

NEEDS EXAMINATION, EVALUATION AND DISSEMINATION (NEED): APPLICABILITY TO RARE DISEASES



NEEDS EXAMINATION, EVALUATION AND DISSEMINATION (NEED): APPLICABILITY TO RARE DISEASES

ZILKE CLAESSENS, ALICE VANNESTE, JOLIEN BROEKMANS, CHARLOTTE VERBEKE, IO WENS, CHARLOTTE VAN ISTERDAEL, ROSANNE JANSSENS, LIESE BARBIER, RANI CLAERMAN, MATS DE JAEGER, ROBBY DE PAUW, LAURENCE KOHN, MURIEL LEVY, CLAUDIA SCHÖNBORN, IRINA CLEEMPUT, CHARLINE MAERTENS DE NOORDHOUT, ISABELLE HUYS



COLOPHON

Title:	Needs Examination, Evaluation and Dissemination (NEED): applicability to rare diseases
Authors:	Zilke Claessens (KU Leuven), Alice Vanneste (KUL), Jolien Broekmans (KUL), Charlotte Verbeke (KUL), Io Wens (KUL), Charlotte Van Isterdael (KUL), Rosanne Janssens (KUL), Liese Barbier (KUL), Rani Claerman (Sciensano), Mats de Jaeger (KCE), Robby De Pauw (Sciensano), Laurence Kohn (KCE), Muriel Levy (KCE), Claudia Schönborn (KCE), Irina Cleemput (KCE), Charline Maertens de Noordhout (KCE), Isabelle Huys (KUL)
Project facilitator:	Nathalie Swartenbroekx (KCE)
Reviewers:	Célia Primus-de Jong (KCE), Marie Dauvrin (KCE)
External experts and stakeholders:	An Bollen (UZ Leuven), Antonella Cardone (Cancer Patients Europe), Sabine Corachan (LUSS - Ligue des Usagers des Services de Santé), Fabio Datri (European Commission), Harlinde De Schutter (Stichting Kankerregister), Martine Delchambre (LUSS), Marion Delcroix (UZ Leuven), Bart Demyttenaere (Solidaris), Franck Devaux (Hôpital Universitaire de Bruxelles), Marc Doods (UZ Leuven), Maggie Galbraith (HAS - Haute Autorité de Santé), Sarah Garner (WHO Europe), Stefan Gijssels (Patient Expert Center), Wim Goettsch (Universiteit Utrecht, the Netherlands), Dimitri Hemelsoet (Universitair Ziekenhuis Gent), Francois Houyez (EURORDIS - European Organisation for Rare Diseases), Stefan Joris (Belgische vereniging voor strijd tegen mucoviscidose), Heini Kanervo (UZ Brussel), Kaja Kantorska (European Commission), Anna Kubina (Kabinet minister Frank Vandenbroucke), Olivia Lacroix (Cliniques universitaires Saint-Luc), Damien Lederer (IPG - Institut de Génétique Humaine), Tim Leest (FAGG – AFMPS – Federaal agentschap voor geneesmiddelen en gezondheidsproducten – Agence fédérale des médicaments et des produits de santé), Joyce Loridan (Solidaris), Kate Morgan (Myeloma Patients Europe), Valentin Mutemberezi (INAMI – RIZIV – Institut national d'assurance maladie-invalidité – Rijksinstituut voor ziekte- en invaliditeitsverzekering), Clara Noirhomme (Mutualité chrétienne), Gauthier Rémiche (HUB - Hôpital Universitaire de Bruxelles, Hôpital Erasme, ULB - Université libre de Bruxelles), Marjolijn Renard (Ziekenhuisfunctie Zeldzame Ziekten, Universitair Ziekenhuis Gent), Eva Schoeters (RaDiOrg – Rare Diseases Belgium), Valentina Strammiello (EPF - European Patient's Forum), Tina Taube (EFPIA - European Federation of Pharmaceutical Industries), Sylvie Taziaux (CHU de Liège), Annemie T'Seyen (Koning Boudewijnstichting), Marc Van De Casteele (RIZIV – INAMI - Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité), Chris Van Haecht (Christelijke mutualiteit), Anne Van Meerbeeck (VPP - Vlaams Patiëntenplatform), Armand Voorschuur (Pharma.be), René Westhovens (KU Leuven), Beate Wieseler (IQWiG - Institute for Quality and Efficiency in Health Care)
External validators:	Olivia Lacroix (Cliniques universitaires St-Luc), Domenica Taruscio (Former director of the National Centre for Rare Diseases, Istituto Superiore di Sanità, Italy), Wendy Van Zelst-Stams (Radboud Universitair Medisch Centrum, the Netherlands)



Acknowledgements:

The authors wish to thank Thomas Vandendriessche, Norin Hamouda, Krizia Tuand and Chayenne Van Meel, the biomedical reference librarians of the KU Leuven Libraries – 2Bergen – Learning Centre Désiré Collen (Leuven), for their help in conducting the systematic literature search. We also would like to thank Elise Schoefs, (Clinical pharmacology & pharmacotherapy, KU Leuven) for her logistic support, Marc Doods (UZ Leuven), Alessandra Blonda (Clinical Pharmacology & Pharmacotherapy, KU Leuven) and René Westhovens, (Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, KU Leuven) for reviewing the list of invites for the stakeholder consultations. We would like to thank the Ethics Committee Research – UZ Leuven for the timely assessment and clearance of the research protocol.

Reported interests KCE experts:

KCE is a federal institution funded by INAMI/RIZIV, by the Federal Public Service of Health, Food chain Safety and Environment, and by the Federal Public Service of Social Security. KCE's mission is to advise policymakers on decisions relating to health care and health insurance on the basis of scientific and objective research. It is expected to identify and shed light on the best possible solutions, in the context of an accessible, high-quality health care system with due regard for growing demand and budgetary constraints. , KCE has no interest in companies (commercial or non-commercial, i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of the recommendations. All experts involved in the writing of the report or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

Reported interests external experts:

All experts and stakeholders consulted within this report were selected because of their involvement in the topic of rare diseases. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report.

RaDiOrg does not support the application of the NEED assessment framework to rare diseases.

Layout:

Ine Verhulst (KCE), Joyce Grijseels (KCE)

Financially supported by BELSPO

**Disclaimer:**

- The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.
- Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.
- Finally, this report has been approved by a majority of votes by the Executive Board (see <http://kce.fgov.be/content/the-board>).
- Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.

Project number: 2023-13-HSR_Needs rare diseases
Publication date: 28 March 2024, 2nd print: 09/09/2024
Domain: Health Services Research (HSR)
MeSH: Needs assessment, Research Design, Rare Diseases
NLM Classification: W84.3
Language: English
Format: Adobe® PDF™ (A4)
Legal depot: D/2024/10.273/08
ISSN: 2466-6459
Copyright: KCE reports are published under a “by/nc/nd” Creative Commons Licence
<http://kce.fgov.be/content/about-copyrights-for-kce-publications>.



How to refer to this document?

Claessens Z, Vanneste A, Broekmans J, Verbeke C, Wens I, Van Isterdael C, Janssens R, Barbier L, Claerman R, de Jaeger M, De Pauw R, Kohn L, Levy M, Schönborn C, Cleemput I, Maertens de Noordhout C, Huys I. Needs Examination, Evaluation and Dissemination (NEED): applicability to rare diseases. Health Services Research



(HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2024. KCE Reports 377C4. D/2024/10.273/08.
DOI: <https://doi.org/10.57598/R377C4>

This document is available on the website of the Belgian Health Care Knowledge Centre.



■ TABLE OF CONTENTS

LIST OF FIGURES	4
LIST OF TABLES	5
LIST OF ABBREVIATIONS	6
GLOSSARY	10
■ SCIENTIFIC REPORT	11
1 INTRODUCTION	11
1.1 MOVING FROM A SUPPLY-DRIVEN TO A NEEDS-DRIVEN HEALTHCARE SYSTEM	11
1.2 THE NEED APPROACH	13
1.3 THE NEED APPROACH AS APPLICABLE TO RARE DISEASES	14
1.3.1 Rare diseases and challenges in research on rare diseases	14
1.3.2 Policies to incentivise research and development in rare diseases	15
1.3.3 Remaining challenges related to diagnosis and care of patients with rare diseases	15
2 RESEARCH QUESTIONS, AIM AND OBJECTIVES	17
2.1 RESEARCH QUESTIONS	17
2.2 AIM AND OBJECTIVES	17
3 METHODOLOGICAL APPROACH	18
3.1 GREY LITERATURE REVIEW	19
3.1.1 Search strategy and screening	19
3.1.2 Data extraction	19
3.1.3 Data synthesis and analysis	19
3.2 RAPID REVIEW	20
3.2.1 Search strategy design	20



3.2.2	Screening and selection.....	21
3.2.3	Data extraction	21
3.2.4	Data synthesis and analysis	21
3.3	STAKEHOLDER CONSULTATIONS	21
3.3.1	Sampling strategy of the stakeholder consultations	21
3.3.2	Data retrieval.....	22
3.3.3	Data analysis.....	22
4	DEFINITIONS OF RARE DISEASES	24
4.1	METHODS.....	24
4.2	RESULTS	26
4.3	DISCUSSION AND CONCLUSION	29
4.3.1	Implications of the diversity of definitions among stakeholders	29
4.3.2	Difficulties of the different elements of rare disease definitions.....	29
4.3.3	Limitations	29
4.3.4	Conclusion	30
5	METHODOLOGICAL CHALLENGES	30
5.1	METHODS.....	30
5.1.1	Rapid Literature Review.....	30
5.1.2	Stakeholder workshops.....	33
5.2	RESULTS	35
5.2.1	Methods to identify unmet needs in rare diseases	36
5.2.2	Challenges related to rare disease research	42
5.3	DISCUSSION AND CONCLUSION	55
6	THE APPLICABILITY OF THE NEED ASSESSMENT FRAMEWORK IN RARE DISEASES	56



6.1	METHODS.....	56
6.2	RESULTS	56
6.2.1	Patient needs	58
6.2.2	Societal needs.....	89
6.2.3	Future needs	105
6.2.4	Transversal dimension: Equity	105
6.3	DISCUSSION AND CONCLUSION	106
7	APPLICABILITY OF THE 4-STEP IMPLEMENTATION MODEL IN THE CONTEXT OF RARE DISEASES	107
7.1	METHODS.....	108
7.2	RESULTS	108
7.2.1	General remarks on the 4-step NEED implementation model.....	111
7.2.2	Step 1: Identification of health conditions with potentially high unmet needs.....	111
7.2.3	Step 2: Prioritisation and selection of health conditions for the NEED assessment exercise.....	116
7.2.4	Step 3: Evidence collection on the criteria of the NEED assessment framework	117
7.2.5	Step 4: Dissemination of NEED results	117
7.3	DISCUSSION AND CONCLUSION	118
8	GENERAL DISCUSSION AND CONCLUSION	119
8.1	SUMMARY OF FINDINGS	119
8.2	STRENGTHS AND LIMITATIONS	121
8.3	FUTURE RESEARCH AND POTENTIAL IMPLICATIONS OF THE STUDY	122
8.4	CONCLUSION.....	124
■	REFERENCES.....	125



LIST OF FIGURES

Figure 1 – The NEED assessment framework	13
Figure 2 – The NEED 4-step implementation model	14
Figure 3 – Visualisation of the methodological approach of the research project.....	18
Figure 4 – Approach of the stakeholder workshop	23
Figure 5 – Flowchart of the grey literature review for the screening of websites	25
Figure 6 – Analysis of stakeholder websites in the EEA and UK on the reporting of a definition for rare diseases	28
Figure 7 – Flowchart of the selection procedure for the scientific literature	31
Figure 8 – Characteristics of stakeholder representatives participating in the workshops.....	33
Figure 9 – Distribution across stakeholder groups of survey completions	34
Figure 10 – Topics covered in research on unmet needs in rare diseases.....	35
Figure 11 – Methodological challenges in rare disease studies	43
Figure 12 – Overview of recruitment strategies obtained from research in rare diseases	46
Figure 13 – The different dimensions, domains, criteria and indicators included in the NEED assessment framework	57
Figure 14 – Overview of the existing and suggested additional patient health needs criteria and indicators relevant for rare diseases	62
Figure 15 – Overview of the existing and suggested additional patient healthcare needs criteria and indicators relevant for rare diseases	70
Figure 16 – Overview of the existing and suggested additional patient social needs criteria and indicators relevant to rare diseases	82
Figure 17 – Overview of the existing and suggested additional societal health needs criteria and indicators relevant to rare diseases	92
Figure 18 – Overview of the existing and suggested additional societal healthcare needs criteria and indicators relevant for rare diseases	98
Figure 19 – Overview of existing and suggested additional societal social needs criteria and indicators relevant for rare diseases	101



Figure 20 – The NEED 4-step implementation model	108
Figure 21 – Stakeholder representatives' recommendations on the open call for proposals.....	113

LIST OF TABLES

Table 1 – Inclusion and exclusion criteria applied in the rapid review.....	20
Table 2 – Overview of prevalence used by different stakeholders when defining a rare disease.	26
Table 3 – Overview of the qualitative criteria used by different stakeholders when defining a rare disease	27
Table 4 – Overview of identified articles including an evaluation of needs in rare diseases.....	32
Table 5 – Example of sources and search engines for literature reviews in identifying unmet needs in rare diseases	36
Table 6 – Overview of databases and registers included in the rapid literature review	38
Table 7 – Overview of selected qualitative research design choices for interviews and focus groups	39
Table 8 – Overview of mixed method approaches in rare disease literature	41
Table 9 – Overview of the different biases that can occur in rare diseases related to the study sample	45
Table 10 – Overview of methodological challenges in rare disease literature	53
Table 11 – Overview of patient needs considered in the NEED assessment framework and (in italic and green) suggested adjustments.....	58
Table 12 – Data sources and methods to assess treatment effectiveness in rare diseases	72
Table 13 – Overview of societal needs criteria, indicators and data collection methods in the NEED assessment framework and suggested adjustments in the context of rare diseases (in italic, and green).....	90
Table 14 – Overview of burden on informal caregivers based on literature	95
Table 15 – Overview of future needs criteria, indicators and data collection methods in the NEED and suggested adjustments in the context of rare diseases (in italic).....	105
Table 16 – Results of the second stakeholder workshop on the NEED 4-step implementation model	109
Table 17 – Stakeholder representatives' most frequent suggestions regarding the minimal information required for the open call for proposals.....	115



LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AADC	Aromatic L-amino Acid Decarboxylase Deficiency
AE-QoL	Angio-Edema Quality of Life Questionnaire
AFQOL	Adult Fabry Quality of Life
AOSD	Adult-Onset Still's Disease
APH	Portuguese Association of Hemophilia
ARG1-D	Arginase 1 Deficiency
AS	Angelman Syndrome / Alstrom Syndrome
BeBOD	Belgian Burden of Disease Study
BIPQ	Brief Illness Perception Questionnaire
BI score	Barthel Index score
CAPS	Cryopyrin-Associated Periodic Syndrome
CARD	Cyprus Alliance for Rare Disorders
CBS	Caregiver Burden Scale
CDG	Congenital Disorders of Glycosylation
CF	Cystic Fibrosis
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMA	Conditional Market Authorization
CMC	Children with Medical Complexity
CPRD	Clinical Practice Research Datalink
CPW	Care Pathway
CSI	Caregiver Strain Index
cTTP	Congenital (Hereditary) Thrombotic Thrombocytopenic Purpura
DT-P	Distress Thermometer for Parents
EC	European Commission
EDS	Ehlers-Danlos syndrome
EEA	European Economic Area



EHR	Electronic Health Records
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERN	European Reference Networks
ESMO	European Society for Medical Oncology
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FOP	Fibrodysplasia Ossificans Progressiva
FMSF	Family Management Style framework
FNAT	Family Needs Assessment Tool
FNRS	Fonds de la Recherche Scientifique
FTEs	Full Time Equivalents
FWO	Fonds Wetenschappelijk Onderzoek
GAS	Goal Attainment Scaling
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HCM	Hypertrophic cardiomyopathy
HCP	Health Care Professionals
HRQoL	Health-related Quality Of Life
HSP	Henoch-Schönlein purpura
HTA	Health Technology Assessment
ICD	International Classification of Diseases
INAMI	Institut national d'assurance maladie-invalidité
ISPOR	Professional Society for Health Economics and Outcomes Research
KCE	Belgian Health Care Knowledge Centre
MCDA	Multi-criteria Decision Analysis



NCCN	National Comprehensive Cancer Network
NCR	The Netherlands Cancer Registry
NEED	Needs Examination, Evaluation and Dissemination
NET	Neuro-Endocrine Tumour
NF-1	Neurofibromatosis type 1
NHS	National Health Service
NIHDI	National Institute for Health and Disability Insurance
OS	Overall Survival
PAG	Patient Advocacy Groups
PNQ	Patient-Need Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
PROMIS	Patient-Reported Outcomes Measurement Information System
PSP	Progressive Supranuclear Palsy
PWH	Patients With Hemophilia
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trials
RD	Rare Disease
R&D	Research and Development
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering
RR	Rapid review
SF-12	12-item Short Form Health Survey
SF-36	36-item Short Form Health Survey
SMA	Spinal Muscular Ataxia



SOC	Standard Of Care
SScQoL	Systemic Sclerosis Quality of Life Questionnaire
SSMG	Société Scientifique de Médecine Générale
ToT	Time on Treatment
UDNI	Undiagnosed Diseases Network International
UHDRS	Unified Huntington's Disease Rating Scale
UK	United Kingdom
UMN	Unmet Medical Need
USA	United States of America
UZ Leuven	Universitair Ziekenhuis Leuven
VAS	Visual Analogue Scale
VNZZ	Vlaams Netwerk Zeldzame Ziekten
VPP	Vlaams Patiëntenplatform
WHO	World Health Organization
WHODAS 2.0	WHO Disability Assessment Schedule
WPAI	Work Productivity and Activity Impairment
WS	Workshop
ZBI	Zarit Burden Interview



GLOSSARY

CONCEPT

DEFINITION

Unmet need

Broad term referring to needs perceived by the patients, society or future generations with an impact on health, healthcare and social life

Unmet health-related needs

Unmet health-related needs cover needs related to health, healthcare, but also non-health(care) needs, which include social or economic aspects.

Unmet patient need

Unmet needs perceived by patients with an impact on patients' health or healthcare condition as well as patients' social context.

Rapid review

A type of knowledge synthesis in which components of the systematic review process are simplified or omitted to produce information in a short period of time.¹

Grey literature review

Literature which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers.²

NEED approach

A specific methodology developed by KCE to identify unmet health-related needs in a variety of health conditions.

NEED 4-step implementation model

The four steps to follow in the NEED approach to identify and assess unmet health-related needs: topic identification, prioritisation, evidence collection, dissemination.

NEED assessment framework

A framework defining dimensions, domains and criteria related to needs, as well as indicators for these criteria and measurement methods to assess the extent to which needs are met.



■ SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Moving from a supply-driven to a needs-driven healthcare system

Good health is a fundamental asset for both individuals and society as a whole. Health systems strive to ensure access to high-quality healthcare with the goal of preserving and promoting good health for its population.³ An important observation made by stakeholders is that the current healthcare system is primarily supply-driven, oriented towards products and treatments, rather than addressing high unmet (health-related) needs as perceived by individual patients or society.⁴ Several factors have contributed to this trend, including advancements in medical technologies and (non-)pharmaceutical developments. New treatments (pharmacological and non-pharmacological) and care pathways are constantly being developed and introduced to the market and/or offered to patients, with a strong emphasis on their market uptake and patient usage, with limited focus on whether this new treatment fulfils the highest needs as perceived by patients.⁵ The consequences of this supply-driven approach can be significant. For instance, it may lead to the overuse of medicines that ultimately are not, marginally or only partly effective in addressing patients' health problems and improving their quality of life. Sometimes, the supply-driven approach might promote interventions that result in negative health outcomes (adverse effects). Such an approach thus leads to suboptimal use of societal resources, and importantly, leaves patients with unaddressed needs.

In recent years, there has been growing recognition that healthcare should be more needs-driven, meaning that care should address individual patient and/or societal needs. The European Commission's (EC) Pharmaceutical Strategy for Europe report in 2020 explicitly addressed this issue by advocating for research priorities to align with the needs of patients and health systems, focusing on the highest unmet medical needs (UMN).⁶

To achieve a more needs-driven healthcare system, it is crucial to have a comprehensive understanding of the **concept of unmet health-related needs**. Unmet health-related needs cover needs related to health, healthcare, but also non-health(care) needs, like social or economic needs.



Hence unmet health-related needs go beyond unmet *medical* needs. At the regulatory level, however, legal texts refer mainly to the concept of unmet *medical* needs instead of unmet *health-related* needs. According to EC regulation (EC726/2004), an UMN refers to a chronically or seriously debilitating condition that is life-threatening and cannot be effectively treated with an authorized medicinal product. Commission Regulation (EC) No. 507/2006 on conditional market authorization (CMA) refers to the concept of UMN as ‘a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected’. The proposed new EU pharmaceutical regulation includes a new definition for the concept UMN. The definition of an unmet medical need in the new proposed regulation reads as follows:

A condition where

(a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;

(b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

The proposed regulation considers orphan medicinal products as addressing a high UMN when they fulfil specific additional requirements such as, aside from ‘having significant benefit’, also ‘bringing exceptional therapeutic advancement’.

The *high UMN definition* reads as follows:

(a) there is no medicinal product authorised in the Union for such condition or where, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement;

(b) the use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

At the national level, the definitions of UMN may be different and are more focused on the treatment reimbursement status. For example, in Belgium, UMN is defined by the law of 7 February 2014⁷ and the Royal Decree of 12 May 2014⁸ as “a severe or life-threatening condition for which no reimbursed alternative treatment is available”.

While at the European level the concept of UMN is used to guide market authorisation, for example to provide conditional market authorisation, at the national level, UMN may determine whether a patient can access a particular treatment. For example in Belgium, the National Institute for Health and Disability Insurance (NIHDI, RIZIV-INAMI) utilizes the concept of UMN in defining a list of indications to give patients early access to treatments not yet authorized at the EU level. It does this by enrolling patient cohorts in compassionate use programs and, in the newly proposed reforms of the reimbursement system, by providing early temporary reimbursement via the early access program.⁹

As a result of the **diverse definitions of UMN and the lack of a definition of unmet health-related needs**, together with the **lack of criteria** that measure unmet health-related needs, **defining and measuring** these at the patient and societal level is a challenging exercise.

1.2 The NEED approach

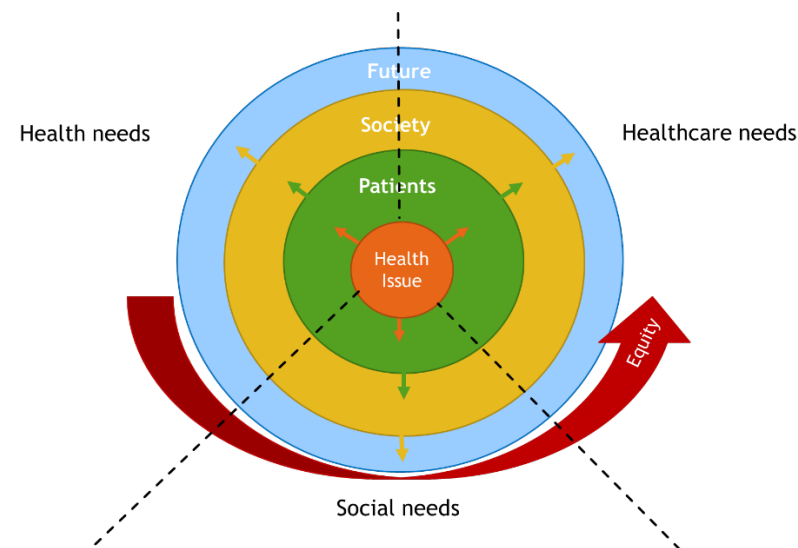
The Belgian Health Care Knowledge Centre (KCE) and Sciensano recently launched the NEED project, whereby NEED means 'Needs Examination, Evaluation, and Dissemination'.^a This project was initiated to prepare for a high-level political European Conference organised in the context of the Belgian Presidency of the Council of the EU (April 2024), which aims to formulate Council conclusions on how to move from a supply-driven to a needs-driven healthcare policy. The ultimate aim of NEED is to set up a European research infrastructure that gathers evidence on unmet health-related needs and to create an evidence database on unmet health-related patient and societal needs across various health conditions to inform further research and other initiatives or activities and hence to support a more needs-driven healthcare policy and innovation system. In particular, NEED aims to support policy decisions on the development, provision and reimbursement of health interventions to ensure that they take into account patients' and society's unmet needs, so that resources are allocated preferentially to the areas of highest need.

In the first phase of the NEED project, KCE and Sciensano designed the overall NEED *approach*. The NEED approach contains two main components, the NEED assessment framework (Figure 1) and a 4-step implementation model (Figure 2).

In the *NEED assessment framework*, unmet needs criteria are defined together with their measurement methods to identify unmet health-related needs in a variety of health conditions, taking equity into account as a principle. The *NEED 4-step implementation model* covers the different steps to follow in order to implement the results from the NEED assessment framework up to the dissemination. These steps are (1) identifying health conditions with potential high unmet needs through (a) databases and (b) a call for proposals, (2) prioritising and selecting health conditions for in-depth unmet needs research, (3) gathering evidence on the unmet health-related needs of the selected health conditions based on the criteria and using the

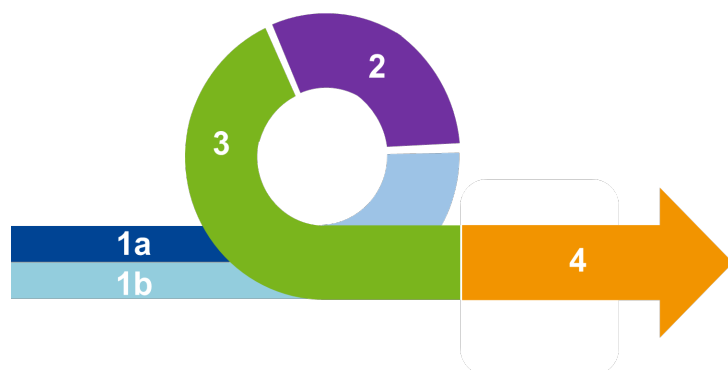
methodologies, and transferring this evidence to a structured evidence database, and (4) disseminating the results.

Figure 1 – The NEED assessment framework



Source: Based on findings from the KCE report 377C1¹⁰

^a NEED; <https://www.health-needs.eu> (last access: 1 February 2024)

**Figure 2 – The NEED 4-step implementation model**

Source: Adapted from KCE report 348 *Identifying patient needs: methodological approach and application* (2022)⁴ (1a) identifying health conditions with potential high unmet needs through databases; (1b) identifying health conditions with potential high unmet needs through a call for proposals, (2) prioritising and selecting health conditions for in-depth unmet needs research, (3) gathering evidence on the unmet health-related needs of the selected health conditions, (4) disseminating the results.

1.3 The NEED Approach as applicable to rare diseases

1.3.1 Rare diseases and challenges in research on rare diseases

Rare diseases are typically health conditions that affect a (very small) group of individuals. These diseases are characterised by wide-ranging very complex health-related needs that extend beyond the purely medical aspects. Such rare health conditions might thereby profoundly affect the individuals themselves, but in many instances also their families or caregivers and future generations.¹¹ Although a single rare disease occurs, by definition, in relatively few patients, multiple rare diseases exist, and taken together represent an important share of the population. The King Baudouin Foundation reports that 6% to 8% of the world's population suffer from a rare disease, and that for Belgium, this would mean more than half a

million people.¹² The Orphanet database currently indexes information on the prevalence or incidence of 6 053 rare diseases.¹³

As a consequence of these small numbers of patients, combined with limited understanding of the disease pathophysiology and progression and a considerable heterogeneity among patients, development of treatments for patients with rare diseases is very challenging. For instance, the small population size can make it more difficult to determine the right dose, because phase 2 clinical trials can often be performed with only a few participants.¹⁴ Moreover, rare disease patients are often in a poor physical condition, making it harder to perform procedures on them.¹⁴ Further, conducting a clinical trial in a population of extremely low numbers of individuals that are often difficult to find or reach, may lead to results that are not statistically sound. Moreover, it is ethically questionable to perform a placebo-controlled clinical trial in a patient population for which no standard treatment exists.¹⁵ In addition, uncertainties to meet regulatory demands or generate commercial impact remain, contributing to a lack of available effective treatments.^{16, 17} This may impact further implementation at the registration or reimbursement level, which leads to a situation where investors refrain from investing in these domains. While some patients suffering from a rare disease may have contacts with a particular patient organisation who can speak up and provide input in studies and hence support the generation of larger samples, patients with the high health-related needs are often invisible, have multiple diagnoses (and hence may not be eligible for a study) or have still not received a diagnosis.

To make regulatory compliance in clinical trials more achievable and to save time and improve resource utilization, adaptive clinical trial designs for rare disease research have been suggested.¹⁸ Both historical data and real-world data can be useful when performing clinical trials is inappropriate, to allow a lower number of participants in clinical trials or as external control when performing a single-arm treatment trial. These two kinds of data can also support submission to regulatory agencies.^{14, 15} Although there are several limitations on the use of external data, regulatory agencies worldwide have recognised their potential in rare diseases.¹⁵ Moreover, the development of a standardised and approved methodology regarding the use of external control is still needed.^{15, 19}



1.3.2 Policies to incentivise research and development in rare diseases

Both in the EU and in the USA, policies aim to incentivize the industry to invest in R&D on rare diseases, as they would otherwise not be commercially viable.²⁰ To this end, the FDA adopted the Orphan Drug Act in 1983 and also the European Union implemented specific policies to compensate for the risk and potential lower return on investment due to small patient populations.^{17, 21} In 1999, the orphan regulation was first adopted, resulting in the possibility of a drug to obtain an orphan designation.²² This initiative has successfully stimulated R&D in orphan diseases resulting in over 230 orphan drugs being registered in the EU in 2023.^{23, 24}

Although these treatments result in significant health gains for particular patient populations, several issues arise on rare disease policies. Firstly, with approximately 7000 rare diseases recognized worldwide, treatment needs remain unmet for the majority of these conditions.²¹ Moreover, a Japanese study has shown that the price of an orphan drug increases as the prevalence of the diseases decreases.²⁵ A third issue is the misuse of the orphan designation, where a company benefits from the orphan designation during R&D, but subsequently adds additional indications for the drug once it is on the market.²¹

Also the reimbursement of orphan drugs poses some challenges. While the orphan drug designation happens on European level, the reimbursement is a matter of the member states. This results in differences in availability of the orphan drugs across member states.²⁶ Furthermore, more than half of the registered orphan drugs are reimbursed in Belgium, while most of them do not meet traditional standards of cost-effectiveness.²⁶ This means that other factors influence the reimbursement decision, like budget impact, price and impact in clinical practice, pricing and reimbursement in other countries and ethical arguments.²⁶

1.3.3 Remaining challenges related to diagnosis and care of patients with rare diseases

As a consequence of the challenges related to research in rare diseases and despite the policies, patients with rare diseases are often overlooked in clinical research and dedicated policy making, leading to a scarcity of treatment options available or affordable for patients. As a result of the low numbers of patients, who often remain unidentified, and the lack of treatments available, medical expertise is scarce or completely absent for these disease areas and needs of rare disease patients therefore remain largely unknown by healthcare professionals.²⁷

A frequently encountered problem in patients with rare diseases is therefore the diagnostic odyssey. Although a growing number of rare disease patients are receiving a diagnosis, a lot of them stay undiagnosed, often their entire lifetime in addition to delayed diagnosis and misdiagnosis.²⁸ An Australian study showed that 38% of the children with a rare disease visit 6 or more different doctors before receiving a diagnosis.²⁹ Another study in the UK reported that 1 in 3 rare disease patients has to wait over 2 years to receive the correct diagnosis.³⁰ In Belgium, the King Baudouin Foundation found that 22% of rare disease patients visited more than 5 physicians before they received a confirmation of the proper diagnosis, 7% visited more than 10 physicians, 44% was misdiagnosed at first and 75% of these misdiagnosed patients received inappropriate and ineffective treatment.³¹ This diagnostic odyssey can lead to medical, physical and mental health burden for the patient. Furthermore, not only patients themselves suffer from the diagnostic odyssey, but also people in their close environment experience financial and emotional burden.²⁸ For example parents from children with undiagnosed diseases not only have to take care of the child, but also have to bear with the consequences of being the “navigator, expert and advocate”.²⁸ In 2014, the Undiagnosed Diseases Network International (UDNI) was developed, aiming to diagnose patients with poorly understood rare diseases.³² In order to obtain a multistakeholder collaboration, clinical, non-clinical, institutional and patient engagement stakeholders are involved in the UDNI.³² Currently almost 50 countries are presented in the UDNI, including Belgium.³³



Even when diagnosed, a study comparing individuals diagnosed with rare and common cancers, showed that those with rare cancers frequently encounter a more complex and uncoordinated care pathway with often inadequate treatments and situations of uncertainty for patients and their informal caregivers looking for care.³⁴

Appointments lack coordination, communication is ineffective and care does not take into account the heterogeneity of patients with rare diseases.³⁵ This can impact the patients' life on all levels, i.e. physical health, financial, mental health and social life.³⁵ Care coordination in rare diseases can be fostered by developing care pathways (CPWs). A CPW is a multidisciplinary plan of care for a specific patient population based on guidelines and/or evidence, translated in concrete steps to be taken.³⁶ But also here, the underlying problem is a lack in scientific evidence as for the majority of rare diseases, scientific uncertainty continues to be the reality and no clinical guidelines are available.³⁷ Moreover, one country cannot tackle all the challenges of all rare diseases on itself, so international collaboration seems crucial. The term "postcode lottery" is used to describe the problem of a patient only being helped if they happen to live in an area where care is available for their rare disease.³⁷

To this end, European Reference Networks (ERNs) were established, which are virtual networks between European HCPs.³⁸ They can provide expertise, ensure economies of scale and provide a quality label for the highest standards in care of rare diseases.³⁷ ERNs are still confronted with some challenges, often caused by their international nature, as it is not easy to find consensus among all the member states.³⁹

Lastly, patient advocacy groups (PAGs) are of utmost importance in rare diseases. Important activities for rare disease PAGs are promoting research on the disease, providing information to patients and their families.⁴⁰ Difficulties facing the PAGs are funding, public awareness, patient engagement and healthcare professional engagement.⁴⁰

The NEED approach was developed with the intention to be potentially applicable to *all* health conditions. However, in view of the above-mentioned complexities related to research, development and care of rare diseases and the need for renewed or additional policy incentives, the NEED approach seeks to ensure inclusivity for such rare disease patients. Therefore, this report aims to assess to what extent the NEED approach is applicable to rare diseases, and how evidence collected on rare diseases according to this approach could be used by decision-makers.



2 RESEARCH QUESTIONS, AIM AND OBJECTIVES

2.1 Research questions

Following the challenges related to conducting studies in a rare disease population, several research questions are formulated.

1. Which **definitions** of 'rare diseases' are currently applied in the healthcare policy domain, across EU countries and relevant European stakeholder organisations (i.e. by regulatory bodies, Health Technology Assessment (HTA) bodies, payer organisations, pharmaceutical industry trade organisations, and patient organisations across Europe and at EU Member State level)?
2. Which **methodological challenges** related to research in rare diseases could impact the assessment of patient and societal needs?
3. What **criteria** are important to consider while assessing unmet health-related needs of patients with rare diseases?
4. What are the points of attention regarding rare diseases when a series of steps are conducted to implement unmet needs research?

2.2 Aim and objectives

To address these research questions, the study has formulated a general aim and four separate sub-objectives. In general, this study aims to contribute to the understanding of and provide practical recommendations on the applicability of the NEED approach to assess unmet health-related needs in the area of rare diseases. It will do this through a comprehensive assessment of rare disease definitions and an assessment of methodological challenges of executing the different steps in the NEED approach and criteria that describe health-related needs specific to rare diseases.

Four sub-objectives are:

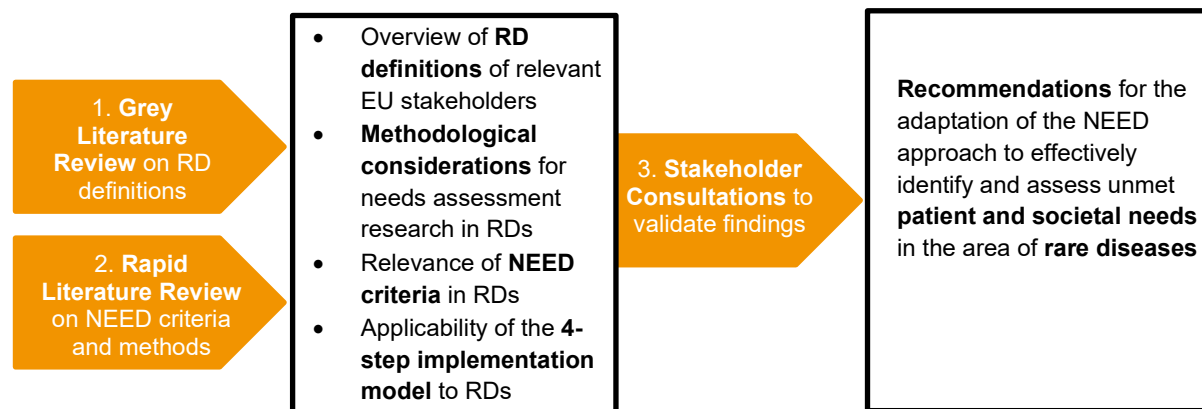
1. To explore the existence and possible variations in **definitions of rare diseases**, as put forward by the relevant stakeholders in the European healthcare policy domain. The study aims to achieve this by mapping and examining the definitions made available by stakeholders in order to identify the complexities and nuances that are used to conceptualise rare diseases.
2. To identify **methodological challenges** related to the methods used in the NEED approach to gather evidence on criteria for rare diseases, evaluate the potential impact of these challenges on the proposed NEED assessment framework, and propose suggestions to adapt or complement the NEED approach to make it more applicable to rare diseases.
3. To identify criteria characteristic to rare diseases that describe patient and societal needs in rare diseases, evaluate the relevance of the existing NEED criteria included in the proposed **NEED assessment framework**, and propose adaptations, additions and/or deletions of criteria to make the NEED assessment framework relevant to rare diseases.
4. To determine whether and how the **NEED 4-step implementation model** should be adapted to effectively address the challenges and specificities of rare diseases.



3 METHODOLOGICAL APPROACH

The study protocol was published in the Open Science Framework database.⁴¹ The study consisted of **three distinct steps** with accompanying methods: (1) a **grey literature review** on rare disease definitions, (2) a **rapid literature review** on the unmet health-related needs in rare diseases and assessment methods and (3) **stakeholder consultations** to validate findings (Figure 3).

Figure 3 – Visualisation of the methodological approach of the research project



RD=Rare Disease, EU=European Union

To investigate the definitions for the concept of rare diseases in the health policy domain across European countries, as formulated by relevant stakeholder organisations, a **grey literature review** was conducted. This grey literature review also tried to identify methodological challenges related to research on rare diseases that could impact the assessment of patient and societal needs (research question 2).

To assess criteria and methods for identifying unmet health-related needs specific to rare diseases, as well as the methodological challenges related to research on rare health conditions that could impact the identification of patient and societal needs in rare diseases, a **rapid review (RR)** was performed, using published scientific literature (research question 2).



Based on the results from the rapid review, the NEED assessment framework and 4-step implementation model were evaluated for their applicability and relevance in the rare disease context, addressing methodological challenges and unmet health-related needs specific to rare diseases (research questions 3 and 4).

To get further input on the NEED approach and its applicability to the context of rare diseases, stakeholders (i.e. regulators, HTA assessors, payers, clinicians, patient organisations, pharmaceutical industry representatives, policy makers) from various relevant organisations were invited for two **stakeholder consultations**. In the first stakeholder consultation, participants were asked to reflect on the appropriateness and feasibility of the criteria and methods included in the NEED assessment framework for rare diseases. They were asked to reflect on whether adaptations were needed (alterations, deletions, additions) in (one of) the criteria and or methods and sources used to assess the criteria (research question 3). In the second stakeholder consultation, participants were asked to share reflections on the appropriateness and feasibility of the NEED 4-step implementation model in the context of rare diseases (research question 4). They were also asked to reflect on whether adaptations were needed (alterations, deletions, additions) in one or more steps of the implementation model.

3.1 Grey literature review

A grey literature review was conducted to answer research questions 1 and 2 (see chapter 2), to identify definitions of rare diseases, along with possible methodological challenges. This review consisted of three main steps.

3.1.1 Search strategy and screening

First, relevant stakeholders that potentially used or developed definitions for rare diseases were identified, their websites were mapped, and subsequently screened for definitions of rare diseases. Websites of the following stakeholder groups were consulted: regulatory agencies, health technology assessment (HTA) bodies and payers, pharmaceutical industry trade organisations, and rare disease patient organisations. HTA bodies and

payers were grouped as for some countries there is no clear separation of the two organisations and these organisations are expected to be aligned in rare disease policy. Websites were searched both at the European level (i.e. websites of European organisations such as the European Medicines Agency (EMA) and EUnetHTA) and at the national Member State level (27 Member States). Furthermore, we searched websites of countries of the European Economic Area (EEA) (Iceland, Liechtenstein, Norway) and of the United Kingdom (total number of countries = 31). An overview of the screened websites is provided in Appendix 1.1. The most comprehensive and significant organisation from each stakeholder group in each country was selected for analysis. Websites that were not available in Dutch or English, were not excluded but translated with DeepL or Google translate.

Firstly, we screened the homepage to verify if there was a direct tab or trajectory for rare diseases. If not, the following search terms were applied to systematically screen the websites: 'rare disease' or 'orphan disease'. The search and screening were performed between May 2023 and August 2023.

3.1.2 Data extraction

Sources (stakeholder websites) were systematically searched and assessed. Data were extracted from the relevant stakeholder websites using a standardised, pre-defined data extraction form in Microsoft Excel (Appendix 1.2). The data extraction form included the stakeholder group (that published the definition on rare diseases), type of organisation, date of publication, the particular location of where the definition was found on the website or in the report or publication, the definition itself and whether any relevant information on methodological challenges related to rare disease research was mentioned.



3.1.3 Data synthesis and analysis

All aggregated results were analysed thematically to identify the different elements used in the definitions and the methodological challenges in defining rare diseases. Data were tabulated and the wording of these definitions as formulated by stakeholders was compared within stakeholder groups as well as between stakeholder groups (i.e. inter- and intra-stakeholder comparison).

3.2 Rapid review

To address research question 2 (see chapter 2), a rapid review was conducted in accordance with the Cochrane guidelines for rapid reviews.⁴² According to these guidelines, a rapid review is “a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting specific methods to produce evidence for stakeholders in a resource-efficient manner”.⁴² Four steps were followed, as described below.

3.2.1 Search strategy design

The search strategy and search strings were designed in collaboration with a trained medical librarian from the KU Leuven Biomedical Libraries (Belgium), in consultation with the KU Leuven research team and the KCE. A comprehensive search was conducted using two scientific databases: PubMed and Embase. Relevant material was also identified by searching the bibliographies of references of included publications (i.e., backward snowballing). Search strings (appendix 2.1.) consisted of a combination of different concepts, taking into account different terminologies relevant for rare diseases, synonyms, MeSH terms (in case of PubMed). Inclusion and exclusion criteria were defined (Table 1).

Table 1 – Inclusion and exclusion criteria applied in the rapid review

Criteria	Inclusion	Exclusion
Article type	All other publication types	Conference abstracts, preprints, clinical trials, editorials
Population	High- and middle-income countries	Low-income countries
Rarity	Focus of the publication is on rare diseases or one specific rare disease	Focus of the publication is not on rare diseases or a specific rare disease
Study type	Focus on methodological studies (primary research), studies that cover methodological aspects related to conducting qualitative or quantitative research in rare diseases (secondary research), which could be in the form of a literature review, meta-analysis, and opinion papers	The research had no methodological nature itself or did not cover any methodological aspects on the broader conduct of research in rare diseases
Outcome	The publication/study conducts an unmet needs assessment or discusses the conduct of needs assessment	No health/care/pharmaceutical needs assessment was conducted or discussed in the publication



3.2.2 Screening and selection

The activity of screening the databases PubMed and Embase was performed by two researchers. This screening of the databases, based on the inclusion and exclusion criteria described in Table 1 involved two phases. In the first phase, 3 218 articles were identified and screened based on title and abstract, up to date until November 2023. In line with the Cochrane rapid review guideline, a joint pilot screening (n= 40) was conducted with two researchers, and ambiguities were discussed with the full team (team members n=5).⁴² This pilot screening was continued by the same researchers but this time blinded and in parallel, the first 5% of the total number of selected articles (n=145) were screened to see whether the researchers would effectively exclude the same articles. A concordance rate of more than 90% was reached after this pilot screening. The remaining articles were screened by one reviewer and controlled by a second researcher. In case of discordance, the two reviewers discussed together until consensus was reached. In the second phase, the selected articles from the first phase were further screened based on their full text. Rayyan software was used to facilitate the process of screening and selection of articles. The data screening and selection process is reported according to the PRISMA guidelines.⁴³

3.2.3 Data extraction

Data from the selected articles were extracted using a predefined data extraction form in Microsoft Excel (appendix 2.4). The data extraction form contained descriptive parameters related to the background parameters of the authors and the articles (e.g. title, year of publication), parameters related to the methods (e.g. primary/meta research) and challenges on applying methods, and parameters related to the criteria to identify unmet health-related needs (e.g. quality of life, mortality, ...). Disease specification and categorization occurred according to the WHO ICD-11 classification system for diseases.⁴⁴ To calibrate the data extraction form and ensure consistency of data extraction in terms of terminology and interpretation during the conduct of the data extraction, a pilot extraction (n=10) was performed by the two researchers and discussed with the full team (team members n=5).

3.2.4 Data synthesis and analysis

Analysis of the data in the Microsoft Excel data extraction sheet was performed using a systematic synthesis approach.⁴² A combined deductive-inductive approach was adopted, whereby predefined themes were searched for, and new themes from the literature itself were included as well. Data were aggregated, grouped, and tabulated.

3.3 Stakeholder consultations

The protocols on the stakeholder consultations were approved by the Ethics Committee Research UZ / KU Leuven (S67909).

3.3.1 Sampling strategy of the stakeholder consultations

Stakeholders from various relevant stakeholder groups were invited to a workshop to reflect on the applicability of the NEED approach to the context of rare diseases. In total, two workshops were organised.

Sampling of participants for the stakeholder consultation workshops was conducted based on the researcher's judgements of participants' ability to provide guidance with regard to the research aim (purposive sampling) and whether invitees were able to participate in one or both the workshop (convenience sampling). To identify suitable participants for the consultations, a systematic approach was followed as illustrated in Figure 4, which involved listing all relevant stakeholder organisations in the field. Consideration was given to factors such as expertise within research or decision making in the field of rare diseases and experience in policy on rare diseases or clinical experience. Stakeholders were categorized into different stakeholder groups: (i) patient organisation, (ii) industry trade organisations, (iii) regulatory authorities & policy makers, (iv) HTA bodies & payers, (v) healthcare providers. From this list, a selection of stakeholders was contacted based on the research teams' selection proposal. Efforts were made to ensure a diverse and balanced representation of the stakeholder groups within each stakeholder workshop (i.e. participation was generally limited to one person per institution). The overall aim was to have 20-30 stakeholders per workshops. Stakeholders were asked to refer to colleagues in case of unavailability, and to propose additional experts from other



organisations that they considered indispensable during this workshop. Sampling was the same for both workshops, all invitees were invited for both workshops.

Prior to the stakeholder workshops, an introductory survey, consisting of open questions with free text response options (appendix 3.1), was developed and distributed to all participating stakeholders. This survey gave the stakeholders the opportunity to reflect on the topics that were to be discussed during the consultations. The surveys were again accessible after the stakeholder workshops for those who wished to provide any additional information.

3.3.2 Data retrieval

In the first stakeholder workshop, participants were asked to reflect on the appropriateness of the criteria, on the measurement methods, and on the data sources included in the NEED assessment framework in the context of rare diseases. To this end, the workshop was structured into two parts: (i) dimensions, domains, criteria and indicators included in the NEED assessment framework and (ii) methodological considerations related to the methods used to assess the indicators. Stakeholders were asked to reflect on the necessity to adapt (i.e. alter, delete or add) any of these.

