.
HAS 2017	Scleroderma	Bosentan	SF-10, Clinical Global Impression	No improvement of quality of life has been demonstrated.
IQWiG 2020	Scleroderma	Nintedanib	EQ-5D-5L, Patient Global Impression of Health, SGRQ, SHAQ	No statistically significant difference between treatment groups for SGRQ
CADTH 2018	Mastocytosis	Midostaurin	MSAS, SF-12	Midostaurin aligned with may offer symptom management and has the potential to maintain HRQoL.
CADTH 2017	Merkel Cell Carcinoma	Avelumab	FACT-M	The content of the FACT-M seems appropriate to assess HRQoL in subjects with Merkel Cell Carcinoma.
CADTH 2018	Mycosis fungoides	Brentuximab Vedotin	Skindex-29, FACT-G, EQ-5D-3L	No validated minimal important difference method applicable to the Skindex-29 questionnaire.
CADTH 2022	Mycosis fungoides	Mogamulizumab	Skindex-29, FACT-G, and EQ-5D-3L	Unable to draw any conclusions on the effect of mogamulizumab on HRQoL.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; DLQI, Dermatology Life Quality Index; EQ-5D-3L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-M, Functional Assessment of Cancer Therapy – Melanoma; HAS, Haute Autorité de Santé; HRQoL, Health Related Quality of Life; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ItchyQoL, Itchy Quality of Life questionnaire; MSAS, Memorial Symptom Assessment Scale; NICE, National Institute for Health and Care Excellence; PedsQL, Pediatric Quality of Life Inventory; PII, Pain Inference Index; PROs, Patient Reported Outcomes; RSD, Rare Skin Disease; SF-10, Short Form-10; SF-12, Short Form-12; SGRQ, St. George's Respiratory Questionnaire; SHAQ, Scleroderma Health Assessment Questionnaire; SMC, Scottish Medicines Consortium.

- HTA comments across 10 submissions noted difficulties in drawing reliable conclusions from HRQoL/PRO data.
- The use of mapped utility estimates in the economic model often failed to capture the benefits of technology, leading to excessive assumptions.
- Certain tools, including the EQ-5D-5L and Skindex-29, were critiqued for their inability to fully capture both the skin-related and physiological symptoms and for containing subjective improvements. Skindex-29 was cited for not having validated thresholds to determine the minimal important difference (MID).

STRENGHTS AND LIMITATIONS

Strengths: The review of HTA submissions followed a rigorous systematic methodology and highlights the need for clarity on tools to assess HRQoL/PROs in RSDs.

Limitations: Only 9 HTA websites were reviewed; there were few submissions detailing the appropriateness of the instruments used; the list of RSDs chosen for this analysis may not comprehensive and is based on only two sources.

CONCLUSIONS

- Among known rare disease affecting the skin, HTA submissions including considerations for HRQoL/PROs are limited.
- Our analysis identified a variety of tools used to assess HRQoL in RSD HTA submissions, even within the same indications.
- Many HRQoL/PRO tools were critiqued for being inappropriate.
- Generic tools are often used despite not capturing dermatologic issues. Thus, the true impact of RSDs on HRQoL may be underestimated. Further research is warranted to validate MID thresholds and to improve the reliability of HRQOL tools in RSDs.

ABBREVIATIONS

AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; CADTH, Canadian Agency for Drugs and Technologies in Health; DFSP, Dermatofibrosarcoma protuberans; DLQI, Dermatology Life Quality Index; EQ-5D-3L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-M, Functional Assessment of Cancer Therapy – Melanoma; HAS, Haute Autorité de Santé; HRQoL, Health Related Quality of Life; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ItchyQoL, Itchy Quality of Life questionnaire; MID, minimal important difference; MSAS, Memorial Symptom Assessment Scale; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PedsQL, Pediatric Quality of Life Inventory; PGI, Patient Global Impression of Health; PII, Pain Inference Index; PROs, Patient Reported Outcomes; RSD, Rare Skin Disease; SF-10, Short Form-10; SF-12, Short Form-12; SGRQ, St. George's Respiratory Questionnaire; SHAQ, Scleroderma Health Assessment Questionnaire; SMC, Scottish Medicines Consortium; SPTCL, Subcutaneous panniculitis-like T-cell lymphoma.

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Presented at ISPOR Europe | Vienna, Austria | November 6–9, 2022