

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



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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:	Joyce Grijseels (KCE)

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- 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>).
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APPENDIX 1. GREY LITERATURE REVIEWS

Appendix 1.1. SCREENED WEBSITES

Stakeholder type	Level of the organisation	Geographical region	Website	Last access date website
Patient organisations				
EURORDIS	EU	EU	https://www.eurordis.org/	13/06/2023
ProRare	National	Austria	https://www.prorare-austria.org/	13/06/2023
RaDiOrg (Rare Diseases Organisation Belgium)	National	Belgium	https://www.radiorg.be/nl/	13/06/2023
Bulgarian National Alliance of People with Rare Diseases	National	Bulgaria	https://rare-bg.com/	17/07/2023
Cyprus Alliance For Rare Disorders	National	Cyprus	http://raredisorderscyprus.com/	18/07/2023
Rare Diseases Croatia	National	Croatia	https://rijetke-bolesti.com/	17/07/2023
Rare Diseases Czech Republic	National	Czech Republic	http://www.vzacna-onemocneni.cz	17/07/2023
Rare Diseases Denmark	National	Denmark	http://www.sjaeldnediagnoser.dk/	17/07/2023
Alliance Maladie Rares	National	France	https://alliance-maladies-rares.org/	13/06/2023
Harvinaiset-Verkosto - Finnish Network for Rare Diseases	National	Finland	http://www.harvinaiset.fi	17/07/2023
ACHSE (Allianz Chronischer Seltener Erkrankungen)	National	Germany	https://www.achse-online.de/de/	13/06/2023
"95" - Rare Alliance Greece	National	Greece	https://rarealliance.gr/	17/07/2023
Rare Diseases Hungary – HUFERDIS	National	Hungary	http://www.rirosz.hu	17/07/2023
Einstök Börn - Support Group for Children with Rare Disorders	National	Iceland	https://www.einstokborn.is/is	17/07/2023
Uniamo - Italian Federation of Rare Diseases	National	Italy	https://uniamo.org/	19/02/2024
Rare Diseases Ireland	National	Ireland	http://rdi.ie/	17/07/2023
Rare Diseases Lithuania	National	Lithuania	http://retosligos.lt/	17/07/2023



ALAN – Maladies Rares Luxembourg	National	Luxembourg	https://alan.lu/	13/06/2023
National Alliance For Rare Diseases Support	National	Malta	http://www.rarediseasesmalta.com	18/07/2023
VSOP (Vereniging Samenwerkende Ouderen Patiëntenorganisaties op het gebied van aangeboren en erfelijke aandoeningen)	National	Netherlands	https://vsop.nl/	13/06/2023
Frambu - Resource Centre For Rare Disorders	National	Norway	http://www.frambu.no	18/07/2023
Polish National Forum on the treatment of Orphan Diseases	National	Poland	http://www.rzadkiechoroby.pl	18/07/2023
Fedra - Federação de Doenças Raras de Portugal	National	Portugal	https://fedra.pt/	13/06/2023
Romanian National Alliance for Rare Diseases	National	Romania	http://bolirareromania.ro	18/07/2023
Slovak Alliance of Rare Diseases	National	Slovakia	http://www.sazch.sk	17/07/2023
Viljem Julijan Association for Children with Rare Diseases	National	Slovenia	http://viljem-julijan.si/	18/07/2023
FEDER - Federación Española De Enfermedades Raras	National	Spain	http://www.enfermedades-raras.org	17/07/2023
Rare Diseases Sweden	National	Sweden	http://www.sallsyntadiagnoser.se	18/07/2023
Rare Disease UK	National	UK	https://www.raredisease.org.uk/	13/06/2023
Pharmaceutical industry/ Trade organisations				
EFPIA (European Federation of Pharmaceutical Industries and Associations)	EU	EU	https://www.efpia.eu/	15/06/2023
IFPMA (International Federation of Pharmaceutical Manufacturers & Associations)	EU	EU	https://www.ifpma.org/	15/06/2023
FCIO (Fachverband der chemischen Industrie Österreichs)	National	Austria	https://www.fcio.at/	14/06/2023
Pharma.BE	National	Belgium	https://pharma.be/nl	13/06/2023
ARPharM (Association of the Research-Based Pharmaceutical Manufacturers in Bulgaria)	National	Bulgaria	http://www.arpharm.org/	29/08/2023

KEFEA (The Cyprus Association of Research and Development Pharmaceutical Companies)	National	Cyprus	http://kefea.org.cy/	29/08/2023
iFI (Innovative Pharmaceutical Initiative)	National	Croatia	https://ifi.hr/en/association/	29/08/2023
AIFP (Asociace inovativního farmaceutického průmyslu)	National	Czech Republic	https://aifp.cz/en/	29/08/2023
LIF (The Danish Association of the Pharmaceutical Industry)	National	Denmark	https://www.lif.dk/en/	14/06/2023
APME (The Association of Pharmaceutical Manufacturers in Estonia)	National	Estonia	http://rtl.ee/map.php?mod_rewrite=/&cmd=en	29/08/2023
Leem (Les Entreprises du médicament)	National	France	https://www.leem.org/	14/06/2023
PIF (Pharma Industry Finland)	National	Finland	https://www.pif.fi/	14/06/2023
VFA (Association of Research-Based Pharmaceutical Companies)	National	Germany	https://www.vfa.de/	14/06/2023
sFEE (Hellenic Association of Pharmaceutical Companies)	National	Greece	https://www.sfee.gr/?lang=en	14/06/2023
AIPM (The Association of Innovative Pharmaceutical Manufacturers)	National	Hungary	https://aipm.hu/en/aipm-english/	29/08/2023
Frumtök	National	Iceland	https://frumtok.is/	29/08/2023
Farindustria	National	Italy	https://www.farindustria.it/english-content/	14/06/2023
IPHA (Irish Pharmaceutical Healthcare Association)	National	Ireland	https://www.ipha.ie/	14/06/2023
SIFFA (Association of International Research-based Pharmaceuticals Manufacturers)	National	Latvia	https://www.siffa.lv/en/	29/08/2023
IFPA (The Innovative Pharmaceutical Industry Association)	National	Lithuania	https://www.ifpa.lt/	29/08/2023
IML (Innovative Medicines for Luxembourg)	National	Luxembourg	https://www.iml.lu/en	29/08/2023
PRIMA (Pharmaceutical Research Based Industry Malta Association)	National	Malta	http://www.prima-malta.com/	29/08/2023
Vereniging innovatieve geneesmiddelen	National	Netherlands	https://www.vereniginginnovatievegeneesmiddelen.nl/	14/06/2023