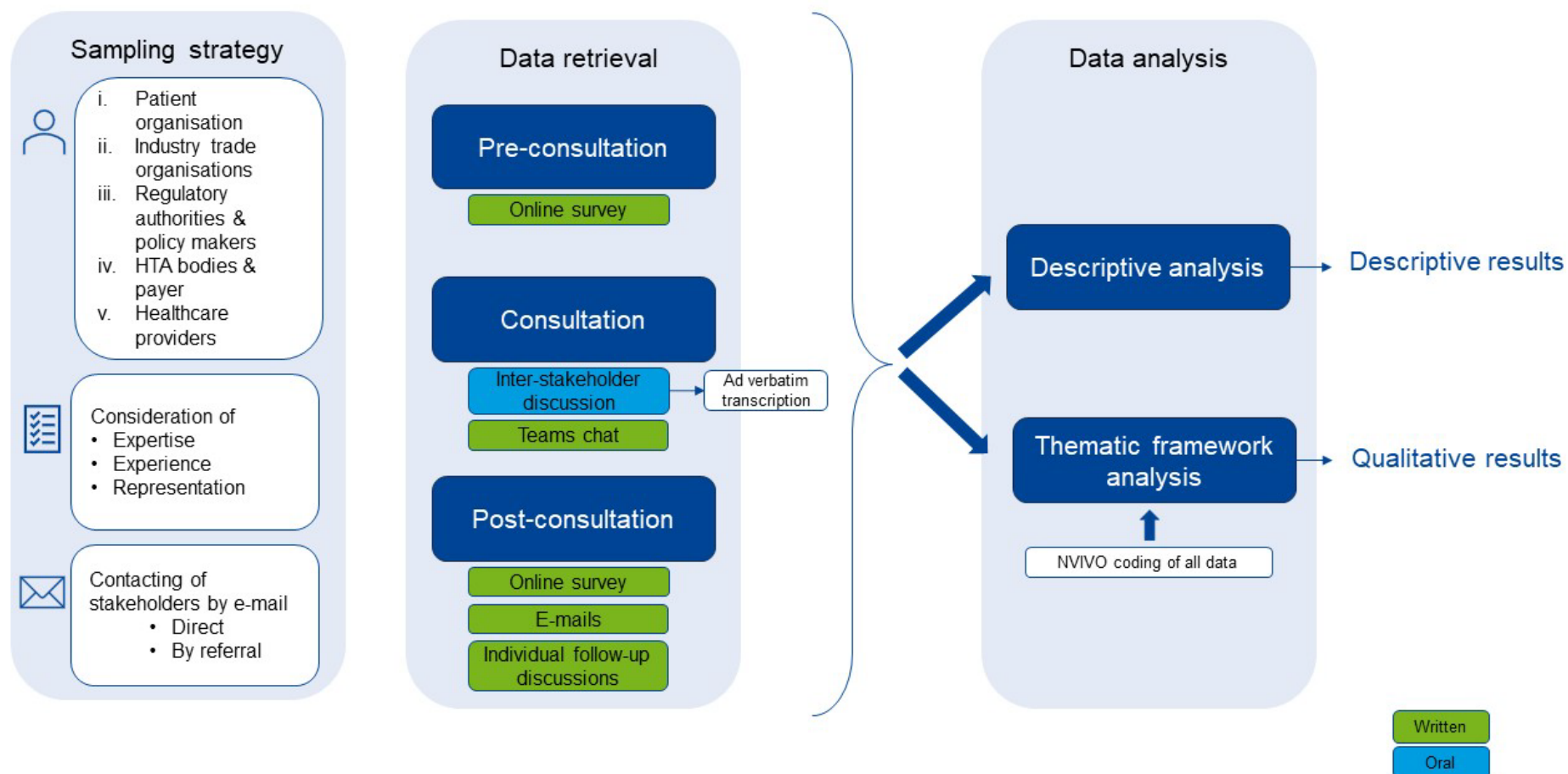
In the second workshop, participants were asked to reflect on the appropriateness and feasibility of the NEED 4-step implementation model for rare diseases. Results of the pre-workshop survey were presented. They were asked to provide feedback on the necessity to adapt (i.e. alter, delete or add) (one of) the steps of the model.

3.3.3 Data analysis

Both a descriptive and a thematic analysis were conducted on all of the data as illustrated in Figure 4. In the descriptive analysis, characteristics of the participating stakeholders were reported.

The thematic framework analysis developed by Lacey & Luff was applied to process all the gathered data.⁴⁵ This analysis encompasses several sequential phases: (i) familiarisation, (ii) establishment of a thematic framework, (iii) coding, (iv) mapping and (v) interpretation. In the first phase or familiarisation-phase, an *ad verbatim* transcript of the stakeholder consultation was generated by one researcher attending the workshop physically, and all other retrieved data were organised. Qualitative input from the surveys, the workshop and written feedback received during and after the workshop were integrated into the analysis as illustrated in Figure 4. The second phase included the establishment of the thematic framework, incorporating both a priori and emerging issues identified during the familiarisation phase. The thematic framework was further refined in subsequent stages, resulting in the code trees (see appendix 3.3). The third phase included the coding phase, where NVIVO software was used to identify specific pieces of data corresponding to distinct themes. In the final phase, the data was investigated for patterns and associations, which are reported in the result section.

Figure 4 – Approach of the stakeholder workshop





4 DEFINITIONS OF RARE DISEASES

Key points

- **There is no consistency among organisations in reporting a definition on rare diseases.**
- **The terms 'rare disease' and 'orphan disease' are often used interchangeably.**
- **When defining a rare disease, reference is frequently made to EC Regulation 141/2000 on orphan drugs.**
- **Disease prevalence and qualitative aspects were the two main elements identified in rare disease definitions**

The aim of this chapter is to explore the existence and possible variations in definitions of rare diseases, as put forward by the relevant stakeholders in the European healthcare policy domain. Four stakeholder groups were identified: HTA bodies and payers, national regulatory authorities or policy makers, pharmaceutical industry trade organisations and patient organisations.

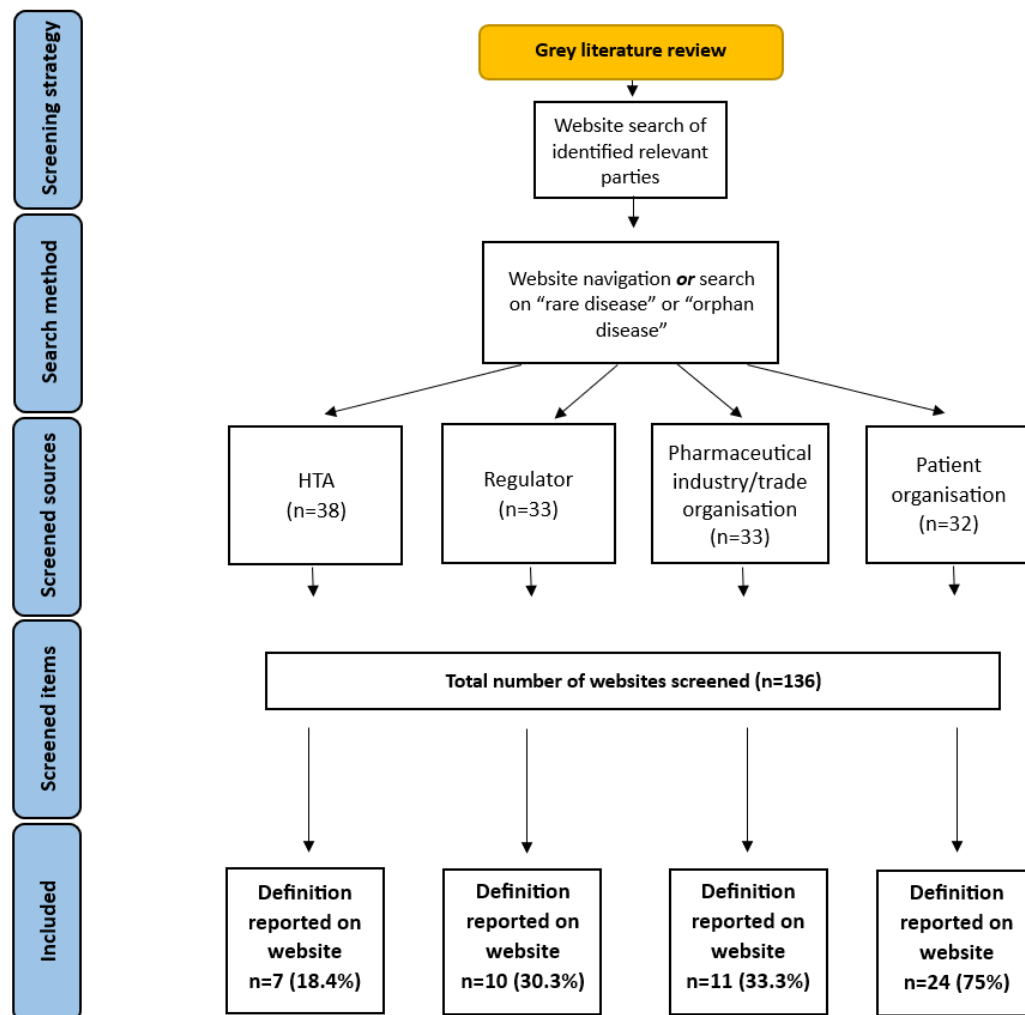
4.1 Methods

A total of 136 websites were screened from the four identified stakeholder groups at European and Member State level (i.e. all countries within the EEA plus the UK, n= 31) (Figure 5). In total, 52 of the 136 websites screened (38.2%) reported a definition on rare diseases.

A table with all the extracted grey literature can be found in appendix 1.2.



Figure 5 – Flowchart of the grey literature review for the screening of websites





4.2 Results

Throughout the included grey literature, stakeholders use the terms 'rare disease' and 'orphan disease' interchangeably while referring to the same or similar definitions. However, Sciensano reported that a disease is considered to be rare in Europe when it affects less than 1 in 2 000 people, while an orphan disease is defined as a disease for which there is no existing treatment. Because rare diseases are so rare, there is often no treatment available for many of them. This entails that a large number of rare diseases are orphan diseases, but a large part of orphan diseases are also rare diseases. However, this does not apply to all of them.⁴⁶ According to the Rare disease special interest group of the Professional Society for Health Economics and Outcomes Research (ISPOR), the absence of a commonly agreed definition of rare diseases lies at the root of the confusion between those two terms.⁴⁷ There are some examples from grey literature where both terms are used e.g., RIZIV – INAMI: "A rare disease or orphan disease is a disease that affects a limited number of people compared to the entire population (1 person in 2 000), listed as a rare disease or orphan disease on the Orphanet website". Stakeholders that did not mention a definition of a rare disease, often did refer to orphan drugs or to the Orphan drug designation (Table 2).

Results of this comparative analysis show differences in the applied rare disease definitions across countries and stakeholder groups. Two main elements were identified to be part of the definition: disease prevalence and qualitative aspects. However, not all stakeholders use both elements in their definition. The included definitions could be divided into four categories based on those elements: (i) a definition solely based on the prevalence of 5 per 10 000, (ii) a definition based on prevalence of 5 per 10 000 and qualitative criteria in line with the definition of an orphan drug in the orphan designation regulation (in some cases supplemented with additional criteria), (iii) a definition based on a prevalence and other qualitative criteria, (iv) a definition solely based on qualitative criteria.

Mostly, when prevalence is part of the definition, it corresponds to a prevalence of no more than 5 in 10 000 people. This is the established EU prevalence threshold.^{48, 49} In three exceptional cases, another prevalence is used e.g. less than 1 in 10 000 people (HTA of Sweden), 1 – 2 in 10 000 people (patient organisation of Denmark) or just low prevalence (HTA of Spain) without specifying any threshold (Table 2).

Table 2 – Overview of prevalence used by different stakeholders when defining a rare disease.

Stakeholder categories	Prevalence
HTA bodies/payers	≤ 5 per 10 000
Spain	Low prevalence
Sweden	< 1 per 10 000
Regulatory authorities	≤ 5 per 10 000
Industry trade organisations	≤ 5 per 10 000
Patient organisations	≤ 5 per 10 000
Denmark	1-2 per 10 000

Countries where investigated definitions diverged from the prevalence of 5 per 10 000 are mentioned under the stakeholder categories.

Besides the prevalence elements, some stakeholders (55.8% of the ones reporting a definition) included additional, qualitative criteria in their definition, which vary significantly. A first part of the included stakeholders consider a rare disease to be 'life-threatening' and 'chronically debilitating', in line with the Regulation (EC) No 141/2000 on orphan medicinal products.⁵⁰ Another part of the stakeholders added some additional elements or used entirely different qualitative criteria in their definition. All these criteria can be divided into four categories: (i) disease characteristics, (ii) knowledge gaps, (iii) disease aetiology and (iv) burden on patients.



Table 3 provides an overview of the different criteria used by stakeholders when defining a rare disease. This overview is exploratory and qualitative in nature.

Table 3 – Overview of the qualitative criteria used by different stakeholders when defining a rare disease

Stakeholder group	Disease characteristics	Knowledge gaps	Disease aetiology	Burden on patients
HTA bodies/payers	Life-threatening Chronically debilitating Progressive	Natural progression unknown		Usually affecting quality of life & daily activities
Regulatory authorities/policy makers	Life-threatening Chronically debilitating	No readily available treatment known		
Industry trade organisations	Life-threatening Chronically debilitating Mostly emerging in childhood		Often genetic in origin	Resulting in a severe burden of illness
Patient organisations	Life-threatening Chronically debilitating Degenerative Progressive Complex Mostly incurable Can impact many body functions	Often no existing effective cures	Major part has a genetic origin and/or is inheritable	Lack of autonomy Causing a lot of pain, stress and suffering

In the figure below (Figure 6), an overview is given of the different elements in the definitions used by the stakeholder groups in all countries. For the majority of organisations no definition could be found on their website (n=76) (59.4% of screened websites, besides the websites that didn't work or were not found) (Figure 6). Moreover, stakeholder groups of countries located in Western or Central Europe were more consistent in reporting a definition of rare diseases compared to stakeholders of Eastern EEA countries. However, this does not apply to patient organisations.



Figure 6 – Analysis of stakeholder websites in the EEA and UK on the reporting of a definition for rare diseases

	Patient organisations	Regulators	HTA & payer	Pharmaceutical industry / trade organisations
EU- level organisations				
Belgium				
Germany				
Italy				
France				
Slovakia				
Croatia				
Finland				
Spain				
Portugal				
Luxembourg				
UK				
Latvia				
Netherlands				
Austria				
Greece				
Bulgaria				
Slovenia				
Norway				
Czech Republic				
Hungary				
Denmark				
Cyprus				
Sweden				
Malta				
Poland				
Ireland				

Estonia	
Iceland	
Liechtenstein	
Romania	
Lithuania	

Some boxes (the ones of the EU-level organisations of regulators and industry

Legend	
	Definition solely based on the prevalence of 5 per 10 000
	Definition based on prevalence of 5 per 10 000 and qualitative criteria in line with the orphan drug designation, in some cases supplemented with additional criteria
	Definition based on a prevalence and other qualitative criteria
	Definition solely based on qualitative criteria
	No definition found
	Website not found/website did not work

trade organisations) represent more than one organisation in a country. The split boxes are the countries for which a website of both an HTA body and a payer has been identified. The left side of the box is always the HTA body, whereas the right side represents the payer.

It is noticeable that patient organisations give a lot of extra explanation about what a rare disease is, compared to other stakeholder groups. In many cases, information on the definition of a rare disease, the challenges associated with rare diseases (e.g. delayed diagnosis, lack of knowledge and diagnostic options) or potential future research avenues could easily be found on patient organisations' homepage and no extensive searches were needed.



4.3 Discussion and conclusion

4.3.1 *Implications of the diversity of definitions among stakeholders*

Several sources confirm the absence of a single globally accepted definition for rare diseases.^{47, 51, 52} In many cases, stakeholders rely on the EC Regulation 141/2000 for orphan drug designation when characterising a rare disease. However, this regulation outlines specific criteria that must be met for a drug to receive orphan designation drug status. Consequently, these criteria may not be universally applicable to all rare diseases. Interchangeability of terminology between an orphan disease and a rare disease is therefore not correct.

However, across different organisations and countries, different terminologies and criteria are used to define rare diseases. Some use only the prevalence, other add qualitative criteria and lean more towards the criteria used in the orphan drug designation. These differences have implications on the European level since incentives are provided for rare diseases with high unmet needs. Therefore, it is important to have an agreement on when a disease is categorised as rare. When the criteria for this categorization vary between different countries, the assessment of the possible unmet needs of a rare disease will turn out differently (e.g. if one country only uses the prevalence, the disease is less likely to be seen as a disease with high unmet needs, than when additional criteria are taken into consideration like chronically debilitating or life-threatening).

4.3.2 *Difficulties of the different elements of rare disease definitions*

Often, the definition is primarily based on the prevalence of the disease.^{47, 51, 52} A study by Nguengang Wakap et al. highlights that performing a thorough methodological analysis to collect robust evidence on what the prevalence in the definition should be, is hard because of several challenges inherent to rare diseases (e.g. scarce epidemiological data, few scientific publications, lack of structured and complete databases).⁵² In that study, the authors did an attempt to perform the first robust evaluation of the

cumulative point prevalence of rare diseases from the Orphanet database, as in a lot of definitions, the term prevalence is used. Our analysis showed that most EEA countries and the UK use the prevalence determined by the European Union.

Furthermore, organisations often report on rare diseases not only using a simple definition, but also giving an extensive explanation which entails that for this analysis it was not always that straightforward to know what criteria organisations consider being part of the actual definition. The qualitative criteria describe what makes a rare disease particularly burdensome, give some extra information or mention what is relevant in the context of for example drug development and reimbursement.

4.3.3 *Limitations*

For the interpretation of the results, three important considerations have to be taken into account. First, only the websites of relevant stakeholders were screened. Regardless of whether a definition was found on the website, other documents or sources from those stakeholders were not explored for definition-related content. In addition, the most comprehensive and significant organization from each stakeholder group in each country was selected for analysis. Consequently, there is no guarantee that the results would remain consistent when considering different organisations or documents or the various fields of application within an organization. In addition, there were instances where websites for certain organisations in specific countries could not be located, preventing their inclusion in the analysis. However, in some cases, more than one organization was included, particularly for the EU-level organisations. It should be made clear that not mentioning a definition or criteria of what a rare disease is on the website, does not imply that the stakeholder does not use it in their decision-making. Lastly, with the translation of some websites there is a risk that small nuances in definitions could be missed.



4.3.4 Conclusion

This analysis points out that definitions still vary across different countries and stakeholders as different definitions of rare diseases were identified. Some definitions only consisted of a prevalence, ≤ 5 per 10 000 seems to be generally accepted with a few exceptions; while other definitions added qualitative criteria, covering the severity of the disease. Agreeing upon a global definition of rare diseases consisting of a clearly defined prevalence and standardized criteria amongst all European countries would be useful. As rare diseases are becoming a public health priority, it is also of importance for policy makers and other stakeholders to put efforts in the harmonization of rare disease definitions.^{47, 52} Additionally, clarity is needed about the difference between rare and orphan diseases.

5 METHODOLOGICAL CHALLENGES

The aim of this chapter is to provide an overview of methods identified from literature to identify and assess unmet needs in rare diseases, as well as to describe challenges reported in literature in the context of the use of such methodologies.

5.1 Methods

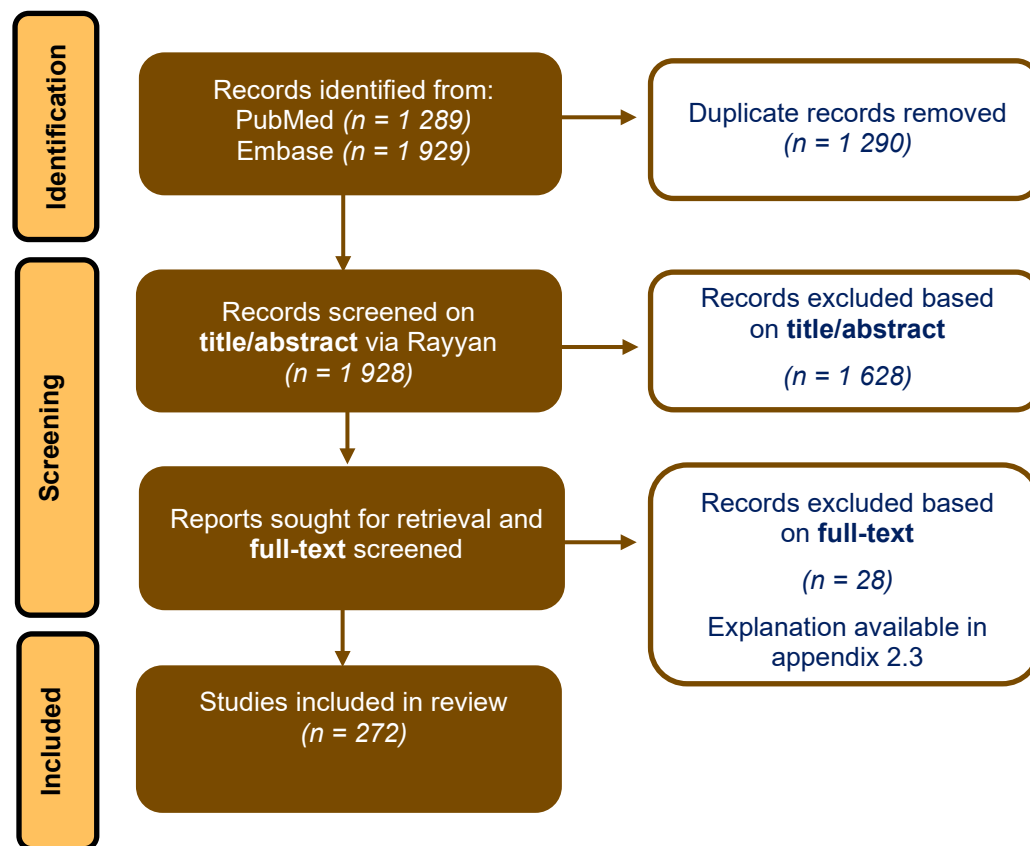
Methods for assessing needs in rare diseases and their associated methodological challenges were investigated using a rapid literature review in combination with stakeholder workshops.

5.1.1 Rapid Literature Review

The PRISMA identification and screening of articles are represented in. Implementing the search string (appendix 2.1) resulted in a total of 3 218 records, including 1 289 records from PubMed and 1 929 records from Embase (Figure 7). After removal of duplicate records ($n=1\ 289$), a total number of 1 929 records remained, which were subsequently screened. A first title-abstract screening resulted in the exclusion of 1 628 articles. After the application of inclusion and exclusion criteria a total of 301 articles remained, and their eligibility was assessed through full-text screening. Out of the 301 full-text screened articles, 28 articles were excluded for varying reasons (e.g. clinical and drug development focus without needs assessment, publication type (e.g. editorials, preprints, clinical trials), out of geographical scope (low-income countries)). This resulted in a total of 272 articles that met the inclusion criteria and were included.



Figure 7 – Flowchart of the selection procedure for the scientific literature





Of all included articles (n=272), most were published after 2014 and half of the studies were conducted in Europe (n=135, 49.6%). Most of the remaining studies were conducted in the United States (n=44, 16.1%) and Australia (n=12, 4.4%). Some studies were conducted across multiple continents (n=30, 11%) and some did not mention the geographical region where the study was conducted (n=35, 12.8%). A range of study designs or methods was applied, including literature reviews (n=31, 11.3%), quantitative methods (n=129, 47.4%), qualitative methods (n=70, 25.7%), mixed methods research (n=28, 10.2%) and other (n=14, 5.1%). From the 272 included records, 56 studies were related to rare diseases in general without focusing on a specific rare disease (n=56, 20.5%). Most articles (n=213, 78.3%) focused on a specific rare disease. Diseases were classified based on the International Classification of Diseases (ICD)-11 system. Most of the included records were related to endocrine, nutritional, and metabolic rare diseases (ICD05, n=62, 22.7%) followed by developmental anomalies (ICD20, n=35, 12.8%) and diseases of the nervous system (ICD08, n=31, 11.3%). Three articles (n=3, 1.1%) did not specify a disease category. A summary of the article characteristics can be found in Table 4.

Table 4 – Overview of identified articles including an evaluation of needs in rare diseases

Study characteristics	Number of included articles (N = 272)
Year of publication	
2006 – 2009	5
2010 – 2013	8
2014 – 2017	33
2018 – 2021	121
2022 – 2023	105
Geographical region	
Europe	135
US	44
Australia	12
Canada	5
Latin-America	3

Asia	8
Inter-continental	30
Unspecified	35
Study design	
Literature review	31
Qualitative methods	70
Quantitative methods	129
Mixed quantitative-qualitative methods	28
Other	14
Disease categorisation (ICD-11)	
Orphan but non-disease specific	56
Disease specific	213
ICD01 - Certain infection diseases	2
ICD02 - Neoplasms	13
ICD03 - Diseases of the blood or blood-forming organs	11
ICD04 - Diseases of the immune system	22
ICD05 - Endocrine, nutritional or metabolic diseases	62
ICD07 - Sleep/wake disorders	1
ICD08 - Diseases of the nervous system	31
ICD09 - Diseases of the visual system	1
ICD11 - Diseases of the circulatory system	3
ICD12 - Diseases of the respiratory system	4
ICD13 - Diseases of the digestive system	4
ICD14 - Diseases of the skin	6
ICD15 - Diseases of the musculoskeletal system or connective tissue	8
ICD16 - Diseases of the genitourinary system	2
ICD18 - Pregnancy, childbirth or the puerperium	1
ICD20 - Development anomalies	35
X - Extension Codes	7
Not specified	3

An overview of the included articles can be found in appendix 2.5.



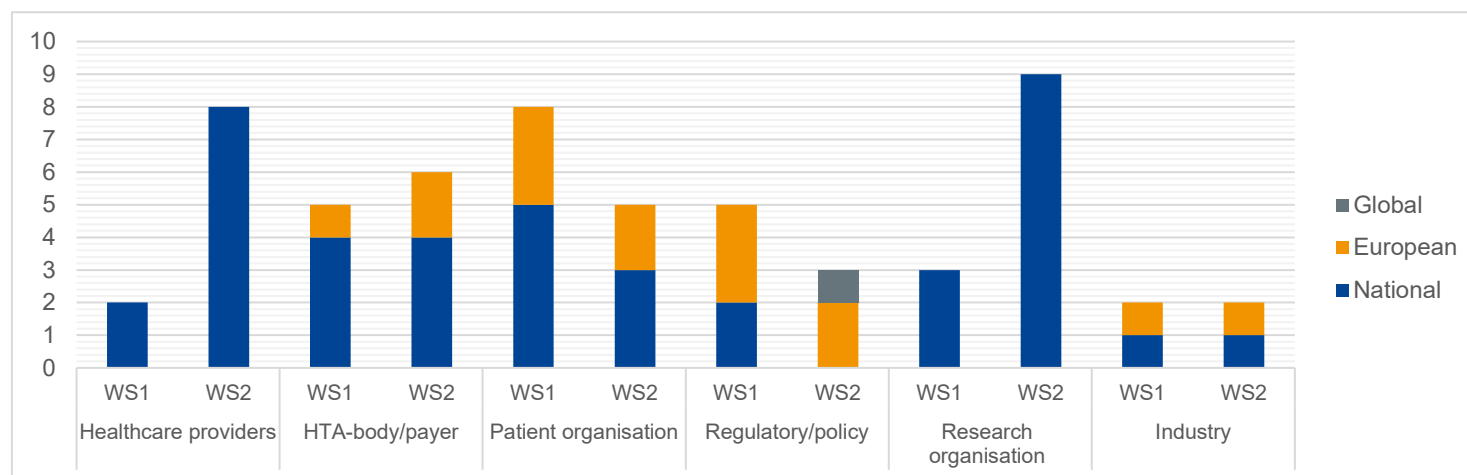
5.1.2 Stakeholder workshops

In the first stakeholder workshop, the NEED framework and its criteria were discussed one by one. In the second stakeholder workshop, the stakeholder representatives were asked about challenges and recommendations on the applicability of the NEED 4-step implementation model on rare diseases. First, stakeholder representatives could reflect on challenges and recommendations on the model in general, whereafter the model was

discussed in a stepwise manner. In total, 72 stakeholder representatives were invited to take part in the stakeholder workshops. Both stakeholder workshops were in a hybrid format (i.e. online and face-to-face).

The distribution of participants across various stakeholder groups is presented in Figure 8 and delineates the (inter)national origin of the organisations they represent.

Figure 8 – Characteristics of stakeholder representatives participating in the workshops

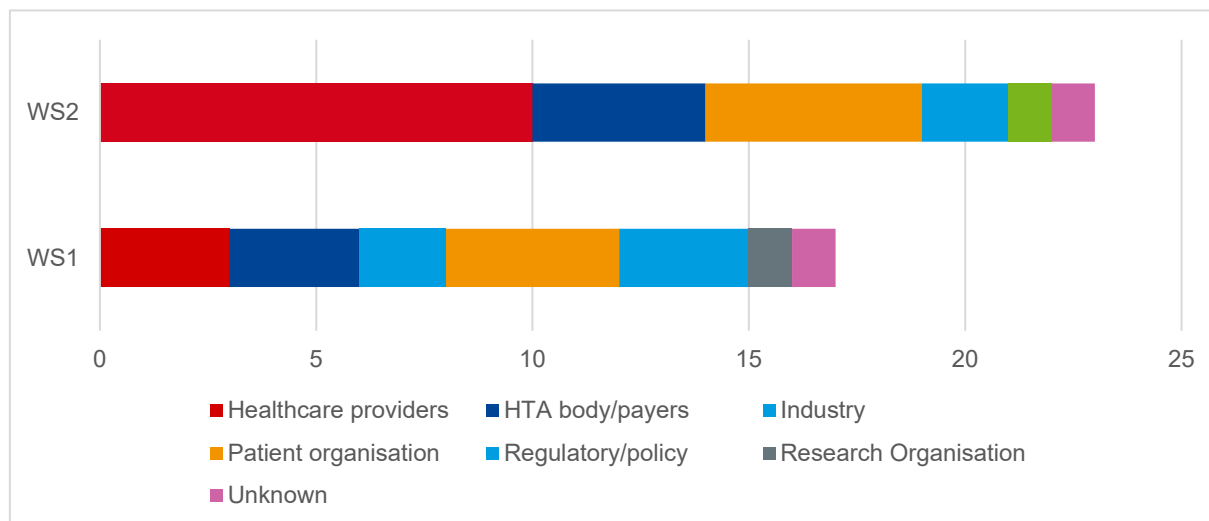


WS = workshop; HTA = health technology assessment

Prior to the workshops, stakeholder representatives were given the possibility to complete a preparatory survey to gauge their initial views on the topics to be discussed in the workshops. Stakeholder representatives who did not complete the survey before the workshop were able to provide written feedback via the survey or by email until one week after the workshop.

Seventeen surveys were completed on the first stakeholder workshop. For the second stakeholder workshop, 23 surveys were completed, 19 of which were completed before and 4 after the stakeholder workshop. Distribution across stakeholder groups is presented in Figure 9.

The surveys and the transcripts of the workshops, as well as chat comments during the workshops, additional stakeholder representative written input received by email following the workshops and one-on-one oral follow-up discussions, were included in the qualitative analysis.

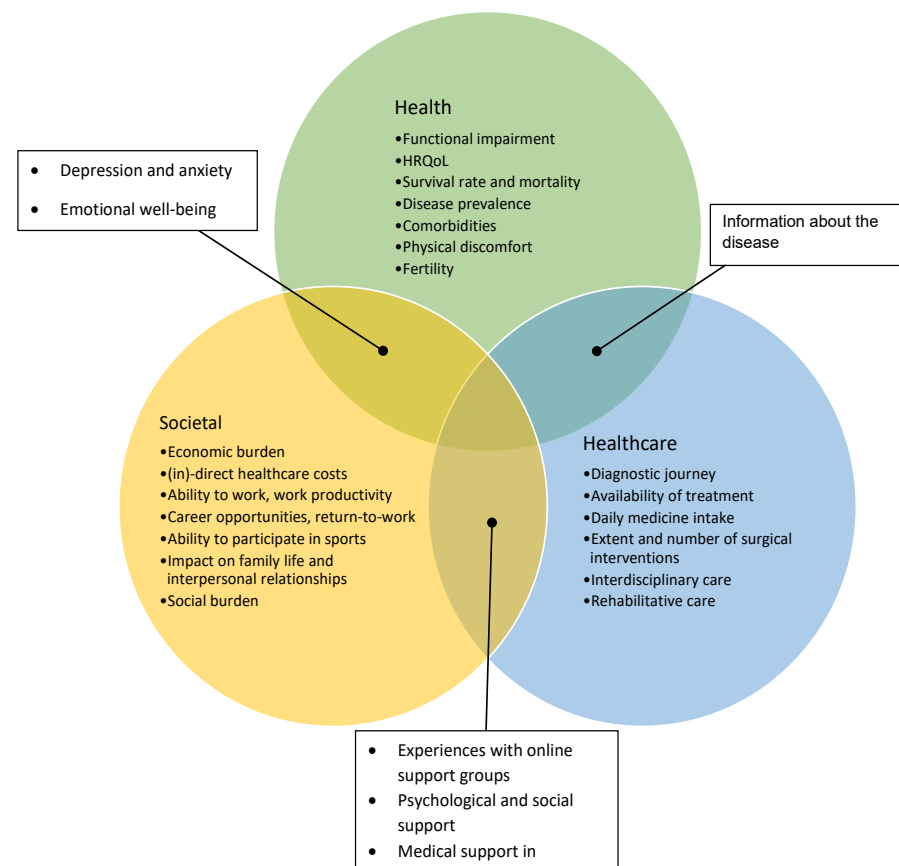
**Figure 9 – Distribution across stakeholder groups of survey completions**

WS = workshop

5.2 Results

The studies of this literature review cover various topics or criteria on unmet needs related to health, healthcare, and social and economic aspects from the patient and societal need dimension. Figure 10 provides an overview of the most dominant topics covered in the literature. An overview of topics studied per type of method can also be found in appendix 2.6.

Figure 10 – Topics covered in research on unmet needs in rare diseases



In this section, we will first present retrieved methods that are used to identify unmet needs in rare diseases (section 5.2.1), followed by challenges and recommendations in rare disease research, related to these methods (section 5.2.2).



5.2.1 Methods to identify unmet needs in rare diseases

Key points

- A variety of qualitative and quantitative methods is applied: literature reviews, database analysis, qualitative studies and survey-based studies
- A total of 70 validated questionnaires, including the generic EuroQoL health-related QoL questionnaires (EQ-5D-3L and EQ-5D-5L), as well as several disease- or symptom-specific questionnaires, such as the Hospital anxiety and depression scale (HADS), are identified
- Methods are often combined in a mixed-method format

The rapid literature review generated an overview of studies applying a variety of methods to identify and measure unmet needs in rare diseases. These methods are grouped in five categories, being (i) literature reviews, (ii) disease-database research, (iii) qualitative research methods, (iv) quantitative methods such as surveys, and (v) mixed-methods research.

5.2.1.1 Literature review

Sources and search engines

Literature reviews made use of diverse sources and search engines. Several reviews focused on scientific databases, others conducted a search of grey literature (Table 5).

Table 5 – Example of sources and search engines for literature reviews in identifying unmet needs in rare diseases

Scientific literature	Clinical trial databases	Systematic review database	Grey literature
• Embase^{53, 54} • Ovid MEDLINE⁵⁵⁻⁵⁷ • ISI Web of Science⁵⁸ • EconLit⁵⁴ • National Health Service (NHS) Economic Evaluation Database⁵⁹ • Cumulative Index to Nursing and Allied Health Literature (CINAHL)⁶⁰ • PsycINFO⁵⁸	• Cochrane Central Register of Controlled Trials⁵⁹	• Cochrane Database of Systematic Reviews⁵⁹	• GreyLit⁶¹ • OpenGrey⁶¹



Literature review design

For rare disease research, a systematic literature review is especially reported as a valuable tool for gaining insights into various critical topics related to rare diseases and allows the identification, evaluation and synthesis of research findings in a structured and reproducible way.^{55, 62-65} Some employ scoping literature reviews to identify and assess unmet needs in rare diseases.⁶⁶ Others adopt mixed methods, such as a combination of systematic review and sequential explanatory narrative synthesis approaches.^{67, 68}

5.2.1.2 Rare disease - database research

Only few rare disease-database research studies were identified in the literature review. Disease databases found were very diverse. The databases are explained more in depth below, classified as i) national disease registries ii) database on electronic health records iii) other databases.

National disease registries

One Italian study combined data from the Italian National Rare Diseases Registry and the National Mortality Database provided by Italy's National Institute of Statistics, to evaluate incidence, survival rate and cause of mortality of patients with primary sclerosing cholangitis.⁶⁹

Another nationally-based study also used a national database, namely the CHES US, to assess the clinical and economic burden of severe haemophilia B in the United States.⁷⁰ The used databases are often generic, but might also be disease-specific, like for cryopyrin-associated periodic syndrome, which has a dedicated registry.^{71 71}

Electronic health records (EHR)

Besides registries, electronic health records at hospital or ambulatory level are a frequently used sources to assess e.g. physical symptoms, medical history, comorbidities, demographics, laboratory results, treatment, and extent and number of surgical interventions.⁷² Such analysis can be retrospective or prospective, collecting real-world data.⁷³ Electronic health records were for instance analysed to study hypertrophic cardiomyopathy (HCM), where from a population based cohort (called CALIBER, linked primary care, hospital and mortality records in England, period 1997–2010), all people diagnosed with HCM were identified and matched by age, sex and general practice with ten randomly selected people without HCM.⁷⁴ Different databases were combined in that study: CALIBER links individual EHR across four data sources, namely primary care data from the Clinical Practice Research Datalink (CPRD), hospital data from the Myocardial Ischaemia National Audit Project disease registry and the Hospital Episodes Statistics and data from the national death registry.⁷⁵ Aside from patient demographic and clinical characteristics at diagnosis, data on treatments (at first and second line), and survival outcomes (overall survival (OS)), data on time on treatment (ToT) analysed by treatment initiation period, and data on cardiac stage and hematologic responses, were collected.⁷³

Other databases

Sometimes, specific databases are used to find information, e.g. in a study to analyse the needs of users contacting a helpline. Here, the electronic database of the national rare disease helpline in Serbia (NORBS) was used as a data source.⁷⁶ Other databases and/or registers used in rare disease literature for any of the step in their needs assessment are listed in Table 6.



Table 6 – Overview of databases and registers included in the rapid literature review

Country	Name register	Rare disease name	Year of launch	Content of the register	Ref
Cyprus	Cyprus Alliance for Rare Disorders (CARD) register	Non-disease specific	2010	Accessibility to care, information needs, infrastructure needs,	77
Global	Cochrane Central Register of Controlled Trials (CENTRAL)	Arginase 1 deficiency (ARG1-D)	1996	QoL, Treatment availability, diagnosis	59, 78
Global	ConnectMPS registry platform	post-stem cell transplant mucopolysaccharidosis type I	2014	QoL, diagnosis, genetics, cost of living, symptoms	79
Europe	The Netherlands Cancer Registry (NCR)	Non-rare disease specific	1989	QoL, treatment availability, accessibility to care, information available, social contacts, diagnosis	80
Norway	TRS National Resource Centre for Rare Disorders	rare, congenital skeletal- and connective tissue disorders, spina bifida and limb deficiency	/	QoL, accessibility to care, information needs	81
UK	Alstrom Syndrome UK register	Alstrom syndrome (AS)	2020	QoL, costs, organisation of care	82
Sweden	Swedish register for rehabilitation medicine (webrehab)	Non-rare disease specific	2007	QoL, accessibility to care, information needs, social impact	83
Australia	Australian Rett Syndrome Database register (AussieRett)	adults with Rett syndrome	1993	QoL, accessibility to care, social impact	84
Portugal	Portuguese Association of Hemophilia (APH) register	Patients with hemophilia (PWH)	2016	QoL, financial impact, impact on work, social impact	85
US	CHESS US+ database	Severe haemophilia	2017	QoL, Financial impact	70
Italy	Italian National Register of Rare Diseases	Primary sclerosing cholangitis	2001	QoL, mortality, incidence	69

QoL= Quality of Life; UK= United Kingdom



5.2.1.3 Qualitative methods

Diverse types of qualitative methods were identified, such as case studies on a patient family or on a particular disease^{86, 87}, a study covering patient diary analysis⁸⁸, studies on an analysis of interactive sessions along a particular rare disease meeting to collect patient data⁸⁹, or workshops (closed or as an open event where anyone is welcome to attend)⁹⁰ and

studies involving ethnography^{b, 91}. One qualitative study included an explorative analysis of online comments and posts made by people with a particular rare disease (rare eosinophil-driven disease) on social media platforms⁹², and developed a search strategy to identify online discussions relating to their disease. Qualitative methods most frequently applied in this literature review are interviews and focus group discussions (Table 7). These two methods are discussed below.

Table 7 – Overview of selected qualitative research design choices for interviews and focus groups

	Interview	Focus group discussions
Medium/Location	• Face-to-face or web-enabled (virtual)⁹³ • At a convenient place⁹⁴	• Face-to-face or web-enabled (virtual)⁹³ • At a convenient place⁹⁴
Participants' profile		• Patients⁹⁵ • Multidisciplinary teams⁷⁷ • HCP⁹⁶ • Informal caregivers (parents)⁹⁵
Design	• One-to-one • Semi-structured using standardised questions⁷¹ or non-structured^{97, 98} • Across different countries⁹⁹ or focus on one country	• One stakeholder group alone¹⁰⁰ or multi-stakeholder • Think tanks¹⁰¹ • World Café methodology¹⁰²

HCP: health care professional

^b a qualitative technique based primarily on patient observation, often complemented by interviews, with detailed

analysis yielding insights into the impact of disease on patients' lives.



Interviews

Interviews were described as a versatile and valuable methodology for studying unmet needs in rare diseases, offering insights into patients' perspectives and experiences.

An interview serves as a means to delve into a wide range of topics relevant to rare diseases, including patients' experiences with online support groups, telephone health services, and the diagnostic process. They can also shed light on current disease management demands, patients' main concerns about disease management, the well-being of affected children, and the impact on family life. Interviews are particularly useful for understanding how patients perceive their illness and associated symptoms, how they cope with these challenges, and how their perceptions and management strategies evolve over time.¹⁰³⁻¹⁰⁵

Focus group discussions

Focus group discussions are also described as a valuable methodology for gaining insights into rare diseases. It might be that additional one-to-one interviews are carried out to complement focus group discussions (as described later).^{77, 95} Some focus groups are organised as 'think tanks'. These are a form of group interviews together with various stakeholders particularly suitable to inquire and elicit debate on previously defined topics among large and heterogeneous stakeholder groups.¹⁰¹ For example, Freitas et al. used for their study on Congenital Disorders of Glycosylation (CDG) a semi-structured interview guide for their think tanks addressing two main topics: 1. What are the challenges experienced by people living with or caring for patients with the rare disease? 2. What strategies can be used to overcome those challenges? Afterwards, when data saturation was reached, core themes were selected and compared between the different think tanks.¹⁰¹ Another approach is to use the 'World Café methodology', which is a consensus-building community participatory tool designed to allow several small-group conversations to take place at separate tables, with participants systematically rotating to different tables approximately every 20 minutes.¹⁰²

5.2.1.4 Surveys

Several studies on rare diseases use surveys to identify unmet needs.

Survey design

Surveys can be designed by research groups or by organisations like the EurordisCare surveys¹⁰⁶, the SURVARC study survey⁸⁰, or the IRDiRC taskforce on patient-centred outcome measures.¹⁰⁷

Such surveys could be organised *online/web-based*¹⁰⁸, using diverse type of *tools* e.g. the EUSurvey tool provided by the European Commission¹⁰⁹ or Google Docs-based survey¹¹⁰ or Lime Survey¹¹¹ or SurveyMonkey platform¹¹¹ or the SmartSurvey platform.¹¹²

Surveys may also include *validated questionnaires* such as the EuroQoL health-related QoL questionnaire EQ-5D-3L or EQ-5D-5L or other specific scales, which are commonly used.¹¹³⁻¹¹⁸ These questionnaires help ensure consistency and reliability in data collection. Besides generic tools, there are some disease-specific questionnaires available, such as the A36 Hemophilia-QoL global mean score.⁸⁵ These disease-specific questionnaires provide validated scores to assess specific aspects of health and quality of life. An overview of disease-specific questionnaires can be found in appendix 2.7.

Surveys were used to collect *qualitative information* as well. In such case, surveys contained open boxes, which allowed participants to provide, in their own words, descriptions of symptoms and complications¹¹⁹ or provide suggestions for important research topics.¹⁰⁹ Such surveys were used to study the unique challenges by people with rare diseases in general (not disease-specific), to explore in participant's own words the nature and frequency of challenges experienced using open ended questions in a cross-sectional survey.¹²⁰ Surveys were also designed as preference surveys, inquiring about most important symptoms and treatment characteristics.^{121, 122}



5.2.1.5 Mixed methods approaches

All methods described in previous sections could theoretically be combined in a mixed method approach or could be organised along other studies like intervention studies.⁷² Some combinations are however more frequent than others. For instance, the combination of literature reviews with qualitative and quantitative methods are common practice.¹²³ This is for example the case in a preference study, wherein first vignettes are designed to be tested out in a discrete choice experiment¹²², as exemplified for Aromatic L-Amino acid decarboxylase deficiency¹²², to generate utilities for use in an economic model. In another study, on Progressive Supranuclear Palsy (PSP), a literature review was combined with qualitative interviews with six PSP experts to map the clinical pathway and identify breakpoints. The pathway was validated by key opinion leaders in seven countries. The approach included self-ethnography, 60-minute telephone interviews and the completion of 7-day smartphone diaries. The smartphone diaries sent daily prompts to participants reminding them to 'Capture a moment' and 'Complete my daily survey'.⁹¹ In one particular study on Congenital (Hereditary) Thrombotic Thrombocytopenic Purpura (cTTP), an initial conceptual model of cTTP symptoms and impacts was derived from a targeted literature review, refined by interviews with expert hematologists, and further refined by concept elicitation telephone interviews with adults with cTTP.¹²⁴

Combining quantitative research methods with complementary qualitative steps has many advantages, particularly in the field of rare diseases where sample sizes tend to be small. Table 8 provides an overview of rationales for identified qualitative-quantitative (mixed) methods combinations.

Table 8 – Overview of mixed method approaches in rare disease literature

Methods	References
Surveys and interviews	125-128
Surveys and focus groups	
First survey, then focus group	90, 102, 127, 129, 130
First focus group, then survey	131, 132
Focus group and survey in parallel	133
Interview and focus group discussion	121, 134-138

Other mixed-methods studies involved **multiple phases**, such as with the ESLAH study, using five different phases: questionnaires, qualitative interviews, participant observations and focus group discussions with relatives, patients and service providers and the evaluation of documentation data.¹³⁹ Another study (in autoimmune diseases) used four phases: expert consultation, scoping review, focus groups and questionnaires.^{130, 140} A study worked on the adaptation of a PROM instrument on self-efficacy in managing medications and treatment in children with medical complexity (CMC), in three different phases: literature review, expert group opinions and interviews.¹⁴¹

Mixed method designs could be used to reveal unmet needs in rare diseases, but they are also useful to develop particular integrated care models in rare diseases.⁹⁸ In addition, such methods are especially useful to *develop disease-specific PROMs or Patient-Need Questionnaire (PNQ)*.¹⁴² Particular steps were taken in terms of content validity, comprehensibility validity, completeness validity, internal consistency, structural validity and reliability. In addition, a supplementary validation was done by comparison of the PNQ with a validated PRO (WHOQOL-BREF). More in particular, due to the disease rarity and the risk of having a sample size too small to detect any significant differences between the test and retest surveys, an additional reliability score was obtained by comparing the PNQ Fabry with a benchmark scale (WHOQOL-BREF). This general quality of life instrument measures physical health, psychological health, social relationships, and environment. This validated, reputable tool has been used



to measure quality of life in a wide variety of medical conditions. It was chosen for its similarity to the PNQ Fabry to help comparative analyses: both have the same 5-Point Likert scale, a “Does not apply to me” option and same number of items. Furthermore, choosing a general health quality of life scale avoided introducing redundant questions and participant boredom. All reliability analyses were performed for both the WHOQOL-BREF and PNQ Fabry.¹⁴²

5.2.2 *Challenges related to rare disease research*

Key points

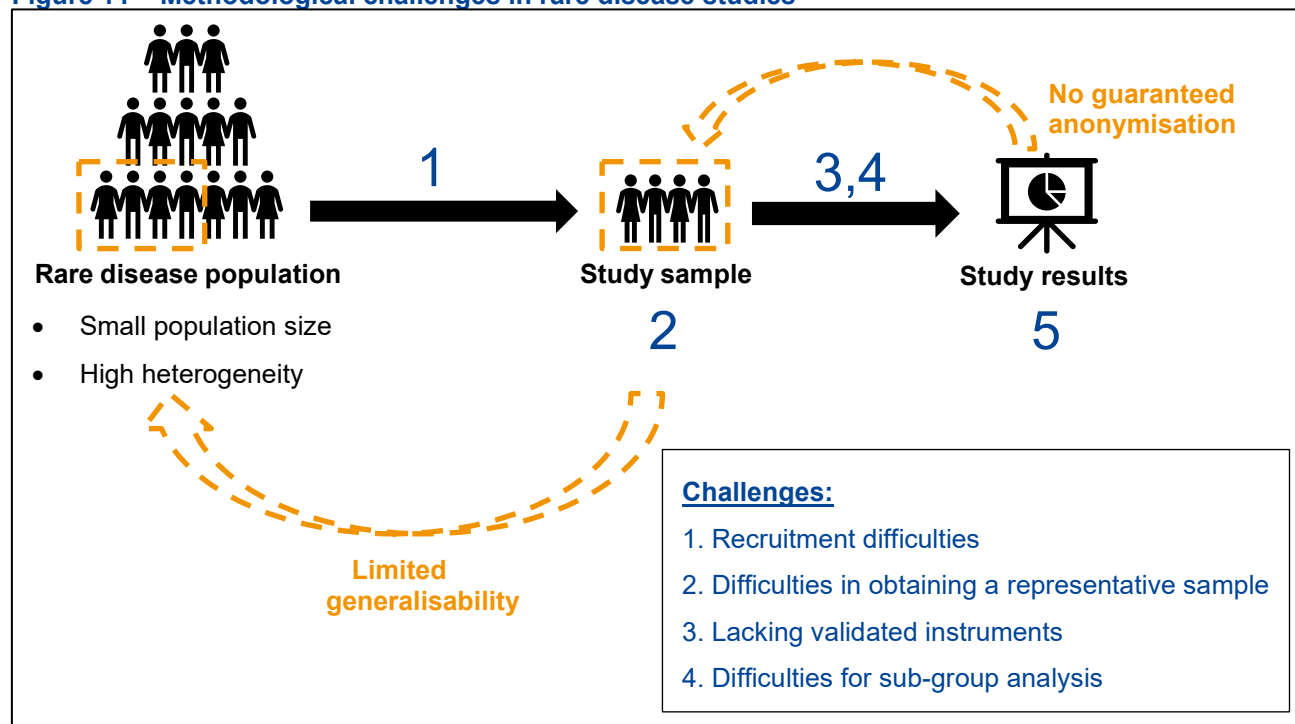
- The small patient population in rare diseases poses difficulties in participant recruitment, leading to limited sample sizes and challenges in generalizability, especially for quantitative methods like patient surveys.
- Challenges arise from the absence of data sources, such as literature and disease-specific registries, for specific indicators. A mixed-method approach is recommended as an effective mitigation strategy, especially for criteria not researched through multiple methods in the NEED assessment framework.
- In cases of extremely rare diseases, considerations for tailoring generic measures may arise. A more qualitative approach, like patient interviews and expert opinions, is proposed as an insightful alternative, particularly when patient numbers are exceptionally low.

Given the rarity of rare diseases, recruitment of large samples sizes is restricted^{137, 143}, therefore the main issues are related to a small sample size.^{72, 98, 125, 140, 144-152} This challenge was also clearly highlighted during the follow-up stakeholder consultation. For both qualitative and quantitative studies, recruiting sufficient participants to generate results of significance is challenging.

Besides the small sample sizes, samples are often heterogeneous^{73, 103, 153-155} and not generalizable or representative of the rare disease population.^{57, 128, 156-161} Figure 11 provides an overview of the main implications of such small and heterogeneous sample in rare disease studies.



Figure 11 – Methodological challenges in rare disease studies



5.2.2.1 Recruitment difficulties

a) Difficulties to find and reach patients

Besides the rarity of the diseases and syndromes,^{74, 162-165} there is also limited access to patient groups,⁹⁶ or no patient organisation/patient advocacy groups exist,^{124, 166} and patients with a particular rare disease are dispersed over different studies and countries.^{93, 130} In addition, the premature mortality rate is very high for certain rare diseases, which hampers the recruitment of patients and in turn affects the

representativeness of the sample.¹⁶⁷ Thus, rare disease patients are often difficult to reach. Recruitment often relies on a limited pool of patients with rare diseases, who also agree to take part in the study.^{99, 168} In the context of paediatric diseases, one study revealed that the limited availability of parents can also be considered challenging when for example, setting-up focus-group discussions.¹⁴⁴

**b) Survey fatigue**

A common challenge with respect to the use of surveys is the general survey fatigue amongst participants. It is a challenge for researchers to ensure that participants remain motivated to participate or to complete a survey until the end if the questionnaire is too extensive.¹⁶⁵ One study in patients with Progressive supranuclear palsy (PSP) indicated that the use of rating scales is time-consuming, whereas simplified versions would be more appropriate.⁹¹ Altogether, a survey that is too long with no honorarium for participants after completing the survey, can contribute to the problem of low response rates.¹⁶⁹ Even though the collection of additional data can help to gain more in-depth information on participants, this may be experienced as burdensome by participants and thus lead to missing data.⁷¹ For example, Amman-Schnell et al., revealed that participants with severe rare chronic neurological disease might not answer the survey at all.¹²³ Moreover, challenges with respect to missing data may also arise when participants indicate the “don’t know” answer options¹⁷⁰ or when they do not fully complete the survey. Furthermore, the fact that answers can be dependent on the physicians’ perception or the memory of patients and that the total number of patients may vary per variable can also result in missing data.¹⁶⁸

c) Biases related to the study sample

Several challenges might result from biases related to the study sample. The chosen recruitment strategy, study design and sample selection can cause different types of biases (Table 9).

**Table 9 – Overview of the different biases that can occur in rare diseases related to the study sample**

Bias	Explanation	Example	References
Selection bias	Selection bias is a consequence of selecting participants by systematically favouring certain individuals over others, as a (direct) result of the study design.	Focusing on one specific outpatient setting or center of expertise responsible for selection and recruitment.	55, 77, 103, 113, 119, 130, 132, 156, 157, 160, 164, 171-186
Referral bias	Referral bias is when some participants are more likely to be referred or selected based on certain characteristics. This can be caused by different approaches for recruitment.	Focusing in the recruitment on collaboration between hospitals and support groups or patients participating in patient organisations leads to limited participation of patients that are less connected and thus a sample not representative for all rare disease patients. Those patients are often more involved, well-informed, more pro-active, more likely to seek help. This may also lead to country selection based on the presence of particular patient organisations.	88, 104, 105, 109, 113, 119, 131, 133, 142, 152, 157, 165, 172, 174, 175, 182, 187-197
(Non)-response bias	A type of bias that occurs when participants are unable or unwilling to respond to a question or when they do not answer questions accurately or truthfully.	Patients suffering from rare diseases are often too young and sick to express themselves.¹³⁹ Parents or informal caregivers are often asked to participate but they are likely to have different perspectives and to under-or overestimate issues^{84, 119, 198, 199} (one of the studies with patients suffering from Cri Du Chat Syndrome showed that parents tend to rate their child's QoL lower than the actual assessment of the child itself.¹⁹⁸) A study on the experience of living with the disease Niemann-Pick type C highlighted that even though participants were open to share their experiences, some aspects were quite emotional and difficult for patients to explain.¹³⁴	80, 85, 95, 117, 150, 187, 200

QoL= Quality of Life

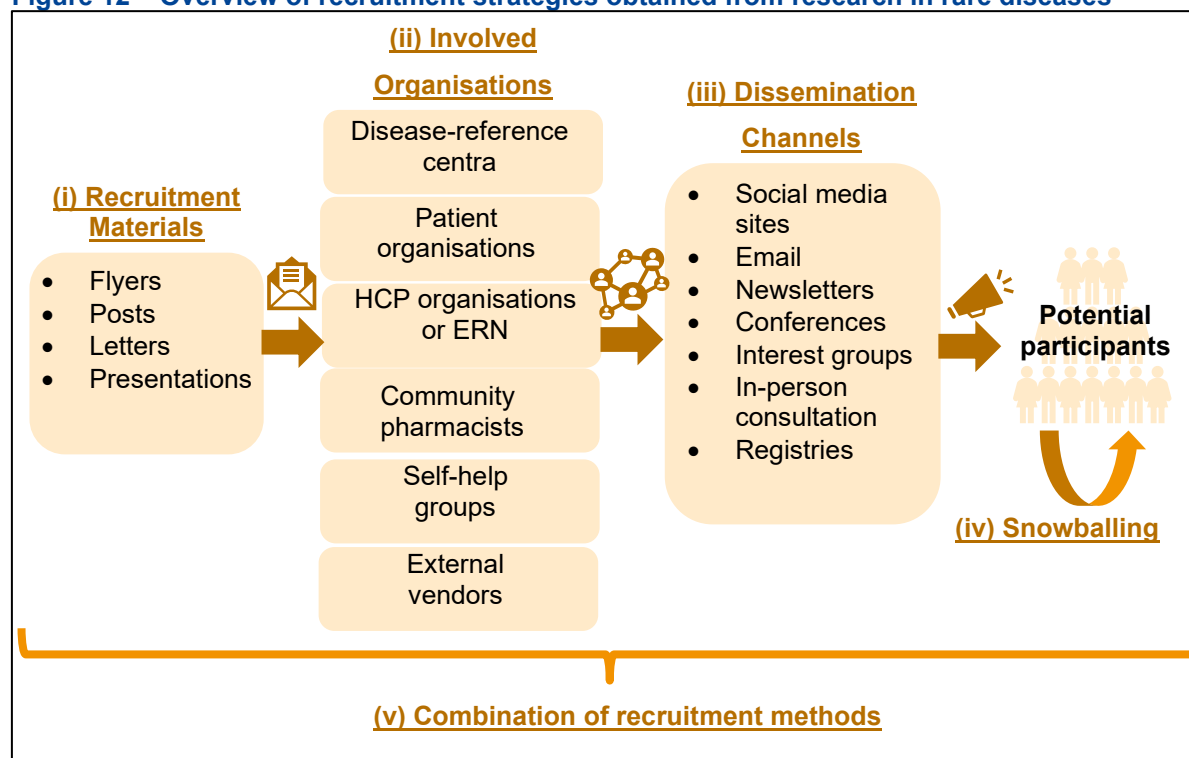


RECOMMENDATIONS

Firstly, to avoid as much as possible survey fatigue, it is required to find a good balance between the collection of necessary and additional data.⁷¹ Herein, it will be important to shorten questionnaires and pick research questions in such a way that there is as little overlap as possible with similar surveys to keep participants motivated.¹⁶⁵

Secondly, various considerations are to be taken in the design of a recruitment strategy, related to (i) used recruitment materials, (ii) involved organisations, (iii) channels to disseminate the materials, (iv) purposive snowballing, and (v) combining recruitment methods. Most recurring approaches are visualised in Figure 12.²²

Figure 12 – Overview of recruitment strategies obtained from research in rare diseases



HCP: health care professional; ERN: European Reference Network



(i) Recruitment Materials: the first step in the recruitment process is the development of the recruitment materials. Materials can be adjusted according to the following steps in the process and hence adjusted to the dissemination channels and intended participants. The exact materials are not frequently explicitly mentioned in the literature. Some studies created flyers to send to clinicians,¹⁶⁶ QR codes,⁹⁰ or in others posters were made available to recruit interviewees.²⁰¹

(ii) Involved Organisations: various organisation can be contacted to disseminate the materials to potential participants, e.g., disease reference centres²⁰¹⁻²⁰³, Individual physicians^{146, 168}, physician organisations or European reference networks (ERN)^{138, 204}, Community pharmacists²⁰⁵, patient organisations^{109, 117, 169, 206}, parents advocacy organisations^{141, 174}, self-help groups and external vendors.¹⁴⁴

(iii) Dissemination channels: the involved organisations can disseminate the materials through various channels. Registries are useful channels to display findings to the wider public in a format that is reproducible and allows subsequent analysis or recruitment of participants.^{79, 80, 121, 178, 207} Newsletters⁹⁷ or patient-oriented social media sites could be useful to identify and recruit participants (e.g. Facebook, LinkedIn, Twitter). A notification about the study can be posted in e.g. disease specific Facebook groups^{74, 114, 131, 158, 174, 178, 208} or published in press releases and short articles.⁹⁷ When primary contacts are available, an invitation can directly be forwarded by e-mail to potential participants^{178, 189, 190} or to known patients, families and advocacy organisations who can be requested to send it further to any potential respondents.¹⁷⁸ However, the challenge with e-mails is that they get lost easily between other e-mails which might lead to a low response rate.²⁰⁵ Other recruitment strategies may involve collaboration with conferences or (online) interest groups²⁰⁹, by e.g. making the questionnaire available during conferences or through their websites.¹⁸⁹ Some recruitment goes via specific days organised for patients with rare diseases¹¹¹, where focus group discussions and interviews can be part of the event.¹²¹ Sometimes, patients are recruited via other projects, for instance when the survey is conducted along a current running or finished project.^{98, 210, 211} In most cases, when persons are selected for an interview based on a previous study, particular selection criteria are applied.¹⁰⁵

(iv) Purposive snowballing: some studies applied purposive snowballing sampling, where researchers select initial participants based on specific criteria and then ask them to refer other eligible individuals.¹¹² This could result in more inclusions in the study to overcome sample issues. Purposive sampling was used to recruit Ehlers-Danlos syndrome (EDS) participants via the Ehlers-Danlos Society International Listserv (a specific mailing software).¹⁹⁷

(v) Combination of recruitment methods: most studies made use of a combination of recruitment methods, like the study on hereditary spastic paraparesis or neurofibromatosis type 1.²¹² In this study, participants were recruited through Frambu Resource Centre for Rare Disorders, one of the national advisory centres for rare disorders in Norway, and the Norwegian patient user associations for NF1 and HSP. Thus, unlike most previous reports about these disorders, the researchers recruited the participants from nonclinical settings.¹⁸⁴ Also in a study on cystic fibrosis (CF), several organisations that serve the CF community are invited for spreading the word about the survey through multiple communication platforms and social media channels.¹⁰² For a study on children with a rare disease, a variety of approaches were used to disseminate the survey to the widest audience possible, including promotion through national and international peak bodies (i.e. patient advocacy groups), paediatric hospitals and genetic departments, and community/support groups.²¹³

5.2.2.2 *Challenge in obtaining a representative sample of the patient population*

Obtaining a representative sample is being complicated by a) high heterogeneity in sample, b) underrepresentation and c) country specific variations.

a) High heterogeneity in sample

The heterogeneity of patients and their symptom experiences are an important challenge to consider.²¹⁴ For example, one study performed a informal caregivers' assessment consisting of a pre-interview ranking activity. Authors revealed that this ranking activity was challenging due to the heterogeneity of symptoms.¹²⁸ In the literature reviews that are available,



there is high variability, heterogeneity and presence of rare subtypes, and an individualised approach is needed.^{106, 154} The lack of large-scale studies for rare diseases is even more problematic when there is such heterogeneity among different subtypes.^{151, 154} The same disease can affect different patients with completely different clinical manifestations, so it is difficult to generalise findings of a few patients.^{215, 216} Moreover, a study specifically on pediatric patients living with a rare disease mentioned the distribution among different age groups and the difficulty to reach a target sample in some age groups.²¹⁷ The disease impact can vary across various ages, especially when considering psychological needs. While similarities exist, subtle variations are present, often attributed to the differing lifestyles and contexts of these age groups.¹²⁴

Specifically in qualitative research, one additional challenge was identified relating to the study sample, which is obtaining data saturation. As a result of the small and heterogenous sample size, in qualitative studies on rare diseases, data saturation might not be reached.¹⁴¹

b) Underrepresentation

Some studies results are not population based¹¹⁶, but focused on one^{103, 138} or only some selected rare diseases groups⁹⁰ or even based on a single or limited subject response per country⁷⁷, with some countries or conditions that can be more represented than others^{122, 168, 175, 192, 218}, or restricted to only Europe^{105, 172} or comprising only or mainly one age category, e.g. adults^{219, 220} or gender.^{55, 100, 141, 160, 182, 221-226} The latter may lead to gender bias.⁵⁵ An additional factor hindering generalisability are situations when the sample mainly consists of one race and/or one specific socio-economic group^{141, 164, 182, 184, 226, 227}. For example, in a qualitative study investigating the impact of caring for an individual with aromatic L-amino acid decarboxylase deficiency (AADC) data saturation was reached, but the data may still not be representative as the sample was predominantly university educated and white.⁹⁹ In addition to this, data generalisability can also be hindered when (i) certain types of specialists that are also involved in patients' care are being disregarded and are not asked about the perceptions of patient disease burden²²⁸ or (ii) patients who already undergo a specific treatment^{229, 230} or have various comorbidities are excluded.¹⁰⁵ Moreover, one particular study raised that challenges regarding data generalisability

may also arise in the context of representing the experiences of newly diagnosed patients, as the majority of study samples include only patients who already have had several years of disease experience.⁹⁸ Furthermore, another study mentioned that by only including patients with an advanced disease stage an underrepresentation of patients with early disease stages occurs.²³¹

c) Country specific variations

Literature is very rarely limited to the Belgian context which makes it difficult to interpret it for policy making at the Belgian level. Moreover, there is a challenge in making a comparison of unmet needs between different countries considering the existing differences between the healthcare systems of different countries^{80, 95, 141, 188, 226, 232, 233} and the provision of supportive care.⁶⁰ For instance, one study that assesses the impact of rare diseases on patients and healthcare systems highlighted that in the US, patients frequently change their healthcare system plans resulting in a lack of continuity of data, making it harder to for example identify original diagnosis dates and the rare disease recognition.¹⁵⁹

RECOMMENDATIONS

This existing heterogeneity is the reason why it is important, according to the stakeholders of the workshop, to get insights of different patients on the impact of the diseases, as their opinions will differ. This makes additional research necessary to explore nuances¹²⁸ and to enrich other findings of earlier studies. Additionally, attempts have to be made to optimize recruitment in order to obtain a sample size as large as possible.

Surveys developed for one country might be adapted to be used in another country. For instance, a survey for spinal muscular ataxia (SMA) was based on a questionnaire developed for a study in the UK and modified to the Canadian context.¹¹⁷ When conducting studies in different countries it is important to take into account the country-specific differences (e.g. patient evaluation, HCP involvement, treatment approaches).⁹¹



5.2.2.3 Lack of validated survey instruments

For rare diseases with a complex and rapidly changing healthcare situation, it is often difficult to measure patients' health status with certain existing instruments.⁵⁸ One questionnaire used in a study in patients with Fabry disease measuring QoL did not include disease-specific information, making it not possible to compare the results within the particular disease types.¹⁶⁹ Another study in cutaneous lupus erythematosus highlighted the fact that QoL questionnaires often lack disease-specific questions.¹⁰⁰ Some of the questionnaires are generic (e.g. the EQ-5D-5L), others are validated for a specific population.¹¹⁷ When non-disease-specific assessments are used, they may not fully capture the nuanced experiences of patients with rare diseases and overlook critical aspects of their health and well-being.¹⁵⁷ However, some questionnaires like the KDQOL-36TM along with the WPAI are not validated but used in a primary hyperoxaluria population, and a scale based on items extracted from a Japanese study needed cross-cultural validation when used for another target population. If used in another context, these questionnaires may be less relevant and not fully capturing the health status of the sample population (e.g. infants and young children).^{117, 169, 229, 234} Furthermore, the EQ-5D is a rough instrument mainly focusing on physical functions, making it less applicable and sensitive to variations in health status in the context of rare diseases as these are characterized by low physical functions.²³⁵ When using this tool in such contexts, where the scores may fall below zero (indicating a status perceives as worse than death), discussing the appropriateness becomes crucial.²³⁵

These findings illustrate that some of the instruments used in the context of rare diseases are too generic and are therefore not adequate to assess the (i) impact of a rare disease on patients^{136, 157} (ii) specific unmet needs of patients with a rare disease⁶⁰ or (iii) symptoms related to the rare disease.²³⁶ It should also be noted that unmeasured variables could affect the generalizability of study results.⁷⁰ Validated questionnaires are not yet available for all types of rare diseases^{178, 182, 237} which emphasizes the need to further develop such instruments.⁶⁰

RECOMMENDATIONS

As most generic (quality of life) instruments are not adequate to assess needs in rare disease contexts, it is suggested to collect more disease- and treatment-specific information in studies on unmet needs in rare diseases, including by means of disease specific instruments.^{9, 182} Pelentsov et al. highlighted several aspects to take into consideration when developing questionnaires, more in particular the importance of understanding potential issues, and to design questionnaires based on literature and clinical experience. Moreover, areas that are not well understood can be further explored via qualitative research with the population of interest.²³⁸ This occurs with mixed-methods designs¹²⁸, for example a quantitative follow up after qualitative studies or vice versa.⁸⁴ Moreover, mixed methods can address internal variations within individual methods, providing a comprehensive approach that not only validates each individual method but also enhances the overall robustness of the research and its findings.⁵⁴ Development and standardisation of disease-specific patient-reported outcomes is recommended.¹⁸²

Some specific scales or validated instruments for rare diseases used in surveys exist and can be found in Appendix 2.7.

5.2.2.4 Difficulties for (subgroup) analysis

In quantitative studies the challenge will be related to getting enough data, between different sub-groups, to allow analyses and obtain statistical power.^{81, 108} When there is a small sample size because patients with rare diseases are e.g. geographically dispersed²³⁹, it can result in an underpowered study.^{93, 164} Such a small sample size can challenge the robustness of the analysed results¹⁶⁹, affect the statistical representativeness of findings and the possibility of correlating results to the sample's characteristics.^{214, 240} A study on Immune Thrombocytopenia mentioned that given the small number of patients included in the study, stating a correlation was impossible.¹⁵⁰ In addition, according to Dermer et al. small sample sizes also prevent researchers from looking at confounding factors.²³⁴ A high participant drop-out rate in some studies²⁴¹ and a common problem of low response percentages on healthcare surveys²⁰⁶ further



complicate this problem.¹⁴² A study measuring the patient experience in rare disorders reported on a challenge of not being able to perform psychometric analysis due to a small sample size, even using special techniques equipped to handle small sample sizes.¹⁵⁵ Having a small sample size in your research limits the ability to make a distinction between different subgroups (e.g. early and late diagnosis)^{120, 134, 157} and to capture sociodemographic data and cultural background of participants, while maintaining anonymity.²⁴² It may be possible that the data of a small sample size study may not capture the overview of important issues for specific rare disease patients.¹⁰⁰ A study investigating psychological well-being in adults with spinal muscular atrophy mentioned the challenge of investigating an understudied subgroup, namely adults with this rare disease, which is limiting for the generalisability of their results.¹⁸⁴ Only limited literature is available.⁶³ Moreover, since the reported studies are conducted with small participant numbers, comparisons of subgroups are limited.^{68, 219} Furthermore, it will not be possible to identify cultural differences when the focus is on one type of participants.²⁴³

RECOMMENDATIONS

For the recommendations of this part reference is made to the recommendations of section 5.2.2. Recruitment difficulties. In addition, attempts can be made to limit the dropout rate of participants by minimising the necessary effort from participants.

5.2.2.5 *Incomplete or unavailable data(sources)*

This category of challenges is related to the sources of the data. A common problem in research on rare diseases is that there is a lack of (scientific) knowledge about rare diseases²⁴⁴⁻²⁴⁷ and a lack of infrastructure for sharing the knowledge. However, the interoperability of those systems and sharing of data and knowledge is crucial to improve the ability to diagnose patients and to foresee in their care.¹⁵⁹ In terms of databases, the challenges are located on two levels: the (un)availability of data(bases) and the quality and usability of the available data.

Unavailability of data

The main challenge with research in rare diseases, highlighted during the stakeholder workshops and reflected in literature, is the unavailability of data in both databases and literature.^{60, 63} For example, a study by Mackay et al. highlighted that there is a lack of data on the QoL for patients diagnosed with Prader-Willi syndrome.⁶² In addition, for most rare diseases there are no disease-specific databases available. The latter was also recognised during the stakeholder consultations, where stakeholders referred to the BeBOD database used in the NEED framework which does not cover all rare diseases but focusses on 38 key diseases.²⁴⁸ In case a database is available, there is still the problem of incompleteness of data, which is also confirmed by the literature.⁶² On top of this, a study by Bell et al., emphasised that certain rare diseases do not even have an ICD-9-CM code and are therefore not included in any rare disease database²⁴⁹, resulting in an underrepresentation of specific rare disease populations. Rare disease patients are often under-recognised and under-estimated in databases which can lead to a lack of recognition of the true situation.¹⁵⁹ In a study with cutaneous T-cell lymphoma patients, purposive sampling was only possible using a local database of people with this disease as there were no (inter)national databases.²³¹ In case there are databases available, the type of data is also of importance. For instance, most adult-onset Still's disease (AOSD) databases solely consist of only retrospective data⁷³, highlighting the lack of prospective data. Also longitudinal data is often not available as several studies on rare diseases identified in the rapid review adopted a cross-sectional study design, only capturing data at a specific point in time. This is a design that leads to particular challenges, since needs and perceptions of patients with rare diseases and the stress of their informal caregivers may evolve throughout the course of the disease.^{177, 234} Also in the context of psychological well-being, needs will transform alongside the evolution of the disease and the progression of time.^{121, 221} With this cross-sectional data, it is not possible to obtain a full picture of patients' needs. Statements about causality cannot be made in these contexts and due to the rarity of the diseases^{156, 177}, there is a paucity of (comparable) data which makes it almost impossible to evaluate an intervention in these contexts.^{250,}



This lack in comparable data is reinforced by a paucity of standard parameters of assessment for certain rare diseases. For the rare disease Angelman syndrome (AS), for instance, there is a lack of consensus on the assessments to measure change in certain aspects of the disease which makes data gathering for this disease challenging.⁶³ Additionally, it contributes to the heterogeneity between articles when performing a systematic review.⁶² Data of studies on rare diseases are also often coming from case reports. In the context of rare diseases, this information is important giving the fact that randomised controlled trials (RCTs) and observational studies with large samples are often not feasible.⁵⁹ Besides that, there is a lack of data on certain topics of rare diseases and on patient needs as a large part of the available rare diseases databases is on the informal caregiver level. There is also a lack of epidemiological studies describing the populations and prevalence of rare diseases.^{239, 252, 253} This makes it difficult to know if the study sample is representative of the general rare disease population.²⁵² A meta-analysis by Wehrli et al. confirmed that the limited number of studies available can be challenging to accurately estimate the between study heterogeneity as well as the extent to which publication bias may occur.¹⁵¹ During the stakeholder consultation, several participants highlighted that the selectivity of journal publication may lead to this bias. In addition, stakeholders emphasized that researchers must be very cautious with interpreting publications that use, for instance, HTA reports as these will not focus on diseases for which there is currently no treatment available. As a result, this can lead to an interpretation bias.

Low quality and usability of data

Lastly, some sources explain that the quality of the evidence available is often low.^{62, 118} This can be explained by the challenging nature of the rare disease field, as mentioned in previous paragraphs. A lot of available data is also outdated. Although literature reviews are believed to be a valuable data source by stakeholders, they cited that a lot of articles are no longer up to date because they are based on past data. Nevertheless, in certain fields there is not as much development as in others so sometimes past data could still be useful.

RECOMMENDATIONS

1. **Combination of databases:** Stakeholders of the workshops suggested to combine several databases in one study, such as the Orphanet database or the National rare disease register, to obtain the full picture. Another suggestion that was mentioned during the stakeholder workshop, going one step further, was to bundle data from existing databases, as proposed by the European platform on rare disease registration that should act as a repository for all registries, and the European Udanet database for medical devices that will soon be available. In order to facilitate this approach, the interoperability of systems and sharing of data and knowledge (open science initiatives) must be improved^{159, 254}, as the current use and dissemination of data is often suboptimal.²³⁹
2. **Broaden the geographical scope:** During the stakeholder consultation, some stakeholders highlighted that in the context of rare disease the scope should be broader than Belgium, in order to obtain sufficient data. Other international examples came up such as the NAVLIN database^c which contains Health technology assessment data from more than 30 countries, and the international horizon

^c NAVLIN database; <https://data.navlin.com/alspc/#/> (last access: 2 February 2024)



scanning initiative. Broadening the geographic scope of data may lead to more data, but also increase heterogeneity in the sample.

3. **Consulting alternative data-sources:** Recommendations and sources of inspirations on the use of databases in the identification of unmet needs in diverse health conditions were highlighted during the second stakeholder consultation: such as (i) the EMA List of orphan designation^d and its FDA counterpart^e, (ii) the European commission community registry of orphan medicinal products^f and (iii) Orphanet^g.
4. To overcome challenges related to missing data (i.e., real-world clinical data), one study performed a used **real-world data** to estimate the disease burden of patients.²⁵⁵
5. Create consensus on and determine **standardised parameters of assessment** for specific rare diseases so that different studies can be compared to each other and the heterogeneity can be reduced.

5.2.2.6 Challenge in anonymization

A study using an Online Bulletin Board (a qualitative research platform) reported a challenge because the study was designed as an anonymous study. As a consequence, sociodemographic and background data was only obtained when this was spontaneously reported by the patient.²⁵⁶ The majority of stakeholders confirmed that complete anonymisation cannot be guaranteed in rare disease research, as there will always be a risk of identification. Nonetheless, one stakeholder pointed to the results of a survey conducted by EURORDIS indicating that rare disease patients are more willing to share their data for research purposes.

RECOMMENDATIONS

Providing patients with thorough information about the potential risks and incorporating this into the informed consent, and thereby making it their individual decision, is of paramount importance. In the table below (Table 10), an overview is given of the challenges related to the methods used to determine unmet health-related needs in rare diseases. Additionally, different criteria measured with those methods are added to get an overview of which challenges are faced when measuring these criteria.

^d EMA List of orphan designation; <https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview> (last access: 2 February 2024)

^e FDA Search Orphan Drug Designations and Approvals: <https://www.accessdata.fda.gov/scripts/opdlisting/ood/> (last access: 2 February 2024)

^f Community Register of orphan medicinal products: https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a (last access: 2 February 2024)

^g Orphanet rare disease: <https://www.orpha.net/consor4.01/www/cgi-bin/Disease.php> (last access: 2 February 2024)



Table 10 – Overview of methodological challenges in rare disease literature

Challenge	Description	Recommendations	Relevant NEED methods	NEED criteria measured with the relevant methods
Recruitment difficulties	RD patients are hard to recruit because of the rarity of their disease.	Find a good balance between the collection of necessary and additional data. Proper design of the recruitment strategy.	Patient survey Patient interview Expert opinion	Impact on general health-related quality of life, Impact on physical health, Impact on psychological health, Impact on autonomy, Effectiveness of treatment, Burden of treatment, Quality of care, Accessibility, Social support, Impact on education, Impact on work, Financial consequences, Antimicrobial resistance, Preventability, Environmental impact of standard of care.
a) <i>Difficulties to find and reach patients</i>	Difficult to reach due to lack of patient organization, geographical dispersion, high premature mortality rate etc.			
b) <i>Survey fatigue</i>	Limited pool of patients, too extensive surveys.			
c) <i>Biases related to the study sample</i>	Selection, referral and (non-)response bias.			
Difficulties in obtaining a representative sample/limited generalisability	Due to the small sample sizes it is difficult to make sure the sample is representative for the RD population and to obtain data saturation.	Get insights of different patients on the impact of the diseases and do additional research to explore nuances and enrich other findings of earlier studies. Optimize recruitment to obtain a sample size When conducting studies in different countries it is important to take into account the country-specific differences.	Patient survey Patient interview	Impact on general health-related quality of life, Impact on physical health, Impact on psychological health, Burden of treatment Quality of care, Accessibility, Social support, Impact on education, Impact on work, Financial consequences, Impact on autonomy.
a) <i>High heterogeneity of the study sample</i>	There is high variability, heterogeneity and presence of rare subtypes. The same disease can have other clinical manifestations in different patients.			
b) <i>Underrepresentation</i>	Some study results are not population based but focused on one or only some selected groups (one country/geographical region, race, socio-economic group, age category, gender).			



c) Country specific differences	There is a challenge in making a comparison of unmet needs between different countries considering the existing differences between the healthcare systems of different countries and the provision of supportive care.			
Lacking validated instruments	Some of the instruments used in the context of rare diseases are too generic and are therefore not adequate to assess the (i) impact of a RD on patients, (ii) specific unmet needs of patients with a RD, (iii) symptoms related to the RD.	Collect more disease- and treatment-specific information in studies on unmet needs in rare diseases, including by means of disease specific instruments and use a mixed-methods study design.	Patient survey Patient interview Literature review	Impact on general health-related quality of life, Impact on physical health, Impact on psychological health, Burden of treatment, Quality of care, Accessibility, Social support, Impact on education, Impact on work, Financial consequences, Impact on autonomy, Burden on informal caregivers.
Difficulties for sub-group analysis	Getting enough data between different sub-groups, to allow analyses and obtain statistical power.	See recommendations for small sample size. In addition, attempts can be made to limit the drop out rate of participants by minimising the necessary effort from participants.	Patient survey Literature review	Impact on general health-related quality of life, Impact on physical health, Impact on psychological health, Burden of treatment, Quality of care, Accessibility, Social support, Impact on education, Impact on work, Impact on autonomy, Burden on informal caregivers
Incomplete or unavailable data(sources)	Lack of (scientific) knowledge of rare diseases and lack of infrastructure for sharing the knowledge.	Combination of databases, broadening of the geographical scope, consulting alternative data sources, a simulation approach with the use of real-world data, create consensus on and determine standardized parameters of assessment for specific rare diseases.	Database analysis Literature review	Impact on general health-related quality of life, Financial consequences, Impact on mortality, Frequency, Antimicrobial resistance, Preventability, Burden on informal caregivers, Value for money of standard of care, Productivity losses, Burden of disease, Economic burden.
a) Unavailability of data	Unavailability of data for rare diseases in both databases and literature and a lack of standardized assessment parameters to measure change in certain aspects of rare diseases which makes data gathering challenging.			
b) Low quality and usability of the available data	Quality of the evidence available is often low.			



No guaranteed anonymisation	Complete anonymisation cannot be guaranteed in rare disease research, as there will always be a risk of identification.	Providing patients with thorough information about the potential risks and incorporating this into the informed consent, and thereby making it their individual decision.	Patient survey Patient interview Expert opinion	Impact on general health-related quality of life, Impact on physical health, Impact on psychological health, Burden of treatment, Quality of care, Accessibility, Social support, Impact on education, Impact on work, Financial consequences, Impact on autonomy Effectiveness of treatment, Antimicrobial resistance, Preventability, Environmental impact of standard of care.
------------------------------------	---	---	---	---

5.3 Discussion and conclusion

Unmet health-related needs in rare diseases have been studied in diverse disease contexts using a variety of methods (surveys, qualitative methods, database and registry analyses, literature reviews). Often a combination of methods is adopted as a strategy to mitigate challenges related to each individual method applied in the context of research on rare diseases.

Most methodological challenges relate to issues in study design, instrument design or study sample and data sources. The majority of challenges in the context of rare diseases arise from the inherent characteristic of a disease being rare and occurring in a small population leading to difficulties in recruitment of rare disease patients. Together with the broad heterogeneity between rare diseases and within a rare disease, this leads to challenges concerning generalisability of data and statistical power, which is a particular problem for quantitative methods. Qualitative methods are therefore potentially more suitable for these small rare disease populations. Other methodological challenges in research on rare diseases relate to data sources, which are often absent or scarce and of low quality.

Recommendations to mitigate methodological challenges include strategies to complete databases with data from patients suffering from rare diseases (preferably at European level, but also at national level), co-creation of methodological approaches together with patients, fostering awareness of researchers on the specificities of rare disease patient populations, generation of disease-specific and validated instruments to collect data and considering diverse types of recruitment strategies when conducting studies on unmet needs.

The majority of studies from this rapid review demonstrated that patient-centered research strategies are key to identify and assess unmet health-related needs in patients with rare diseases.



6 THE APPLICABILITY OF THE NEED ASSESSMENT FRAMEWORK IN RARE DISEASES

Rare diseases have been described to be associated with wide-ranging health-related needs that extend beyond purely medical aspects (such as diagnosis, pharmaceutical intervention, or clinical care) to other aspects, such as psychosocial aspects. Rare diseases profoundly affect individuals, their families and society across the health, healthcare, and social dimensions.¹¹ Figure 13 presents these different dimensions as included in the NEED assessment framework.¹⁰ Within each dimension the framework identifies a variety of domains, which in turn include diverse criteria which assess health-related needs that matter to patients, society, or future generations. To do this, each criterion uses one or more indicators that measure to what extent the needs criteria are met or unmet.

This chapter aims to identify and describe the dimensions, domains, criteria and indicators from the NEED assessment framework that are relevant to assess unmet health-related needs associated with rare diseases. Recommendations are also formulated to adapt the NEED assessment framework, making it more applicable and relevant to the specific patient and societal needs in rare diseases.

Box 1 – Building blocks of the NEED framework

- Dimensions: relate to the perspectives taken to identify and measure needs: patient, societal, or future (with equity as a transversal dimension).
- Domains: relate to the type of health-related need: health, healthcare, or social.
- Criteria: represent the different needs by domain and within each dimension.

- Indicators: assess to what extent health-related needs identified by the criteria are met or unmet.

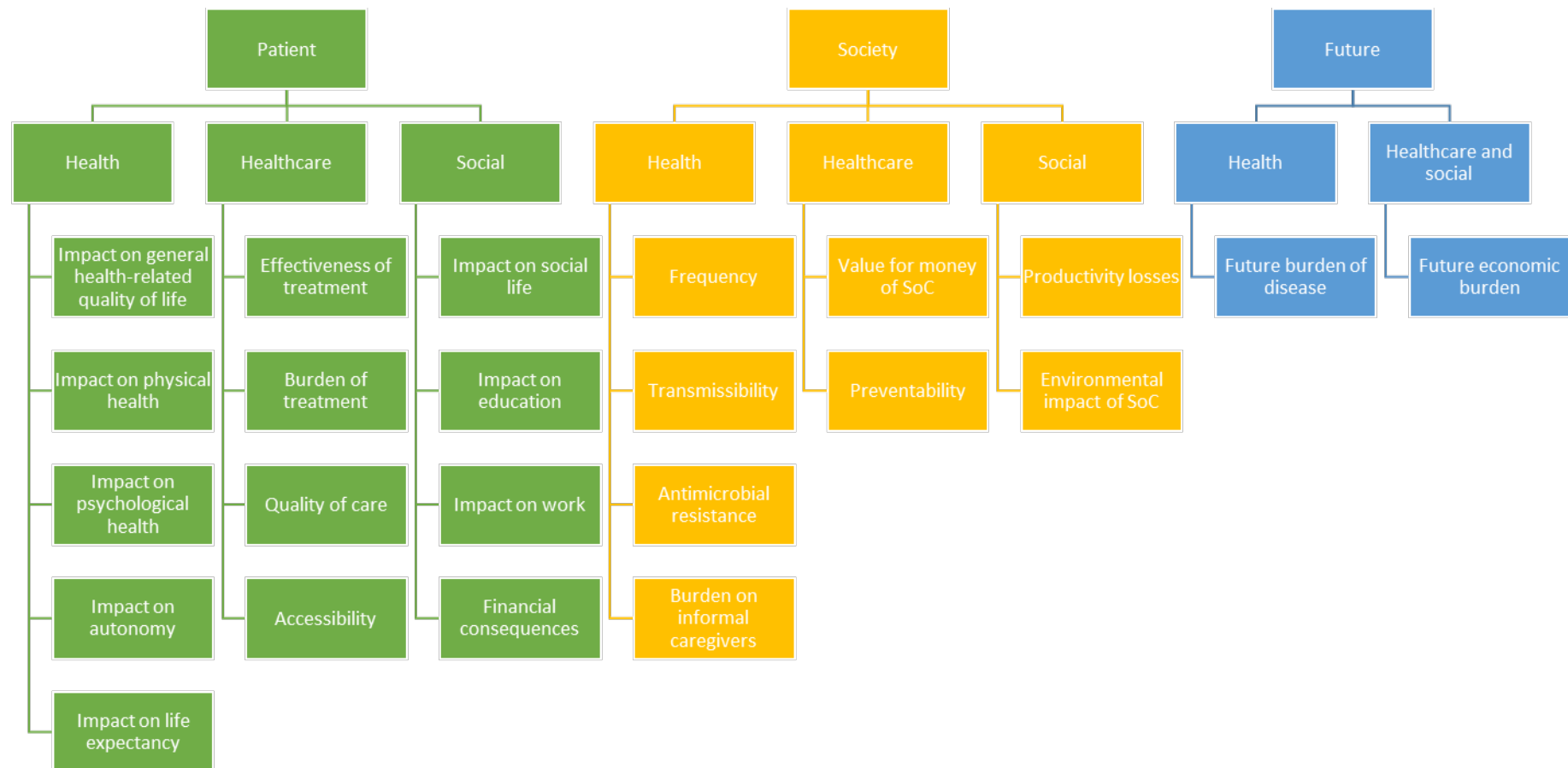
6.1 Methods

The methods used to address the aim of this chapter are a rapid literature review in combination with qualitative stakeholder workshops. Information on the methods and descriptive results for the rapid literature review (i.e. countries covered, disease areas) and stakeholder workshops (i.e. stakeholder groups) were described previously in chapter 5.

For each criterion, we summarised the findings from the literature review and stakeholder workshops related to the corresponding indicators and measurement or data collection methods. Suggestions are also made on how to adjust the criteria, indicators and measurement or data collection methods in the NEED assessment framework for them to be more relevant in the context of rare diseases.

6.2 Results

The results section is structured according to the different dimensions, domains, criteria and indicators of the NEED assessment framework (Figure 13). For each dimension, we provided an overview of the indicators and methods used in the literature to assess the needs in the context of that dimension. For each domain, a box with key points summarises findings and recommendations which can be useful for the NEED framework in the context of rare diseases. These key points are described in more detail further in the text. For each criterion, the following results are reported: i) a summary of the findings with respect to that criterion and its respective indicators, ii) the methods that can be used to assess the indicators, and iii) the key points and recommendations for adapting the NEED assessment framework to rare diseases based upon the literature and workshops.

**Figure 13 – The different dimensions, domains, criteria and indicators included in the NEED assessment framework**

SOC: Standard of care



6.2.1 Patient needs

The first dimension of the NEED assessment framework is “patient needs”. This dimension is then further divided into the following domains: (1) health, (2) healthcare, and (3) social needs. Each of these contain various criteria and indicators to identify them. Table 11 provides an overview of the (sub-)criteria, indicators and the proposed methods to gather evidence on these criteria in the general NEED framework, together with suggested additions, some of which might be applicable for the general framework, while others may be rare-disease specific.

Table 11 – Overview of patient needs considered in the NEED assessment framework and (in italic and green) suggested adjustments

Criterion	Indicator	Data collection method*	Suggestion applicable to general or rare-disease framework
Domain: Health needs			
Impact on general health-related quality of life	Years of life lived with disability (per case)	Database analysis	
	EQ-5D-5L average score	Patient survey	
	Associated comorbidities	Literature review	
	<i>Unpredictability</i>	<i>Patient survey + interviews</i>	<i>General framework</i>
Impact on physical health	Experienced burden of physical symptoms related to the health issue	Patient survey + interview	
	Pain/discomfort before vs today	Patient survey	
Impact on psychological health	Experienced burden of psychological symptoms related to the health issue	Patient survey + interview	
	Anxiety/depression before vs today	Patient survey	
	<i>Self-esteem before vs today</i>	<i>Patient survey</i>	<i>General framework</i>
Impact on autonomy	Mobility before vs today	Patient survey	
	Self-care before vs today	Patient survey	



	Usual activities before vs today	Patient survey	
Impact on life expectancy	Years of life lost (per death)	Database analysis	
<i>Impact on reproductive health</i>	<i>Reproductive health needs</i>	<i>Patient survey + literature review</i>	General framework
Domain: Healthcare needs			
Effectiveness of treatment	Treatment effectiveness	Expert opinion, <i>patient survey</i>	
Burden of treatment	Experienced burden of treatment	Patient survey + interview	
	Experienced burden of side-effects of treatment	Patient survey + interview	
	<i>Treatment adherence</i>	<i>Patient survey</i>	General framework
Quality of care	Experience with the organisation of care	Patient survey + interview	
	Quantity of information	Patient survey + interview	
	Clarity of information	Patient survey + interview	
	Involvement of patients in treatment choice	Patient survey + interview	
	Diagnostic timing	Patient survey + interview	
	<i>Availability of diagnostic methods</i>	<i>Expert opinion</i>	Rare-disease framework
Accessibility	Treatment availability	Expert opinion	
	Forgone care	Patient survey + interview	
	<i>Waiting time for medical appointment</i>	<i>Patient survey + interview</i>	Rare-disease framework



	<i>Distance to healthcare centre</i>	<i>Patient survey + interview</i>	<i>Rare-disease framework</i>
<i>Research needs</i>	<i>Availability of research and information</i>	<i>Expert opinion</i>	<i>Rare-disease framework</i>
	<i>Existence of clinical practice guidelines</i>	<i>Expert opinion + database analysis</i>	<i>General framework</i>
<u>Domain: Social needs</u>			
Impact on social life	Social support needs	Patient survey + interview	
	<i>Social connection needs</i>	<i>Patient survey + interview</i>	<i>General framework</i>
Impact on education	Years of education lost	Patient survey + interview	
Impact on work	Changes in working conditions	Patient survey + interview	
Financial consequences	Average out-of-pocket healthcare costs per patient	Database analysis, Patient interview	
	Average non-healthcare costs per patient	Patient interview	
<i>Stigma</i>	<i>Stigma</i>	<i>Patient survey + interview</i>	<i>General framework</i>

**It is important to note that literature review as a data collection method is applicable to all indicators. HCP: healthcare professionals.*

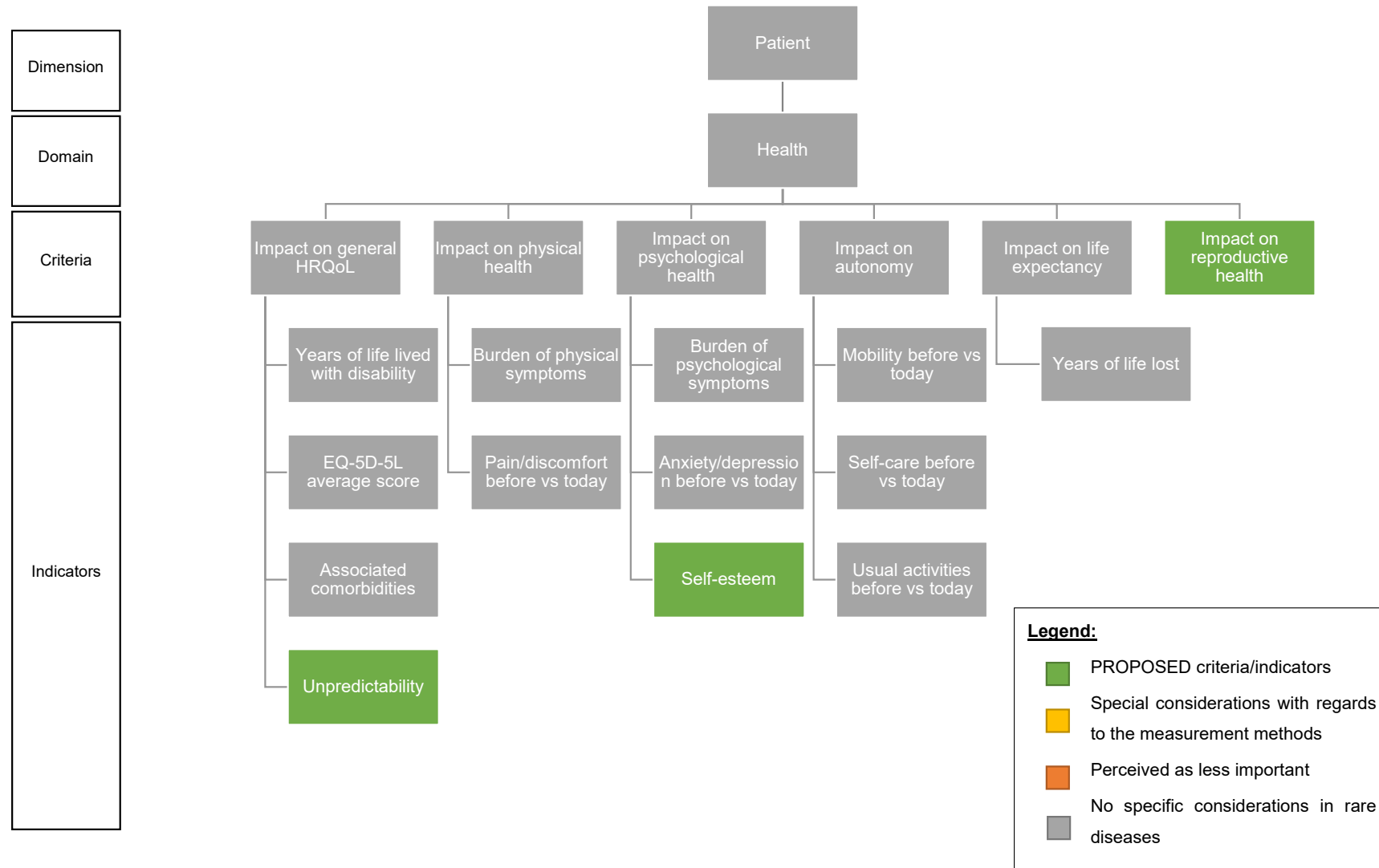


6.2.1.1 *Health needs*

Key Points

- **The invisible toll on the psychological level, such as a low self-esteem within the rare disease community, is often profound and can exert an important negative influence on individuals' lives, warranting careful consideration in rare disease needs assessment.**
- **The unpredictability of rare diseases introduces many uncertainties, for instance regarding the trajectory of the illness and its implications for the future.**
- **In addition, morbidity, disease status, as well as reproductive health, are essential elements in the context of rare diseases.**

Based upon the rapid literature review and findings from the stakeholder workshops, we suggest to include the criterion “impact on reproductive health” to increase the applicability of the NEED framework towards identifying health needs of patients with rare diseases. Figure 14 provides an overview of the existing NEED criteria and indicators, together with the additional suggested criterion (in green). Further details regarding these suggestions can be found under ‘Suggestions for the adjustment of the NEED framework’.

**Figure 14 – Overview of the existing and suggested additional patient health needs criteria and indicators relevant for rare diseases**



CRITERION 1: Impact on general health-related quality of Life (HRQoL)

Similar to common diseases, patients suffering from a rare disease often experience impairments in their HRQoL due to their disease. Their impairments in HRQoL are not only related to the restrictions in their physical capabilities, mobility, self-care, and ability to perform their usual activities, but the disease also impacts their psychological well-being. Examples of HRQoL impairments mentioned in the literature are a lack of energy, cognitive difficulties (e.g., memory deficits, lack of concentration), motor function impairment, and psychosocial problems (e.g., anxiety, verbal communication difficulties, loss of autonomy, loss of interest in sexuality, and social exclusion).^{134, 156, 236, 257}

Indicators

To cover all of the aforementioned problems, the criterion 'impact on general HRQoL' contains three indicators: (i) years of life lived with disability (per case), (ii) EQ-5D-5L average score, and (iii) associated comorbidities. The importance of addressing quality of life comprehensively was stressed by many. Two participants further noted that not only morbidity but also the issue of co-morbidities should be considered. One participant emphasized that particularly patients over 60 years old often face multiple diseases and that this complexity should be taken into account when considering morbidity. Another participant highlighted the importance of considering morbidity as a consequence of the primary disease, often leading to secondary issues like pain, digestive problems, among others. Participants emphasized the significance of accounting for such consequences in the assessment.

During the stakeholder workshops, multiple participants emphasized the substantial burden posed by the unpredictability of how a disease will manifest over days, weeks, and throughout one's life. It was noted that not all rare diseases, even those with high mortality rates, have guaranteed fatal outcomes, and predicting the remaining time for living for patients can be challenging. This unpredictability can compound the psychological stress experienced by patients. They highlighted how unpredictability affects the

daily lives of individuals with the disease, impacting their quality of life, psychological well-being, and ability to plan and manage their condition. The example of epilepsy was mentioned as an illustration of this unpredictability: *"People can have good weeks, and then all of a sudden it falls apart"*. There was a suggestion to consider categorizing unpredictability under "invisible" symptoms, alongside issues like fatigue and exhaustion. Stakeholders noted that invisible symptoms, including pain and discomfort, can be challenging to deal with due to the misunderstandings they may create. Also, other studies report on the impact of unpredictability on various aspects of patients' lives, such as mental health, autonomy, and family life.^{53, 68, 85} The unpredictability was for example included in the Angioedema Control Test, where patients were asked how much the unpredictability of angioedema bothered them.¹⁷⁵

Measurement and data collection methods

The EQ-5D-5L average score is measured via the general EQ-5D-5L questionnaire. Both the EQ-5D-3L and EQ-5D-5L questionnaire are frequently used in studies on rare diseases to assess patients' QoL. The EQ-5D is often used in combination with other tools or methods, such as the SF-36²⁵¹, SF-12¹⁰⁸ or Barthel Index (BI) score.¹¹⁴ The BI score is an ordinal scale used to measure performance in activities of daily living. In other instances, the EQ-5D was combined with disease-specific tools, such as Myasthenia Gravis QoL 15-item revised scale²⁵⁸ or Unified Huntington's Disease Rating Scale (UHDRS).²⁵⁹ In the latter study, participants felt that the disease-specific questionnaires were more relevant and more useful than the generic SF-12 and EQ-5D.¹⁰⁸

The NEED framework uses databases analysis to assess the years of life lived with disability (per case) (e.g. disability weight), a patient survey to assess EQ-5D-5L average score and the literature to assess associated comorbidities. These methods align well with the existing literature on rare diseases, making them suitable choices for evaluating the indicators of this criterion.

**Adjustment suggestions for the criterion 'Impact on HRQoL'**Indicators:

- (i) **Years of life lived with disability (per case):** no proposed adaptations
- (ii) **EQ-5D-5L average score:** no proposed adaptations
- (iii) **Associated comorbidities:** no proposed adaptations
- (iv) **PROPOSED: Unpredictability**

Measurement or data collection methods:

- Add question to the patient survey on proposed indicator 'unpredictability'

*CRITERION 2: Impact on physical health***Indicators**

The criterion 'Impact on physical health' contains two indicators, being (i) the experienced burden of physical symptoms, and (ii) pain/discomfort before vs today.

- (i) **Experienced burden of physical symptoms** in rare diseases can range from anaphylaxis, abdominal pain, diarrhea in mastocytosis¹⁸³ to swelling, itching, and photosensitivity in patients with Cutaneous Lupus Erythematosus.^{100, 183} The burden of fatigue and exhaustion was also highlighted during stakeholder workshops.
- (ii) **Pain and discomfort** are common symptoms in rare diseases, significantly affecting patients' QoL.^{56, 81, 146, 183, 256} For instance, patients with the rare disease Pigmented Villonodular Synovitis frequently reported pain, stiffness, inflammation, and disrupted sleep, highlighting the profound impact of pain on daily activities.²⁵⁶

Measurement or data collection methods

In some studies, generic tools (meaning not specific to a particular rare disease, treatment or symptom) (e.g. AE-QoL, SF-36, mean global HRQoL or VAS) were used to measure the physical impact of the rare disease on patients.^{136, 163, 175, 236} Several studies highlighted the importance of using disease-specific tools, along with more generic tools, to assess physical

symptoms and discomfort.^{98, 161, 169, 175, 185, 251, 260} For instance, in patients with Systemic Sclerosis, the Systemic Sclerosis Quality of Life Questionnaire (SScQoL) was associated with self-reported comorbidities, emphasizing its relevance in assessing physical well-being.⁹⁸ Similarly, in Fabry disease, the Adult Fabry QoL (AFQOL) tool focused on cardiovascular and renal symptoms, which are highly relevant to patients' daily lives.¹⁶⁹

Measuring physical needs in rare diseases poses several challenges, including discrepancies between patient and physician assessments.²⁶¹ For instance, patients with rheumatoid arthritis valued fatigue and pain differently compared to physicians, who prioritised (other) clinical features. Physicians' assessments frequently rely on objective laboratory data, creating a gap in understanding the patient's experience.²⁶¹

Adjustment suggestions for the criterion 'Impact on physical health'Indicators:

- (i) **Experienced burden of physical symptoms:** no proposed adaptations
- (ii) **Pain/discomfort before vs today:** no proposed adaptations

Measurement or data collection methods:

No proposed adaptations

CRITERION 3: Impact on psychological health

Included studies highlighted the importance of addressing psychological, mental (cognitive) and emotional issues in patients with rare diseases. Mental or psychological impairments were sometimes described as the main concerns by patients or informal caregivers. For example, Langhinrichsen-Rohling et al. reported mental health concerns to be the most common indicator of an unmet need, expressed by a substantial share of respondents (83%, n=87) living with Ehlers-Danlos syndrome.¹⁹⁷ Another study found that in patients living with Locked-in syndrome in Sweden, although scores varied between the participants followed-up, overall higher scores (as QoL outcomes) were seen in cognitive and mental domains than in physical domains.²³⁵ A last study on this matter reported a divergent perception of concerns between clinicians and patients. While clinicians tended to indicate the impact of more practical implications of the diseases, such as traveling,



and physical impact, patients referred more to emotional impacts, such as anxiety, depression and mood swings, as part of their main concerns.¹²⁴

Indicators

The sub-criterion 'Impact on psychological health' contains two indicators: (i) the experienced burden of psychological symptoms, and (ii) anxiety/depression before vs today. An additional indicator being (iii) self-esteem is proposed based on the literature review and stakeholder workshops.

- **Experienced burden of psychological symptoms** often results from patients' unmet health, healthcare or social needs as defined in the NEED assessment framework. Two participants of the stakeholder workshop mentioned the importance of differentiating between neuro-psychiatric/psychological symptoms that can be primary manifestations of a rare disease and psychological symptoms as a secondary consequence of having a specific disease. This notion is reflected in literature, where causes of psychological symptoms are grouped into three categories:
 - Physical symptoms: Patients with rare diseases often experience profound physical symptoms, which can have a profound psychological impact. Physical symptoms can be debilitating, causing distress and affecting their overall psychological well-being.^{169, 243} Further, coping with physical problems such as chronic pain, limited mobility, or other challenging physical manifestations can lead to emotional distress and feelings of helplessness.
 - Financial concerns: Besides physical symptoms, financial concerns have been described to add to the psychological stress experienced by patients and their families. The high costs of medical treatments, therapies, and specialised care may result in financial strain and anxiety about the future.²⁵¹
 - Lack of information: The third cause is very specific to the rare disease context, being a lack of information regarding multiple aspects, such as diagnosis, rare disease outcomes or treatments, resulting in uncertainties among patients and their informal

caregivers. Generally little clinical data is available, and combined with the unpredictable nature of rare disease, this often leads to uncertainty about disease progression, treatment outcomes and future care needs.^{100, 121, 221} Besides the limited availability of clinical data, (i) documented information (e.g. on rare diseases, diagnosis, treatments), (ii) education of physicians, patients and the general public, and (iii) communication to patients is believed to be limited in the literature. A lack of adequate support and access to accurate information about their condition can leave patients feeling isolated and overwhelmed and can fuel feelings of anxiety and stress.^{101, 129, 161, 227} Lack of support and understanding may hinder their ability to cope with the challenges they face, amplifying their mental health concerns.¹⁶¹ This was emphasized during the stakeholder workshops, where a participant mentioned that the psychological impact differs between patients without a diagnosis and patients with a diagnosis.

- **Anxiety and depression** emerged from the literature as the most recurring forms of psychological impairments for patients with rare diseases.^{53, 56, 68, 81, 95, 98, 105, 119, 129, 146, 164, 169, 197, 225, 259, 262} These conditions are closely linked to the fear of disease progression⁹⁸, feelings of hopelessness regarding future encounters¹⁹⁷ and the desire for controllability in patients' lives.¹⁰⁵ Other significant concerns are decreased sexual satisfaction, intellectual disabilities and cognitive impairments, loneliness, increases in aggression, anger, annoyance, and/or irritability.^{63, 68, 98, 197, 198, 262} The inclusion of anxiety and depression in the NEED framework is aligned with the common practice in rare diseases, where these mental health aspects are crucial for assessing patients' overall well-being. Therefore, retaining this separation ensures a comprehensive evaluation of psychological needs in the context of rare diseases.
- **Suggested additional indicator: Impact on self-esteem**, including but not limited to aesthetic concerns was mentioned by participants in the stakeholder workshop. Also in the literature low self-esteem was mentioned for patients with rare diseases.²⁵⁷ In addition to anxiety and



depression, self-esteem is believed to be of equal importance as an indicator of psychological health.

Measurement or data collection methods

In the literature, various tools have been used to measure the psychological well-being of patients with rare diseases. Some of these tools encompass a holistic approach, integrating a psychological component as an integral part of their assessment. An example is the Patient-Reported Outcomes Measurement Information System (PROMIS) tool, where one specific part is designed to evaluate anxiety and depression.^{85, 172} Other examples include the SF-36 tests and the WHO Disability Assessment Schedule (WHODAS 2.0).^{172, 263} The literature also reports on tools that are specifically tailored to measure psychological aspects, such as the Brief Illness Perception Questionnaire (BIPQ) and the Hospital Anxiety and Depression Scale (HADS).^{86, 175} The HADS offers a specialised means of assessing the psychological state of patients.¹⁷⁵ These tools, whether encompassing a wider scope or focusing only on psychological aspects, can play a pivotal role in understanding the psychological problems experienced by individuals with rare diseases and could contribute to a more comprehensive understanding of the needs and well-being of patients with rare diseases. Thus, general questionnaires, such as the SF-36, WHO DAS 2.0, and PROMIS tool, could be incorporated into the Patient survey to measure psychological needs and more specific tools such as the HADS could be used for anxiety and depression.

Rare diseases often present unique psychological challenges, and patients and HCPs may interpret the severity of these concerns differently. To address this gap, the NEED framework employs patient surveys to assess the psychological burden. This approach is particularly suitable for rare diseases where limited literature may exist. Since the literature on psychological impairments in rare diseases can be limited, the NEED framework can leverage well-documented psychological issues from other conditions as a starting point. Beyond patient surveys and literature, psychological problems and symptoms can be explored using qualitative methods with rare disease patients or HCP experts to ensure their relevance and adaptability.

Adjustment suggestions for the criterion 'Impact on psychological health'

Indicators:

- (i) **Experienced burden of psychological symptoms:** no proposed adaptations
- (ii) **Anxiety/depression before vs today:** no proposed adaptations
- (iii) **PROPOSED: self-esteem before vs today**

Measurement or data collection methods:

Add a question on self-esteem before versus today to the patient survey.

CRITERION 4: Impact on autonomy

The autonomy of individuals with rare diseases can be compromised, because of the symptoms of the condition and the medical interventions necessary for treatment. It is important to acknowledge that medical care itself can also exert an influence on patients' autonomy. Literature highlights instances where patients must navigate challenges, such as the need to adapt their schedules to accommodate medical appointments during working hours¹⁸⁹ and the intrusion of hospital visits into their personal lives.²⁶⁴

Indicators

Within the NEED framework, the criterion 'Impact on autonomy' consists of three indicators: impact on (i) mobility before vs today, (ii) self-care before vs today, and (iii) usual activities before vs today. Based on literature review and stakeholder workshops, an additional fourth indicator is proposed: independent housing.

- **Mobility before vs today:** Walking and mobility challenges manifest as recurrent autonomy impairments in the context of the rare disease literature, as illustrated by several studies.^{84, 108, 172, 251, 259} The literature presents a spectrum of mobility difficulties: some rare disease patients retain the capacity for independent movement, while others necessitate assistance, and some are constrained to wheelchairs or even bedridden states.¹⁰⁸



- **Self-care before vs today:** The indicator on self-care, which pertains to an individual's capacity to independently manage washing and dressing, is less extensively addressed in the existing literature. A study investigating the social economic costs, health-related QoL, and disability in individuals with the rare disease 'Cri Du Chat syndrome' found that 98% of patients reported problems in washing and dressing.¹⁹⁸ Further, a literature review assessing the burden of disease associated with X-linked hypophosphatemia in adults highlighted an interview study that examined patients' ability to dress themselves as an indicative measure of disease burden.¹¹⁸ In another study, lack of independence was associated with being reliant on other people for activities of daily living such as eating, dressing, showering, and using the bathroom.¹⁸⁵
- **Usual activities before vs today:** Rare diseases impact patients' daily activities, affecting both personal and professional activities. Professional functioning appears to be a commonly affected aspect in rare diseases for adults.^{82, 118, 166, 175, 183, 190, 243} In the context of rare diseases in children, the usual activities that are affected by their disease include schooling. Various studies have assessed the impact of rare diseases in children on their schooling.^{79, 213, 243} Rare diseases also affect the social functioning of patients and patients' personal interactions.^{166, 190, 256} The ability to communicate effectively and participate in routine activities can also be constrained by a rare disease. Specifically, the neurocognitive challenges posed by certain conditions can necessitate special support for communicating and routine activities.⁷⁹ Besides general autonomy constraints, very specific symptoms related to rare diseases may result in specific challenges. For instance, attacks that target the hands and feet can hinder work productivity and the ability to engage in everyday tasks like typing on a computer.⁷⁹ Another example is comorbid epilepsy which may complicate patients' transition to autonomy and hinder self-management skills, such as the pursuit of obtaining a driver's license.⁹⁵

Measurement or data collection methods:

The literature reports how assessing the extent of autonomy impairment in individuals living with rare diseases is a complex endeavour, necessitating the utilisation of suitable measurement tools. The EQ-5D has been employed to assess the impact of autonomy deficits in rare disease patients.¹¹⁷ Furthermore, the assessment of pain, discomfort, and emotional well-being through this tool elucidated the complex intersections between autonomy and mental health.¹¹⁷ During the stakeholder workshops, one participant referred to the BelRAI tool^h to assess autonomy.

The use of a patient survey combined with patient interviews to assess autonomy needs among patients, as suggested in the NEED framework, is aligned with the existing literature on rare diseases. This data collection method is a suitable choice for evaluating autonomy needs for rare diseases.

In the NEED framework, questions about "usual activities" are focused on identifying whether patients have problems with these activities, the support they require, and the type of support received. However, the framework does not delve into the specifics of these problems. Considering the wide range of autonomy impairments documented in the literature for rare disease patients, it would be beneficial to incorporate questions that inquire patients about the different types and potential causes of these problems. Such additional insights can provide a more comprehensive understanding of autonomy needs within the rare disease population.

^h BelRAI Tool ; <https://belrai.org/nl> (last access: 1 February 2024)

**Adjustment suggestions for the criterion 'Impact on autonomy'**Indicators:

- (i) **Mobility before vs today:** no proposed adaptations
- (ii) **Self-care before vs today:** no proposed adaptations
- (iii) **Usual activities before vs today:** no proposed adaptations

Measurement or data collection methods

- Add question to the patient survey on the type of impairment that patients experience / find important that challenge their usual activities.
- Add question to the patient survey on independent housing.
- Investigate the usefulness of the BelRAI tool.

CRITERION 5: Impact on life expectancy**Indicators**

The NEED assessment framework includes the criterion 'impact on mortality' and its indicator 'years of life lost'. Mortality appears to have received relatively limited attention within the included literature.⁸³ Several participants of the stakeholder workshops provided alternative terms or complementary measures for mortality. One participant for example proposed the "potential life years lost". Another workshop participant suggested "conditional survival", defined as the expected survival at the moment where the patient survived a certain period of time after diagnosis. Still, another participant proposed use of disability-adjusted life years as a replacement of mortality and another alternatively proposed "the age at death" as a complement to mortality. Further research is needed to identify the best suited indicator.

Measurement or data collection methods

In the literature, one study assessed mortality as the total deaths during follow-up using the CALIBER platformⁱ (primary care data, Hospital Episode Statistics and Office for National Statistics mortality data), which links 5.37 million people's records from 225 general practices primary care, hospital and mortality records in England in the period of 1997 to 2010.⁷⁵ CALIBER data were obtained from the Clinical Practice Research Datalink^j. Further, no specific measurement methods in the context of rare diseases were identified in the literature review or during the stakeholder workshops.

Adjustment suggestions for the criterion 'Impact on life expectancy'Indicators:

- (i) **Years of life lost (per death):** no proposed adaptations

Measurement or data collection methods:

- No proposed adaptations

PROPOSED ADDITIONAL CRITERION: Impact on reproductive health**Indicators**

One workshop participant referred to reproductive health as an important element to include and more specifically the impact on whether a patient with a rare disease can have children. In a survey with patients living with various rare diseases, participants suggested to perform research on fertility preservation and reproductive technology.¹⁰⁹ Another study in patients living with hypothalamic dysfunction reported that for 13.3% of patients, pubertal delay or gonadal insufficiency/infertility was one of the most important health problems.²⁶⁵ Both findings highlight the importance of considering the impact of rare diseases on the reproductive health for patients. As such, 'impact on reproductive health' may be relevant to include as a criterion in the NEED framework.

ⁱ CALIBER platform; <http://www.caliberresearch.org> (last access: 1 February 2024)

^j Clinical practice Research datalink; www.cprd.com (last access: 1 February 2024)



Measurement or data collection methods

To estimate the reproductive health, a literature review and the patient survey can be used as data collection methods to estimate the reproductive health impact of the rare disease. However, further investigation on measurement methods is needed.

Adjustment suggestions for the criterion 'Impact on reproductive health'

Indicator:

PROPOSED: Reproductive health needs

Measurement or data collection methods:

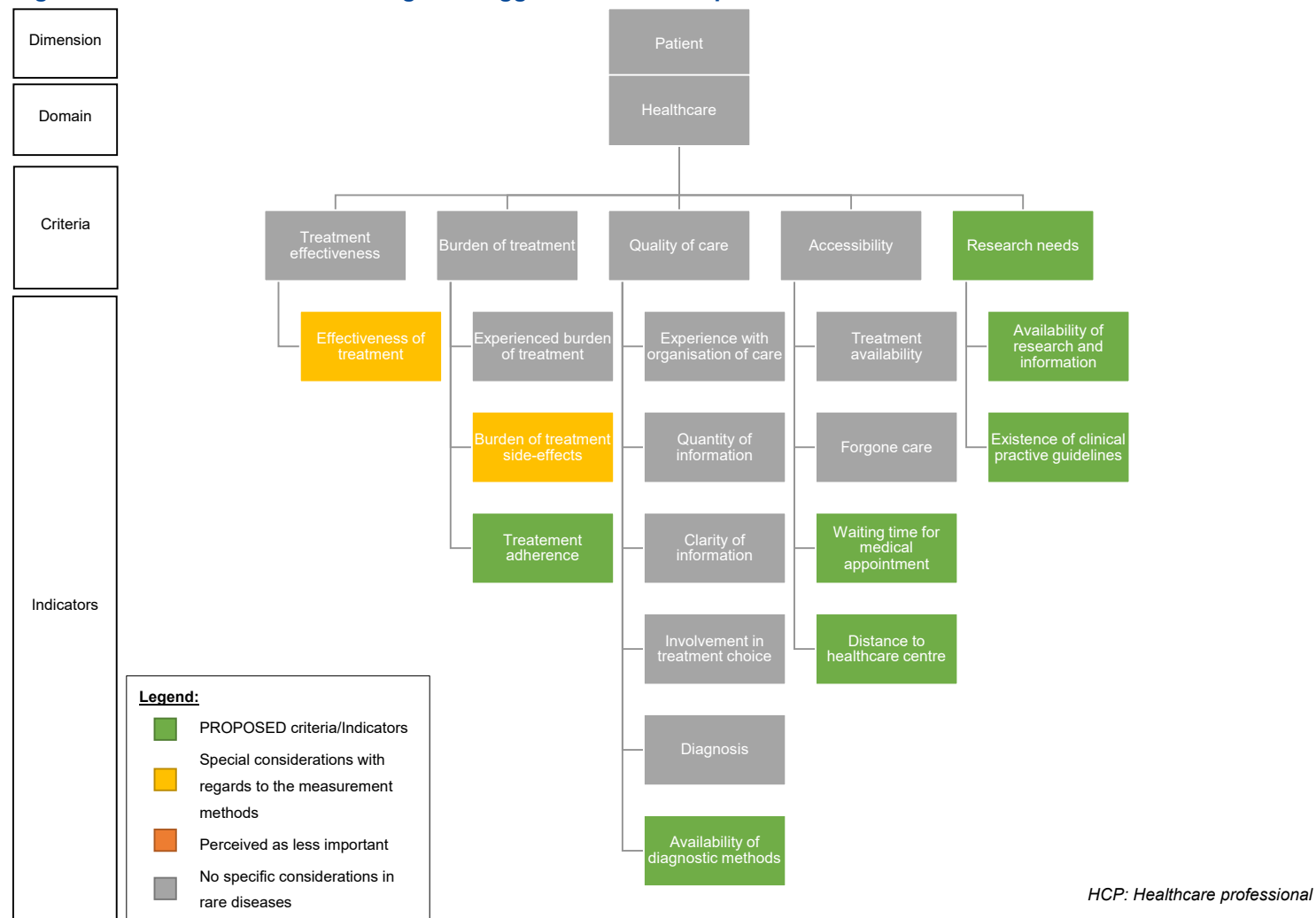
- Add question on impact of rare diseases on reproductive health in the patient survey and review the published literature to collect evidence on this criterion.

6.2.1.2 Healthcare needs

Key Points

- Lack of knowledge about rare diseases as well as lacking information on adequate treatments are critical challenges, impacting timely diagnosis and the adequate management of rare diseases.
- Diagnostic delay or even lack of diagnosis is an important problem in rare diseases because it delays access to treatment.
- Non-pharmacological treatments are essential in the context of rare diseases and should not be ignored.
- Addressing the complexity of rare diseases requires collaboration among healthcare providers, integrating medical, psychological, and social aspects.

To identify patient healthcare needs, four criteria are suggested in the NEED framework: (i) treatment effectiveness, (ii) burden of treatment, (iii) quality of care, and (iv) accessibility. Figure 15 provides an overview of the current set of patient healthcare needs criteria and indicators, together with the proposed new criteria and indicators that may make the NEED framework more relevant in the context of rare diseases.

**Figure 15 – Overview of the existing and suggested additional patient healthcare needs criteria and indicators relevant for rare diseases**



CRITERION 1: Treatment effectiveness

Box 2 – Definition of treatment¹⁰

Treatment of a health condition involves the use of therapeutic or secondary preventive measures that are based on scientific evidence and that have been prescribed or recommended by a healthcare professional with the goal of promoting healing, relieving symptoms, preventing complications, repairing injury, or restoring health.

This may include various components such as medications, surgery, medical procedures (e.g., joint aspiration), medical devices (e.g. pacemaker), physical therapy, psychological therapy, and other forms of (clinical) interventions (e.g., hydration, artificially provided nourishment) to target the specific disease or condition, to target symptoms caused by the disease/condition, or to prevent complications.

However, interventions or services that are purely supportive, such as those that increase access to care, provide health information, or aid in medication adherence, are excluded from this definition of treatment. Palliative care, which focuses on improving the quality of life and managing symptoms in incurable diseases, is also excluded in the definition of “available treatment” in this context as it does not provide curative or disease-modifying effects.

In the literature, the interpretation of “treatment” in the rare disease context expands beyond pharmaceutical interventions to encompass a broader spectrum, including physical therapy, psychological support, treatment using medical devices, and technical assistance.⁶³ This broad interpretation is emphasized in the treatment of Pelizaeus-Merzbacher Disease, where therapy services and assistive devices play integral roles.¹⁹² This consideration was also repeatedly expressed during the stakeholder workshops, when participants pointed out that rare diseases can be treated using various non-pharmacological approaches, such as surgery, medical devices, radiation therapy, and dietary modifications. It was emphasized that the absence of an orphan drug should not imply the absence of treatment options.

Indicators

During the workshop, stakeholders underlined the significance of considering the benefits of available treatments when assessing the magnitude of the “Unmet Need” gap. They noted that neglecting the benefits of existing treatments could potentially overestimate the unmet needs. Furthermore, the importance of considering relative effectiveness was brought up, particularly in cases where multiple treatments are available for a rare disease. Stakeholders noted that evaluating relative effectiveness is crucial for making informed decisions about treatment options.

Consequently, this indicator should exceed the merely clinical effectiveness parameters and also consider other factors that contribute to patient well-being, include relative effectiveness and focus on the expected long-term efficacy of the treatment.

Measurement or data collection methods

The effectiveness of treatment is subject to high variability, due to variations in treatment response, change in effectiveness over time, methods used and treatment regimen. As described in Chapter 5, rare diseases are characterised by small population sizes which is typically translated into low sample sizes. The high variability in the sample complicates evidence generation and generalisability. Variation can be caused by a variation in treatment regimen, treatment responses, change of the effectiveness over time, and methods.^{54, 73, 135, 168}

During the stakeholder workshops, one participant raised the question of who would determine the effectiveness of a treatment, emphasizing the various outcomes and assessments that may exist. Stakeholders emphasized the importance of considering multiple perspectives on treatment effectiveness, including those of patients, and the use of various resources, such as public assessment reports, health technology assessment reports, and databases (Table 12). They highlighted that patient experiences may differ, and their input can provide valuable insights into the real-world effectiveness of a treatment. For instance, the incorporation of patient satisfaction as a metric for assessing treatment effectiveness is applied in the example of Hereditary Angioedema, where clinical efficacy



may not fully encompass patients' lived experiences.²⁶¹ In a study on the unmet needs of patients with Cushing's syndrome, patient satisfaction with treatment was also assessed.⁸² In one survey study, patients were involved in the assessment of efficacy by asking them whether they were still experiencing symptoms while they were being treated.¹⁷⁰ Besides patient's perspectives on the effectiveness of a treatment, expert opinions were also assessed in the literature to shed light on the effectiveness of existing treatments.¹⁹⁴ In the latter study, experts gave their opinion about e.g. the therapy's effectiveness but also therapy adherence, disease control and patient management, and treatment withdrawal.¹⁹⁴

Currently, the framework collects data for the criterion "treatment effectiveness" solely based on expert opinions. The literature also suggests making use of particular sources such as the EPARs and other EMA documents. However, due to potential data gaps, including patient input on treatment effectiveness through the patient survey presents a valuable alternative.

Table 12 – Data sources and methods to assess treatment effectiveness in rare diseases

Data source	Explanation
Public Assessment Reports	A suggestion was made to include public assessment reports available on the EMA website ^k as a valuable resource for evaluating treatment effectiveness. These reports are believed to provide detailed information on the assessment and approval process of orphan drugs. Another participant cautioned that the EMA database contains reports from different committees, each with a distinct approach to evaluating medicines. They advised careful consideration of the specific reports and data used from the EMA database and emphasized the potential for

^k European Medicines Agency. Advanced Search.
https://www.ema.europa.eu/en/search?f%5B0%5D=ema_search_categories%3A83&f%5B1%5D=ema_search_categories%3A84&f%5B2%5D=ema_se

	variability in assessment criteria. Further, another participant suggested incorporating HTA reports and databases into the assessment of treatment effectiveness. These reports, available in various countries, may provide comparative effectiveness data, offering additional information for evaluating treatments.
Databases	Stakeholders mentioned the existence of databases and initiatives for collecting information on healthcare assessments and orphan drugs. These resources, such as the NAVLIN database ^l and the international horizon scanning initiative ^m , may be valuable sources for gathering data on rare diseases and their treatments.
Patient Survey	The need to include treatment effectiveness in the patient survey was raised. It was suggested that patient feedback on the effectiveness of their treatments should be collected and considered in the assessment. The Goal Attainment Scaling (GAS), developed in the Asterix project ⁿ , was recommended by a participant as a potential approach for assessing treatment effectiveness. The goal is described by Gaasterland et al. as "an instrument that is intended to evaluate the effect of an intervention by assessing change in daily life activities on an individual basis". ²⁶⁶
Consensus guidelines	Stakeholders suggested that consensus guidelines from reputable organisations could serve as another important source of information when assessing the effectiveness of treatments. They mentioned the existence of valuable resources in areas like oncology, such as the European Society for Medical Oncology (ESMO) guidelines in Europe and the National Comprehensive Cancer Network (NCCN) consensus guidelines in America. These guidelines often provide recommendations for preferred treatments in both rare and non-rare oncology cases.

arch_categories%3A85&landing_from=73303 (last access: 2 February 2024)

^l <https://data.navlin.com/alspc/#/> (last access: 2 February 2024)

^m <https://ihsi-health.org/> (last access: 2 February 2024)

ⁿ <https://www.asterix-fp7.eu/> (last access: 2 February 2024)

**Adjustment suggestions for the criterion 'Effectiveness of treatment'**Indicators:

- (i) **Effectiveness of current overall treatment:** broaden the scope of the effectiveness interpretation

Measurement or data collection methods:

Besides an expert opinion, it is suggested to add a question to the patient survey.

CRITERION 2: Burden of treatment**Indicators**

The current NEED framework includes two indicators for the criterion "burden of treatment": (i) experienced burden of treatment, and (ii) experienced burden of side effects. Based on this literature review and stakeholder workshops, an additional third indicator is proposed: treatment adherence.

The experienced burden of the treatment itself is only mentioned in two reviewed studies.²²⁸ The complexity of treatment regimens in rare diseases, often involving a combination of therapies, contributes significantly to the overall burden experienced by patients. This multipronged approach amplifies treatment-related challenges and side effects (see next indicator).²²⁸ Therefore, this indicator and the next one are important in the context of rare diseases. One participant of the stakeholder workshops stressed that the burden of treatment is contextual, for instance, the burden differs when there is no homecare organisation and treatment is administered in a hospital.

The experienced burden of the side effects of treatment is often mentioned in the literature and appears to be an important concern for patients and informal caregivers.^{168, 190, 258} Rare disease treatments often bring about a diverse array of side effects, encompassing both physical and psychological manifestations. This diversity of side effects complicates the standardised comparison process. Patients frequently navigate a complex

interplay between their disease symptoms and the side effects of treatments. For instance, individuals with myasthenia gravis experience ongoing unmet needs due to the burdensome nature of treatments and their side effects²⁵⁸, while treatment options for cutaneous lupus erythematosus entail a multitude of medications with problematic side effects, leading to concerns about their long-term impact on their health.¹⁰⁰ These subjective experiences and the varying severity of side effects make uniform weighting challenging.

Suggested additional indicator: Treatment adherence. A last factor influencing the effectiveness of a treatment is the impact of patients' behaviour. Literature highlights that long-term adherence to treatment might strongly impact the results of a treatment regimen.¹⁶⁴ This was echoed during the stakeholder workshops where a suggestion was made to potentially include treatment adherence in the assessment framework. Low treatment adherence is likely a result of the treatment burden or burden of the side effects of the treatment.

Measurement or data collection methods

A high variance in treatment regimens was observed caused by the diversity of treatment approaches, the range of side effects, and the overall burden of disease. Patients subjected to multiple treatment lines frequently experience increased functional impairments and symptom burden, potentially attributed to factors such as the introduction of specific medications or shifts in disease progression.²³⁶ Moreover, aside from necessary changes in treatment regimens due to a lack of response, patients' decision to discontinue treatment due to the burden of treatment-induced side effects might also occur. This conscious choice to prioritise QoL often materialises when the side effects outweigh the perceived benefits, thereby triggering a search for alternative treatment strategies to cope with the treatment-associated challenges.²⁵⁷ These individualised treatment schemes make direct comparisons and the generalisability of side effects difficult. Another challenge reported in the literature is the nuanced recognition of treatment efficacy and its associated side effects by physicians.²⁰⁹ Understanding these complexities is crucial for comprehending the potential impacts of treatment regimens.²⁵⁷ If this is



reported as a challenge for physicians, it might also be difficult for patients to differentiate the impact of the disease from the side effects of the treatment.

A patient's perceived impact or relative importance of a certain side effect also differs based on their stage in life. Younger patients might care more about life expectancy and long-term consequences while older patients might care more about their current QoL. This difference is reported in a study with osteogenesis imperfecta patients receiving bisphosphonate therapy.⁸³

As a result, the diversity of perceptions related to the burden of treatment within a small patient population poses challenges to generalisation. Additionally, the long-term repercussions of side effects are currently not included in the patient survey. While patients may not currently encounter side effects, the potential for substantial long-term effects exists. Incorporating patients' perceived requirements along with the anticipated impact on their lives can provide a more comprehensive perspective of their experienced needs.

Adjustment suggestions for the criterion 'Burden of treatment'

Indicators:

- (i) **Experienced burden of treatment:** no proposed adaptations
- (ii) **Experienced burden of side-effects of treatment:** extend the focus to the expected long-term burden of the side-effects
- (iii) **PROPOSED: Treatment adherence:** Firstly, it offers insights into the actual use of the current SOC and signals potential issues at that level. Secondly, it can be utilised as a confounding factor when testing treatment efficacy or burden of the treatment and treatment side-effects, given that these indicators depend on the patient's adherence to the prescribed treatment.

Measurement or data collection methods:

- Add a question to the patient survey covering the indicator on treatment adherence.
- Perform a dedicated literature review on the expected long-term side effects of the treatment.

CRITERION 3: Quality of care

Indicators

In the NEED assessment framework, the criterion 'Quality of care' covers five indicators: (i) experience with the organisation of care, (ii) quantity of information received, (iii) clarity of information received, (iv) involvement of patients in treatment choice, and (v) diagnostic timing.

During the stakeholder workshop, one participant questioned if the five indicators of quality of care in the original NEED framework sufficiently cover the question of whether the disease is managed optimally with true expert knowledge and experience, and infrastructure. The participant adds that *"A patient needs to feel secure that he/she is getting state-of-the-art care and that the care he/she is receiving is truly the best possible care for his/her condition. Many rare disease patients are not referred optimally and/or are treated by medical professionals that do not have a sincere interest in the rare condition."*

(i) **Experience with the organisation of care:** All stakeholders in the workshop agreed with the importance of including this sub-criterion in the framework but one stakeholder proposed to change the name to satisfaction with the organisation of care. When it comes to the organisation of care, the literature regularly refers to the lack of integrated care (namely HCPs that collaborate, incorporating medical, psychological, and social aspects). Also during the stakeholder workshops, the importance of a good coordination of care and collaboration between general practitioners (GPs) and specialist care was mentioned. The literature review further showed that multidisciplinary teams are crucial for rare diseases, but a lack of familiarity among HCPs with the wide range of rare conditions contributes to fragmented care.^{82, 95, 112, 131, 201, 242} Coordinated care addressing both medical and non-medical aspects is consistently emphasized, underscoring the urgency for integrated approaches.⁹⁵ For instance, one study showed that patients' experiences were shaped by their access to multidisciplinary care, where the lack of well-coordinated clinics resulted in multiple trips to various specialists, impacting the quality of their care.²⁵⁷ In particular, the transition from paediatric to adult services for those with rare diseases remains problematic, leading to a loss of specialised services available to



paediatric patients.^{57, 162, 201} During the stakeholder workshop, one participant referred to the quality of the relationship between HCPs and patients, as an indicator of experience with the organisation of care. The participant mentioned, *“We frequently hear that doctors do not listen nor trust the patients? This impacts the management of the disease and the patient's trust in professionals.”*. The literature also reports that patients feel that they are not taken seriously by HCPs or that HCPs are ignorant and overwhelmed.^{55, 217, 267}

(ii) **Quantity of information:** Within the context of rare diseases, addressing the information needs of patients emerges as a pivotal criterion. The literature extensively highlights the challenges posed by inadequate and ineffective information dissemination. Patients frequently seek information on disease manifestations, treatments, psychological issues, and prognosis⁹⁵, as well as wider support services such as financial assistance and access to equipment.⁵⁸

Patients living with rare diseases encounter substantial hurdles in obtaining accurate and comprehensive information concerning their conditions e.g., available treatments, ongoing research, support networks, and available resources.^{58, 68, 95, 141, 188, 268, 269} HCPs play a critical role as sources of information but there are systemic challenges that hinder effective information sharing.^{76, 135} Patients' experiences with information provided by HCPs vary depending on the interaction context. In a study with parents of children with rare bleeding disorders, the majority of parents are satisfied with the knowledge and expertise offered by HCPs within specialised centres, but some (19%) express dissatisfaction with the limited understanding exhibited by professionals outside these specialised settings.²⁷⁰ Information provided by HCPs to patients with diffuse cutaneous systemic sclerosis is overall reported to be insufficient and sometimes generalised, leaving patients with a limited understanding of their conditions.²⁵⁷ As experts in their conditions, some patients feel that HCPs are unable to provide them with sufficient information, leading to a situation where patients are left to take charge of their own healthcare journey.^{257, 271} This discrepancy in knowledge gives rise to patient frustration and poses barriers to effective HCP-patient communication. This paucity of information

prompts patients to turn to online sources, such as search engines, online communities, and forums, to satisfy their need for information.^{68, 76, 135}

Several participants of the stakeholder workshops stressed that the unavailability of information contributes to low health literacy among patients. Therefore, they proposed to include a separate indicator of health literacy in the NEED framework.

(iii) **Clarity of information:** The literature highlights a differentiation between various types of information.¹⁴⁰ Examples of information categories reported in the literature include: (i) general knowledge about the disease, prognosis, and management, (ii) information about the social security system, encompassing legal, financial, and social support, (iii) guidance on family planning, (iv) information about existing research that patients or their relatives could engage in. The first category would address the already mentioned lack of general knowledge among patients on specific rare diseases. Besides the lack of general knowledge, several studies report patients being not informed about the applicable social security laws and social rights, indicating the urgent need for information sharing networks empowering patients with rare diseases.^{127, 140, 186, 226} Furthermore, the lack of information about pregnancy and family planning is regularly recurring in literature in the context of rare diseases.^{127, 208} Lastly, patients would like to know if there are any research efforts in which they or their relatives could participate.^{96, 119, 272}

(iv) **Involvement in treatment choice:** Participants of the stakeholder workshop agree that the involvement of patients in their treatment choices is of paramount importance as patients have unique experiences with their disease and involvement may lead to increased compliance to the treatment decision made. Workshop participants referred to the concept of “shared decision making” to be considered, specifically in the rare disease context, where there are limited evidence sources and absence of treatment guidelines for many rare diseases.

(v) **Diagnosis timing:** Articles included in the literature review point to the importance of timely diagnosis in rare diseases, and to its far-reaching implications for patients and society in terms of inefficient resource use, poorer well-being and health outcomes for patients and families.^{56, 87, 120, 160,}



^{164, 273} In the context of rare diseases, delays in diagnosis are frequently attributed to factors like non-specific symptoms, insidious onset, and multisystem involvement which hinders early diagnosis by HCPs.^{62, 269} These challenges are further investigated in a study on myasthenia gravis, where fluctuating symptoms complicate clinical assessments, leading to potential misdiagnoses, particularly in primary care and non-neurology settings.¹⁶⁸ This underscores the need for improved education and more reliable diagnostic methods within myasthenia gravis, and rare diseases is general. Moreover, heterogeneous presentations and limited clinician awareness contribute to the diagnostic hurdles faced in identifying these conditions.^{62, 134} During the stakeholder workshop, one participant stressed that not all patients living with rare diseases will ever come to a clear-cut diagnosis. Therefore, this participant explains that a correct diagnosis for a rare disease may in certain cases be too complex. It seems not appropriate to limit the sub-criterion "Diagnostic timing" to the time to come to a diagnosis. We therefore propose some extra indicators.

(vi) Suggested additional indicator: Availability of diagnostic methods: A diagnostic delay can be caused by the lack of availability or use of diagnostic tests or the inexistence of screening programmes, both mentioned in literature as well as during stakeholder workshops.^{195, 206} A survey study on genetic diagnostic testing in Europe reports that in many cases (40% to 60%) patients have no access to certain diagnostic analyses.¹⁹⁵ Another survey study reports that the availability of screening methods across European countries is uneven, highlighting the need for easy access to information about the techniques used for screening and their availability.²⁰⁶ Several stakeholders from the workshops stressed that in various rare diseases, there are no specific diagnostics tests or systematic screening programmes, which delay the diagnosis. Moreover, one participant explained that the guidelines for diagnostic tests differ between countries (e.g. the Netherlands and Belgium) and between regions within Belgium.

Measurement or data collection methods:

(i) Experience with the organisation of care: Survey and interview methods were most commonly applied to assess patients' experience with

the organisation of care.^{55, 57, 82, 95, 112, 131, 162, 180, 201, 217, 242, 267} In the current NEED framework, the measurement method includes a patient survey complemented with patient interviews. To cover both proposed indicators, more specific questions are to be added to the patient survey.

(ii) Quantity of information AND (iii) clarity of information: In the literature, surveys were most regularly applied to assess the information needs experienced by patients (and/or informal caregivers, parents). What exactly was assessed differed, a study by Behan et.al. for instance measured the experienced awareness about the diseases among GPs²⁷⁴, and Buttner and Bogart et.al. similarly assessed the level of information/explanation received from GPs and specialists.^{177, 252} Some surveys distinguish between the different information types, such as (i) long-term effects of treatment, (ii) new treatments/therapies, (iii) treatment side effects, (iv) information on nutrition, (v) disease itself, (vi) physical activity/sport, and (vi) social and legal support or question what information is most desired.²⁷⁵ Another survey study focuses on gathering and understanding medical information, including feeling prepared for appointments, ability to understand medical information, whether they leave appointments with care plans and next steps, whether they feel all their questions are answered, and whether the clinic clearly explained extent they can be involved in care.¹⁸⁰ Interviews and/or focus groups were also organised to gain in-depth insights into the information needs^{230, 276, 277}, and lastly a combination of survey methods with interviews was applied.²¹⁴

In the NEED framework, the patient survey in combination with patient interviews seems a good measurement method to assess information needs in rare diseases. Furthermore, a review of the literature and expert opinion can be consulted to assess the availability and quality of information and evidence on rare diseases.

(iv) Involvement in treatment choice: In literature, no studies focus specifically on assessing the involvement of patients in the treatment choice nor did participants of the stakeholder workshop propose specific measurement methods.

(v) Diagnostic timing: One study defined "diagnostic delay" as a span of more than one year from symptom onset to diagnosis confirmation.¹²⁰



Nevertheless, the literature reveals various ways to express diagnostic delays, which should be considered as possible indicators:

- i. **Time from symptom onset until diagnosis:** patients often experience delays between symptom onset and the actual diagnosis, which was the most common indicator for diagnostic delay in the rare disease literature.^{59, 63, 73, 74, 91, 159, 160, 265, 278, 279} Moreover, participants from the stakeholder workshops similarly proposed to assess the “diagnostic odyssey” as the time between the onset of the symptoms and the diagnosis.
- ii. **Stage of disease at diagnosis:** diagnosis frequently occurs later in the course of the disease, resulting in delayed intervention.⁷³
- iii. **Perceived effort to obtain diagnosis:** patients with a rare disease often spend significant effort to receive the final diagnosis, with multiple referrals and second opinions.⁸⁰
- iv. **Number of misdiagnoses:** instances of misdiagnosis before arriving at the correct diagnosis contribute to delays.^{74, 168, 229, 278} Assessing misdiagnosis was proposed by stakeholders during the workshops but one stakeholder also provided the insight that this can only be done via “medicovigilance”.
- v. **Number of experts or doctor visits before final diagnosis**^{160, 187}: Stakeholders proposed to include ‘Number of visits to healthcare providers/physicians/specialists before the correct diagnosis is reached’. Some studies in the literature also assess the number of visits. For instance, in a survey study on primary ciliary dyskinesia, authors reported that 34% of the total respondents visited their doctor on more than 40 occasions before the disease was considered a possible diagnosis.²⁷⁴ Other studies assess the number of experts contacted^{150, 280}, as seen in a survey study including 344 different rare diseases, where it was reported that nearly a quarter of patients saw six or more doctors before receiving a diagnosis.²⁵²

Some studies in the literature also use a combination of measures to provide the full picture of the diagnostic odyssey. For instance, Wolin et al. report on the mean patient-reported time from first symptom onset to clinical diagnosis, mean number of HCPs visited before the diagnosis, and number of doctor visits.¹⁷⁶

(iv) **Suggested additional indicator: Availability of diagnostic methods:** the availability of diagnostic methods was mostly in literature identified via patient surveys.^{195, 206}

Adjustment suggestions for the sub-criterion ‘Experience with the organisation of care’

Indicators:

- (i) **Experience with the organisation of care:** no adaptations proposed
- (ii) **Quantity of information received:** no adaptations proposed
- (iii) **Clarity of information received:** no adaptations proposed
- (iv) **Involvement in treatment choice:** no adaptations proposed
- (v) **Diagnosis timing:** no adaptations proposed
- (vi) **PROPOSED: Availability of diagnostic methods**

Measurement or data collection methods:

- Add question to the patient survey to assess the availability of diagnostic methods and include expert opinions on this indicator.
- Evaluate the alternative measurement methods for diagnosis and diagnostic delay.

CRITERION 4: Accessibility

Indicators

The patient healthcare criterion “Accessibility” encompasses two indicators:

- treatment availability, and (ii) forgone care. This report suggests to add two indicators, (i) waiting time, (ii) distance to healthcare centre, to provide a more nuance picture of the challenges and needs in terms of accessibility.
- **Treatment availability:** The landscape of rare diseases is often characterised by the absence of curative interventions, leaving symptomatic management as the principal recourse for affected individuals. An example is the condition known as Fibrodysplasia Ossificans Progressiva (FOP), where the lack of approved disease-modifying treatments compels the focus toward supportive measures that minimize flare-up risks, manage pain, address comorbidities, and



provide assistive care.²⁵¹ This is echoed in the context of treatment options for conditions such as Genetic Mucopolysaccharidoses, where approved therapies remain limited.¹²⁸ These findings were reflected during the stakeholder workshops as multiple stakeholders emphasized the absence of approved treatments for many rare diseases.

Besides the existence of a treatment, it must be accessible to patients to benefit them. Based on a focus group study on hyperemesis Gravidarum in Ireland, access to treatment appeared limited because of difficulty in obtaining prescriptions from local GPs and limited medication stocks in pharmacies.²²⁰ One stakeholder noted that in some cases, medications are used off-label, and patients resort to vitamin/mineral supplementation. Additionally, multiple stakeholders mentioned that patients may seek treatment in other EU countries. The question was raised about whether the assessment would consider these various forms of treatment, including those acquired abroad. Lastly, stakeholders expressed concerns about how the framework addresses the issue of medications accessible in other countries but not available in Belgium. Thus, treatment availability to patients depends on various factors, such as reimbursement of the drug, geographical accessibility, supply in a particular county, and prescription by physicians.

Box 3 – NEED definition of availability¹⁰

Availability of treatment refers to treatment that is largely accessible to the patient population, encompassing both logistical and financial considerations. Availability problems might concern key treatments that are:

- not authorised in Belgium,
- authorised but not commercialised,
- commercialised but expensive and not reimbursed, or
- treatments that have regular stock problems.

(ii) **Forgone care:** Based on the literature review and the stakeholder workshops, it became clear that in the context of rare diseases, it is important to not only focus on medical care but also other forms of paramedical care to obtain the full picture. However, the literature underscores challenges faced by rare disease patients in obtaining timely and appropriate care. To comprehensively assess and address the needs of rare disease patients, a holistic approach is essential, taking into account the multifaceted barriers identified in this report.

The literature highlights several specific care needs that rare disease patients regularly experience:

- **Psychological care needs:** despite its crucial role, psychological support remains insufficient due to long waiting times and a scarcity of professionals.¹⁷⁶ The psychosocial aspect of care is frequently overlooked, leaving patients and informal caregivers without adequate support for emotional challenges.^{88, 95, 120}
- **Medication and treatment needs:** obtaining necessary medications, particularly therapeutic formulas and unfinanced products, poses difficulties for patients.^{55, 127, 130, 188} The high costs and limited availability of these treatments exacerbate the challenge.
- **Holistic care needs:** Rare disease patients require holistic care that extends beyond medical treatment, encompassing psychological support, family assistance, and lifestyle adjustments.^{111, 146} Patients frequently report unmet needs for physiotherapy, occupational therapy, and speech therapy.^{189, 218} The lack of access to these rehabilitation services hampers their ability to manage their conditions effectively. A comprehensive approach is crucial for addressing the diverse needs of these patients.
- **Dietary/nutritional needs:** For individuals with rare metabolic disorders, access to specialised food supplements and dietary integrators can be important.^{81, 111, 172, 218} However, resources for the assessment of dietary needs can be limited as also the knowledge about cost coverage, which can hamper access.^{111, 146, 218}

**Box 4 – NEED definition of forgone care¹⁰**

Forgone care refers to not using health care despite perceiving a need for it. This can be due to several reasons, including costs, waiting lists or travel difficulties.

(iii) **Suggested additional indicator: waiting time for medical appointment** The availability of experts and specialised centres emerges as a critical need in the context of rare diseases, with far-reaching implications for patients' healthcare journeys.^{186, 218} These findings in the literature were echoed during the stakeholder workshops by multiple participants. The availability of experts was mentioned by multiple participants during the stakeholder workshops as a high need, specifically in the context of rare diseases. General waiting time was mentioned in the context of rheumatology and central diabetes lipidus.^{74, 186, 204} Furthermore, despite being recognised as an essential service, access to psychological care appears to be hindered by long waiting times and a shortage of professionals.²⁰⁹

(iv) **Suggested additional indicator: travel distance to healthcare centre:** during the stakeholder workshop one participant mentioned distance to the healthcare centre as a possible measure for access, explaining that 12% of people living with a rare disease change their region of residence after diagnosis. Moreover, other participants stressed that even many people living with rare diseases are forced to go to other countries to access the care they need. Also in the literature travelling distance was assessed, a survey study with patients representing 344 different rare diseases reported that 47% of participants travelled more than 60 miles.²⁵² Also other studies, more specifically in primary sclerosing cholangitis and paediatric rheumatology, highlighted the burden of traveling travel great distances to reach specialist centres on patients.²⁵² Geographic disparities between urban and rural regions can exacerbate the availability of specialists, as infrastructure discrepancies contribute to uneven access to expert care.^{105, 270, 281}

Measurement or data collection methods

(i) **Treatment availability:** A survey study in patients with NET questioned whether patients had access to all therapies of which they had heard and then specifically asked the patients if they had heard of every specific treatment that exists for the specific disease and if they had received it.^{281, 282} This is a possible measurement method to assess treatment availability via the use of a survey.

The NEED framework uses expert opinion to assess availability of treatments, but this sub-criterion could also potentially be assessed via the patient survey, but further research is necessary. Literature, pricing and reimbursement assessment documents could also be consulted.

(ii) **Forgone care:** No specific measurement methods were identified from literature or stakeholder workshops.

(iii) **Suggested additional indicator: waiting time for a medical appointment:** Measurement methods from a survey study included the time between first appointment with HCPs and the referral to a specialist and waiting time between scheduling an appointment and being seen.¹⁸⁰

(iv) **Suggested additional indicator: travel distance to healthcare centre:** Both quantitative (survey) and qualitative assessments (interviews) were performed to assess the travel distance to specialist centres.^{105, 252, 270, 281} One way of assessing the travel distance and its impact on accessibility, is by asking the patient how far they have to travel or alternatively whether they perceive the distance to obtain care as long or not.^{105, 252, 270, 281}

Suggestions for the adjustment for criterion 'accessibility'Indicators:

- (i) **Treatment availability:** no proposed adaptations
- (ii) **Forgone care:** no proposed adaptations
- (iii) **PROPOSED: Waiting time for a medical appointment**
- (iv) **PROPOSED: Travel distance to healthcare centre**

Measurement or data collection methods:

- For the assessment method on treatment availability, expert opinion is the only assessment method currently applied in the framework. Based on the



literature it is proposed to also add a question to the patient survey as perceptions of patients on availability of treatments can differ with the perceptions from experts.

- Add two questions to the patient survey, one specifically covering the indicator 'waiting time' and one covering 'travel distance'.

PROPOSED CRITERION: Research needs

Within the stakeholder workshops, several participants mentioned the important lack of evidence and research as such, wondering whether this should be included in the framework as a separate criterion.

Indicators

- **Suggested additional indicator: availability of research and information:** The treating HCP can be confronted with a lack of knowledge, resulting from several factors, including inadequate documentation (e.g., brochures, information sources) about rare diseases, limited medical schooling (e.g. conferences, webinars) on these conditions, and a lack of practical expertise with rare diseases.^{91, 94, 141, 146, 197} A participant of the stakeholder workshop explains that for rare diseases, there is still a lot of trial and error and mistreatment in the clinical practice, due to the lack and low quality of available information. The latter was also confirmed in the literature.^{133, 188} Furthermore, one study reported that 99% of survey respondents felt that an improvement in awareness of their specific disease amongst general practitioners and local doctors is needed to encourage early referral.²⁷⁴
- **Suggested additional indicator: Existence of clinical practice guidelines:** Limited clinical guidance for individuals with rare diseases presents a challenge within the healthcare landscape. HCPs tend to experience a lack of available clinical guidance for various rare diseases.^{63, 85, 90, 141, 283} A participant of the stakeholder workshops

emphasized that an important criterion could be the absence of consensus guidelines for the care management of the disease considered (See European Reference Networks). This was echoed in an interview study in children living with rare diseases, proposing to develop "A guide with additional addresses of experts, information on the information needs of those affected, and possible therapy offers" to assist the treating specialists.²¹⁷

Measurement or data collection methods

In the literature, both patient and expert interviews and surveys were the most regularly applied measurement methods to assess the existence of clinical practice guidelines.^{63, 85, 90, 141, 283}

Suggestions for the adjustment of the criterion 'research needs'

Indicators:

- (i) **PROPOSED: Availability of research and information**
- (ii) **PROPOSED: Existence of clinical practice guidelines**

Measurement or data collection methods:

The proposed measurement method for both proposed indicators is expert opinions, complemented for clinical practice guidelines with a search in databases (e.g. guidelines international network (GIN)^o, orphanet^p, and GuidelineCentral^q).

^o Guidelines International Network (GIN): <https://g-i-n.net/international-guidelines-library>

^p Orphanet: <https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN>

^q GuidelineCentral: <https://www.guidelinecentral.com/guidelines/>

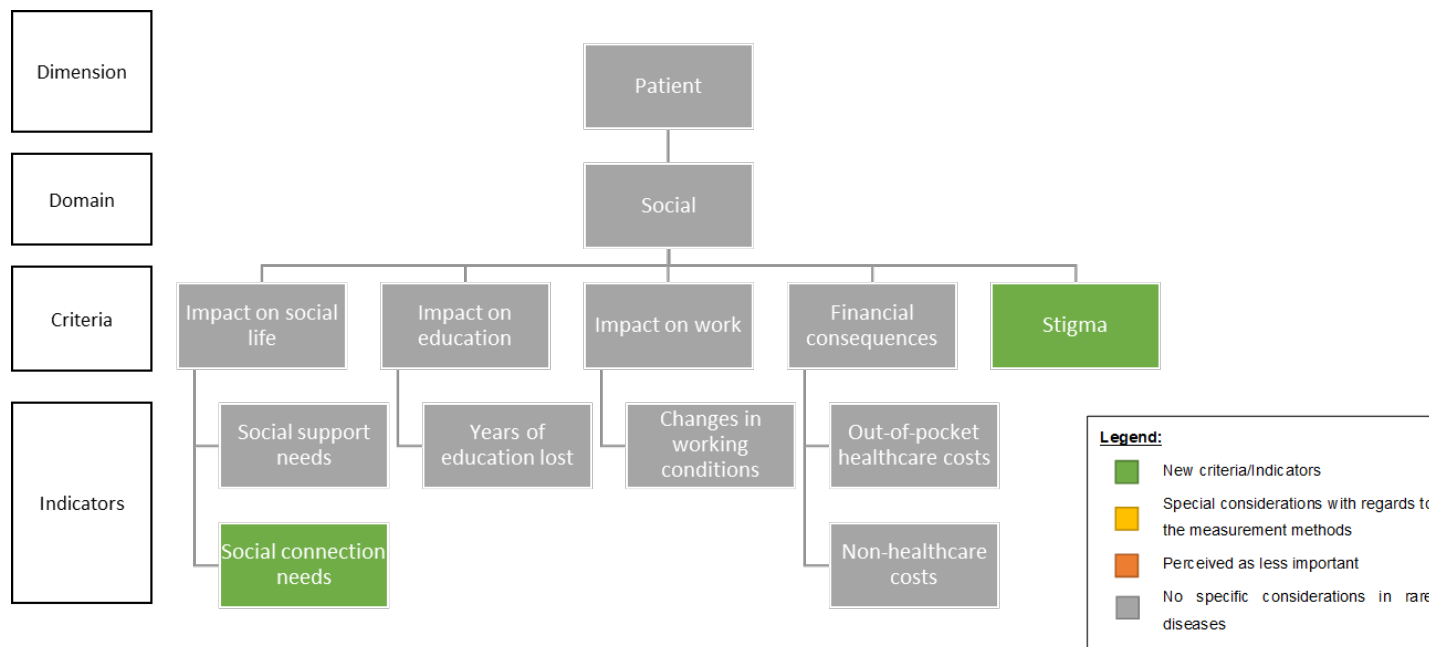


6.2.1.3 Social needs

Key Points

- **Rare diseases exert a significant impact on the social life of patients, influencing various facets such as work conditions, education, romantic relationships, family dynamics, and hobbies.**
- **The extent of this impact varies depending on the life stage of the patient, highlighting the need for a nuanced understanding of the specific challenges faced at different points in their lives.**
- **Stigma emerges as a substantial factor, exerting a profound influence on social integration and the overall well-being of patients.**

Patient social needs can be identified through four criteria: (i) impact on social life, (ii) impact on education, and (iii) impact on work and (iv) financial consequences. Each of these criteria encompasses one or two indicators, as illustrated in Figure 16. We propose the additional indicator “social connections needs” under the criterion (i) impact on social life. Each of these criteria encompasses one or two indicators, as illustrated in Figure 16.

**Figure 16 – Overview of the existing and suggested additional patient social needs criteria and indicators relevant to rare diseases**



CRITERION 1: Impact on social life

Indicator

The criterion 'impact on social life' encompasses one indicator: social support needs. Based on this literature review and stakeholder workshops, a second indicator is proposed: social connection needs.

(i) Social support needs: Some studies assessed the level of support obtained and the remaining gap that exists for patients.^{128, 280} A European Survey study in the mucopolysaccharidosis type VII patient population showed that access to social support varies across countries.²⁸⁰ Notably, the RARE-e-CONNECT platform is highlighted as a versatile tool that serves various purposes, from patient education to informed decision-making in critical situations.⁷⁷ Such platforms can bridge gaps in access to information and support. In addition to online platforms, it was observed that (1) peer support groups and (2) non-clinical guidance are immensely important in the context of rare diseases, yet tend to be lacking.

(1) Peer support groups emerge as a lifeline for people living with rare diseases in various stages of their disease.^{77, 274, 284} They provide a platform for sharing experiences and knowledge, offering psychosocial support, and helping patients manage their conditions better.^{101, 103, 251} For those dealing with the stress of an undiagnosed condition, peer support groups offer support and reduce feelings of isolation.²⁴² While there is a growing recognition of the importance of peer support groups, the literature also highlights challenges. Condition-specific support groups may not exist for undiagnosed diseases, leaving these patients and their families without a sense of community.²⁴² Where in-person support groups might lack to provide the needed help, online peer-support groups might make the difference.¹⁰³ Technology, particularly social media and online communities, has proven effective in connecting rare disease patients and their families. These platforms offer a safe space for interaction and information sharing, mitigating feelings of isolation.²⁷⁸ Besides the frequently mentioned need for peer support groups, patients and informal caregivers from patients living with rare diseases reported a need for educational support and self-help support.^{111, 189, 285}

(2) The scarcity of non-clinical guidance translates into a greater dependence of patients on healthcare provision, amplifying the impact of inappropriate care delivery and further frustrating patients and their families.¹⁰¹ The lack of guidance and strategies for independent self-management strengthens the challenges faced by patients living with a rare disease, highlighting gaps in care coordination and support.^{74, 186} Patients often find themselves lacking essential resources such as psychological support and practical information.²⁰⁴ One study showed that while some areas, like diet and supplements, may receive reasonable management advice, others such as physical activity, social care access, and mental health support exhibit gaps or even complete absence of guidance.¹³³ This unmet need for holistic support is emphasized, underscoring the need for comprehensive assistance that encompasses health system navigation, physical well-being, patient care, daily living, and emotional needs.¹³³ A participant of the stakeholder workshops stressed that *"all patients should get access to the social services at local, regional and national level. Many patients do not get access to these services or too late. The public health authorities should make a list of who is entitled to which services and how many citizens actually use them."*

The current indicator 'social support needs' seems appropriate in the context of rare diseases, as it is broadly interpreted and covers logistical support, peer support, administrative or social help, support in returning to work, and spiritual or religious support.

(ii) Social connection needs: Besides the criterion 'social support', the literature often discusses the social aspects affected by rare diseases. The latter impact is however missing in the NEED framework. One finding in the literature is that patients often struggle with feelings of isolation and concern about burdening others. The disease not only makes it difficult for them to interact with others but also affects their romantic relationships and friendships, leading to a thinning of their social circle.^{100, 166}

Participants of the stakeholder workshop agreed on the broad importance of social relations for individuals living with a rare disease, encompassing the capacity for leisure activities and maintaining friendships as reflected in literature.^{84, 230, 231, 286} During the stakeholder workshop there was a focus on individuals' ability to participate in normal societal activities. The literature reports fear among people living with rare diseases to no longer be able to



fulfil their roles in traditional roles in society.^{230, 286} Moreover, an interview study in primary biliary cirrhosis reports the challenge woman experience with their identity because of their self-images, centred on their domestic duties, which can no longer be fulfilled.²⁸⁶

Additionally, considerations extended to family planning, recognising the unique challenges faced, including potential isolation. The discussions also touched upon family dynamics, emphasizing the importance of understanding and addressing relational issues within families. One study reports side effects of treatment and long-term effects of the disease causing relationship problems and loss of libido as a cause of disruption of relationships.²³⁰

One study identified various domains reflecting the social impact of rare diseases, including: i) social connectedness, described as “personal relationships with others within social settings such as at home, or in day or community programs”, (ii) the natural environment, described as “interaction with the elements of nature and the outdoors, which was frequently associated with exhibiting settled behaviours. This included time spent at the beach, local park, or with animals”, and (iii) variety of activities, described as “the enjoyment generated by involvement in different interactive activities including community day programs, family activities, horse riding, sailing, looking at books, listening to music, watching television, and time spent in water”.⁸⁴

Measurement or data collection methods

(i) Social support needs: In the literature, surveys and interviews were the most commonly applied methods to assess the social support needs of patients living with rare diseases.^{111, 189, 280, 285}

As a result, the current data collection methods (patient survey and interviews) seem suitable.

(ii) Social connection needs: During the stakeholder workshop, one participant mentioned the HTx PROM select app, which would provide tools to measure the impact on social life in the broad sense.²⁸⁷ In the literature, studies with a predominant focus on social impact of a rare disease applied interviews^{84, 217, 231, 286}, and a combination of interview, focus group²³⁰ or survey^{252, 276, 288} (i.e. mixed-methods).

Adjustment suggestions for the criterion ‘Impact on social life’

Indicator

- (i) **Social support needs:** special attention is to be paid to the unavailability of peer support groups and scarcity of non-clinical guidance for patients and sources of social support needs.
- (ii) **PROPOSED: Social connection needs**

Measurement methods

- Add a question on social connection need to the patient survey and to the interview guide.

CRITERION 2: Impact on education

Rare diseases often manifest early in life, affecting children and young adults who are still in school and therefore frequently impacting productivity losses in educational pursuits.^{85, 179, 217} The cognitive, physical and emotional challenges associated with rare diseases can disrupt the patient’s ability to concentrate, fully participate in class or complete assignments. Frequent medical appointments, hospitalisations, and periods of illness can lead to missed school days, impacting the patient’s continuity of learning and may necessitate for catch-up efforts. Pinto et al. report school absenteeism to be a common issue among children with haemophilia in Portugal, with more than half of participants reporting missed school days due to their conditions.⁸⁵ This absenteeism not only hinders academic progress but also affects social integration and development, putting affected children at an academic and social disadvantage.²²⁹ Furthermore, patients suffering from tuberous sclerosis complex also reported lots of efforts to obtain good results at school as they require more effort and time for their school tasks.¹⁵⁷ The importance of assessing the impact on education was by multiple participants of the stakeholder workshops acknowledged.



Indicators

The indicator of use in the current NEED framework is Year of education lost. Alternatively, the impact of the rare disease could be measured based on the number of school days missed in a month.²²⁹ This assessment was applied in the study of Banerji et. al. where patients suffering from hereditary angioedema reported missing an average of two school days for their last attack and 48% believed that their disease hindered educational attainment.⁵³

Further dedicated research on the topic is needed to identify the most appropriate indicator.

Measurement or data collection methods

Most studies with a specific focus on educational needs used a survey²⁸⁰ or interviews¹⁷⁹. Consequently, the method (patient survey and interviews) suggested in the NEED framework seems appropriate.

Adjustment suggestions for the criterion 'Impact on education'

Indicators:

- (i) **Years of education lost:** could potentially be replaced by the number of school days missed, to obtain a more nuanced picture of the impact of the disease.

Measurement or data collection methods

- No proposed adjustments.

CRITERION 3: Impact on work

Patients coping with rare diseases often encounter significant limitations in their professional activities.^{85, 166} A substantial body of evidence underscores the profound influence of these conditions on work life.⁸⁵ For instance, Goldfarb et al. highlighted in 2023 that 25% of patients with primary hyperoxaluria reported a moderate amount of impairment while working due to their health condition.²²⁹ Furthermore, in a study on unmet needs in Cushing's syndrome approximately three-quarters of patients report that their professional activities have been notably affected.⁸² Disease-related challenges lead to changes in job responsibilities, absenteeism, and, in

some cases, voluntary or involuntary job termination.^{85, 190} Despite the acknowledged importance of the impact of rare diseases on work, several participants of the stakeholder workshops stressed that its impact extends beyond work. The impact on reintegration of a person, social inclusion, or self-development is perceived by some as more suited.

Indicators

The current indicator for the criterion 'impact on work' is 'changes in working conditions'. Rare diseases can hinder career progression and limit the types of jobs patients can perform. They may need to switch to part-time roles, accept lower-paying positions, or forgo promotions due to the uncertainty of their health condition. The impact on working conditions can be characterised by (i) the impact on job type, (ii) the impact on the intensity of the work, (iii) financial impact, and (iv) Reintegration into work life.

- **Impact on job type:** Depending on the severity and nature of the rare disease, patients may find it difficult to find a suitable new job as they find themselves restricted to certain job types or industries that accommodate their health condition.¹⁷⁹ This was also illustrated by Siden et al., revealing that 58% of patients suffering from hereditary angioedema reported that their rare disease affected career advancements.²⁸⁹ This limitation can result in lower-paying jobs or underemployment.¹⁸¹ This issue was further highlighted by the study of Both et al., where patients with tuberous sclerosis complex struggled with finding a suitable job since they often experience difficulties in coping with stress and therefore need a structured work environment.⁹⁵
- **Impact on work intensity:** Many patients have experienced changes in work responsibilities, necessitating reductions in working hours or taking unpaid leave.^{117, 177, 179, 190} Patients may even lose their jobs due to their health-related limitations affecting their ability to work or maintain a consistent work schedule or choose for early retirement.^{176, 179} The choice for early retirement can have substantial financial consequences, such as reduced income, reliance on savings, pensions or disability benefits, and the necessity to revise retirement plans.^{70, 113, 171, 198} Loss of work days is a measure of the impact of the rare diseases on working conditions used under the form of a survey.²⁹⁰



- **Financial impact:** Literature reports that changes in work conditions regularly impact the financial situation of the individuals living with the disease. For instance, in a study on patients living with Pulmonary arterial hypertension, 73% of patients (N=326) reported a major impact on finances, leaving many families with below average incomes.²⁷⁶ Another study in Australia, reports that more than half of the patients relying on financial support of the government regarded it as inadequate to establish an acceptable quality of life, raise a family or access local and wider communities.²⁹¹
- **Reintegration into work life:** Furthermore, individuals with rare diseases encounter barriers when seeking employment or attempting to reintegrate into work life.¹¹⁷ The reintegration of a person after the disease was also spontaneously mentioned by multiple participants during the stakeholder workshops. Some participants perceived the focus on work to be limited as normal social integration evolves with age. While work might be a crucial aspect for some, it may not be universally applicable across all age groups. This perspective advocates for a broader focus on social re-integration, including work, rather than solely assessing the impact on work, acknowledging the diverse ways individuals navigate societal engagement post-disease. One could opt to replace the criterion with the new proposed criterion on social impact or include both separate criteria.

Measurement or data collection methods

Most studies from the literature review applied interviews^{179, 190, 291} or surveys^{177, 176, 275, 276, 290} to assess the impact of rare diseases on work conditions. Topics that were regularly covered to assess working conditions related to the following topics:

- Part-time versus full-time job^{176, 275}
- Ability to work²⁷⁵
- Mean days of sick leave during the last year²⁷⁵
- Need to take days off¹⁷⁶
- Asking the employer to make accommodations¹⁷⁶

- Reduction of working hours¹⁷⁶
- Early retirement¹⁷⁶

The data collection methods (patient survey and interviews) currently included in the NEED framework seem appropriate. Survey questions could be added to cover the full picture.

Adjustment suggestions for the criterion 'Impact on work'

Indicators:

- (i) **Changes in working conditions:** attention must be paid to all four characteristics of working conditions:
 - the impact on job type,
 - the impact on the work intensity,
 - financial impact, and
 - Reintegration into work life

Measurement or data collection methods

- Add questions to the patient survey to cover the impact on the job type and work intensity.

CRITERION 4: Financial consequences

Research has underscored the profound economic challenges faced by individuals living with rare diseases. For instance, Valassi et al. found that 37% of patients with Cushing syndrome (N=326) reported a negative impact on their economic situation.⁸² Moreover, regardless of their professional status, a substantial proportion of adults (N=146, 55%) with haemophilia indicated that their financial income had been adversely affected.⁸⁵



Indicators

The two indicators used to measure the criterion “Financial consequences” seem appropriate:

- **Average healthcare out-of-pocket payments per patient:** A semi-structured questionnaire study with rare disease patients and families in the Valencian region in Spain showed that rare disease patients often encounter significant financial challenges related to their healthcare needs.¹²⁰ Access to specialised care and treatments may be hindered by the financial burden patients and families face. These challenges contributed to the inequalities experienced by individuals with rare diseases.¹²⁰ One study reported that psychological care, which is essential for emotional well-being, is unaffordable for over 22% of families (N=163) in this specific Spanish region, exacerbating emotional disorders such as anxiety and depression.¹²⁰ Physiotherapy, a frequently unmet need for those with chronic rare diseases, posed a considerable challenge due to limited accessibility despite being a common expense.¹²⁰ Although medication costs make up a significant portion of expenditures, non-medicinal therapies remain neglected, highlighting the financial challenges faced by patients.¹²⁰ Diagnostic tests, treatments, and specific nutritional needs, such as therapeutic formula, sometimes lack full insurance coverage, placing additional financial stress on patients.^{92, 131, 186} This financial uncertainty further impacts patients, who frequently report their inability to afford necessary therapeutic drugs and other medical care.⁷⁴ This issue is exemplified in a study conducted by Anderson et al. which revealed that half of the patients confronted with rare genetic metabolic disorders face insufficient financial assistance to cover their needs and costs.⁹⁰ Financial uncertainties extend throughout different stages of the disease journey, including diagnosis, pre-treatment, and long-term management, affecting job security, career advancement, and future planning.¹⁵⁸
- **Average non-healthcare costs per patient:** Studies revealed that rare disease management often involves costs associated with specialised clothing or equipment (e.g., easy access clothing, mobility aids and specialised devices to support the patient) and adaptations to the living

spaces through home modifications, e.g., to make it more accessible to the patient.^{157, 223, 232, 280} Furthermore, high non-medical expenses are often attributed to informal caregiver costs, encompassing both professional and informal caregivers, as many individuals affected with rare diseases necessitate support and assistance.^{61, 70, 156, 171} Another noteworthy non-healthcare costs that is specific to rare diseases are the substantial expenditures related to travel and accommodations required to access the specialised treatment. Patients and their informal caregivers frequently find themselves travelling long distances or even relocating temporarily to access the specialised care and expertise crucial for managing their rare disease effectively. These travel and accommodation costs can place an additional financial burden on those already coping with the challenges of rare diseases, underscoring the unique financial challenges associated with these conditions.^{11, 53, 74, 90, 104, 117, 123, 128}

In conclusion, the financial burden of out-of-pocket payments for healthcare services and treatments significantly affects patients living with rare diseases.¹²⁰ In some countries such as Spain, the lack of coverage for essential services like psychological care and therapies, along with expenses related to diagnostic tests and specialised treatments, exacerbates the financial challenges faced by individuals with rare diseases.^{92, 120, 161, 186}

Measurement or data collection methods

To enhance the understanding of the financial landscape associated with rare diseases, one participant of the stakeholder consultations suggested to incorporate targeted questions in the patient survey for out-of-pocket payments. One study by Bogart et al. used a survey method to assess the out-of-pocket payments of patients living with rare diseases, they applied cost-categories (i.e. \$500–999, \$1000–1499, \$1500–1999, \$2000–2999, over \$3000) and asked patients in what cost category they would put themselves.²⁵² Nevertheless, considering the challenges faced by patients in reliably estimating their out-of-pocket healthcare costs and their non-healthcare costs, the suggested data collection methods in the NEED framework (databases analysis, patient interviews and literature review) seemed appropriate.

**Adjustment suggestions for the criterion 'Financial consequences'**Indicators:

- (i) **Average healthcare out-of-pocket payments per patient:** No proposed adjustments
- (ii) **Average non-healthcare costs per patient:** No proposed adjustments

Measurement or data collection methods:

No proposed adjustments

PROPOSED ADDITIONAL CRITERION: Impact on stigma

Suggested indicator: Stigma. During the stakeholder workshops, multiple participants mentioned stigma as an important burden on patients, which was echoed in the literature review. A large-scale survey study (n=1 128 adults with a non-specified rare disease) reported a correlation between stigma and depression and anxiety, stressing the significant impact of stigma on patients' lives.²⁵² Similarly, in a literature review on psychosocial implications of rare genetic skin diseases, a negative impact on psychosocial conduction was reported resulting from stigma or even discriminatory acts.²¹⁶ Lastly, a survey study in complex vascular anomalies found that patients' physical and mental health care was associated with perceived stigma, which was expressed via social isolation or avoidance, embarrassment or judgment.²⁸⁸

Moreover, an international, large-scale, self-reported survey in patients with Pulmonary arterial hypertension showed that over half of patients (N=326, 55%) felt socially isolated due to the lack of understanding of the disease among family and friends, as well as the general public.²⁷⁶ A lack of awareness, understanding, and familiarity with rare diseases lays at the basis of this stigmatisation resulting from less attention for particular rare diseases and insufficient information due to limited research in this disease area. Therefore, the general population is not aware of the impact of rare diseases on patients and the challenges they may face. As a result, patients, informal caregivers, and family members did not feel understood by their social environment, causing less support and feeling of loneliness.^{93, 107, 127, 129, 217, 286}

Adjustment suggestions for the criterion 'stigma'Indicators:

- (i) **PROPOSED: add stigma**

Measurement or data collection methods:

- Add question to the patient survey and to the interview guide.

PROPOSED ADDITIONAL INDICATOR: Impact on social connections

Besides the criterion 'social support', the literature often discusses the social aspects affected by rare diseases. The latter impact is however missing in the NEED framework. One finding in the literature is that patients often struggle with feelings of isolation and concern about burdening others. The disease not only makes it difficult for them to interact with others but also affects their romantic relationships and friendships, leading to a thinning of their social circle.^{100, 166}

Indicators

Participants of the stakeholder workshop agreed on the broad importance of social relations for individuals living with a rare disease, encompassing the capacity for leisure activities and maintaining friendships as reflected in literature.^{84, 230, 231, 286} During the stakeholder workshop there was a focus on individuals' ability to participate in normal societal activities. The literature reports fear among people living with rare diseases to no longer be able to fulfil their roles in traditional roles in society.^{230, 286} Moreover, an interview study in primary biliary cirrhosis reports the challenge woman experience with their identity because of their self-images, centred on their domestic duties, which can no longer be fulfilled.²⁸⁶



Additionally, considerations extended to family planning, recognising the unique challenges faced, including potential isolation. The discussions also touched upon family dynamics, emphasizing the importance of understanding and addressing relational issues within families. One study reports side effects of treatment and long-term effects of the disease causing relationship problems and loss of libido as a cause of disruption of relationships.²³⁰

One study identified various domains reflecting the social impact of rare diseases, including: i) social connectedness, described as “personal relationships with others within social settings such as at home, or in day or community programs”, (ii) the natural environment, described as “interaction with the elements of nature and the outdoors, which was frequently associated with exhibiting settled behaviours. This included time spent at the beach, local park, or with animals”, and (iii) variety of activities, described as “the enjoyment generated by involvement in different interactive activities including community day programs, family activities, horse riding, sailing, looking at books, listening to music, watching television, and time spent in water”.⁸⁴

Measurement or data collection methods

During the stakeholder workshop, one participant mentioned the HTx PROM select app, which would provide tools to measure the impact on social life in the broad sense.²⁸⁷ In the literature, studies with a predominant focus on social impact of a rare disease applied interviews^{84, 217, 231, 286}, and a combination of interview, focus group²³⁰ or survey^{252, 276, 288} (i.e. mixed-methods).

6.2.2 Societal needs

Similarly to the ‘Patient needs’, the ‘Societal needs’ dimension encompasses three domains: (1) health, (2) healthcare, and (3) social, including various (sub)criteria and indicators. Table 13 provides an overview of the (sub-)criteria, indicators and the proposed methods to evaluate them.

A stakeholder during the workshop underscored the frequently overlooked but pivotal role of informal caregivers, particularly for family members and relatives caring for patients with rare diseases. Recognising and considering this impact on society is therefore considered imperative for a comprehensive understanding of the significant burden faced, extending beyond the patients to encompass the informal caregivers as well.



Table 13 – Overview of societal needs criteria, indicators and data collection methods in the NEED assessment framework and suggested adjustments in the context of rare diseases (in italic, and green)

Criterion	Indicator	Data collection method	Suggestion applicable to general or rare-disease framework
<i>Domain: Health needs</i>			
Frequency	Prevalence or incidence	Database analysis + Literature review	
Transmissibility	Contagiousness	Database analysis + Literature review	
	<i>Heritability</i>	<i>Expert opinion + Literature review</i>	<i>Rare-disease framework</i>
Antimicrobial resistance	Existing antimicrobial resistance to treatments used	Expert opinion + Literature review	
	Volume of antibiotic delivered to treat disease (proxy)	Database analysis + Literature review	
Burden on informal caregivers	<i>Impact on physical health</i>	Literature review + <i>interviews</i>	<i>General framework</i>
	<i>Impact on psychological health</i>	Literature review + <i>interviews</i>	<i>General framework</i>
	<i>Impact on autonomy</i>	Literature review + <i>interviews</i>	<i>General framework</i>
<i>Domain: Healthcare needs</i>			
Value for money of standard of care	Healthcare costs per unit of health gain (disaggregated presentation of total healthcare expenditures and total health effects of standard of care)	Database analysis + Literature review	
Preventability	Implementation of effective primary prevention strategies	Expert opinion + Literature Review	
<i>Domain: Social needs</i>			
<i>Impact on informal caregivers</i>	<i>Impact on social connections</i>	<i>Literature review + interviews</i>	<i>General framework</i>
	<i>Financial consequences</i>	<i>Literature review + interviews</i>	<i>General framework</i>



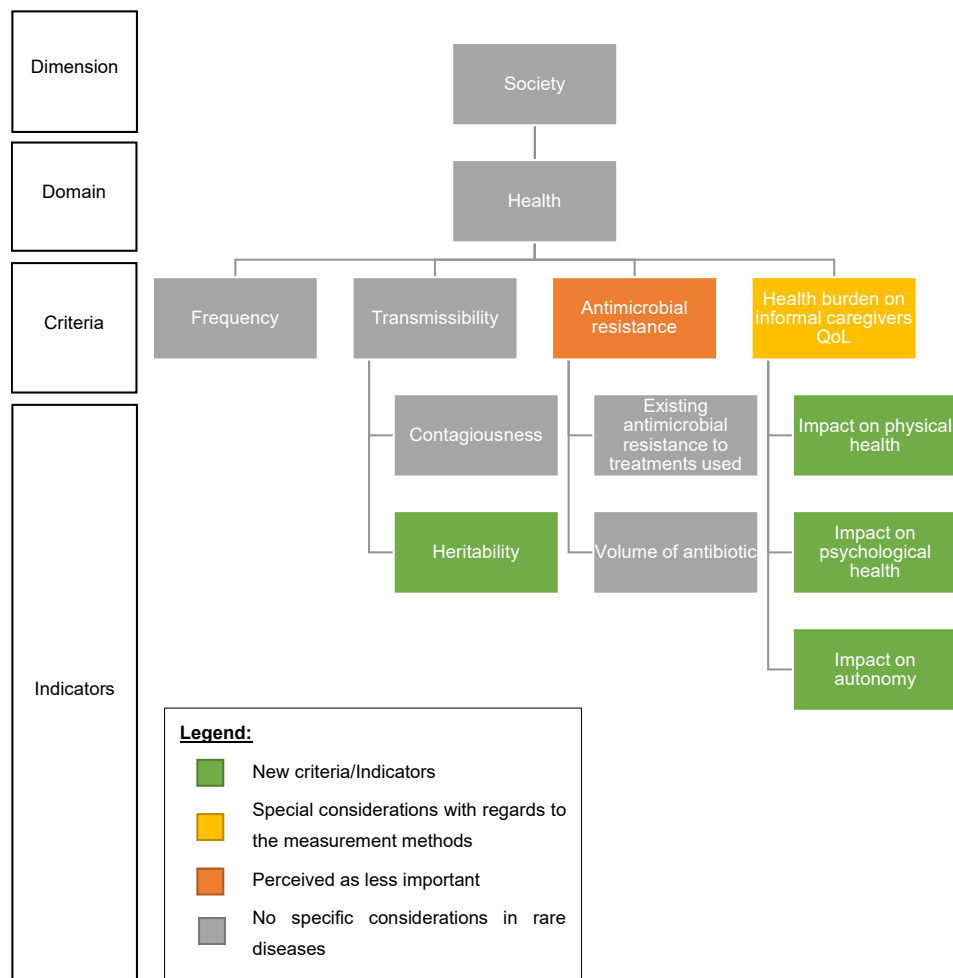
Productivity losses	Costs related to work absenteeism, presenteeism, early labour force exits of patients	Database analysis + Literature review + <i>patient survey</i>	<i>General framework</i>
	Costs related to work absenteeism, presenteeism or/and early labour force exits of informal caregivers	Literature review + <i>interviews</i>	<i>General framework</i>
Environmental impact of standard of care	Greenhouse gas emissions related to the standard of care	Expert opinion + Literature review	
	Hazardous waste related to standard of care	Expert opinion + Literature review	
	Use of natural resources and raw materials related to standard of care	Expert opinion + Literature review	

6.2.2.1 Health needs

Key Points

- In the context of rare diseases, a potential source of unmet needs is related to the hereditary component of certain rare genetic disorders.
- Informal caregivers of rare disease patients grapple with a substantial health burden, encompassing physical, psychological and autonomy-related challenges. This emphasises the need for a comprehensive assessment of informal caregivers' quality of life.

Societal health needs are identified through four criteria: (i) frequency, (ii) transmissibility, (iii) antimicrobial resistance, and (iv) health burden on informal caregivers QoL. The proposed NEED criteria and indicators are provided in Figure 17, together with suggested adapted or added criteria and indicators to make the NEED assessment framework more applicable to rare diseases.

**Figure 17 – Overview of the existing and suggested additional societal health needs criteria and indicators relevant to rare diseases**



CRITERION 1: Frequency

Indicator

Incidence and prevalence play pivotal roles in understanding the epidemiological burden and societal impact of rare diseases. However, measuring incidence and prevalence rates for rare diseases poses some challenges. These difficulties arise from factors such as the scarcity of cases, underreporting, and potential for underdiagnosis.^{101, 252} Rare diseases encompass a wide range of disorders with diverse clinical manifestations, contributing to the complexity of data collection. Moreover, the lack of awareness among healthcare professionals as well as the general public further complicate the hurdles associated with obtaining comprehensive data. These challenges are inherent due to the unique nature of rare diseases, which are characterised by a low frequency of occurrence in the population. Therefore, the lack of sufficient data makes it difficult to accurately estimate incidence and prevalence rates for rare diseases.^{56, 252, 292}

Measurement or data collection method

While databases appear to be the most suitable measurement method to measure incidence and prevalence, considerations should be made with this measurement method in the context of rare diseases.

Adjustment suggestions for the criterion 'Frequency'

Indicators

(i) **Incidence and prevalence:** No proposed adjustments

Measurement or data collection methods

- No proposed adjustments.

Applicability in the context of rare diseases should be carefully considered since incidence and prevalence rates are difficult to estimate.

CRITERION 2: Transmissibility

Indicator

Transmissibility is a relevant factor to consider in the context of common diseases, like the flu, common cold, and sexually transmitted infections, where contagious diseases can easily be transmitted. When focusing on rare diseases, the relevance of this criterion diminishes, given that these conditions affect only a small proportion of the population. Most of such diseases do not spread in the same way as infectious diseases. Rare diseases often result from a genetic mutation or other distinct factors, making transmissibility uncommon. Consequently, existing literature on rare diseases tends to scarcely address the concept of transmissibility.

While transmission within the general population remains largely irrelevant for rare diseases with a hereditary component, the criterion can focus on the transmission of the disease-causing genetic mutation from the parent to the child. As genetic rare diseases can be passed down through families such as Von Hippel–Lindau disease, Lysosomal Storage Diseases and rare genetic skin diseases, understanding the hereditary aspects and the likelihood of a child inheriting the condition becomes relevant.¹²⁷ Therefore, for genetic rare diseases, transmissibility within the broader community might not be relevant but transmission from parent to child becomes an essential aspect of managing and addressing rare genetic disorders, e.g., via carrier testing, prenatal screening, and genetic counselling. During the stakeholder workshop, some participants highlighted the absence of genetic inheritance as a crucial factor in the context of rare diseases, noting its significance for society. The participants emphasized that early detection through carrier and neonatal screening could not only prevent the inheritance but also mitigate the subsequent impact of the disease. Notably, participants of the stakeholder workshop regarded infectious transmissibility as less relevant in the context of rare diseases.

To augment the comprehensiveness of the NEED framework for rare diseases, consideration should be given to the hereditary component. This addition will enable a more thorough understanding of the health impact on society, including the children of individuals with rare diseases who may be susceptible to inheriting the genetic disorder gene.



Measurement or data collection method

No specific data was found on measurement methods.

No adaptations are proposed for the measurement method of the transmissibility basic reproduction number. To estimate the heritability indicator, a literature review and expert opinion can be used as measurement methods to estimate the heritability of the rare disease, revealing the genetic burden of the rare disease and the impact of genetic factors on its occurrence.

Adjustment suggestions for the criterion 'Transmissibility'

Indicators:

- (i) **Contagiousness**
- (ii) **PROPOSED: Heritability**

Measurement or data collection methods

- Add literature review and expert opinion as additional measurement methods for the indicator heritability.

CRITERION 3: Antimicrobial resistance

Indicator

Antimicrobial resistance primarily arises from the overuse or misuse of antibiotics and other antimicrobial agents in the treatment of bacterial infections. While antimicrobial resistance is a critical concern for public health, its relevance is only seldomly assessed in rare disease literature since rare diseases do not generally result from microbial factors. Nevertheless, it is noteworthy that in some cases of rare diseases, infections may occur.¹⁶³ Patients with rare diseases might be more susceptible and vulnerable to infections due to compromised immune systems or underlying health issues, resulting in the necessity to follow chronic antibiotic treatment, e.g. patients suffering from a severe combined immunodeficiency.¹⁵⁸ In these instances, existing antimicrobial resistance to treatment used and volume of antibiotics delivered to treat the disease might be pertinent considerations. However, in the literature, no references addressing antimicrobial resistance in the context of rare diseases were identified. Participants of the stakeholders workshop also perceived this criterion to be of lesser relevance.

Measurement or data collection method

Specific data on measurement methods were not identified in the literature. Nevertheless, during the workshop, some participants mentioned Farmaflux^r as a promising method for measuring the indicator related to the volume of antibiotics delivered to treat the disease. Farmaflux records both reimbursed and not-reimbursed medications delivered by pharmacists. Although access to these data might pose challenges, it is a noteworthy source that can be taken into account.

^r Farmaflux; <https://www.farmaflux.be/nl-BE> (last access: 2 February 2024)

**Adjustment suggestions for the criterion 'Antimicrobial resistance'**Indicators

- (i) **Existing antimicrobial resistance to treatment used:** no proposed adaptations
- (ii) **Volume of antibiotic delivered to treat disease:** no proposed adaptations

Measurement or data collection methods

- Investigate usefulness of 'Farmaflux' as a data collection method for the indicator "volume of antibiotic delivered to treat disease".

CRITERION 4: Burden on informal caregiversIndicator

For most rare diseases, informal caregivers provide crucial support, assistance, and care to those affected. However, this indispensable role often results in a substantial health burden on informal caregivers themselves. This burden on informal caregivers is reflected in the literature, where three key aspects of the multifaceted impact on informal caregivers' QoL are emphasized: impact on physical health, impact on psychological health and impact on autonomy (Table 14). Building upon these findings, the participants from the stakeholder workshop further highlighted the extensive burden on informal caregivers. Notably, a participant emphasized that siblings are also undeniably affected by the challenges posed by rare diseases.

Table 14 – Overview of burden on informal caregivers based on literature

Health burden on informal caregivers QoL	Aspects	Sources
Impact on physical health	- Fatigue and exhaustion. - Sleep-related issues - Pain	58, 61, 63, 67, 68, 107, 117, 201, 222, 226, 276 63, 67, 74, 99, 107, 108, 117, 174, 182, 222, 226, 229, 293 117, 207, 294
Impact on psychological health	- Anxiety - Depression - Stress - Worrying - Self-blame and guilt - Other emotions such as feelings of frustrations, mental exhaustion, fear, grief, sadness, and helplessness	58, 67, 68, 104, 107, 108, 117, 128, 132, 158, 207, 222, 223, 229, 270, 289, 294, 295 14, 58, 61, 67, 68, 108, 117, 158, 184, 207, 222, 289, 290, 294, 295 63, 65, 67, 90, 104, 107, 108, 128, 153, 186, 222, 226, 234, 289 58, 61, 68, 99, 107, 116, 127, 153, 158, 162, 180, 242 67, 68, 87, 91, 107, 127, 158, 201, 213, 270, 296 65, 67, 91, 104, 107, 158, 213, 222, 242, 270
Impact on autonomy	Changes in personal plans	11, 58, 61, 65, 99, 107, 116, 117, 213, 219, 226, 243, 289, 297



Based on the literature and stakeholder workshops, we propose changing the current indicator 'Loss in informal caregivers' QoL' to the following three indicators for the criterion 'Burden on informal caregivers':

- **Impact on physical health:** Informal caregivers often experience significant physical challenges resulting from the demanding caregiving responsibilities, including pain associated with tasks like lifting and transferring patients.^{117,207} This issue was further highlighted in the study by Lima et al. where the majority of informal caregivers for children with rare chronic kidney diseases reported pain in their bodies.²⁹⁴ In this context, a staggering 73.5% attributed changes in their bodies to the demands of caregiving tasks. Sleep-related issues were also often mentioned due to the scarcity of leisure time. Furthermore, the literature highlighted the prevalence of fatigue and exhaustion among informal caregivers.²⁷⁶
- **Impact on psychological health:** The caregiving responsibilities can have a toll on informal caregivers' psychological well-being. Predominantly highlighted in the literature, informal caregivers reported high levels of anxiety associated with witnessing patients' clinical deterioration, especially in severe cases or absence of a definite diagnosis or effective treatment.^{99,117} Depression is also a significant concern, with informal caregivers often experiencing moderate to severe symptoms. Informal caregivers endure significant stress, arising from concerns about the patient's health, uncertainty in caregiving, lack of guidance, inadequate support, and time commitment leading to insufficient self-care. Furthermore, informal caregivers express worries about the patient's future and safety, comprehension of their needs, and effective disease management. Feelings of self-blame and guilt are also common, rooted in the transmission of a defective gene resulting in the rare disease. Additionally, feelings of frustrations, mental exhaustion, fear, grief, sadness, and helplessness contribute to the complex emotional impact of caregiving in the context of rare diseases. Informal caregivers articulated that the impact on their mental well-being often exceeded the impact on their physical health, due to the management of their myriad caregiving responsibilities.⁹⁹ Participants in the stakeholder workshop also underscored the burden posed by mental

health challenges among informal caregivers, emphasizing the critical importance of addressing the psychological impact.

- **Impact on autonomy:** The demanding nature of caregiving, including numerous appointments and extensive travels to consult specialists or receive treatments, also severely limits informal caregivers' personal plans, including employment, usual activities and opportunities for respite, self-care or holidays. For instance, a striking majority (77%) of informal caregivers for individuals afflicted with Dravet syndrome reported having less than a solitary hour each day for personal respite.¹¹⁶

By assessing the impact of informal caregiving on the physical, psychological, and autonomy level, a more comprehensive assessment of informal caregivers' QoL can be obtained. This differentiation becomes especially pertinent given the often profound dependency of individuals afflicted with a rare disease on the supportive care provided by their families or informal caregivers. The informal caregivers' lived experiences and well-being exert a profound impact on their own lives. Hence, it is imperative to consider and thoroughly assess the different factors, as underscored in the literature.

Measurement or data collection method

In the literature, informal caregiver burden is measured using various tools. The Family Management Style framework (FSMF) provides a conceptual understanding of how families integrate chronic disease management into their daily lives.²⁹⁸ The Zarit Burden Interview (ZBI-22), a 22-item survey, delves into the psychological aspects of informal caregiver burden and explores the caregiver-patient relationship.^{74, 180, 237} To quantify informal caregivers' stress, various studies use specific tools such as the Distress Thermometer for Parents (DT-P) and the Caregiver Strain Index (CSI).^{117, 226} Assessing parental support needs for children with rare diseases involves tools like the Parental Needs Scale and the Caregiver Burden Scale (CBS).^{270, 294} The latter, encompasses five domains to categorise informal caregivers' burden: general tension, isolation, disappointment, emotional involvement and environment, provides a comprehensive understanding of informal caregivers' burden.²⁹⁴ Whether offering broad insights into the



overall informal caregiver burden or focusing on specific dimensions, these tools provide valuable perspectives into the multifaceted challenges faced by informal caregivers.

Although the informal caregiver burden is described in literature, relying solely on literature as a measurement method to understand the informal caregiver burden in the context of rare diseases has limitations. Literature may not capture the multifaceted and dynamic experiences of informal caregivers, especially for rare diseases with each rare disease having its distinct caregiving demands and specific challenges. Furthermore, a review of the literature may not sufficiently reflect the perspectives of informal caregivers who may not actively engage with healthcare systems or research. This challenge is exacerbated by the fact that the informal caregiver burden is frequently overlooked and not consistently assessed for every rare disease. To achieve a more comprehensive understanding of the informal caregiver burden in the context of rare diseases, literature-based insights can be supplemented with insights from qualitative research, including interviews and focus group discussions. This approach ensures a more holistic understanding of the unique needs of informal caregivers facing the complexities of rare diseases. Many participants in the stakeholder workshops strongly advocated to include interviews, focus group discussions or surveys, underscoring the recognition of the need for a more comprehensive understanding of the challenges faced by informal caregivers in the context of rare diseases. One participant further highlighted the drawbacks of relying solely on literature, indicating that *“It is too late, too limited, and often too foreign”*.

Adjustment suggestions for the criterion ‘Burden on informal caregivers’

Indicators:

- (i) **PROPOSED: Impact on physical health**
- (ii) **PROPOSED: Impact on psychological health**
- (iii) **PROPOSED: Impact on autonomy**

Measurement or data collection methods

- Add interviews with informal caregivers as data collection method.

6.2.2.2 Healthcare needs

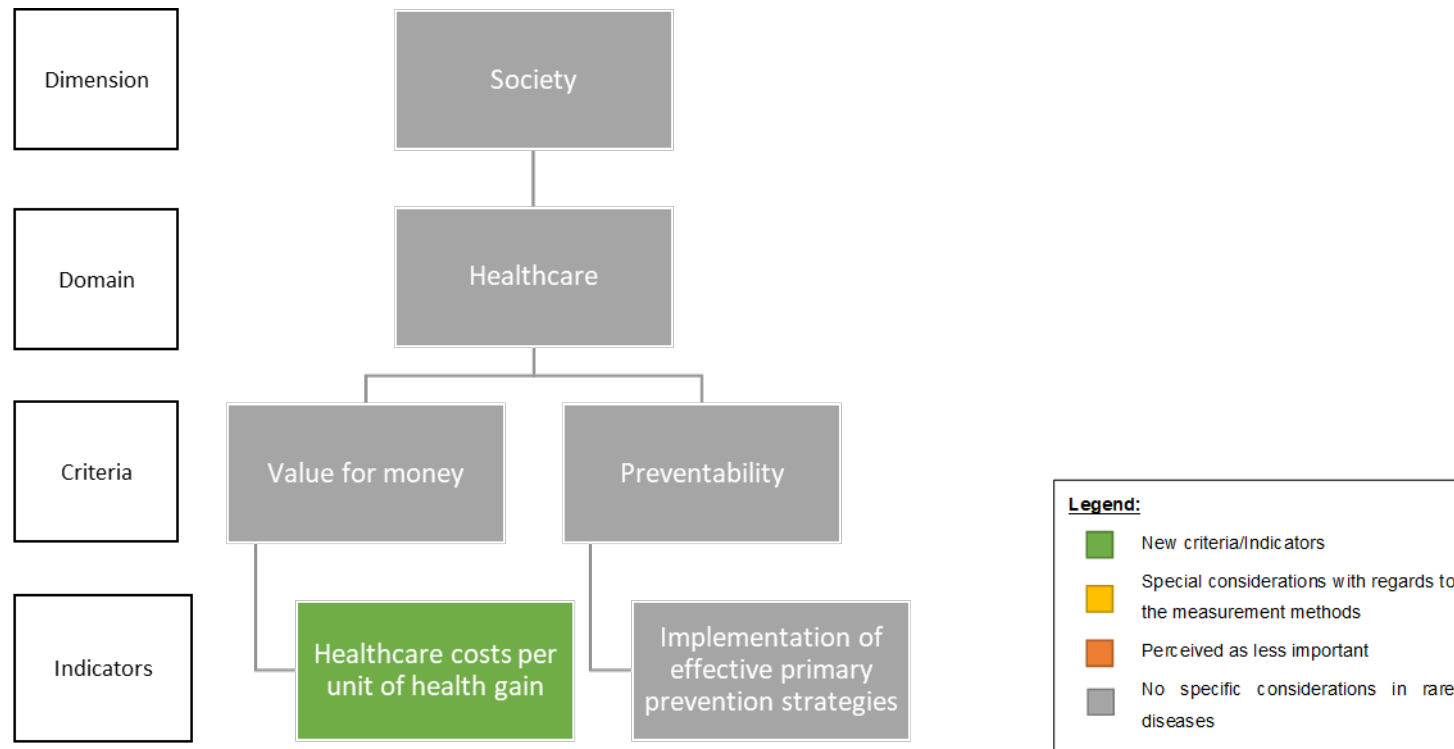
Key Points

- **Rare diseases represent a significant public health challenge with a profound economic impact for healthcare systems.**
- **Evaluating the healthcare cost per unit of health gained for rare diseases is challenging due to their low prevalence, limited data, and uncertainties in clinical outcomes. Due to their high costs, rare disease treatments are seldom cost-effective.**

Societal healthcare needs comprise one criterion “value for money of standard of care”, which is further measured by one indicator as illustrated in Figure 18.



Figure 18 – Overview of the existing and suggested additional societal healthcare needs criteria and indicators relevant for rare diseases





CRITERION 1: Value for money of standard of care

Indicator

Rare diseases may individually affect a small number of people, but collectively, they represent a significant public health challenge with profound economic impact on a societal level. The management and treatment of these conditions presents a unique challenge for healthcare systems, as they are sometimes associated with substantial healthcare costs per unit of health gained. Therefore, understanding the economic burden of rare diseases from a societal perspective is essential. However, evaluating the healthcare cost required to gain one year of high-quality life of interventions for rare diseases is challenging due to their low prevalence, limited data and uncertainties in clinical outcomes.

Direct health-related costs from a societal perspective were mentioned in the literature related to rare diseases. One of the most immediate apparent economic burden of rare diseases is the cost of diagnosis and treatment. Due to the limited prevalence and complexity of many rare diseases, patients often endure a lengthy and costly diagnostic odyssey with multiple rounds of testing and consultations with various specialists before receiving a definitive and correct diagnosis.^{123, 171, 295} Notably, the study of Teare et al. underscored that the high costs associated with the diagnosis can vary significantly depending on the speed of diagnosis and the complexity of the underlying aetiology.¹²³ Once diagnosed, patients necessitate access to highly specialised and long-term healthcare services, including frequent hospitalisations, regular monitoring in specialised centres, consultations with expert clinicians, genetic testing, advanced imaging, and expensive medications.^{74, 90, 99, 133, 156, 171, 270} The cost associated with these specialised medical treatments can reach exorbitant levels. Furthermore, these treatments often focus on managing symptoms and improving the patient's QoL as many rare diseases lack a cure for the disease.^{68, 70, 94, 99, 188, 256, 281, 295} For instance, patients suffering from cystic fibrosis bear high treatment costs due to the type, quantity and frequency of the prescribed medication, particularly for recently licensed drugs.⁹⁴

Depending on the nature of the rare disease, patients may require ongoing rehabilitation and physical therapy to maintain their functional abilities. These services can be both costly and time-consuming.¹⁹⁸ The stress, anxiety, and depression that can result from living with a rare disease can lead to increased healthcare utilization and costs related to mental health services.^{61, 91}

Overall, the convergence of the conditions' rarity and the steep healthcare costs associated with rare diseases poses a challenge in distributing these expenses equitably across a broader population. The high costs per unit of health underscore the seldom cost-effectiveness of rare disease treatments, raising concerns about the sustainability and accessibility of healthcare services in resource allocation. This not only affects the affordability of healthcare for all but also exacerbates the economic strain associated with these rare diseases.⁹⁹

Participants in the stakeholder workshop highlighted the challenges associated with the availability of standard of care for rare diseases. Furthermore, one participant addressed the importance of going beyond the provision of standard of care by considering the uptake of preventive measures, screening, and the associated societal costs to help mitigate the impact of rare diseases.

Measurement or data collection method

One participant of the stakeholder workshop mentioned the importance of considering evidence beyond data obtained through large randomised clinical trials, including phase IV real-world data to complement clinical findings, particularly in demonstrating effectiveness.

While databases appear to be the most suitable measurement method to define the cost per QALY, the high costs associated with rare disease treatments often make them seldom cost-effective, necessitating careful considerations with this measurement method in the context of rare diseases.

**Adjustment suggestions for the criterion 'Value for money of standard of care'**Indicators:

- (ii) **Value for money of standard of care:** No proposed adjustments
Applicability in the context of rare diseases is questioned since most rare disease treatments are expensive and thus seldom cost-effective.

Measurement or data collection methods:

- No proposed adjustments.

CRITERION 2: Preventability**Indicator**

Preventability is a crucial aspect in the context of rare diseases, extending beyond the patient level to encompass societal and economic aspects. Rare diseases can lead to substantial healthcare costs, both in terms of diagnosis and ongoing medical care. Preventative measures not only alleviate the financial burden on healthcare systems but also enhance the overall well-being of patients. Unlike more common diseases, rare diseases often lack established measures, early detection methods, and accessible treatment options. Consequently, preventative measures in the context of rare diseases are needed for early detection, treatment, and ultimately a lower burden on patients and society. Literature shows that the availability of screening methods over European countries is uneven, pointing at a need for easy access to information about the techniques used for screening and their availability to improve application.²⁰⁶ Moreover, one participant explains that the guidelines for diagnostic tests differ between countries (e.g. the Netherlands and Belgium) and in Belgium between regions. Several stakeholders from the workshops stressed that in various rare diseases there are no specific diagnostics tests or systematic screening programmes, which delays the diagnosis. Participants in the stakeholder workshops further explain that sufficient attention must go to the prevention of diseases. They explained that prevention could for instance be in the form of information campaigns, screening programmes, and family disease identification.

Measurement or data collection methods

No specific data was found on measurement or data collection methods.

Adjustment suggestions for the criterion 'Preventability'Indicators:

- (i) **Implementation of effective primary prevention strategy:** No proposed adjustments

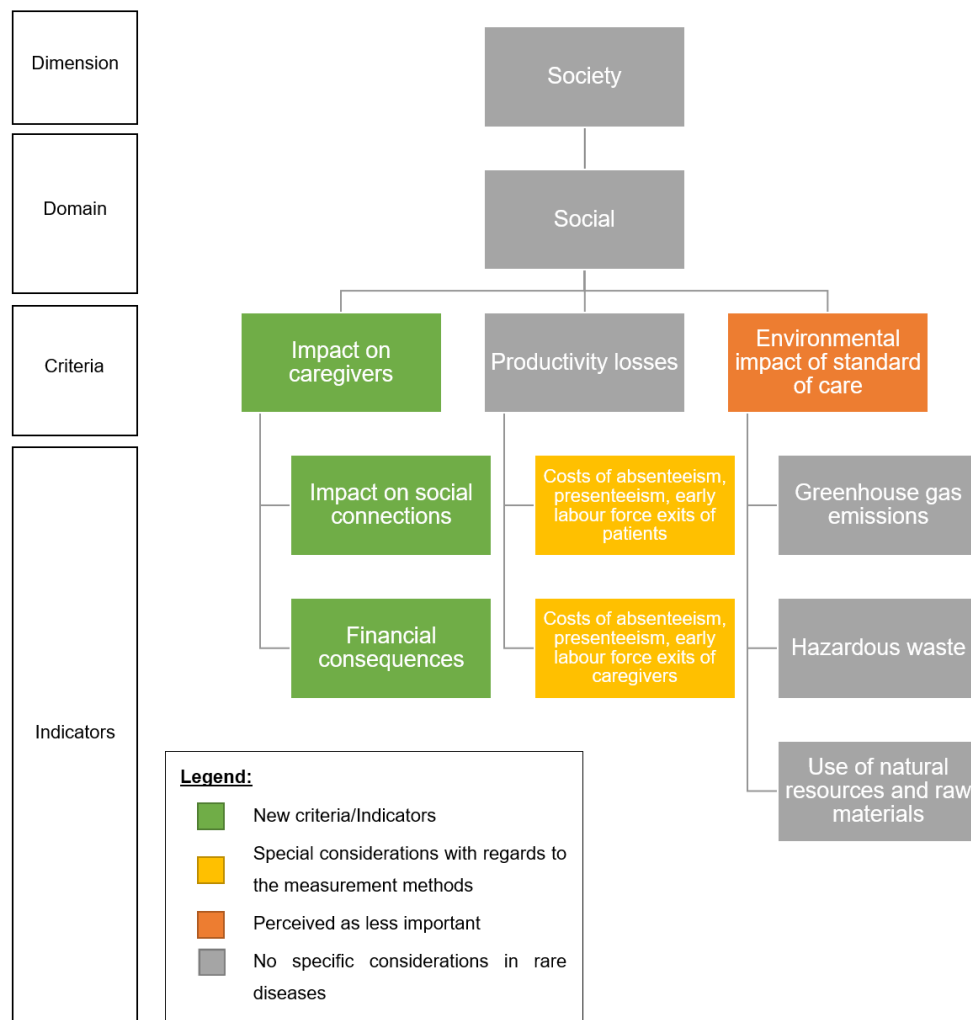
Measurement or data collection methods:

- No proposed adjustments.

6.2.2.3 Social needs**Key Points**

- **Rare diseases often disrupt patients and informal caregivers' ability to work, leading to substantial losses in work-related productivity. These productivity losses not only impose costs on the patients directly affected but also extend to their informal caregivers and have broader economic implications for society.**
- **The impact of rare diseases on society goes beyond productivity losses for informal caregivers, affecting society through profound social implications such as isolation, strained partner relationships, and potential marriage breakdowns, as well as substantial financial burdens for informal caregivers.**

At the societal level, the identification of social needs comprises two criteria: (i) productivity losses, encompassing two indicators, and (ii) environmental impact of standard of care, encompassing three indicators. We propose a third criterion: (iii) impact on informal caregivers, encompassing two indicators, as illustrated in Figure 19.

**Figure 19 – Overview of existing and suggested additional societal social needs criteria and indicators relevant for rare diseases**



CRITERION 1: Productivity losses

Indicator

The criterion 'Impact on productivity losses' contains two indicators, being costs related to work absenteeism, presenteeism, and early labour force exits of (i) patients, and (ii) informal caregivers.

- **Cost related to work absenteeism, presenteeism or/and early labour force exits of patients:** Rare diseases often disrupt patients' ability to work due to frequent medical appointments, and limitations caused by symptoms of the disease and side effects of the treatment.^{53, 229} Consequently, individuals with rare diseases may be frequently absent for medical reasons, experience reduced work efficiency, and partially or completely withdraw from work, as discussed in the patient social need criterion 'Impact on work'. Additionally, for young patients, rare diseases can disrupt education, leading to missed school days and potential difficulties in pursuing higher education or specific career paths.^{53, 95} These collective challenges not only affect individual patients but also have broader implications for society. Reduced workforce productivity, whether due to absenteeism, job limitations, or job loss, can result in economic losses for both employers and the broader economy, impacting overall economic output and growth.
- **Cost related to work absenteeism, presenteeism or/and early labour force exits of informal caregivers:** Informal caregivers, often family members or close friends, may also experience significant productivity losses when caring for individuals with rare diseases. Frequently, informal caregivers need to reduce their working hours or take extended leaves to fulfil caregiving responsibilities.¹⁹⁹ This leads to decreased income and potential harm to their own careers, as highlighted by Lagaea et al., where 65% of informal caregivers reported taking time off work to provide care for their child, e.g., emergency care or routine visit to the HCP.¹¹⁶ The emotional and mental toll of caregiving further impact a informal caregiver's job performance, affecting their ability to concentrate and be productive. Informal caregivers grappling with stress, anxiety, and burnout become more

susceptible to absenteeism.^{79, 157} Furthermore, long-term caregiving responsibilities can result in career interruptions or permanent departures from the workforce, as indicated by Acaster et al., where 56% of informal caregivers for patients with hereditary transthyretin amyloidosis reported changes in their employment, with only 42% working full-time or part-time.¹⁰⁸ These career interruptions hinder professional development and opportunities for career advancements, highlighting the significant challenge of balancing caregiving responsibilities with professional growth as frequently described in the literature.^{157, 223, 229, 241, 269, 289} The significance of informal care provided by informal caregivers and the consequential productivity losses impose a burden on informal caregivers that is currently insufficiently explored in research.²⁹⁹

While some participants in the stakeholder workshop raised concerns about using the term 'productivity', it was acknowledged that the term also encompasses days missed at work and various other factors illustrating the broader impact of rare diseases on patients and informal caregivers, which was deemed relevant.

Measurement or data collection method

In the literature, the Work Productivity and Activity Impairment (WPAI) and its adapted version specific for caregiving (WPAI:CG) serves as a tool to measure lost productivity experienced by patients and informal caregivers. This validated tool captures the extent of impairment in work and non-work-related activities of daily living. The survey generates four distinct subscales presented as percentages: absenteeism, presenteeism, overall work impairment, and activity impairment.^{223, 229, 237}

For estimating the time devoted by informal caregivers to their responsibilities, a participant proposed measuring the Full Time Equivalents (FTEs) of informal caregiving, emphasizing its particular importance in the context of rare diseases where informal caregiving demands can be notably extensive. Furthermore, another participant emphasised the significant value of incorporating surveys and interviews as complementary methods to enrich the data collection method suggested in the NEED framework.



To assess the costs related to work absenteeism, presenteeism, and early labour force exits of patients, databases serve as a suitable resource. Nevertheless, the assessment can be complemented with questions in the patient survey that specifically address patients' perspectives regarding their absenteeism, presenteeism and early labour force exits. Furthermore, relying solely on literature for assessing the costs related to work absenteeism, presenteeism or/and early labour force exits of informal caregivers may not be sufficient, particularly given the limited literature on informal caregivers for rare diseases. To complement this data collection method, interviews could be added to provide a more comprehensive understanding of the economic implications.

Adjustment suggestions for the criterion 'Productivity losses'

Indicators

- (i) **Costs related to work absenteeism, presenteeism, early labour force exits of patients:** no proposed adaptations
- (ii) **Costs related to work absenteeism, presenteeism or/and early labour force exits of informal caregivers:** no proposed adaptations

Measurement or data collection methods

- Add patient survey and interviews as additional data collection methods.

CRITERION 2: *Environmental impact of standard of care*

Indicators

In the literature, the focus has primarily been on the medical, economic, and social aspects related to rare diseases. However, environmental implications may be relevant in the context of rare diseases as often specialised treatments, medications and medical devices require resource-intensive manufacturing processes with production in limited quantities. Furthermore, the transportation and logistics to access these treatments, medications and medical devices can be substantial, including the travelling required by patients and their families to reach these specialised services.

Despite these environmental implications, no evidence on greenhouse gas emissions, hazardous waste, or use of natural resources and raw materials related to the standard of care for rare diseases was found in the rare disease literature. Participants in the stakeholder workshop also noted that this criterion was perceived as less relevant.

Measurement or data collection methods

No specific data was found on measurement or data collection methods.

Adjustment suggestions for the criterion 'Environmental impact of standard of care'

Indicators:

- (i) **Greenhouse gas emissions related to the standard of care:** no proposed adaptations
- (ii) **Hazardous waste related to standard of care:** no proposed adaptations
- (iii) **Use of natural resources and raw materials related to standard of care:** no proposed adaptations

Measurement methods

- No proposed adjustments.

PROPOSED ADDITIONAL CRITERIA

CRITERION: *Impact on informal caregiver*

The impact on society, encompassing both patients, informal caregivers and beyond, surpass considerations of productivity losses and environmental impact, as emphasized by a participant in the stakeholder workshop. The participant suggested a broader interpretation of the term 'social', acknowledging its relevance to various dimensions of life beyond a strictly economic perspective.



Indicators

Based on the literature and stakeholder workshops, we propose the following two indicators for the additional criterion 'Impact on informal caregiver':

- **Suggested indicator: Impact on social connections.** The burden of caregiving extends beyond the immediate challenges of providing care, also encompassing profound social implications for informal caregivers on both relationships external and internal to the family.³⁰⁰ The social impact is often expressed through a perceived sense of isolation for informal caregivers, resulting from the overwhelming demands of their responsibilities.^{14, 61, 65, 68, 99, 107, 144, 223, 270, 294, 295} Moreover, the demanding nature of caregiving, including numerous appointments and extensive travels to consult specialists or receive treatments, compounds the social implications by not only limiting informal caregivers' employment opportunities but also disrupting their personal plans, necessitating adaptations in lifestyle and leaving minimal room for respite or holidays.^{11, 58, 61, 65, 99, 107, 116, 117, 213, 226, 243, 289, 297} Illustrating this constraint, a striking majority (77%) of informal caregivers for individuals afflicted with Dravet syndrome reported having less than a solitary hour each day for personal respite.¹¹⁶

Another profound social implication is the strain on partner relationships, with many parents experiencing growing apart or even the breakdown of their marriage due to the burdens of caregiving.^{99, 144, 219, 223} Participants in the stakeholder workshops emphasized the profound impact on families, noting that many marriages do not endure the challenge posed by an untreatable disease without a prognosis. The breakdown of marriages also carries economic consequences, imposing additional financial burdens on informal caregivers and family members. The lasting impact of living with a serious disease resonates across generations, underscoring the need to consider these social implications as highlighted by numerous participants in the stakeholder workshops.

- **Suggested indicator: Financial consequences:** Participants in the stakeholder workshops highlighted the importance of considering the multifaceted financial impact associated with rare diseases, extending the focus beyond the impact on patients, as outlined in the NEED assessment framework, to include the impact on informal caregivers and the entire family. These financial implications encompass costs incurred due to for instance marriage breakdown.²¹⁷ The financial impact extends beyond non-healthcare costs such as household adaptations and travel costs, as informal caregivers also face substantial financial strains due to uncovered healthcare costs.²⁹⁰ The significance of the financial impact was further underscored in literature, with Applebaum et. al. reporting that nearly half of the informal caregivers had utilised most or all of their family's savings on care for patients with Erdheim-Chester disease.²⁹⁵

Measurement or data collection methods

The assessment of informal caregivers' impact, encompassing both social and financial implications, can be conducted through surveys or qualitative interviews. For instance, the Family Needs Assessment Tool (FNAT), a validated self-reported tool on social support, can be used for evaluating family coping and functioning based on parents' perceptions.⁵⁸ These measurement methods allow to gather a comprehensive understanding of informal caregivers' experiences, shedding light on the intricacies of their social dynamics and financial challenges.

Social impact could potentially be assessed via a literature review and interviews.

Adjustment suggestions for the criterion 'Impact on informal caregiver'

Add the criterion 'Impact on informal caregiver', with as indicators:

- PROPOSED: impact on social connections**
- PROPOSED: financial consequences**

Measurement or data collection methods:

- Add literature review and interviews with informal caregivers as data collection method.



6.2.3 Future needs

Similarly to the two other dimensions of the NEED assessment framework, “future needs” encompass health, healthcare and social needs. Table 15 provides an overview of the criteria, indicators and the proposed methods to gather evidence on such criteria.

Table 15 – Overview of future needs criteria, indicators and data collection methods in the NEED and suggested adjustments in the context of rare diseases (in italic)

Criterion	Indicator	Data collection method
Domain: Health needs		
Burden of disease	Future prevalence/incidence	Database analysis + Literature review
	Future years of life lost	Database analysis + Literature review
	Future years lived with disability	Database analysis + Literature review
Domains: Healthcare and social needs		
Economic burden	Future direct costs attributable to the health condition	Database analysis + Literature review
	Future indirect costs attributable to the health condition	Database analysis + Literature review

In the literature review, no studies focus specifically on assessing the future needs at the patient or societal level related to rare diseases nor did participants of the stakeholder workshop propose specific adaptations to the NEED framework.

6.2.4 Transversal dimension: Equity

In the context of equity, the literature review and stakeholder consultations identified five crucial elements: (i) sex and gender differences, (ii) socio-cultural conditions, (iii) intellectual disability, (iv) geographical disparities, (v) disease area, and (vi) diagnosis.

(i) Sex and gender differences: During the stakeholder workshops, some participants emphasised the importance of incorporating gender as a criterion within the equity transversal criteria. This suggestion stems from the recognition that not all rare diseases affect both genders equally and a lot of clinical research and development tends to be disproportionately male-oriented. Literature further supports this perspective; for instance, a meta-analysis on osteogenesis imperfecta in adults underscores the growing importance of sex differences with age, attributed to biological, psychological, and social changes.¹⁵¹ An additional study points to gender roles influencing the expression of disease burden, emphasizing the need to consider societal expectations in healthcare contexts.²⁸⁶ The latter is explained as follows “a traditional gender view, women are expected to carry out the household chores and other responsibilities implied by their gender roles which may turn into a reason for underestimating fatigue and justifying the lack of understanding of the impact of fatigue within the family context”.²⁸⁶

(ii) Socio-cultural conditions: Findings from stakeholder consultations and existing research reveal that socio-cultural conditions significantly impact healthcare navigation.¹⁸⁸ For instance, one study indicates that more educated individuals tend to benefit more from treatment programs due to the literacy requirements associated with manuals and computer usage.³⁰¹ Additionally, certain demographic groups, including Black, Indigenous, and People of Colour, encounter limited access to innovative medications, as evidenced by a survey study in the US with individuals with Cystic Fibrosis.¹⁷⁸



(ii) Intellectual disability: During the stakeholder consultations, a participant underscored that individuals with intellectual disability are vulnerable to receiving inappropriate care when faced with other health issues, especially within the context of rare diseases where mental impacts on patients are prevalent.

(iii) Geographical inequity: Geographical disparities pose challenges to equitable healthcare access. A qualitative study in informal caregivers of patients with GM1-gangliosidosis reports that parents from South America experienced less timely and adequate communication among healthcare professionals and were less informed about the genotype of their child as compared to parents on other continents.¹²⁸ Another study in China with families of patients with Gaucher disease, shows that health care covers differs between regions.¹⁴⁸ More rural areas tend to have no drug coverage resulting in high financial burdens on families.¹⁴⁸ Also in Europe, this could be expected as healthcare coverage differs between member states, resulting in inequitable healthcare access.

(iv) Disease area: Inequality in the provision of care is observed across different disease areas. A qualitative study in Australia on parents of children with rare diseases reveals that parents of children diagnosed with cancer receive more comprehensive support compared to those with other rare conditions.¹⁴⁴ The support includes medical team assistance, coordinated care, financial aid, and counselling, indicating discrepancies in the level of care provided to different disease groups.¹⁴⁴

(v) Undiagnosed patients: A critical concern raised during consultations pertains to the majority of rare disease patients who remain unidentified within the healthcare system. This invisibility stems from the lack of studies, data, and registers, resulting in the often overlooked needs of this invisible group. Addressing this issue is paramount for achieving true equity in rare disease healthcare.

6.3 Discussion and conclusion

In this study, both scientific peer-reviewed and grey literature sources were assessed to explore how unmet health-related patient and societal needs are presently defined and measured within the context of rare diseases. In a second step, findings were discussed with stakeholders during two stakeholder consultations. The literature review resulted in 272 scientific publications that examined the indicators associated with unmet health related needs in the context of rare diseases. These studies explored how these indicators are measured and outlined the diverse challenges encountered in this measurement process. This report highlights the relevance of the already included criteria and indicators in the NEED assessment framework and proposes adjustments and additions to the framework to make it relevant in the context of rare diseases.

The existing NEED assessment framework, with its established criteria and indicators, proved to be well-suited for measuring the unmet health-related needs of patients and society in the context of rare diseases.

In enhancing the comprehensiveness of the framework, this report suggests additional criteria to provide a more nuanced understanding of the diverse needs experienced by patients and society in the context of rare diseases. However, most recommendations also apply to more common diseases. These suggested additional criteria (n=4) and indicators (n=17) span across the three dimensions and recurring domains. Within the health domain, recommendations include introducing a criterion focused on impact on reproductive health, along with indicators addressing unpredictability and impact on self-esteem. In the healthcare domain, the literature consistently emphasizes criteria related to the availability of information and diagnosis, necessitating special attention. Suggestions in this domain primarily centre on refining the framework's granularity, especially in the context of rare diseases. For instance, challenges such as limited access to care due to extensive travel distances to expert centres were identified, but this level of detail was not previously incorporated into the framework. Therefore, the findings suggest to introduce the criteria "travel distance" and "waiting times". As research and evidence in rare diseases are often lacking, another criterion on "research needs" was proposed, with as recommended indicators "availability of research and information", "existence of clinical



practice guidelines" and "possibility to participate in clinical trials". Within the social domain, the report suggests introducing two criteria: "stigma" and "impact on social connections" recognizing the substantial burden rare diseases place on these aspects of life. Regarding societal needs, the primary suggestions revolve around the disease's impact on informal caregivers' lives, advocating for the inclusion of new criteria and indicators pertaining to specific aspects of informal caregivers' well-being i.e. impact on physical health, psychological health, autonomy, social connections, and financial consequences.

Building upon the findings of this study, additional criteria and indicators have been proposed. However, there is a need for further research to identify the most appropriate measurement and data collection methods to effectively employ these criteria. Additionally, the feasibility of the proposed criteria and indicators must be rigorously assessed in practical settings to ensure their validity and reliability.

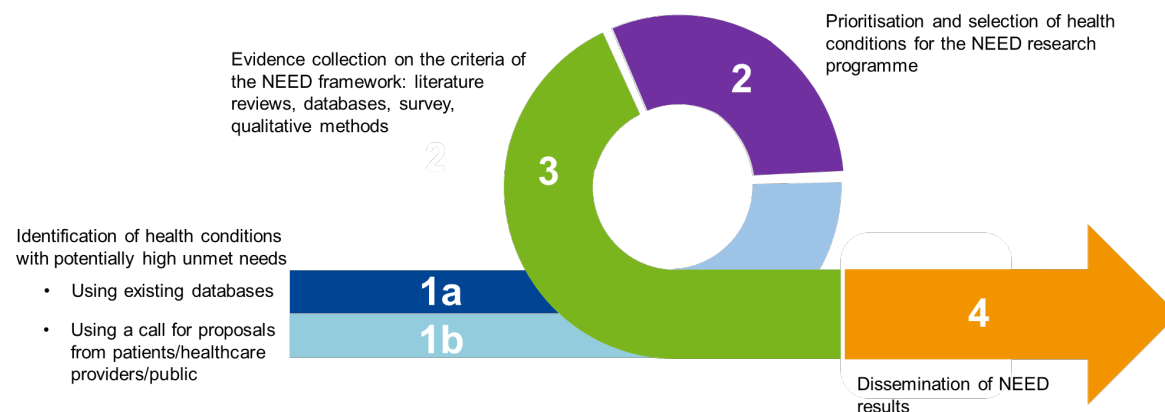
While some criteria within the NEED framework may be perceived as less pertinent in the context of rare diseases, they are no less relevant than for certain common diseases. Moreover, considering potential additions to the framework could offer a more nuanced understanding of specific unmet health-related needs. It is crucial to note that these proposed adjustments are not prerequisites for the applicability of the NEED framework in the rare disease context but rather recommendations aimed at further enriching its relevance.

7 APPLICABILITY OF THE 4-STEP IMPLEMENTATION MODEL IN THE CONTEXT OF RARE DISEASES

Key Points

- **The 4-step implementation model should be conceived as inclusive as possible aiming to develop strategies that effectively reach individuals with rare diseases and gather information, especially for those who are challenging to access.**
- **Only focusing on databases or existing sources in step 1 is insufficient to reach that goal, a mixed-method approach (combination with call for proposals) is recommended.**
- **Collaboration between NEED researchers and national and European networks is essential, like ERNs, EC networks, VNZZ, RadiOrg, EURORDIS, Orphanet and other.**

The objective of this chapter is to assess the applicability of the different steps included in the NEED 4-step implementation model (Figure 20) in the context of rare diseases and provide recommendations for improvement. To this end, a rapid review was conducted, enriched with insights from the two stakeholder workshops.

**Figure 20 – The NEED 4-step implementation model**

Source: Adapted from KCE report 348 *Identifying patient needs: methodological approach and application* (2021)³⁰²

7.1 Methods

The methods used to evaluate the applicability of the NEED 4-step implementation model in the context of rare diseases include a rapid literature review and stakeholder workshops. Information on the methods and descriptive results for the rapid literature review (i.e. countries covered, disease areas) and stakeholder workshops (i.e. stakeholder groups) can be found in the previous chapter (Chapter 5 section 1.2).

7.2 Results

An overview of the results of the second stakeholder workshop on the NEED 4-step implementation model is presented in Table 16. These results are discussed in the following paragraphs.


Table 16 – Results of the second stakeholder workshop on the NEED 4-step implementation model

Steps in implementation model	Mentioned challenges and considerations	Stakeholder representatives' recommendations
General impressions	- The focus on specific rare health conditions rather than general disease symptoms may risk to neglect patients - The terms "condition" or "rare disease" are too restrictive	- Grouping of diseases - o Based on symptoms - o Based on organs
Step 1a + Step 1b: identification of health conditions with potentially high unmet needs		
Step 1a: Identification of health conditions using databases	- Lack of rare disease and rare disease-specific databases - Incompleteness & insufficient quality of existing databases	Additional sources of inspiration: - EMA list of orphan designations - EC community registry of orphan medicinal products - Orphanet - Literature
Step 1b: Identification of health conditions using a call for proposals from patients/healthcare providers/public	- Risk to only hear the loudest voices - Reaching insufficient patients and HCPs with experience/expertise in rare diseases	<u>Channels</u> - Online (e.g. social media and websites) along off-line communication - Appropriate materials (e.g. flyers and posters) - Oral (e.g. GPs, specialists, patient networks) <u>Design</u> - Include open and closed questions - Make use of surveys, focus groups, interviews, mixed methods <u>Involved stakeholders</u> - Patients - o Individuals - o Organisations (national and European) - HCPs: ERNs, VNZZ, SSMG, Domus Medica
Step 2: Prioritisation and selection of health conditions for the NEED research program	- Risk of inequity between patient populations - Difficulty of inclusion of specific/vulnerable populations (e.g. pregnant women, children)	In the prioritisation process, avoid pure quantitative assessment, and consider different weighing of criterion on "prevalence". Proposed additional prioritisation criteria (on top of current NEED prioritisation criteria):



		- Level of evidence available - Severity of the disease or its symptoms - Burden of disease - Availability of treatment options - Prognosis - Impact on QoL - Representation through patient organisations (to express needs) - Diagnostic odyssey - Time to reach a doctor - Budgetary impact
Step 3: Collection of evidence on the criteria of the NEED framework: literature reviews, databases, surveys, qualitative methods	- Anonymisation is difficult to guarantee in rare diseases - Obtaining a representative sample and sufficient statistical power is challenging	- Enable larger samples via - o Disease grouping - o International collaboration - o Collaboration with other organisations - Transparent communication via informed consent forms
Step 4: Dissemination of NEED results	- Challenge to keep the NEED database up-to-date when new information on rare disease emerges - Difficulties with accessibility of the data (inter)nationally - Difficulty to disseminate complex information in a way that is both understandable and useful to various stakeholders	- Dedicated NEED team to keep the database up-to-date - Update the database depending on the disease context

EMA = European Medicines Agency; HCP = Health Care Professional; GP = General Practitioners, QoL = Quality of life; ERN = European Reference Network; VNZZ = Vlaams Netwerk voor Zeldzame Ziekten, SSMG = Société Scientifique de Médecine Général



7.2.1 General remarks on the 4-step NEED implementation model

According to stakeholder representatives, a commonly encountered challenge in the context of rare diseases was the tendency of the 4-step model to focus on specific health *conditions*, rather than general disease *symptoms*. Several stakeholder representatives felt that the term “condition” or “rare disease” was too restrictive, as these terms solely assume diagnosed disorders. Many agreed that a strict focus on confirmed diagnoses may not cover the groups that possibly encounter the largest unmet health-related needs, such as (i) those awaiting diagnosis (ii) those with multiple diagnoses (iii) those without a precise diagnosis of their disease and (iv) those whose diagnosis has not yet been included in the Orphanet database. One stakeholder representative proposed not to work with groups of rare diseases instead of with specific diseases. Considering rare diseases as a group with specific needs would be a better approach according to this stakeholder representative because it is impossible to develop one guideline on how to identify unmet needs of rare disease patients applicable to all rare diseases. Furthermore, stakeholders emphasised a broader argument not specific to rare diseases, pointing out that the needs arising from symptoms, disease manifestation, and comorbidities can vary among patients with the same disease. Lastly, it is important to mention that misdiagnosis happens regularly in rare diseases and often leads to an unnecessary financial burden on the patient and the healthcare system. This might bias the evidence on unmet needs.

Although several stakeholder representatives supported a symptom-based approach for the 4-step model, two counterarguments were presented:

1. One stakeholder representative expressed concerns about including undiagnosed individuals, arguing that there is already a substantial amount of work to be done with those who have received a diagnosis.
2. Moreover, stakeholder representatives emphasised that the orphan regulation (EC 141/2000) and European databases provide definitions and set the framework for the use of the terms “condition” or “rare disease”, which could be an approach to follow.

7.2.2 Step 1: Identification of health conditions with potentially high unmet needs

The initial phase of the NEED 4-step implementation model covers the identification of health conditions with potentially high unmet needs. This phase is divided into two parallel steps. Step 1a focuses on the use of existing databases, and step 1b on a call for proposals. Some stakeholder representatives highlighted the high potential of combining databases and open calls for proposals to identify potential unmet needs, while others emphasised the importance of other methods such as literature search (including case reports) for a comprehensive approach.

7.2.2.1 Step 1a: Identification of health conditions using databases

Challenges with research based on databases and/or registries are discussed under 5.2.2. and stress the absence of data and evidence for many rare diseases. Only few disease-specific databases exist for specific rare diseases, an overview of rare disease include in the literature review are given under Table 6. It is advised to, besides generic databases and registries such as BeBOD, to also include disease-specific databases when available. National or European databases on rare diseases can complement the disease-specific databases and are thus suited for the purpose, provided that they exist and are comprehensive. These broader databases are likely to offer a more holistic view of rare diseases, and must encompass health-related quality of life, mortality and morbidity.

Stakeholder representatives expressed varying opinions regarding the use of international databases to identify rare diseases. Some advocated for considering databases from other European countries as they offer more extensive data compared to Belgian databases. They argued that cross-border research is particularly crucial in rare diseases. In contrast, others stressed that this is a Belgian project and that the potential international variation in prevalence as well as specifics in terms of medical support organised at the national level, may call for the need for a national approach. Some additional sources of inspiration are mentioned in Table 16.



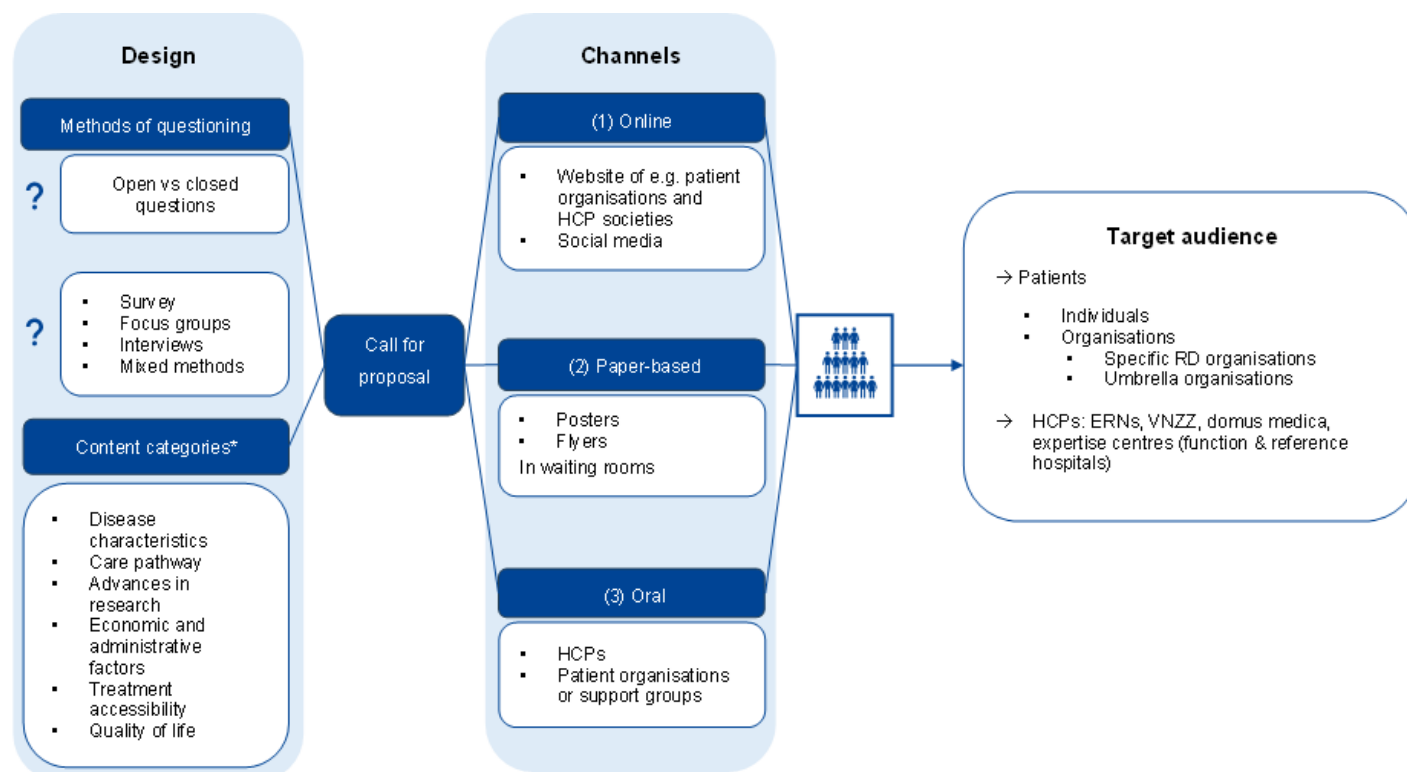
7.2.2.2 *Step 1b: Identification of health conditions using an open call for proposals*

Together with consulting databases, an open call for proposals is used in Step 1 to identify health conditions with potentially high unmet needs. The main concern regarding Step 1b was that only patients with the loudest voices would be heard, rather than those with the highest unmet needs like individuals who are exhausted from their battle with the disease as well as those lacking representation or diagnosis. In the field of rare diseases, many people are underdiagnosed, as stated during the stakeholder workshops but also reflected in the literature.¹⁵⁹ It is common for rare disease patients to stay for a long time undiagnosed or are even misdiagnosed (diagnostic delay, due to a lack of e.g. scientific knowledge of healthcare professionals¹¹¹ and little quality information¹¹¹, diagnostic tools¹⁵⁹). This may contribute to variability across healthcare systems in prevalence and disease management.¹⁵⁹ For instance, due to difficulties related to the diagnosis but also the management of patients with light chain amyloidosis,

these patients are often treated in referral centres when the disease is already advanced. Notably, comprehensive and reliable data collection is feasible only in centres equipped with the requisite expertise, resources, and knowledge for conducting systematic and accurate data gathering.⁷³ Additionally, another challenge regarding diagnosis is that for some rare diseases, e.g. cryopyrin-associated periodic syndrome (CAPS), recruitment for clinical trials can be difficult because patients can be diagnosed not only by paediatricians or paediatric rheumatologists but also by other specialists. Encouragement is needed here, to extend the net of participating centres as widely as possible.⁷¹ However, it is better to include multiple centres of expertise when identifying unmet needs instead of relying on a single-centre experience.^{270, 303}

Figure 21 provides an overview of the stakeholder representatives' recommendations regarding the open call for proposals, categorised into three main areas: design, channels and target audience. Below, these three points will be further discussed.

Figure 21 – Stakeholder representatives' recommendations on the open call for proposals



*Specific proposals for each content category are illustrated in Figure 17

HCP= healthcare provider, RD= rare disease, ERN= European Reference Network, VNZZ= Vlaams Netwerk Zeldzame Ziekten



Design of open calls for proposals

Two topics of discussion emerged regarding the design of the open call for proposals, including (i) the type of questions and (ii) the content of the open call. First of all, the design of the open call for proposals was discussed and this revealed that stakeholder representatives held different opinions regarding the types of questions to include. Some stakeholder representatives favoured closed-ended questions, arguing that open-ended questions might lead to extensive personal narratives. Herein, one stakeholder representative referred to the patient survey included in the NEED framework, as an example of a standardised approach mainly including closed questions. Contrarily, one stakeholder representative highlighted the benefits of open questions as they might facilitate obtaining a comprehensive view of individuals' unmet needs. Both arguments are valid for all disease types but are especially important to consider in the context of rare diseases as little is known about these. Furthermore, various methods for the conduct of the call for proposals were suggested, including interviews or a combination of surveys with focus groups. Some stakeholder representatives suggested a standardised template to simplify both the submission and the analysis of the call for topics. In literature, some survey studies also applied a non-disease-specific approach, where populations were defined based on the symptoms²⁸⁹ that these patients experienced or similar care needs.²¹³ Moreover, interviews can be interesting for identifying the needs of undiagnosed patients.^{184, 188, 242, 268}

Regarding the content of the call for proposals, stakeholder representatives had different opinions on whether there should be uniform or distinct information requests for rare diseases compared to common diseases. Those favouring the same information requests emphasised that rarity does not necessarily mean more invalidating, and thus prioritisation should be

comparable across rare and common diseases and the same information should be required. Moreover, some stakeholder representatives were reluctant to request quantitative information in the call for proposal because the rarity of certain conditions can lead to their needs being less apparent and measurable.

Contrarily, those in favour of including different information in a call for proposals for rare diseases vs common diseases argued that the difference in information requested should underscore the specific challenges inherent to rare diseases, including the diagnostic and therapeutic odyssey as well as the lack of expertise, training and awareness among professionals.

When stakeholder representatives were asked about the minimal information required in the open call for proposals, a whole range of suggestions were made. The most frequent suggestions can be grouped into six categories: disease characteristics, care pathway, advances in research, economic and administrative factors, treatment accessibility and quality of life. Stakeholder representatives' suggestions for every category are presented in Table 17. It is important to note that while these suggestions will be taken into consideration, they may not all be incorporated in the call for proposals, considering the length of the questionnaire. One stakeholder representative pointed out the potential differentiation between the minimum information that could be provided and the minimum requested information. This consideration holds particular relevance for rare diseases, as they lack significant representation from individuals with a strong scientific background to provide comprehensive responses. The stakeholder representative therefore suggested to require a minimal amount of information, with the possibility to provide additional information if available. A stakeholder representative also mentioned that it is important to recognise that not being able to provide information reflects a need in itself.

**Table 17 – Stakeholder representatives' most frequent suggestions regarding the minimal information required for the open call for proposals**

Content category	Stakeholder representatives' suggestions
Disease characteristics	- Name of the disease - Prevalence of the disease - Disease complexity - Natural history of the disease - Prognosis - Orphacode
General information	- Declaration of conflict of interest related to the person submitting the information (declaration of any commercial interests linked to the provided information)
Care pathway	- Name of expert consulted - Diagnostic and treatment odyssey including availability of diagnostic facilities, expertise, awareness - Involvement of different stakeholders in the care pathway (different types of informal caregivers to provide care) - o Follow-up with the centre of expertise or rare disease centre - o Algology centre involvement - o Need for supportive care (psychological and paramedical support) - Need for 24-hour assistance - Number of HCPs seen before and after diagnosis
Advances in research	- Overview of research done or ongoing - Overview of treatment options in the pipeline - Knowledge about the pathogenic pathway
Economic factors	- Financial burden - Average cost of treatment
Treatment accessibility	- Availability and accessibility of treatment options - Whether the shortcoming is medical, multidisciplinary medical team, technical, geographical
Quality of life	- What they miss the most in their daily life

HCPs= Health Care Professionals



Channels for open calls for proposals

Stakeholder representatives indicated that the call for proposals should be as inclusive as possible to ensure its value. The suggested channels can be divided into three main categories as illustrated in Figure 21.

For online communication (1), stakeholder representatives proposed strategies such as posting invitations on patient associations' websites (e.g., EURORDIS, RaDiOrg, Vlaams Patiëntenplatform (VPP)) and strategically utilising various social media platforms. For paper-based materials (2), the distribution of flyers and posters in waiting rooms of HCPs and specialised rare disease centres were considered effective strategies by stakeholder representatives to reach individuals for the open call for proposals. Furthermore, stakeholder representatives reported the importance of establishing direct contacts (3) with patients through HCPs or umbrella organisations like RaDiOrg and rare disorders Belgium (RDB).

Furthermore, a shared vision among stakeholder representatives was the challenge of reaching out to patients and involving them in the call for proposals. Particularly, individuals affected by conditions lacking extensive networks or patient organisations may be unreachable. This could lead to a biased overview of unmet needs, with an overrepresentation of well-organised rare diseases, potentially overshadowing the needs of less represented rare diseases.

Target audience to whom the open call for proposals should be addressed

Lastly, input was given regarding which people to invite for the open call for proposals. Several stakeholder representatives agreed upon a call for proposals without the involvement of the pharmaceutical industry. However one stakeholder representative expressed his concern and suggested to include proposals from pharmaceutical companies. In general, the target audience can be classified into two main groups: patients and HCPs. Patients' input can be gathered through individuals as well as through organisations, including specific rare disease organisations or broader umbrella organisations (e.g. RaDiOrg and rd-b, EURORDIS, Orphanet). Input from HCPs can be collected through individual HCPs, ERNs, VNZZ,

Domus Medica, SSMG and expertise centres (function and reference centres). Specifically, VNZZ covers diverse organ specific networks of rare disease expert physicians. In this step, it is crucial to engage a broad spectrum of relevant stakeholders, ensuring that anyone who wishes to give input is allowed to do so.

7.2.3 Step 2: Prioritisation and selection of health conditions for the NEED assessment exercise

After the identification of rare health conditions with potentially high unmet needs, the next step involves prioritising and selecting the conditions to include in the NEED assessment exercise. Both prioritisation criteria and the prioritisation process were extensively discussed during the second stakeholder workshop. Several stakeholder representatives expressed their concerns regarding the potential risk of inequity arising from the prioritisation procedure. According to them, the use of criteria like prevalence, incidence or treatment cost may lead to inequities, especially because we need them to determine the burden of disease. Additionally, they argued that the prioritisation step might reinforce the existing pattern where known conditions with identified needs receive more attention.

Eight specific criteria for prioritisation were suggested by stakeholder representatives. The current NEED prioritisation criteria include:

1. impact of the health condition on patients' quality of life,
2. impact of the health condition on patients' life expectancy,
3. frequency of the health condition,
4. economic impact of the health condition on patients and society, and
5. impact of the health condition on vulnerable population groups.

Several stakeholder representatives recommended incorporating the level of available evidence on the disease pathophysiology and disease management as a prioritisation criterion, particularly due to the limited understanding of many rare diseases. Other suggestions included severity of the disease or its symptoms, burden of disease, prognosis, existence of patient organisation for the disease, and budgetary impact.



Two concerns were raised regarding the prioritisation criteria: the inclusion of rare disease populations on one hand, and the criterion “frequency of the health condition” on the other hand.

- Firstly, stakeholder representatives emphasised the need to focus on hard-to-reach patient groups, as well as vulnerable and less extensively studied patient groups such as children and pregnant women. Some stakeholder representatives argued that these patient groups should be given more weight in the prioritisation process.
- Secondly, opinions differed regarding the inclusion of “frequency of the health condition” as a prioritisation criterion. Stakeholder representatives advocating for its exclusion argued that rare conditions would never receive priority if frequency of the health condition was considered. A stakeholder representative proposed to initially exclude frequency of the health condition for both common and rare diseases, allowing them to be prioritised together in the same evaluation, with frequency taken into account in a later step to establish separate rankings for rare and common diseases. However, some argued that the prioritisation criteria for rare and common diseases could remain the same if the weighting of different criteria was adjusted, for instance, by placing more weight on severity than on frequency for rare diseases.

7.2.4 Step 3: Evidence collection on the criteria of the NEED assessment framework

Following the identification, prioritisation and selection of health conditions with potential high unmet need, it is essential to gather evidence on the indicators of the NEED framework, discussed in Chapter 6 (section 6.2). Nevertheless, challenges have emerged concerning ethical considerations. In Chapter 5 (section 5.2.2), anonymisation in rare disease research was discussed. A study among patients with NKX-1-related disorders highlighted the fact that raw data will not be published given the rarity of the disease and the fact that participants could easily be identified.¹³⁸

Recommendations were provided concerning three topics: disease grouping (see under section 1.1.1), collaboration with other organisations. Opinions differed among stakeholder representatives regarding international

collaboration for evidence collection on the criteria of the NEED framework for rare diseases. Those in favour of international collaboration suggested that European networks could facilitate survey dissemination and establish contact with patients. Additionally, they proposed to work with the European Reference Networks (ERN) structures³⁰⁴, which aim to connect HCP from across Europe to address complex or rare diseases.

7.2.5 Step 4: Dissemination of NEED results

The final step of the 4-step implementation model involves the dissemination of the results on the identified unmet needs. Recommendations were given on (i) keeping the database up-to-date, (ii) who should get access to the database, (iii) ensuring visibility of the database, and (iv) using the database.

(i) Updating the NEED database

According to the stakeholder representatives, keeping the database up-to-date is crucial as unmet needs may evolve over time, new ones may emerge, or existing ones may have been (partially) met. To do so, stakeholder representatives proposed to set up a team that maintains close connections with patient organisations and HCPs, and stays up-to-date with ongoing research. This team would ultimately conduct routine reviews of the database, through a three- to five year cycle. Other stakeholder representatives suggested doing these reviews on an ongoing basis through a shortened cycle of the 4-step implementation model.

(ii) Accessing the NEED database

There were varying perspectives regarding the extent of access to the NEED database. Some participants suggested to grant access to the evidence on an international scale, i.e. to European policy makers, EURORDIS, EMA and the ERNs because it is crucial to include, collaborate and inform on an international level in order to achieve optimal outcomes for rare diseases. Concrete suggestions from stakeholder representatives for national dissemination included: utilising networks from academic institutions, Research Foundation - Flanders (FWO), Fonds de la Recherche Scientifique (FNRS), industry, patient communities, HCPs, the general public, RIZIV – INAMI, and all the stakeholders who participated in the project.



Some stakeholder representatives underscored that mere access to the database is insufficient. They argued that it is necessary to disseminate the gathered evidence in a manageable way, both comprehensibly and practically. This could be through scientific articles on one hand, and public awareness campaigns through social media or television on the other hand. The latter is considered crucial as rare diseases often receive less media attention compared to common diseases. Other suggestions were annual information days, a presentation on the bi-annual European Conference for Rare Diseases and Orphan Drugs, and a debate in the Belgian federal parliament.

(iv) Use of the NEED database

The database can be used in several decision-making processes. A stakeholder representative highlighted the conventions and reference centers in Belgium as a concrete example of the use of the NEED database. Reference centers comprise multidisciplinary teams specialized in treating specific diseases. Presently, eight groups of rare diseases have access to reference centers under NIHDI agreements (conventions), which facilitate the reimbursement of care pathways. However, while new conventions could be allocated to four diseases with significant unmet needs, the current system of assigning these conventions tends to be influenced by political and societal preferences rather than by the actual needs. This situation underscores the importance of developing an objective tool, possibly utilizing the NEED database, to identify rare diseases with the highest unmet needs or complexity, ensuring that resources are allocated more effectively and based on unmet medical needs. The database can also be used for the development of multi-criteria decision analysis (MCDA), which is used to aid complex decision-making where multiple, often conflicting, criteria must be considered. The database can be useful in the selection and structuration of quantitative and qualitative criteria in MCDA.

7.3 Discussion and conclusion

In conclusion, the stakeholder workshops provided new insights regarding the application of the NEED 4-step implementation model in rare diseases. In general, the workshop yielded insights into addressing undiagnosed health conditions, emphasizing proactive measures to encompass overlooked patients and health issues. For step 1, it is important to reconsider whether the identification should focus towards a particular rare disease, or towards a group of rare diseases with similar symptoms or organ disfunctions. Recommendations emerged regarding diverse channels for call for proposals, international registry utilisation and the required content of the open call for proposals. Collaboration with patient groups was highlighted. Regarding step 2, the need to reconsider the criteria for prioritization was highlighted, recognizing that prevalence should not be the primary focus whereas a lack of knowledge about a disease was identified as a more significant criterion for prioritization.

For the evidence collection (Step 3), international collaboration may be essential to enlarge sample sizes. Finally, in terms of dissemination (Step 4), it is key to keep the NEED database up to date, appoint a dedicated team to manage this effort, and to develop a dissemination plan to actively communicate about the unmet needs evidence to the wider public and inform decision-making.



8 GENERAL DISCUSSION AND CONCLUSION

Orphanet and EURORDIS are key resources for rare diseases and list over 6 000 rare diseases, which is potentially an underestimation due to undiagnosed cases.^{52, 305} The European Medicines Agency has approved 235 orphan drugs for rare diseases, but a notable number of conditions still lack appropriate pharmaceutical treatments. Patients affected by rare diseases face challenges due to inadequate diagnosis and treatment and often rely on non-orphan medications, surgery and various alternative approaches like physiotherapy or dietary adaptations. The complex nature and rarity of these diseases create challenges resulting in unmet health-related needs. These intricacies hinder investments, as stakeholders are hesitant to support high-risk products for a small market with uncertain regulatory acceptance. Research in rare diseases is challenging, and their unique needs differ from more common diseases. To respond to the unmet health-related needs of this population, this study aimed to explore variations in the definitions of rare diseases and assess whether the NEED approach could be applied to rare diseases.

The NEED approach, including the NEED assessment framework and the 4-step implementation model stands out as the first practical application to address the identification of patient and societal unmet health-related needs.¹⁰ This approach has been established independently, free from any conflict of interest, with the purpose of supporting scientific and governmental initiatives. Its objective is to provide valuable insights to stakeholders regarding unmet health-related needs across various health conditions. In order to reach its full potential and based on learnings from this study, some are for future research are proposed below.

8.1 Summary of findings

Definitions of rare diseases

There are variations in how a rare disease is defined across countries, among different stakeholder groups, and between organisations. It is important to highlight that the terms "orphan disease" and "rare disease" are often used interchangeably among various organisations and stakeholders. This interchangeable use may lead to confusion, especially when stakeholders refer to the orphan designation's definition of an orphan medicinal product when discussing a rare disease.⁵⁰ Most definition encompass one or two components. The first component concerns the prevalence of the disease and the second concerns qualitative criteria, such as the severity of a specific disease or the existence of alternative treatments. For this report, the emphasis is specifically on rare diseases, defined as conditions occurring in fewer than 5 out of 10 000 people, without any other criteria, thus ensuring a high inclusivity.

Methodological challenges

The NEED assessment framework encompasses 23 needs criteria and 46 related indicators to estimate if the needs are met or unmet. For each indicator, a measurement method and data source is proposed. Data collection methods can be summarised into four types: (i) patient survey, (ii) qualitative methods, such as patient interviews and expert opinions, (iii) database and registry analyses, and (iv) literature reviews. Each of these methods presents specific challenges, some of which may overlap.

In the context of rare diseases, a notable challenge arises from the small patient population, leading to difficulties in recruiting participants, which regularly results in a limited sample size. Furthermore, this can have repercussion on the generalisability of quantitative data (i.e. patient survey). To tackle this challenge, a strong recruitment strategy is crucial, utilising diverse channels and collaborating with various organisations. Qualitative methods, which require smaller sample sizes, may present a more suitable alternative in the context of rare diseases.



Additionally, challenges may arise from the absence of data sources, such as literature and disease-specific registries or databases, particularly when specific indicators of unmet needs rely solely on these methods (e.g. years of life lived with disability, years of life lost, value for money of standard of care, future prevalence/incidence). To address this, the report recommends to reinforce the application of open science initiatives in practice. Further, the use of real-world data simulations to estimate disease parameters could also serve as a solution in case of missing data. Furthermore, the application of a mixed-method approach is highlighted in the literature as an effective mitigation strategy, already successfully implemented in the NEED assessment framework for most criteria.

It is important to note that the proposed adjustments are envisioned as complementary rather than essential for making the framework applicable to rare diseases. However, in certain instances, particularly with very rare diseases, considerations may arise for tailoring generic measures. For example, a more qualitative approach, such as patient interviews and expert opinions, could replace the patient survey, offering a more insightful perspective, especially in cases where patient numbers are exceptionally low.

NEED assessment framework

The existing NEED assessment framework, with its established criteria and indicators, proved to be well-suited for measuring the unmet health-related needs of patients and society in the context of rare diseases.

In enhancing the comprehensiveness of the framework, this report suggests additional criteria to provide a more nuanced understanding of the diverse needs experienced by patients and society in the context of rare diseases, but most could also be applied to more common diseases. These suggested additional criteria (n=4) and indicators (n=17) span across the three dimensions and recurring domains. Most recommendations are applicable in the context of rare diseases but also apply for more common diseases. Within the health domain, recommendations include introducing a criterion focused on impact on reproductive health, along with indicators addressing unpredictability and impact on self-esteem. In the healthcare domain, the literature consistently emphasizes criteria related to the availability of

information and diagnosis, necessitating special attention. Suggestions in this domain primarily centre on refining the framework's granularity, especially in the context of rare diseases. For instance, challenges such as limited access to care due to extensive travel distances to expert centres were identified, but this level of detail was not previously incorporated into the framework. The findings suggest an inclusion of this granularity by introducing specific criteria, such as "travel distance" and "waiting times". Another criterion on "research needs" was proposed, as in rare diseases research and evidence is often lacking. This criterion would include indicators "availability of research and information", "existence of clinical practice guidelines" and "possibility to participate in clinical trials" are recommended. Within the social domain, the report suggests introducing two criteria: "stigma" and "impact on social connections" recognising the substantial burden rare diseases place on these aspects of life. Regarding societal needs, the primary suggestions revolve around the disease's impact on informal caregivers' lives, advocating for the inclusion of new criteria and indicators pertaining to specific aspects of informal caregivers' well-being i.e. impact on physical health, psychological health, autonomy, social connections, and financial consequences.

NEED 4-step implementation model

The NEED 4-step implementation model consists of identification of health conditions with potentially high unmet needs (step1), prioritisation and selection of health conditions for the NEED research program (step2), collection of evidence on the criteria of the NEED framework: literature reviews, databases, surveys, qualitative methods (step3), and dissemination of NEED results (step4). For each step suggestions and considerations for its application in the context of rare diseases were proposed.

For step 1, stakeholder consultations revealed concerns about potential inequities between patient populations, with fears that those with the "loudest voice" would dominate in the prioritisation process. The identification is currently to be performed via two parallel steps, being (i) databases and (ii) a call for proposals directed to patients, healthcare providers and the general public. Regarding the identification based on



databases, challenges included the lack of rare disease and rare disease-specific databases and incompleteness & insufficient quality of existing databases. Therefore, additional sources were proposed to include in the assessment (e.g. EMA list of orphan designations, orphaned and scientific literature). Regarding the call for proposals main challenge included the risk of better-represented and more reachable individuals having greater influence, necessitating additional efforts to engage vulnerable, rare, populations. Therefore, a well-designed recruitment strategy, using a variation of channels, disseminating organisation, and materials is advised.

The step 2, i.e. involving the prioritisation and selection of health conditions for the NEED research program, has sparked significant discussion, particularly concerning its application in the rare disease context. It was proposed to consider different weighing of the criterion on “prevalence”. A complementary suggestion was to adopt more inclusive prioritisation criteria for the assessments. Proposed prioritisation criteria encompass, but are not limited to, the level of available evidence, severity of disease symptoms, and the diagnostic odyssey experience.

For step 3, the main challenges reported for performing the NEED assessment were the difficulty to guarantee anonymisation in rare diseases and obtain a representative sample and sufficient statistical power. Therefore, it was proposed to transparently report on the challenge of anonymisation in informed consent forms and enable a larger sample via for instance international collaboration.

For step 4, challenges related to the dissemination of NEED results were also applicable to more common diseases, and included the challenge to keep the database up-to-date, accessibility of data and the format of the dissemination.

8.2 Strengths and limitations

To the best of our knowledge, this study represents the first comprehensive assessment of the methodologies applied to evaluate unmet health-related needs of patient and society in the context of rare diseases. The utilisation of multiple methods, including an extensive literature review and stakeholder workshops, strengthens the quality of the study. This multi-method approach allowed for the incorporation of the perspective of e.g. patients, informal caregivers, healthcare professionals, and society. Further, collaboration among multiple researchers at different stages, from the literature review to screening and extraction, enriched the study with diverse interpretations. Although interpretations varied, comprehensive team discussions facilitated fruitful insights that considered various perspectives, enhancing the robustness of the study.

Five particular limitations are to be considered when interpreting the data:

- (i) The research's iterative process, with revisions to the NEED assessment framework, required a flexible report writing approach that allowed for the incorporation of specific findings and recommendations into the evolving NEED framework, while certain elements such as the extraction table and search strategy remained rooted in the initial framework.
- (ii) Another limitation but at the same time a strength involves the use of Google Translate for articles in foreign languages (N= 5). While this approach was adopted to prevent the oversight of potentially valuable data, it introduces a reliability concern for the translated papers. However, most studies in foreign languages were available in languages familiar to the researchers, who could check for translation errors.
- (iii) The study acknowledges the potential existence of substantial unpublished data on rare diseases due to small sample sizes (publication bias). The applied approach may not capture this valuable information, thus potentially missing crucial insights and perspectives. Nevertheless, to make up for this potential lack in insights, the literature review was complemented with qualitative insights from stakeholders via the stakeholder consultations.



(iv) For participant recruitment in the stakeholder workshop, a convenience sampling method was employed, wherein involved researchers generated a list of relevant stakeholders based on their knowledge. This approach raises the possibility of overlooking some stakeholders, potentially leading to missed insights. However, in both consultations, at least one representative from each identified stakeholder group participated. To enhance inclusivity, an expert in the field reviewed and validated the stakeholder list, ensuring representation of the most influential experts. Invitees were also encouraged to suggest additional participants for a comprehensive and diverse representation.

(v) Due to time constraints, not all stakeholder representatives had the opportunity to provide their input during the workshop, as a considerable number of representatives participated. Moreover, the subject matter was for many participants not general knowledge, requiring some preparation and time to think about the subject in advance. Consequently, the questions posed during the workshop may have been challenging for those stakeholder representatives who did not complete the preparatory survey. In response to this limitation, we offered the participating stakeholders the option to fill out the survey post-workshop. Additionally, for those expressing a desire to provide more information during the workshop, we organised additional one-on-one interviews.

8.3 Future research and potential implications of the study

Definitions of rare diseases

This report highlights that there still exists divergence on the definition and use of the term “rare disease”. As rare diseases are becoming a public health priority, it is important for policy makers and other stakeholders to have a globally accepted definition with clear criteria. More transparency and alignment could be generated by providing a list of rare diseases.

NEED assessment framework & Methodological challenges

Building upon the findings of this study, additional criteria and indicators have been proposed. However, there is a need for further research to identify the most appropriate measurement and data collection methods to

effectively employ these criteria. Specific statistical models could provide a solution to deal with low sample sizes but must be further investigated. Additionally, the feasibility of the proposed criteria and indicators must be rigorously assessed in practical settings to ensure their validity and reliability. A promising avenue for future research involves the application of the revised NEED framework to a specific rare disease to pilot the framework. This practical exploration could help to shed further light on potential challenges or inefficiencies that may arise when performing the NEED assessment in the context of rare diseases.

The research highlighted specific challenges in applying the framework to rare diseases, a category that frequently includes children as a particularly vulnerable population. However, while this study broadly covered the paediatric population, it did not specifically address the differences in applying the framework to children versus adults. To address this gap, an in-depth exploration of the unique challenges associated with needs assessment in paediatric cases is deemed essential. A thorough examination of the criteria, indicators, and methodologies within the NEED assessment framework tailored to the paediatric population, would provide valuable insights for future research.

To facilitate access to data on rare diseases, the application of open science initiatives and artificial intelligence should be reinforced, the exact opportunities and applications of which must further be investigated.

NEED 4-step implementation model

An essential avenue for future research lies in a more nuanced exploration of the 4-step implementation model. This involves conducting a thorough examination of the decisions guided by the model and the practical implications arising from its application. The NEED 4-step implementation model, while theoretically robust, lacks practical demonstrations, leading to scepticism among stakeholders, particularly within the rare disease domain. Concerns have surfaced regarding the overemphasis on common diseases in the assessment process, potentially reducing attention for rare diseases. To address these concerns, the implementation of pilot studies becomes imperative. Anticipated pilots present a crucial opportunity to validate and refine the NEED 4-step implementation model. To conduct a pilot study and



apply the complete 4-step implementation model, special attention must be given to steps 1 and 2, focusing on the inclusiveness of rare diseases. Questions regarding how the approach will be specifically applied to rare diseases and the criteria for prioritisation, ensuring fair inclusion of rare diseases, need thorough exploration.

Application of the NEED database

Additionally, investigating the impact of the NEED database on decision-making is an important research area, aiming to understand its added value for decision-makers and stakeholders. The implementation could take place by various healthcare stakeholders and society, including (i) developers and research funders, (ii) regulators, (iii) HTA bodies and payers, (iv) HCPs, (v) patients and patient-organisations.

(i) Addressing the current lack of evidence-based research funding from public instances is another critical area where the NEED database could play a transformative role, potentially improving the rigor and validity of research funding decisions in rare diseases. Also for-profit companies can benefit from the results of the database, as this could serve as a tool to redirect investment decisions to the highest needs.

(ii) The orphan designation is a prominent measure included in regulatory decision making at the European level and enables incentives for medicinal products that are eligible.⁵⁰ It must be noted that this regulation is currently undergoing reform as per the 2023 EU pharmaceutical legislation.³⁰⁶ In this proposal for the new pharmaceutical legislation, roots for a new and more clear definition of the unmet medical need concept are laid out.³⁰⁶ This definition serves as a prerequisite for various incentives within drug development, market authorisation, and reimbursement processes. This inclusion in the new legislation aims to encourage stakeholders toward a treatment development pathway that is rooted in addressing identified unmet needs. The NEED database could potentially inform decisions at the level of the orphan designation granting process but also further in the regulatory process at the level of the marketing authorisation assessment and the application of expediting regulatory measures (i.e. PRIME scheme, conditional marketing authorisation, accelerated assessment). Examining the possible application in those processes and consecutive impact of the

results of a NEED assessment in the context of potential new drug market entry could underscore its value for regulatory agencies like the EMA.

(iii) Simultaneously, at the national level, Belgium has incorporated the concept of unmet medical needs into several regulatory and market access procedures. These procedures include initiatives to expedite access to unapproved indications, such as compassionate use programs (CUP) and medical need programs (MNP), along with early temporary reimbursement procedures for innovative therapies targeting unmet medical needs.^{307, 308} Furthermore, also drugs that obtained an orphan designation at the European level may receive additional incentives at the national level, issued by HTA bodies or payers. These and possible other application opportunities for the NEED database at the level of national HTA, regulation and pricing and reimbursement are still to be show-cased in the future. Similarly to the European level, case-studies of the application of the data could provide stakeholders and organisation with the potential added value and further stimulate the adaptation in their decision making practices.

(iv) In clinical practice, the NEED database and its results can be utilised, particularly in scenarios where additional funding for care pathways in rare diseases is requested. The Belgian government allocates funds to hospitals for a limited number of rare diseases, and the decision-making process for these allocations could potentially benefit from more evidence-based insights provided by the data in the NEED database.

(v) As for common diseases, also in rare diseases patient organisations could benefit from the NEED database to provide better support to patients living with the respective disease. The database could also serve as a valuable tool for patients seeking peer support. Additionally, in the long run, patients will benefit as their identified needs may potentially be addressed through systemic changes in healthcare systems, governmental adjustments, or advancements in research and development, particularly in areas where needs are most pronounced.



8.4 Conclusion

The applicability of the NEED approach, encompassing its 4-step implementation model and assessment framework has been demonstrated in the context of rare diseases.

Despite challenges posed by certain methodologies within the framework, such as patient surveys, database research, and literature reviews, in gathering evidence on unmet needs in the context of rare diseases—attributed to limited data sources and difficulties in patient recruitment—the increased use of qualitative methods is seen as a strategy to enhance the framework's applicability to rare diseases. Moreover, considering the suggested additions to the framework could offer a better understanding of specific unmet health-related needs for rare diseases. It is important to note that these proposed adjustments are not prerequisites for the approach's applicability in the context of rare disease but rather recommendations aimed at further enriching its relevance.



■ REFERENCES

1. Tricco AC, Antony J, Zarin W, Striffler L, Ghassemi M, Ivory J, et al. A scoping review of rapid review methods. *BMC Medicine*. 2015;13(1).
2. Paez A. Gray literature: An important resource in systematic reviews. *Journal of Evidence-Based Medicine*. 2017;10(3):233-40.
3. OECD. Unmet needs for health care: Comparing approaches and results from international surveys. 2020 January 2020. OECD Report Better Policies for Better Lives, 2020. Available from: <https://www.oecd.org/health/health-systems/Unmet-Needs-for-Health-Care-Brief-2020.pdf>
4. Maertens De Noordhout C. DJ, Primus-De Jong, C., Kohn L., Devleesschauwer B., Charafeddine R., Cleemput I. Identifying patient needs: methodological approach and application. Brussels: Belgian Health Care Knowledge Centre (KCE); 2021 13 January 2022. D/2021/10.273/51 Available from: https://kce.fgov.be/sites/default/files/2022-02/KCE_348_Patient_Needs_Report.pdf
5. Lubl6y  . Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Services Research*. 2014;14(1):469.
6. Commission E. Pharmaceutical Strategy for Europe. 2020. Available from: https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf
7. Wet houdende diverse bepalingen inzake de toegankelijkheid van de gezondheidszorg. 2014
8. Koninklijk besluit tot uitvoering van de artikelen 25 en volgende van de wet betreffende de verplichte verzekering voor geneeskundige verzorging en uitkeringen. 2014
9. invaliditeitsverzekering R-Rvz-e. Onbeantwoorde medische behoeften - Unmet Medical Need [Web page].2023 [updated 30/08/2023]. Available from: <https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/Paginas/unmet-medical-need.aspx>



10. Maertens de Noordhout C, Levy M, Claerman R, De Jaeger M, De Pauw R, Kohn L, et al. Needs Examination, Evaluation and Dissemination (NEED): assessment framework. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Center (KCE); 2024 03/2024. KCE Reports 377C1 (377C1) Available from: <https://doi.org/10.57598/R377C1>
11. McMullan J, Crowe AL, Bailie C, Moore K, McMullan LS, Shamandi N, et al. Improvements needed to support people living and working with a rare disease in Northern Ireland: current rare disease support perceived as inadequate. Orphanet journal of rare diseases. 2020;15(1):315.
12. KB. STANDING UP FOR PEOPLE WITH RARE DISEASES. ZOOM 2018.
13. Prevalence and incidence of rare diseases: Bibliographic data. 2022. Orphanet Report Series, Rare Diseases collection (Number 1: Diseases listed in alphabetical order) Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
14. AE M, C B-R, J G, D J, FK J, Q L, et al. Regulatory strategies for rare diseases under current global regulatory statutes: a discussion with stakeholders. Orphanet journal of rare diseases. 2019;14(1):36.
15. AM G. Using real world data to support regulatory approval of drugs in rare diseases: A review of opportunities, limitations & a case example. Current problems in cancer. 2021;45(4):100769.
16. A G-P, J T-F, A C, A P, M F, R P-P, et al. DRUG EVALUATION AND DECISION MAKING IN CATALONIA: DEVELOPMENT AND VALIDATION OF A METHODOLOGICAL FRAMEWORK BASED ON MULTI-CRITERIA DECISION ANALYSIS (MCDA) FOR ORPHAN DRUGS. International journal of technology assessment in health care. 2017;33(1):111-20.
17. AMCP Partnership Forum: Preparing for and managing rare diseases. United States; 2021.
18. A W, SC G, JR T, J K, BR D, CS C, et al. Clinical Trial Design for Alpha-1 Antitrypsin Deficiency: A Model for Rare Diseases. Chronic obstructive pulmonary diseases (Miami, Fla.). 2015;2(2):177-90.
19. Ghadessi M, Tang R, Zhou J, Liu R, Wang C, Toyoizumi K, et al. A roadmap to using historical controls in clinical trials - by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). Orphanet J Rare Dis. 2020;15(1):69.
20. Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23(1):36-42.
21. A D, L M, C F, I C, S S. Issues surrounding orphan disease and orphan drug policies in Europe. Applied health economics and health policy. 2010;8(5):343-50.
22. EMA. Legal framework: orphan regulation [Web page].2023 [cited 1st december]. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation/legal-framework-orphan-designation>
23. Pharma.be. Facts & Figures over weesgeneesmiddelen (februari 2022) [Web page]. [cited 28th november 2023]. Available from: [https://pharma.be/nl/expertise/zeldzame-ziekten-en-weesgeneesmiddelen#:~:text=Facts%20%26%20Figures%20over%20weesgeneesmiddelen%20\(februari,op%20Europees%20nivea u%20geregistreerde%20geneesmiddelen](https://pharma.be/nl/expertise/zeldzame-ziekten-en-weesgeneesmiddelen#:~:text=Facts%20%26%20Figures%20over%20weesgeneesmiddelen%20(februari,op%20Europees%20nivea u%20geregistreerde%20geneesmiddelen)
24. EMA. Orphan medicines in the EU [Web page]. [cited 1st december 2023]. Available from: https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf
25. A K, K M. The actual status of drug prices and adjustment factors for drug price calculation: an analysis of ultra-orphan drug development in Japan. Orphanet journal of rare diseases. 2022;17(1):408.
26. Picavet E, Cassiman D, Simoens S. Reimbursement of orphan drugs in Belgium: what (else) matters? Orphanet J Rare Dis. 2014;9:139.



27. Development IoMCoARDR, Product O. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington (DC): National Academies Press (US); 2010.
28. A B, C S, C M, C F. The diagnostic odyssey: insights from parents of children living with an undiagnosed condition. Orphanet journal of rare diseases. 2022;17(1):233.
29. Zurynski Y, Deverell M, Dalkeith T, Johnson S, Christodoulou J, Leonard H, et al. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. Orphanet Journal of Rare Diseases. 2017;12(1):68.
30. Muir E. The Rare Reality - an insight into the patient and family experience of rare disease. 2016.
31. KB. Nieuwe perspectieven op gelijke kansen. ZOOM zeldzame ziekten 2014.
32. D T, G B, H C, SC G, EW K, K K, et al. The Undiagnosed Diseases Network International: Five years and more! Molecular genetics and metabolism. 2020;129(4):243-54.
33. UDNI. Members of the UDNI [Web page]. 2023 [cited 1st december]. Available from: <https://www.udninternational.org/schede-14-members>
34. de Heus E, van de Camp K, Driehuis E, van der Zwan JM, van Herpen CML, Merkx MAW, et al. The solitary versus supported experience: Care inequality between rare and common cancer patients. Psycho-oncology. 2023;32(11):1667-74.
35. A S, L B, NJ F, E H, K L-B, S M, et al. How are patients with rare diseases and their carers in the UK impacted by the way care is coordinated? An exploratory qualitative interview study. Orphanet journal of rare diseases. 2021;16(1):76.
36. Lawal AK, Rotter T, Kinsman L, Machotta A, Ronellenfisch U, Scott SD, et al. What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review. BMC Medicine. 2016;14(1):35.
37. B T, H G. Rare disease care pathways in the EU: from odysseys and labyrinths towards highways. Journal of community genetics. 2021;12(2):231-9.
38. EC. European Reference Networks [Web page]. [cited 1st december 2023]. Available from: https://health.ec.europa.eu/european-reference-networks/overview_en
39. B T, H G, IM M, AM P, F S, M S, et al. European Reference Networks: challenges and opportunities. Journal of community genetics. 2021;12(2):217-29.
40. AM P, M OB, GE V, KA D. Emerging roles and opportunities for rare disease patient advocacy groups. Therapeutic advances in rare disease. 2023;4:26330040231164425.
41. Claessens Z. VA, Broekmans J., Janssens R., Barbier L. Cleemput I., Maertens C., Schoenborn C. De Jaeger M., Kohn L., Levy M., Huys I. NEED (Needs Examination, Evaluation and Dissemination) – Applicability of Framework to Rare Diseases / protocol. 2023.
42. Chantelle G, Gerald G, Barbara N-S, Valerie JK, Candyce H, Chris K, et al. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. Journal of Clinical Epidemiology. 2021;130:13-22.
43. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-73.
44. WHO. ICD-11 International Classification of Diseases 11th Revision [Web page]. Available from: <https://icd.who.int/en>
45. <Lacey & Luff Qualitative_Data_Analysis_Revision_2009.pdf>.
46. Sciensano. Rare diseases [Web page]. Available from: <https://www.sciensano.be/en/health-topics/rare-diseases>
47. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value Health. 2015;18(6):906-14.



48. Commission E, Research D-Gf, Innovation. Collaboration – A key to unlock the challenges of rare diseases research. Publications Office; 2021.
49. Commission E. EU research on rare diseases [Web page]. Available from: https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en
50. Regulation (EC) 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, 2000.
51. Denis A SS, Fostier C, Mergaert L, Cleemput I. Policies for Rare diseases and Orphan Drugs. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. (D/2009/10.273/32)
52. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet*. 2020;28(2):165-73.
53. Banerji A. The burden of illness in patients with hereditary angioedema. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2013;111(5):329-36.
54. Monga N, Garside J, Quigley J, Hudson M, O'Donovan P, O'Rourke J, et al. Systematic literature review of the global burden of illness of mantle cell lymphoma. *Curr. Med. Res. Opin*. 2020;36(5):843-52.
55. Spencer-Tansley R, Meade N, Ali F, Simpson A, Hunter A. Mental health care for rare disease in the UK - recommendations from a quantitative survey and multi-stakeholder workshop. *BMC health services research*. 2022;22(1):648.
56. Kwon CS, Daniele P, Forsythe A, Ngai C. A systematic literature review of the epidemiology, health-related quality of life impact, and economic burden of immunoglobulin a nephropathy. *J. Health Econ*. 2021;8(2):36-45.
57. Simpson A, Bloom L, Fulop NJ, Hudson E, Leeson-Beevers K, Morris S, et al. How are patients with rare diseases and their carers in the UK impacted by the way care is coordinated? An exploratory qualitative interview study. *Orphanet journal of rare diseases*. 2021;16(1):76.
58. Brandt M, Johannsen L, Inhestern L, Bergelt C. Parents as informal caregivers of children and adolescents with spinal muscular atrophy: a systematic review of quantitative and qualitative data on the psychosocial situation, caregiver burden, and family needs. *Orphanet journal of rare diseases*. 2022;17(1):274.
59. Bin Sawad A, Pothukuchy A, Badeaux M, Hodson V, Bubbs G, Lindsley K, et al. Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. *JIMD reports*. 2022;63(4):330-40.
60. de Heus E, van der Zwan JM, Husson O, Frissen AR, van Herpen CML, Merks MAW, et al. Unmet supportive care needs of patients with rare cancer: A systematic review. *European journal of cancer care*. 2021;30(6):e13502.
61. McMullan J, Lohfeld L, McKnight AJ. Needs of informal caregivers of people with a rare disease: a rapid review of the literature. *BMJ Open*. 2022;12(12):e063263.
62. Efthimiou P, Kontzias A, Hur P, Rodha K, Ramakrishna GS, Nakasato P. Adult-onset Still's disease in focus: Clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. *Semin. Arthritis Rheum*. 2021;51(4):858-74.
63. Wheeler AC, Sacco P, Cabo R. Unmet clinical needs and burden in Angelman syndrome: a review of the literature. *Orphanet journal of rare diseases*. 2017;12(1):164.
64. Painous C, van Os NJH, Delamarre A, Michailoviene I, Marti MJ, van de Warrenburg BP, et al. Management of rare movement disorders in Europe: outcome of surveys of the European Reference Network for Rare Neurological Diseases. *Eur. J. Neurol*. 2020;27(8):1493-500.
65. McMullan J, Crowe AL, Downes K, McAneney H, McKnight AJ. Carer reported experiences: Supporting someone with a rare disease. *Health & social care in the community*. 2022;30(3):1097-108.



66. Morel T, Cano SJ. Measuring what matters to rare disease patients - reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. *Orphanet journal of rare diseases*. 2017;12(1):171.
67. Hassall S, Smith DM, Rust S, Wittkowski A. A systematic review and integrative sequential explanatory narrative synthesis: The psychosocial impact of parenting a child with a lysosomal storage disorder. *Journal of inherited metabolic disease*. 2022;45(3):406-16.
68. Hill M, Lewis C, Riddington M, Crowe B, DeVile C, Götherström C, et al. Exploring the impact of Osteogenesis Imperfecta on families: A mixed-methods systematic review. *Disability and health journal*. 2019;12(3):340-9.
69. Carbone M, Kodra Y, Rocchetti A, Manno V, Minelli G, Gerussi A, et al. Primary sclerosing cholangitis: Burden of disease and mortality using data from the national rare diseases registry in Italy. *Int. J. Environ. Res. Public Health*. 2020;17(9).
70. Burke T, Asghar S, O'Hara J, Sawyer EK, Li N. Clinical, humanistic, and economic burden of severe hemophilia B in the United States: Results from the CHES US and CHES US+ population surveys. *Orphanet J. Rare Dis*. 2021;16(1).
71. Tilson H, Primates P, Kim D, Rauer B, Hawkins PN, Hoffman HM, et al. Methodological challenges in monitoring new treatments for rare diseases: Lessons from the cryopyrin-associated periodic syndrome registry. *Orphanet J. Rare Dis*. 2013;8(1).
72. Roghmann F, Von Bodman C, Löppenberg B, Hinkel A, Palisaar J, Noldus J. Is there a need for the Fournier's gangrene severity index? Comparison of scoring systems for outcome prediction in patients with Fournier's gangrene. *BJU Int*. 2012;110(9):1359-65.
73. Palladini G, Schönland S, Merlini G, Milani P, Jaccard A, Bridoux F, et al. The management of light chain (AL) amyloidosis in Europe: clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018. *Blood Cancer J*. 2023;13(1).
74. Qi X, Xu J, Shan L, Li Y, Cui Y, Liu H, et al. Economic burden and health related quality of life of ultra-rare Gaucher disease in China. 2021.
75. Pujades-Rodriguez M, Guttmann OP, Gonzalez-Izquierdo A, Duyx B, O'Mahony C, Elliott P, et al. Identifying unmet clinical need in hypertrophic cardiomyopathy using national electronic health records. *PLoS ONE*. 2018;13(1).
76. Joldic M, Todorovic J, Terzic-Supic Z. The needs of patients with rare disease in Serbia. Why do we need National Strategy for rare disease? *Health & social care in the community*. 2019;27(5):e861-e70.
77. Antoniadou V, Hadjipanayis A. Co-constructing effective collective intelligence networks in rare diseases: a mixed method approach to identify the parameters that matter for patients, professionals and policy-makers, piloted in Cyprus. *Orphanet J. Rare Dis*. 2023;18(1).
78. Lanar S, Acquadro C, Seaton J, Savre I, Arnould B. To what degree are orphan drugs patient-centered? A review of the current state of clinical research in rare diseases. *Orphanet J. Rare Dis*. 2020;15(1).
79. Conner T, Cook F, Fernandez V, Rascati K, Rangel-Miller V. An online survey on burden of illness among families with post-stem cell transplant mucopolysaccharidosis type I children in the United States. *Orphanet journal of rare diseases*. 2019;14(1):48.
80. Drabbe C, Grünhagen DJ, Van Houdt WJ, Braam PM, Soomers VLMN, Van der Hage JA, et al. Diagnosed with a rare cancer: Experiences of adult sarcoma survivors with the healthcare system—results from the survsarc study. *Cancers*. 2021;13(4):1-16.
81. Johansen H, Velvin G, Lidal I. Adults with Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome: a cross-sectional study of patient experiences with physical activity. *Disability and rehabilitation*. 2022;44(10):1968-75.
82. Valassi E, Chiodini I, Feelders RA, Andela CD, Abou-Hanna M, Idres S, et al. Unmet needs in Cushing's syndrome: the patients' perspective. *Endocrine connections*. 2022;11(7).



83. Swezey T, Reeve BB, Hart TS, Floor MK, Dollar CM, Gillies AP, et al. Incorporating the patient perspective in the study of rare bone disease: insights from the osteogenesis imperfecta community. *Osteoporosis Int.* 2019;30(2):507-11.
84. Strugnell A, Leonard H, Epstein A, Downs J. Using directed-content analysis to identify a framework for understanding quality of life in adults with Rett syndrome. *Disability and rehabilitation.* 2020;42(26):3800-7.
85. Pinto PR, Paredes AC, Pedras S, Costa P, Crato M, Fernandes S, et al. Sociodemographic, Clinical, and Psychosocial Characteristics of People with Hemophilia in Portugal: Findings from the First National Survey. *TH Open.* 2018;2(1):e54-e7.
86. Twigg J, Methley A, Lavin T, Dickinson G, Teager A. Living with Polyneuropathy Organomegaly Endocrinopathy Monoclonal gammopathy Skin changes (POEMS) syndrome: a case study of healthcare experiences and quality of life. 2021.
87. Gioldasi O, Vlachou C, Argyriadis A, A. A. Case study of a patient family with multiple endocrine neoplasia syndrome. *Evaluation of Stress levels.* 2022.
88. Gutenbrunner C, Schiller J, Goedecke V, Lemhoefer C, Boekel A. Screening of Patient Impairments in an Outpatient Clinic for Suspected Rare Diseases—A Cross-Sectional Study. *Int. J. Environ. Res. Public Health.* 2022;19(14).
89. Devi GR, Hough H, Barrett N, Cristofanilli M, Overmoyer B, Spector N, et al. Perspectives on inflammatory breast cancer (IBC) research, clinical management and community engagement from the duke IBC consortium. *J. Cancer.* 2019;10(15):3344-51.
90. Anderson M, Elliott EJ, Zurynski YA. Australian families living with rare disease: Experiences of diagnosis, health services use and needs for psychosocial support. *Orphanet J. Rare Dis.* 2013;8(1).
91. Respondek G, Breslow D, Amirghiasvand C, Ghosh B, Bergmans B, van Wyk L, et al. The Lived Experiences of People with Progressive Supranuclear Palsy and Their Caregivers. *Neurology and therapy.* 2023;12(1):229-47.
92. Strobel MJ, Alves D, Roufosse F, Antoun Z, Kwon N, Baylis L, et al. Insights from Social Media on the Patient Experience of Living With Rare Eosinophil-Driven Diseases. *Journal of patient experience.* 2022;9:23743735221143953.
93. Dwyer AA, Uveges M, Dockray S, Smith N. Advancing qualitative rare disease research methodology: a comparison of virtual and in-person focus group formats. *Orphanet journal of rare diseases.* 2022;17(1):354.
94. Lowton K, Ballard KD. Adult cystic fibrosis patients' experiences of primary care consultations: A qualitative study. *Br. J. Gen. Pract.* 2006;56(528):518-25.
95. Both P, Ten Holt L, Mous S, Patist J, Rietman A, Dieleman G, et al. Tuberous sclerosis complex: Concerns and needs of patients and parents from the transitional period to adulthood. *Epilepsy & behavior : E&B.* 2018;83:13-21.
96. Litzkendorf S, Hartz T, Göbel J, Storf H, Pauer F, Babac A, et al. Conceptualization and Implementation of the Central Information Portal on Rare Diseases: Protocol for a Qualitative Study. *JMIR research protocols.* 2018;7(5):e112.
97. Hiltrop K, Heidkamp P, Halbach S, Brock-Midding E, Kowalski C, Holmberg C, et al. Occupational rehabilitation of male breast cancer patients: Return patterns, motives, experiences, and implications-A qualitative study. *European journal of cancer care.* 2021;30(4):e13402.
98. Kocher A, Simon M, Dwyer AA, Blatter C, Bogdanovic J, Künzler-Heule P, et al. Patient Assessment Chronic Illness Care (PACIC) and its associations with quality of life among Swiss patients with systemic sclerosis: a mixed methods study. *Orphanet journal of rare diseases.* 2023;18(1):7.
99. Skrobanski H, Williams K, Werner C, O'Neill S, Buesch K, Acaster S. The impact of caring for an individual with aromatic l-amino acid decarboxylase (AADC) deficiency: a qualitative study and the development of a conceptual model. *Current medical research and opinion.* 2021;37(10):1821-8.



100. Ogunsanya ME, Brown CM, Lin D, Imarhia F, Maxey C, Chong BF. Understanding the disease burden and unmet needs among patients with cutaneous lupus erythematosus: A qualitative study. *International journal of women's dermatology*. 2018;4(3):152-8.
101. de Freitas C, Dos Reis V, Silva S, Videira PA, Morava E, Jaeken J. Public and patient involvement in needs assessment and social innovation: a people-centred approach to care and research for congenital disorders of glycosylation. *BMC health services research*. 2017;17(1):682.
102. Godfrey EM, Kazmerski TM, Brown G, Thayer EK, Mentch L, Pam M, et al. Educational Needs and Preferences for Patient-Centered Outcomes Research in the Cystic Fibrosis Community: Mixed Methods Study. *JMIR formative research*. 2021;5(3):e24302.
103. Ashtari S, Taylor AD. The Internet Knows More Than My Physician: Qualitative Interview Study of People With Rare Diseases and How They Use Online Support Groups. *J. Med. Internet Res*. 2022;24(8).
104. Cardão C, Barros L, Francisco R, Silva D, Ferreira VR. Experiences of parents with children with congenital disorders of glycosylation: What can we learn from them? *Disability and health journal*. 2021;14(3):101065.
105. Loesken C, Maehder K, Buck L, Hartl J, Löwe B, Schramm C, et al. Understanding illness experiences of patients with primary sclerosing cholangitis: a qualitative analysis within the SOMA.LIV study. *BMC gastroenterology*. 2023;23(1):12.
106. Applequist J, ., Burroughs C, Merkel P, Rothenberg M, Trapnell B, R D, et al. Direct-to-Consumer Recruitment Methods via Traditional and Social Media to Aid in Research Accrual for Clinical Trials for Rare Diseases: Comparative Analysis Study. 2023.
107. Pelentsov LJ, Laws TA, Esterman AJ. The supportive care needs of parents caring for a child with a rare disease: A scoping review. *Disability and health journal*. 2015;8(4):475-91.
108. Acaster S, Lo SH, Nestler-Parr S. A survey exploring caregiver burden and health-related quality of life in hereditary transthyretin amyloidosis. 2023.
109. de Graaf JP, de Vries F, Dirkson A, Hiort O, Pereira AM, Korbonits M, et al. Patients with rare endocrine conditions have corresponding views on unmet needs in clinical research. *Endocrine*. 2021;71(3):561-8.
110. Dinur T, Istaiti M, Frydman D, Becker-Cohen M, Szer J, Zimran A, et al. Patient reported outcome measures in a large cohort of patients with type 1 Gaucher disease. *Orphanet journal of rare diseases*. 2020;15(1):284.
111. Tejada-Ortigosa EM, Flores-Rojas K, Moreno-Quintana L, Muñoz-Villanueva MC, Pérez-Navero JL, Gil-Campos M. [Health and socio-educational needs of the families and children with rare metabolic diseases: Qualitative study in a tertiary hospital]. *Anales de pediatria*. 2019;90(1):42-50.
112. Caputo A. Exploring quality of life in Italian patients with rare disease: a computer-aided content analysis of illness stories. *Psychology, health & medicine*. 2014;19(2):211-21.
113. Chevreul K, Brigham KB, Gandré C, Mouthon L, Serrano-Aguilar P, Linertová R, et al. The economic burden and health-related quality of life associated with systemic sclerosis in France. *Scand. J. Rheumatol*. 2015;44(3):238-46.
114. Efthymiadou O, Mossman J, Kanavos P. Differentiation of health-related quality of life outcomes between five disease areas: Results from an international survey of patients. *Int. J. Technol. Assess. Health Care*. 2018;34(5):498-506.
115. Efthymiadou O, Mossman J, Kanavos P. Health related quality of life aspects not captured by EQ-5D-5L: Results from an international survey of patients. *Health Policy*. 2019;123(2):159-65.
116. Lagae L, Irwin J, Gibson E, Battersby A. Caregiver impact and health service use in high and low severity Dravet syndrome: A multinational cohort study. *Seizure*. 2019;65:72-9.
117. McMillan HJ, Gerber B, Cowling T, Khuu W, Mayer M, Wu JW, et al. Burden of Spinal Muscular Atrophy (SMA) on Patients and Caregivers in Canada. *J. Neuromusc. Dis*. 2021;8(4):553-68.



118. Seefried L, Smyth M, Keen R, Harvengt P. Burden of disease associated with X-linked hypophosphataemia in adults: a systematic literature review. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2021;32(1):7-22.
119. Cheung M, Rylands AJ, Williams A, Bailey K, Bubbear J. Patient-Reported Complications, Symptoms, and Experiences of Living With X-Linked Hypophosphatemia Across the Life-Course. *Journal of the Endocrine Society*. 2021;5(8):bvab070.
120. Gimenez-Lozano C, Páramo-Rodríguez L, Cavero-Carbonell C, Corpas-Burgos F, López-Maside A, Guardiola-Villarrog S, et al. Rare Diseases: Needs and Impact for Patients and Families: A Cross-Sectional Study in the Valencian Region, Spain. *International journal of environmental research and public health*. 2022;19(16).
121. Jimenez-Moreno AC, van Overbeeke E, Pinto CA, Smith I, Sharpe J, Ormrod J, et al. Patient Preferences in Rare Diseases: A Qualitative Study in Neuromuscular Disorders to Inform a Quantitative Preference Study. *Patient*. 2021.
122. Hanbury A, Smith AB, Buesch K. Deriving Vignettes for the Rare Disease AADC Deficiency Using Parent, Caregiver and Clinician Interviews to Evaluate the Impact on Health-Related Quality of Life. Patient related outcome measures. 2021;12:1-12.
123. Teare H, Argente J, Dattani M, Leger J, Maghnie M, Sherlock M, et al. Challenges and improvement needs in the care of patients with central diabetes insipidus. *Orphanet journal of rare diseases*. 2022;17(1):58.
124. Oladapo AO, Ito D, Hibbard C, Bean SE, Krupnick RN, Ewenstein BM. Patient Experience with Congenital (Hereditary) Thrombotic Thrombocytopenic Purpura: A Conceptual Framework of Symptoms and Impacts. *The patient*. 2019;12(5):503-12.
125. Rajmil L, Perestelo-Pérez L, Herdman M. Quality of life and rare diseases. *Advances in experimental medicine and biology*. 2010;686:251-72.
126. Dabbous O, Chachoua L, Aballéa S, Sivignon M, Persson U, Petrou S, et al. Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies. *Advances in therapy*. 2023;40(2):393-424.
127. Kasparian NA, Rutstein A, Sansom-Daly UM, Mireskandari S, Tyler J, Duffy J, et al. Through the looking glass: an exploratory study of the lived experiences and unmet needs of families affected by Von Hippel-Lindau disease. *European journal of human genetics : EJHG*. 2015;23(1):34-40.
128. Bingaman A, Waggoner C, Andrews SM, Pangonis D, Trad M, Giugliani R, et al. GM1-gangliosidosis: The caregivers' assessments of symptom impact and most important symptoms to treat. *American journal of medical genetics. Part A*. 2023;191(2):408-23.
129. Depping MK, Uhlenbusch N, Löwe B. Acceptance and commitment therapy meets peer-support. Development of a supportive self-care intervention for patients with rare diseases: A multistage development process. *BMJ Open*. 2021;11(7).
130. Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: Implications for online interventions and peer-to-peer support. *Orphanet J. Rare Dis*. 2014;9(1).
131. Hiremath G, Kodroff E, Strobel MJ, Scott M, Book W, Reidy C, et al. Individuals affected by eosinophilic gastrointestinal disorders have complex unmet needs and frequently experience unique barriers to care. *Clinics and research in hepatology and gastroenterology*. 2018;42(5):483-93.
132. Porter KA, O'Neill C, Drake E, Parker S, Escolar ML, Montgomery S, et al. Parent Experiences of Sanfilippo Syndrome Impact and Unmet Treatment Needs: A Qualitative Assessment. *Neurol. Ther*. 2021;10(1):197-212.
133. Long JC, Best S, Hatem S, Theodorou T, Catton T, Murray S, et al. The long and winding road: perspectives of people and parents of



- children with mitochondrial conditions negotiating management after diagnosis. *Orphanet journal of rare diseases*. 2021;16(1):310.
134. Golden E, van Gool R, Cay M, Goodlett B, Cao A, Al-Hertani W, et al. The experience of living with Niemann-Pick type C: a patient and caregiver perspective. *Orphanet journal of rare diseases*. 2023;18(1):120.
135. Güeita-Rodríguez J, Famoso-Pérez P, Salom-Moreno J, Carrasco-Garrido P, Pérez-Corrales J, Palacios-Ceña D. Challenges Affecting Access to Health and Social Care Resources and Time Management among Parents of Children with Rett Syndrome: A Qualitative Case Study. *International journal of environmental research and public health*. 2020;17(12).
136. Aiyegbusi OL, Isa F, Kyte D, Pankhurst T, Kerecuk L, Ferguson J, et al. Patient and clinician opinions of patient reported outcome measures (PROMs) in the management of patients with rare diseases: A qualitative study. *Health Qual. Life Outcomes*. 2020;18(1).
137. Simoes E, Sokolov AN, Kronenthaler A, Hiltner H, Schaeffeler N, Rall K, et al. Information ranks highest: Expectations of female adolescents with a rare genital malformation towards health care services. *PLoS ONE*. 2017;12(4).
138. Martín-Gómez C, Ortigoza-Escobar JD, Nou-Fontanet L, Molina-Linde JM, Bachoud-Lévi AC, Léger J, et al. Exploring the values, preferences, and information needs of patients with NKX2-1-related disorders: A qualitative study protocol. *PloS one*. 2023;18(2):e0281573.
139. Engler J, Schütze D, Hach M, Ploeger C, Engler F, Erler A. [Specialized outpatient palliative care for children, adolescents, and their families-the special needs of the target group. Results of the ELSAH study]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*. 2022;65(3):357-66.
140. Erbis G, Schmidt K, Hansmann S, Sergiichuk T, Michler C, Kuemmerle-Deschner JB, et al. Living with autoinflammatory diseases: identifying unmet needs of children, adolescents and adults. *Pediatric rheumatology online journal*. 2018;16(1):81.
141. Olischläger DLT, den Boer LXY, de Heus E, Brom L, Dona DJS, Klümpen HJ, et al. Rare cancer and return to work: experiences and needs of patients and (health care) professionals. *Disability and rehabilitation*. 2022:1-12.
142. Noël E, Dussol B, Lacombe D, Bedreddine N, Fouilhoux A, Ronco P, et al. Treatment needs and expectations for Fabry disease in France: development of a new Patient Needs Questionnaire. *Orphanet journal of rare diseases*. 2019;14(1):284.
143. Geneesmiddelen VI. 'Zorg zeldzame ziekten kan en moet beter!' [Web page]. 2023 [updated 07/03/2023]. Available from: <https://www.vereniginginnovatievegeneesmiddelen.nl/actueel/zorg-zeldzame-ziekten-kan-en-moet-beter>
144. Pelentsov LJ, Fielder AL, Esterman AJ. The Supportive Care Needs of Parents With a Child With a Rare Disease: A Qualitative Descriptive Study. *Journal of pediatric nursing*. 2016;31(3):e207-18.
145. Petracca F, Tempere R, Cucciniello M, Ciani O, Pompeo E, Sannino L, et al. An Electronic Patient-Reported Outcome Mobile App for Data Collection in Type A Hemophilia: Design and Usability Study. *JMIR formative research*. 2021;5(12):e25071.
146. Izquierdo-García E, Escobar-Rodríguez I, Moreno-Villares JM, Iglesias-Peinado I. Social and health care needs in patients with hereditary fructose intolerance in Spain. *Necesidades sociosanitarias en pacientes con intolerancia hereditaria a la fructosa en España*. 2020;67(4):253-62.
147. Strober B, Kotowsky N, Medeiros R, Mackey RH, Harrold LR, Valdecantos WC, et al. Unmet Medical Needs in the Treatment and Management of Generalized Pustular Psoriasis Flares: Evidence from a Survey of Corrona Registry Dermatologists. *Dermatology and therapy*. 2021;11(2):529-41.
148. Xu J, Bao H, Qi X, Wang J, Yin H, Shang C, et al. Family caregivers of rare disease: A survey on health-related quality of life in family caregivers for Gaucher disease patients in China. *Molecular genetics & genomic medicine*. 2021;9(9):e1760.



149. Jindal NL, Harniman E, Prior N, Perez-Fernandez E, Caballero T, Betschel S. Hereditary angioedema: Health-related quality of life in Canadian patients as measured by the SF-36. *Allergy Asthma Clin. Immunol.* 2017;13(1).
150. Alesci R, Hecking C, Weissmann M. Identification of an Unmet Medical Need: Height of Depression, Hypersomnia, and Sleep Apnea Positively Correlate With the Level of Fatigue in Patients With Immune Thrombocytopenia. *Cureus.* 2023;15(10):e47003.
151. Wehrli S, Rohrbach M, Landolt MA. Quality of life of pediatric and adult individuals with osteogenesis imperfecta: a meta-analysis. *Orphanet J. Rare Dis.* 2023;18(1).
152. Ballesteros-Sayas C, Muñoz-Montero A, Giorgi S, Cardenal-Muñoz E, Turón-Viñas E, Pallardó F, et al. Non-pharmacological therapeutic needs in people with Dravet syndrome. *Epilepsy & behavior : E&B.* 2023;150:109553.
153. Moretti A, Cianci P, De Paoli A, Meroni F, Tajè S, Mariani M, et al. Burden of care in families of patients with rare genetic diseases: analysis of a large Italian cohort. *European journal of medical genetics.* 2021;64(7):104230.
154. Connolly EA, Grimison PS, Horvath LG, Robinson PJ, Reddel RR. Quantitative proteomic studies addressing unmet clinical needs in sarcoma. *Frontiers in oncology.* 2023;13:1126736.
155. Ciesluk A, Voorhaar M, Barrett L, Baldasaro J, Griebisch I, Marquis P. Measuring the Patient Experience in Rare Disorders: Benefit of Pragmatic Mixed-Methods Research in NUT Carcinoma. *Oncology and therapy.* 2022;10(1):263-77.
156. Martins AM, Pessoa ALS, Quesada AA, Ribeiro EM. Unmet needs in PKU and the disease impact on the day-to-day lives in Brazil: Results from a survey with 228 patients and their caregivers. *Molecular genetics and metabolism reports.* 2020;24:100624.
157. Al Mukaddam M, Toder KS, Davis M, Cali A, Liljesthröm M, Hollywood S, et al. The impact of fibrodysplasia ossificans progressiva (FOP) on patients and their family members: results from an international burden of illness survey. *Expert review of pharmacoeconomics & outcomes research.* 2022;22(8):1199-213.
158. Raspa M, Kutsa O, Andrews SM, Gwaltney AY, Mallonee E, Creamer A, et al. Uncertainties experienced by parents of children diagnosed with severe combined immunodeficiency through newborn screening. *European journal of human genetics : EJHG.* 2023;1-7.
159. Tisdale A, Cutillo C, Nathan R, Russo P, Laraway B, Haendel M, et al. The IDeaS initiative: pilot study to assess the impact of rare diseases on patients and healthcare systems. 2021.
160. Molster C, Urwin D, Di Pietro L, Fookes M, Petrie D, Van Der Laan S, et al. Survey of healthcare experiences of Australian adults living with rare diseases. *Orphanet J. Rare Dis.* 2016;11(1).
161. Yamaguchi K, Wakimizu R, Kubota M. Difficulties in Daily Life and Associated Factors, and QoL of Children with Inherited Metabolic Disease and Their Parents in Japan: A Literature Review. *JIMD reports.* 2017;33:1-10.
162. Kleinendorst L, van den Heuvel LM, Henneman L, van Haelst MM. Who ever heard of 16p11.2 deletion syndrome? Parents' perspectives on a susceptibility copy number variation syndrome. *European journal of human genetics : EJHG.* 2020;28(9):1196-204.
163. Fasshauer M, Schuermann G, Gebert N, Von Bernuth H, Goldacker S, Krueger R, et al. A structured patient empowerment programme for primary immunodeficiency significantly improves general and health-related quality of life. *Cent. Eur. J. Immunol.* 2021;46(2):244-9.
164. Dzemaili S, Tiemensma J, Quinton R, Pitteloud N, Morin D, Dwyer AA. Beyond hormone replacement: quality of life in women with congenital hypogonadotropic hypogonadism. *Endocrine connections.* 2017;6(6):404-12.
165. Ammann-Schnell L, Groeschel S, Kehrer C, Frölich S, Krägeloh-Mann I. The impact of severe rare chronic neurological disease in childhood on the quality of life of families-a study on MLD and PCH2. *Orphanet journal of rare diseases.* 2021;16(1):211.



166. Hoenig C, van der Laan R, Reimann A, Hoffmann M, Tyler S, Wiesmann C, et al. Eliciting Patient Insights on the Burden of Nontuberculous Mycobacterial Lung Disease (NTM-LD) and Healthcare Gaps in Germany Through Qualitative Semi-structured Interviews. *Adv. Ther.* 2023.
167. Kuman Tunçel Ö, Kayıkçioğlu M, Pırıldar Ş, Yılmaz M, Kaynar L, Aktan M, et al. Mental status and physical activity in patients with homozygous familial hypercholesterolemia: A subgroup analysis of a nationwide survey (A-HIT1 registry). *J. Clin. Lipidology.* 2020;14(3):361-70.e2.
168. Mahic M, Bozorg AM, DeCourcy JJ, Golden KJ, Gibson GA, Taylor CF, et al. Physician-Reported Perspectives on Myasthenia Gravis in the United States: A Real-World Survey. *Neurology and therapy.* 2022;11(4):1535-51.
169. Koto Y, Yamashita W, Lee Y, Hadano N, Kokubu C, Sakai N. Development and validation of a disease-specific quality of life scale for adult patients with Fabry disease in Japan. *Journal of patient-reported outcomes.* 2022;6(1):115.
170. Mahic M, Bozorg A, DeCourcy J, Golden K, Gibson G, Taylor C, et al. Physician- and patient-reported perspectives on myasthenia gravis in Europe: a real-world survey. *Orphanet J. Rare Dis.* 2023;18(1).
171. Angelis A, Kanavos P, López-Bastida J, Linertová R, Serrano-Aguilar P. Socioeconomic costs and health-related quality of life in juvenile idiopathic arthritis: A cost-of-illness study in the United Kingdom. *BMC Musculoskelet. Disord.* 2016;17(1).
172. Bolte FJ, Langenstroer C, Friebe F, Hüsing-Kabar A, Dugas M, Schmidt HH. Patient-reported outcomes on familial amyloid polyneuropathy (FAP). *Orphanet J. Rare Dis.* 2020;15(1).
173. Henderson SL, Packman W, Packman S. Psychosocial aspects of patients with Niemann-Pick disease, type B. *Am. J. Med. Genet. Part A.* 2009;149(11):2430-6.
174. Landlust AM, Koza SA, Carbin M, Walinga M, Robert S, Cooke J, et al. Parental perspectives on Phelan-McDermid syndrome: Results of a worldwide survey. *European journal of medical genetics.* 2023;66(7):104771.
175. Mendivil J, Murphy R, de la Cruz M, Janssen E, Boysen HB, Jain G, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. *Orphanet journal of rare diseases.* 2021;16(1):94.
176. Wolin EM, Leyden J, Goldstein G, Kolarova T, Hollander R, Warner RRP. Patient-reported experience of diagnosis, management, and burden of neuroendocrine tumors: Results from a large patient survey in the United States. *Pancreas.* 2017;46(5):639-47.
177. Büttner M, Krogh D, Führer D, Fuß CT, Willenberg HS, Luster M, et al. Hypoparathyroidism – management, information needs, and impact on daily living from the patients' perspective: results from a population-based survey. *Horm.* 2023;22(3):467-76.
178. Kramer-Golinkoff E, Camacho A, Kramer L, Taylor-Cousar JL. A survey: Understanding the health and perspectives of people with CF not benefiting from CFTR modulators. *Pediatric pulmonology.* 2022;57(5):1253-61.
179. Hill M, Hammond J, Sharmin M, Lewis C, Heathfield M, Crowe B, et al. Living with osteogenesis imperfecta: A qualitative study exploring experiences and psychosocial impact from the perspective of patients, parents and professionals. *Disabil. Health J.* 2022;15(1).
180. Chappell M, Parikh S, Reynolds E. Understanding the impact of pediatric single large-scale mtDNA deletion syndromes on caregivers: Burdens and challenges. *JIMD reports.* 2023;64(5):375-86.
181. Mease C, Fermaglich LJ, Jackler K, Shermer S, Miller KL. Determining Commonalities in the Experiences of Patients with Rare Diseases: A Qualitative Analysis of US Food and Drug Administration Patient Engagement Sessions. *Patient.* 2023.
182. Bonnekoh H, Jelden-Thurm J, Butze M, Krause K, Maurer M, Kolkhir P. In Urticarial Vasculitis, Long Disease Duration, High Symptom Burden, and High Need for Therapy Are Linked to Low



- Patient-Reported Quality of Life. The journal of allergy and clinical immunology. In practice. 2022;10(10):2734-41.e7.
183. Mesa RA, Sullivan EM, Dubinski D, Carroll B, Slee VM, Jennings SV, et al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. *Cancer*. 2022;128(20):3691-9.
184. Fischer MJ, Asselman FL, Kruitwagen-van Reenen ET, Verhoef M, Wadman RI, Visser-Meily JMA, et al. Psychological well-being in adults with spinal muscular atrophy: the contribution of participation and psychological needs. *Disabil Rehabil*. 2020;42(16):2262-70.
185. Schuster ALR, Crossnohere NL, Fischer R, Furlong P, Bridges JFP. Unmet Therapeutic Needs of Non-Ambulatory Patients with Duchenne Muscular Dystrophy: A Mixed-Method Analysis. *Therapeutic innovation & regulatory science*. 2022;56(4):572-86.
186. Sestini S, Paneghetti L, Lampe C, Betti G, Bond S, Bellettato CM, et al. Social and medical needs of rare metabolic patients: results from a MetabERN survey. *Orphanet journal of rare diseases*. 2021;16(1):336.
187. Tkachuk V, Balbuena Aguirre ME, Alonso R, Barboza A, Liwacki SDV, Mainella C, et al. Barriers to access and unmet needs to neuromyelitis optica spectrum disorders care in an Argentinean cohort. *Mult. Scler. Relat. Disord*. 2023;70.
188. Baumbusch J, Mayer S, Sloan-Yip I. Alone in a Crowd? Parents of Children with Rare Diseases' Experiences of Navigating the Healthcare System. *Journal of genetic counseling*. 2018.
189. Depping MK, Uhlenbusch N, von Kodolitsch Y, Klose HFE, Mautner VF, Löwe B. Supportive care needs of patients with rare chronic diseases: multi-method, cross-sectional study. *Orphanet J. Rare Dis*. 2021;16(1).
190. Potter AM, Bentz B, Crue L, Leiby S, Bashir S, Maguire K, et al. Men's Lived Experiences of Breast Cancer and Changes in Occupation. *Occupational therapy international*. 2023;2023:9641922.
191. Ebert AK, Zwink N, Schwarzer N, Brunner L, Reutter H, Jenetzky E, et al. Needs Assessment in Care of Adults With Anorectal Malformations and Exstrophy-Epispadias Complex in Germany. *Frontiers in pediatrics*. 2018;6:392.
192. Moore KM, Wolf NI, Hobson G, Bowyer K, McSherry J, Hartin G, et al. Pelizaeus-Merzbacher Disease: A Caregiver Assessment of Disease Impact. *Journal of child neurology*. 2023;38(1):78-84.
193. Griffiths J, Willard C, Burgess A, Amir Z, Luker K. Meeting the ongoing needs of survivors of rarer cancer. *Eur. J. Oncol. Nurs*. 2007;11(5):434-41.
194. Pivonello R, Scaroni C, Polistena B, Migliore A, Giustina A. Unmet needs on the current medical management of Cushing's syndrome: results from a Delphi panel of Italian endocrinologists. *J. Endocrinol. Invest*. 2023;46(9):1923-34.
195. Mancuso M, Houlden H, Molnar MJ, Filla A, Breza M, Graessner H, et al. How to approach a neurogenetics diagnosis in different European countries: The European Academy of Neurology Neurogenetics Panel survey. *Eur. J. Neurol*. 2022;29(7):1885-91.
196. Senn KC, Thiele S, Kummer K, Walter MC, Nagels KH. Patient-Reported Health-Related Quality of Life, Anxiety and Depression in Patients with Inclusion Body Myositis: A Register-Based Cross-Sectional Study in Germany. *J. Clin. Med*. 2023;12(15).
197. Langhinrichsen-Rohling J, Lewis CL, McCabe S, Lathan EC, Agnew GA, Selwyn CN, et al. They've been BITTEN: reports of institutional and provider betrayal and links with Ehlers-Danlos Syndrome patients' current symptoms, unmet needs and healthcare expectations. *Therapeutic advances in rare disease*. 2021;2:26330040211022033.
198. Kodra Y, Cavazza M, de Santis M, Guala A, Liverani ME, Armeni P, et al. Social economic costs, health-related quality of life and disability in patients with cri du chat syndrome. *Int. J. Environ. Res. Public Health*. 2020;17(16):1-14.
199. Mooney J, Graham K, Watts RA. Impact of caring for someone with a rare rheumatic condition, views from patients and informal carers-



- the need for cat-like vigilance. *Rheumatology Advances in Practice*. 2019;3(1).
200. Nagamatsu Y, Oze I, Aoe K, Hotta K, Kato K, Nakagawa J, et al. Physician requests by patients with malignant pleural mesothelioma in Japan. *BMC cancer*. 2019;19(1):383.
201. Feng JC, Wu WW, Chwo MJ, Liang SY, Cheng SF. [The Long-Term Care Experiences and Care Needs of Parents Caring for Children With Adrenoleukodystrophy]. *Hu li za zhi The journal of nursing*. 2019;66(1):27-37.
202. Babac A, Frank M, Pauer F, Litzkendorf S, Rosenfeldt D, Lühns V, et al. Telephone health services in the field of rare diseases: a qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany. *BMC health services research*. 2018;18(1):99.
203. Majoor BCJ, Andela CD, Bruggemann J, van de Sande MAJ, Kaptein AA, Hamdy NAT, et al. Determinants of impaired quality of life in patients with fibrous dysplasia. *Orphanet journal of rare diseases*. 2017;12(1):80.
204. Kocher A, Simon M, Dwyer AA, Villiger PM, Künzler-Heule P, De Geest S, et al. Developing a rare disease chronic care model: Management of systemic sclerosis (MANOSS) study protocol. *Journal of advanced nursing*. 2019;75(12):3774-91.
205. Saglio M, Peter-Derex L, Franco P, Ricordeau F, Bastuji H, Rozaire O, et al. Narcolepsy and idiopathic hypersomnia: Assessment of pharmacists' need for information and relevance of using secure messaging to ensure the link community-hospital. *Narcolepsie et hypersomnie idiopathique: évaluation du besoin d'information des pharmaciens d'officine et de la pertinence de l'usage d'une messagerie sécurisée pour assurer le lien ville-hôpital*. 2020;17(4):231-43.
206. Lamy F, Ferlini A, Athanasiou D, Reviers E, Lamy F, Plançon JP, et al. Survey on patients' organisations' knowledge and position paper on screening for inherited neuromuscular diseases in Europe. *Orphanet J. Rare Dis*. 2021;16(1).
207. Landfeldt E, Lindgren P, Bell CF, Guglieri M, Straub V, Lochmüller H, et al. Quantifying the burden of caregiving in Duchenne muscular dystrophy. *J. Neurol*. 2016;263(5):906-15.
208. Marinello D, Zucchi D, Palla I, Aguilera S, Galetti I, Holmner M, et al. Exploring patient's experience and unmet needs on pregnancy and family planning in rare and complex connective tissue diseases: a narrative medicine approach. *RMD open*. 2022;8(2).
209. Stubbs LA, Ferry AM, Guffey D, Loccke C, Wade EM, Pour P, et al. Barriers to care in juvenile localized and systemic scleroderma: an exploratory survey study of caregivers' perspectives. *Pediatric rheumatology online journal*. 2023;21(1):39.
210. Schut ARW, de Bruin LE, de Rooij BH, Lidington E, Timbergen MJM, van der Graaf WTA, et al. Physical symptom burden in patients with desmoid-type fibromatosis and its impact on health-related quality of life and healthcare use. *Cancer Med*. 2023.
211. Ruiz-Casas L, O'Hara S, Mighiu C, Finnegan A, Taylor A, Ventura E, et al. Burden of illness of progressive familial intrahepatic cholestasis in the US, UK, France, and Germany: study rationale and protocol of the PICTURE study. *Expert review of pharmacoeconomics & outcomes research*. 2021;21(2):247-53.
212. Fjermestad KW, Kanavin Ø, Nyhus L, Hoxmark LB. Health service experiences among adults with hereditary spastic paraparesis or neurofibromatosis type 1. *Molecular genetics & genomic medicine*. 2020;8(10):e1399.
213. Silibello G, Vizziello P, Gallucci M, Selicorni A, Milani D, Ajmone PF, et al. Daily life changes and adaptations investigated in 154 families with a child suffering from a rare disability at a public centre for rare diseases in Northern Italy. *Ital. J. Pediatr*. 2016;42(1).
214. Hughes T, Anderson AEL, Habib AA, Perez K, Bergin C, Suchotliff S, et al. Impact of social determinants of health on individuals living with generalized myasthenia gravis and implications for patient support programs. *Front Public Health*. 2023;11:1147489.



215. Meyer A, Scirè CA, Talarico R, Alexander T, Amoura Z, Avcin T, et al. Idiopathic inflammatory myopathies: Narrative review of unmet needs in clinical practice guidelines. *RMD Open*. 2019;4.
216. Fournier H, Calcagni N, Morice-Picard F, Quintard B. Psychosocial implications of rare genetic skin diseases affecting appearance on daily life experiences, emotional state, self-perception and quality of life in adults: a systematic review. *Orphanet J. Rare Dis*. 2023;18(1).
217. Witt S, Schuett K, Wiegand-Grefe S, Boettcher J, Quitmann J. Living with a rare disease - experiences and needs in pediatric patients and their parents. *Orphanet J. Rare Dis*. 2023;18(1).
218. Webb SM, Kristensen J, Vitali D, van Klink S, van Beuzekom C, Santos A, et al. EndoERN patient survey on their perception of health care experience and of unmet needs for rare endocrine diseases. *Endocrine*. 2021;71(3):569-77.
219. Brod M, Waldman LT, Smith A, Karpf D. Assessing the Patient Experience of Hypoparathyroidism Symptoms: Development of the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom). *Patient*. 2020;13(2):151-62.
220. Beirne ER, Andrews LB, Murtagh LP, Browne S, Curran SB, O'Brien EC. The far-reaching burden of Hyperemesis Gravidarum - an exploration of women's experiences and perceptions of healthcare support. *Women Health*. 2023;63(7):485-94.
221. Kleitsch J, Weiner JD, Pandya R, Concha JS, Lim D, Werth VP. The physical and emotional impact of cutaneous dermatomyositis: a qualitative study. *Archives of dermatological research*. 2023.
222. Wu YH, Sun FK, Lee PY. Family caregivers' lived experiences of caring for epidermolysis bullosa patients: A phenomenological study. *Journal of clinical nursing*. 2020;29(9):1552-60.
223. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17:88.
224. Foster CC, Blackwell CK, Kan K, Morales L, Cella D, Shaunfield S. Parental self-efficacy managing a child's medications and treatments: adaptation of a PROMIS measure. *Journal of patient-reported outcomes*. 2023;7(1):10.
225. Witt S, Kolb B, Bloemeke J, Mohnike K, Bullinger M, Quitmann J. Quality of life of children with achondroplasia and their parents - a German cross-sectional study. *Orphanet journal of rare diseases*. 2019;14(1):194.
226. Rihm L, Dreier M, Rezvani F, Wiegand-Grefe S, Dirmaier J. The psychosocial situation of families caring for children with rare diseases during the COVID-19 pandemic: results of a cross-sectional online survey. *Orphanet journal of rare diseases*. 2022;17(1):449.
227. Bryson B, Bogart K, Atwood M, Fraser K, Locke T, Pugh K, et al. Navigating the unknown: A content analysis of the unique challenges faced by adults with rare diseases. *Journal of health psychology*. 2021;26(5):623-35.
228. Mesa RA, Sullivan EM, Dubinski D, Carroll B, Slee VM, Jennings SV, et al. Perceptions of patient disease burden and management approaches in systemic mastocytosis: Results of the TouchStone Healthcare Provider Survey. *Cancer*. 2022;128(20):3700-8.
229. Goldfarb DS, Modersitzki F, Karafilidis J, Li-McLeod J. Healthcare utilization, quality of life, and work productivity associated with primary hyperoxaluria: a cross-sectional web-based US survey. *Urolithiasis*. 2023;51(1):72.
230. Husson O, Younger E, Dunlop A, Dean L, Strauss DC, Benson C, et al. Desmoid fibromatosis through the patients' eyes: time to change the focus and organisation of care? *Supportive Care Cancer*. 2019;27(3):965-80.
231. Beynon T, Selman L, Radcliffe E, Whittaker S, Child F, Orlowska D, et al. We had to change to single beds because i itch in the night: A qualitative study of the experiences, attitudes and approaches to coping of patients with cutaneous T-cell lymphoma. *Br. J. Dermatol*. 2015;173(1):83-92.



232. Scharping M, Brennenstuhl H, Garbade SF, Wild B, Posset R, Zielonka M, et al. Unmet Needs of Parents of Children with Urea Cycle Disorders. *Children* (Basel, Switzerland). 2022;9(5).
233. Boettcher J, Denecke J, Barkmann C, Wiegand-Grefe S. Quality of Life and Mental Health in Mothers and Fathers Caring for Children and Adolescents with Rare Diseases Requiring Long-Term Mechanical Ventilation. *International journal of environmental research and public health*. 2020;17(23).
234. Dermer E, Spahr A, Tran LT, Mirchi A, Pelletier F, Guerrero K, et al. Stress in Parents of Children With Genetically Determined Leukoencephalopathies: A Pilot Study. *Journal of child neurology*. 2020;35(13):901-7.
235. Svernlind K, Törnblom M, Nordin Å, Sunnerhagen KS. Locked-in syndrome in Sweden, an explorative study of persons who underwent rehabilitation: A cohort study. *BMJ Open*. 2019;9(4).
236. Eichler M, Pink D, Menge F, Jakob J, L H, S R, et al. Quality of life of GIST patients with and without current tyrosine kinase inhibitor treatment: Cross-sectional results of a German multicentre observational study (PROSa). 2021.
237. Yang X, Yoo HK, Amin S, Cheng WY, Sundaresan S, Zhang L, et al. Burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN) in the United States: A Cross-Sectional Study. *Neurol. Ther.* 2022;11(3):1221-33.
238. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. Development of the parental needs scale for rare diseases: A tool for measuring the supportive care needs of parents caring for a child with a rare disease. *J. Multidiscip. Healthc.* 2016;9:425-33.
239. Farindustria. Position paper on rare diseases. Available from: https://www.farindustria.it/app/uploads/2021/01/Malattie_rare_PositionPaper_ENG_DEFIN.pdf
240. Rispoli V, Díaz Crescitelli ME, Cavallieri F, Antonelli F, Meletti S, Ghirrotto L, et al. Needs and Perceptions of Patients With Dystonia During the COVID-19 Pandemic: A Qualitative Framework Analysis of Survey Responses From Italy. *Frontiers in neurology*. 2022;13:808433.
241. Skrobanski H, Vyas K, Bowditch S, Hubig L, Dziadulewicz E, Fish L, et al. Shared decision-making and the caregiver experience in tuberous sclerosis complex: results from a UK survey. *Orphanet journal of rare diseases*. 2023;18(1):78.
242. Bauskis A, Strange C, Molster C, Fisher C. The diagnostic odyssey: insights from parents of children living with an undiagnosed condition. *Orphanet journal of rare diseases*. 2022;17(1):233.
243. Randall JA, Sutter C, Wang S, Bailey E, Raither L, Perfetti R, et al. Qualitative interviews with adults with Classic Galactosemia and their caregivers: disease burden and challenges with daily living. *Orphanet journal of rare diseases*. 2022;17(1):138.
244. Diseases BNAoPwR. Rare diseases [Web page]. Bulgarian National Alliance of People with Rare Diseases. Available from: https://rare-bg.com/?page_id=234
245. Diseases VJAfCwR. Rare diseases [Web page]. Viljem Julijan Association for Children with Rare Diseases. Available from: <https://viljem-julijan.si/redke-bolezni/>
246. Diseases SAoR. Rare diseases general information [Web page]. Available from: <https://sazch.sk/zriedkave-choroby/vseobecne-informacie/>
247. Diseases CAfR. Rare Diseases [Web page]. Croatian Association for Rare Diseases. Available from: <https://rijetke-bolesti.com/rijetke-bolesti/>
248. Belgium Fah. Burden of Disease [Web page]. 2023 [cited 18/09/2023]. Available from: <https://www.healthybelgium.be/en/health-status/burden-of-disease#:~:text=The%20Belgian%20national%20burden%20of,du e%20to%20morbidity%20and%20mortality>
249. Bell C, Ajmera M, Meyers J. Retrospective Analysis of the Burden of Illness of Eosinophilic Granulomatosis With Polyangiitis (EGPA) Versus Asthma in Commercially Insured US Patients. *Cureus*. 2023;15(7):e42241.



250. Van Groenendael S, Giacobazzi L, Davison F, Holtkemper O, Huang Z, Wang Q, et al. High quality, patient centred and coordinated care for Alstrom syndrome: A model of care for an ultra-rare disease Rare systemic diseases. *Orphanet J. Rare Dis.* 2015;10(1).
251. Aubry-Rozier B, Richard C, Unger S, Hans D, Campos-Xavier B, Schneider P, et al. Osteogenesis imperfecta: Towards an individualised interdisciplinary care strategy to improve physical activity and quality of life. *Swiss Med. Wkly.* 2020;150(28).
252. Bogart K, Hemmesch A, Barnes E, Blissenbach T, Beisang A, Engel P, et al. Healthcare access, satisfaction, and health-related quality of life among children and adults with rare diseases. *Orphanet J. Rare Dis.* 2022;17(1).
253. Luxembourg DdISdG-Dd. Plan National Maladies Rares Luxembourg 2018-2022. 2018
254. Duda H, Hesse J, Haschberger B, Hilger A, Keipert C. The german hemophilia registry: Growing with its tasks. *J. Clin. Med.* 2020;9(11):1-11.
255. Kolbin AS, Vlodavets DV, Kurylev AA, Balykina YY, Proskurin MA, Mishinova SA, et al. The social-economic burden of spinal muscular atrophy in Russia. Анализ социально-экономического бремени спинальной мышечной атрофии в Российской Федерации. 2020;13(4):337-54.
256. Cook NS, Landskroner K, Shah B, Walda S, Weiss O, Pallapotu V. Identification of Patient Needs and Preferences in Pigmented Villonodular Synovitis (PVNS) Using a Qualitative Online Bulletin Board Study. *Advances in therapy.* 2020;37(6):2813-28.
257. Khanna D, Allanore Y, Denton CP, Matucci-Cerinic M, Pope J, Hinzmann B, et al. Patient perception of disease burden in diffuse cutaneous systemic sclerosis. *Journal of scleroderma and related disorders.* 2020;5(1):66-76.
258. Berrih-Aknin S, Claeys K, Law N, Mantegazza R, H M, F S, et al. Patient-reported impact of myasthenia gravis in the real world: Protocol for a digital observational study (MyRealWorld MG). 2021.
259. van Walsem MR, Howe EI, Ruud GA, Frich JC, Andelic N. Health-related quality of life and unmet healthcare needs in Huntington's disease. *Health Qual. Life Outcomes.* 2017;15(1).
260. Kontogeorgos G, Mamasoula Z, Krantz E, Trimpou P, Landin-Wilhelmsen K, Laine C. Low health-related quality of life in hypoparathyroidism and need for PTH analog. 2022.
261. Rose E, Ferrada M, Quinn K, Arnaud L, Goodspeed W, Kim J, et al. Discordance in patient and physician global assessment in relapsing polycondritis. 2021.
262. Auchus RJ, Courtillot C, Dobs A, El-Maouche D, Falhammar H, Lacroix A, et al. Treatment patterns and unmet needs in adults with classic congenital adrenal hyperplasia: A modified Delphi consensus study. *Frontiers in endocrinology.* 2022;13:1005963.
263. Fang S, Shen X, Chen AJ, Li S, Shan K. Health-related quality of life in patients with primary cutaneous amyloidosis. *PLoS ONE.* 2015;10(3).
264. de Dios García-Díaz J, López-Rodríguez M, Morales-Conejo M, Riera-Mestre A. Understanding the ecosystem of patients with lysosomal storage diseases in Spain: a qualitative research with patients and health care professionals. *Orphanet J. Rare Dis.* 2022;17(1).
265. van Roessel IMAA, de Graaf JP, Biermasz NR, Charmandari E, van Santen HM. Acquired hypothalamic dysfunction in childhood: 'what do patients need?' – an Endo-ERN survey. *Endocr. Connect.* 2023;12(10).
266. Gaasterland CMW, van der Weide MCJ, Roes KCB, van der Lee JH. Goal attainment scaling as an outcome measure in rare disease trials: a conceptual proposal for validation. *BMC Med Res Methodol.* 2019;19(1):227.
267. Smits RM, Vissers E, te Pas R, Roebbers N, Feitz WFJ, van Rooij IALM, et al. Common needs in uncommon conditions: a qualitative study to explore the need for care in pediatric patients with rare diseases. *Orphanet J. Rare Dis.* 2022;17(1).



268. Courbier S, Dimond R, Bros-Facer V. Share and protect our health data: An evidence based approach to rare disease patients' perspectives on data sharing and data protection - Quantitative survey and recommendations. *Orphanet J. Rare Dis.* 2019;14(1).
269. Gaite L, García Fuentes M, González Lamuño D, Alvarez J. [Needs in rare diseases during paediatric age]. *Anales del sistema sanitario de Navarra.* 2008;31:165-75.
270. Khair K, Pelentsov L. Assessing the supportive care needs of parents with a child with a bleeding disorder using the Parental Needs Scale for Rare Diseases (PNS-RD): A single-centre pilot study. *Haemophilia.* 2019;25(5):831-7.
271. Adams C, Stears A, Savage D, Deaton C. "We're stuck with what we've got": The impact of lipodystrophy on body image. *J Clin Nurs.* 2018;27(9):1958-68.
272. Pauer F, Schmidt K, Babac A, Damm K, Frank M, von der Schulenburg JM. Comparison of different approaches applied in Analytic Hierarchy Process - an example of information needs of patients with rare diseases. *BMC medical informatics and decision making.* 1 ed. England; 2016. p. 117.
273. Ragan LA, Duffett-Leger L, Laing CM, Bector DL. Exploring Informational Needs of Parents of Children with Intestinal Failure: A Thematic Analysis. *Journal of pediatric nursing.* 2021;60:230-7.
274. Behan L, Galvin AD, Rubbo B, Masfield S, Copeland F, Manion M, et al. Diagnosing primary ciliary dyskinesia: An international patient perspective. *Eur. Respir. J.* 2016;48(4):1096-107.
275. Weiss M, Holzer MT, Muehlensiepen F, Ignatyev Y, Fiehn C, Bauhammer J, et al. Healthcare utilization and unmet needs of patients with antisynthetase syndrome: An international patient survey. *Rheumatol. Int.* 2023;43(10):1925-34.
276. Guillevin L, Armstrong I, Aldrighetti R, Howard LS, Ryftenius H, Fischer A, et al. Understanding the impact of pulmonary arterial hypertension on patients' and carers' lives. *Eur. Respir. Rev.* 2013;22(130):535-42.
277. Mooney J, Poland F, Spalding N, Scott DGI, Watts RA. 'In One Ear and Out the Other - It's a Lot to Take in': A Qualitative Study Exploring the Informational Needs of Patients with ANCA-Associated Vasculitis. *Musculoskelet. Care.* 2013;11(1):51-9.
278. Pignolo RJ, Bedford-Gay C, Cali A, Davis M, Delai PLR, Gonzales K, et al. Current challenges and opportunities in the care of patients with fibrodysplasia ossificans progressiva (FOP): an international, multi-stakeholder perspective. *Orphanet journal of rare diseases.* 2022;17(1):168.
279. van Geest FS, Groeneweg S, Popa VM, Stals MAM, Visser WE. Parent perspectives on complex needs in patients with MCT8 deficiency: an international, prospective, registry study. *J Clin Endocrinol Metab.* 2023.
280. Morrison A, Oussoren E, Friedel T, Cruz J, Yilmaz N. Pathway to diagnosis and burden of illness in mucopolysaccharidosis type VII-A European caregiver survey. *Orphanet J. Rare Dis.* 2019;14(1).
281. Howley E, Graham Davies E, Kreins AY. Congenital Athymia: Unmet Needs and Practical Guidance. *Ther. Clin. Risk Manage.* 2023;19:239-54.
282. Hilker C, Tizek L, R  th M, Schielein M, Biedermann T, Zink A. Leveraging internet search data to assess prevalence, interest, and unmet needs of sarcoidosis in Germany. *Scientific reports.* 2021;11(1):20841.
283. Snijders R, Assis DN, Oo YH, Sebode M, Taubert R, Willemse J, et al. Research gaps and opportunities in autoimmune hepatitis-Results of the international autoimmune hepatitis group research workshop 2022. *Liver international : official journal of the International Association for the Study of the Liver.* 2023.
284. Pak HYV, Lansdown A, Taylor P, Rees DA, Davies JS, Hayhurst C. Acromegaly and the information gap: Patient perceptions of the journey from primary to tertiary care. *Endocr. Connect.* 2020;9(10):971-7.
285. Palikara O, Ashworth M, Van Herwegen J. Addressing the Educational Needs of Children with Williams Syndrome: A Rather



- Neglected Area of Research? Journal of autism and developmental disorders. 2018;48(9):3256-9.
286. Montali L, Frigerio A, Riva P, Invernizzi P. 'It's as if PBC didn't exist': The illness experience of women affected by primary biliary cirrhosis. *Psychol. Health*. 2011;26(11):1429-45.
287. The HTx vision: a nex generation of healthcare decision-making [Web page]. [cited 26/01/2024]. Available from: <https://www.htx-h2020.eu/>
288. Kerr AM, Lin S, Sisk BA. Mental and physical health of adult patients affected by complex vascular anomalies. *Patient Educ. Couns*. 2023;117.
289. Siden H, Steele R. Charting the Territory: Children and families living with progressive life-threatening conditions. *Paediatr. Child Health*. 2015;20(3):139-44.
290. Abeni D, Rotunno R, Diociaiuti A, Giancristoforo S, Bonamonte D, Schepis C, et al. A multicenter study on quality of life of the "greater patient" in congenital ichthyoses. *Orphanet J. Rare Dis*. 2021;16(1).
291. Maxfield M, Cooper MS, Kavanagh A, Devine A, Gill Atkinson L. On the outside looking in: a phenomenological study of the lived experience of Australian adults with a disorder of the corpus callosum. *Orphanet J. Rare Dis*. 2021;16(1).
292. Videnovic A, Pfeiffer HCV, Tyłki-Szymańska A, Berry-Kravis E, Ezgü F, Ganju J, et al. Study design challenges and strategies in clinical trials for rare diseases: Lessons learned from pantothenate kinase-associated neurodegeneration. *Front. Neurol*. 2023;14.
293. Mackay J, McCallum Z, Ambler GR, Vora K, Nixon G, Bergman P, et al. Requirements for improving health and well-being of children with Prader-Willi syndrome and their families. *J. Paediatr. Child Health*. 2019;55(9):1029-37.
294. Lima AGT, Sales CCDS, Serafim WFL. Burden, depression and anxiety in primary caregivers of children and adolescents in renal replacement therapy. *J Bras Nefrol*. 2019;41(3):356-63.
295. Applebaum AJ, Polacek LC, Walsh L, Reiner AS, Lynch K, Benvengo S, et al. The unique burden of rare cancer caregiving: caregivers of patients with Erdheim-Chester disease. *Leukemia & lymphoma*. 2020;61(6):1406-17.
296. Gasol M, Paco N, Guarga L, Bosch J, Pontes C, Obach M. Early Access to Medicines: Use of Multicriteria Decision Analysis (MCDA) as a Decision Tool in Catalonia (Spain). *Journal of clinical medicine*. 2022;11(5).
297. Kocova H, Dvorackova O, Vondracek P, Haberlova J. Health-related quality of life in children and adolescents with spinal muscular atrophy in the Czech Republic. *Pediatric neurology*. 6 ed. United States; 2014. p. 591-4.
298. Granero-Molina J, Sánchez-Hernández F, Fernández-Sola C, Jiménez-Lasserrotte MDM, Antequera-Raynal LH, Hernández-Padilla JM. The Diagnosis of Hereditary Angioedema: Family Caregivers' Experiences. *Clin Nurs Res*. 2020;29(2):117-26.
299. Buchholz M, Weber N, Borel S, Sayah S, Xie F, Schulz JB, et al. Patient-reported, health economic and psychosocial outcomes in patients with Friedreich ataxia (PROFA): protocol of an observational study using momentary data assessments via mobile health app. *BMJ Open*. 2023;13(8).
300. Ragusa L, Crinò A, Grugni G, Reale L, Fiorencis A, Licenziati MR, et al. Caring and living with Prader-Willi syndrome in Italy: Integrating children, adults and parents' experiences through a multicentre narrative medicine research. *BMJ Open*. 2020;10(8).
301. Bardon C, Guillemette A, Rioux M-E, Rivard M. Group intervention programs and their impact on well-being and quality-of-life for adults living with a rare or orphan disease - realist review of literature. *Disabil Rehabil*. 2023;45(16):2567-77.
302. Maertens de Noordhout C, Detollenaere J, Primus-de Jong C, Kohn L, Devleeschauwer B, Charafeddine R, et al. Identifying Patient needs: methodological approach and application. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2022. KCE Reports (348)
303. Giordano P, Netti GS, Santangelo L, Castellano G, Carbone V, Torres DD, et al. A pediatric neurologic assessment score may drive



- the eculizumab-based treatment of Escherichia coli-related hemolytic uremic syndrome with neurological involvement. *Pediatr. Nephrol.* 2019;34(3):517-27.
304. C G, R B, V B, S G. Clinical research on rare diseases of children: neuroblastoma. *Cancer chemotherapy and pharmacology.* 2017;79(2):267-73.
305. EURORDIS. What is a rare disease? [Web page]. EURORDIS. Available from: <https://www.eurordis.org/information-support/what-is-a-rare-disease/>
306. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, European Commission 2023. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0193>
307. RIZIV. Onbeantwoorde medische behoeften - Unmet Medical Need [Web page]. Rijksinstituut voor ziekte-en invaliditeitsverzekering. Available from: <https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/geneesmiddelen/geneesmiddel-terugbetalen/onbeantwoorde-medische-behoeften-unmet-medical-need#.WhgUoFWnGpo>
308. FAMHP. Compassionate use - Medical need [Web page]. Federal Agency for Medicines and Health products [updated 11/12/2023]. Available from: https://www.famhp.be/en/human_use/medicines/medicines/research_development/compassionate_use_medical_need