LMI (Legemiddelindustriforeningen)	National	Norway	https://www.lmi.no/	14/06/2023
Infarma	National	Poland	https://en.infarma.pl/	14/06/2023
Apifarma	National	Portugal	https://apifarma.pt/	14/06/2023
ARPIM (The Romanian Association of International Medicines Producers)	National	Romania	https://arpim.ro/	29/08/2023
Association of Innovative Pharmaceutical Industry (AIFP)	National	Slovakia	https://www.aifp.sk/sk/kto-sme/	29/08/2023
Forum of International Research and Development Pharmaceutical Companies, EIG (Forum)	National	Slovenia	https://www.farmaforum.si/en	29/08/2023
Farmaindustria	National	Spain	https://www.farmaindustria.es/web_en/	14/06/2023
LIF (Läkemedelsindustriföreningen)	National	Sweden	https://www.lif.se/	14/06/2023
ABPI (Association of the British Pharmaceutical Industry)	National	UK	https://www.abpi.org.uk/	14/06/2023
Regulators				
EMA (European Medicines Agency)	EU	EU	https://www.ema.europa.eu/en	19/06/2023
European Commission	EU	EU	https://commission.europa.eu/index_en	10/07/2023
AGES (Österreichische Agentur für Gesundheit und Ernährungssicherheit)	National	Austria	https://www.ages.at/	15/06/2023
FAMHP-FAGG (Federal Agency for Medicines and Health Products)	National	Belgium	https://www.fagg-afmps.be/nl	15/06/2023
BDA (Bulgarian Development Agency)	National	Bulgaria	https://www.bda.bg/en/	15/06/2023
Ministry of health - Pharmaceutical services	National	Cyprus	https://www.moh.gov.cy/moh/phs/phs.nsf/home_en?openform	15/06/2023
HALMED (Agency for Medicinal Products and Medical Devices)	National	Croatia	https://www.halmed.hr/en/	15/06/2023
State institute of drug control	National	Czech Republic	https://www.sukl.eu/	15/06/2023
Danish Medicines Agency	National	Denmark	https://laegemiddelstyrelsen.dk/en/	16/06/2023
State agency of medicines	National	Estonia	https://www.ravimiamet.ee/	16/06/2023
ANSM (Agence nationale de sécurité du médicament et des produits de santé)	National	France	https://ansm.sante.fr/	19/06/2023

FIMEA (Finnish Medicines Agency)	National	Finland	https://www.fimea.fi/web/en/marketing_authorisations/marketing_authorisation_application/orphan-drugs	16/06/2023
Federal institute for drugs and medical devices	National	Germany	https://www.bfarm.de/DE/Home/_node.html	19/06/2023
National organisation of medicines	National	Greece	https://www.eof.gr/web/guest;jsessionid=a02e77764bf00575807ad868ad27	19/06/2023
National institute of pharmacy and nutrition	National	Hungary	https://ogyei.gov.hu/	19/06/2023
Icelandic Medicines Agency	National	Iceland	https://www.ima.is/	19/06/2023
AIFA (Agenzia italiana del farmaco)	National	Italy	https://www.aifa.gov.it/	10/07/2023
HPRA (Health Products Regulatory Authority)	National	Ireland	https://www.hpra.ie/	19/06/2023
State agency of medicines	National	Latvia	https://www.zva.gov.lv/en	19/06/2023
Office of health/Department of pharmaceuticals	National	Liechtenstein	https://www.llv.li/de	19/06/2023
State Medicines Control Agency (VVKT)	National	Lithuania	Website does not work	/
Ministry of Health	National	Luxembourg	https://sante.public.lu/fr.html	06/07/2023
Malta Medicines Authority	National	Malta	https://medicinesauthority.gov.mt/	10/07/2023
CBG – MEB (College ter Beoordeling van Geneesmiddelen)	National	Netherlands	https://www.cbg-meb.nl/	19/06/2023
Norway Medicines Agency	National	Norway	https://legemiddelverket.no/	10/07/2023
Office for registration of Medicinal products, medical devices and biocidal products	National	Poland	https://www.urpl.gov.pl/pl	10/07/2023
Servico Nacional de Saúde	National	Portugal	https://www.sns.gov.pt/	05/07/2023
National Authority of Medicines and medical devices	National	Romania	https://www.ms.ro/en/	10/07/2023
SUKL (SIDC, State Institute for Drug Control)	National	Slovakia	https://www.sukl.sk/	10/07/2023
JAZMP (Javna agencija Republike Slovenije za zdravila in medicinske pripomočke)	National	Slovenia	https://www.jazmp.si/en/	10/07/2023
AEMPS (Agencia Española de Medicamentos y Productos Sanitarios)	National	Spain	https://www.aemps.gob.es/	19/06/2023
Swedish Medicinal Products Agency	National	Sweden	https://www.lakemedelsverket.se/sv	10/07/2023



Medicines & Healthcare products Regulatory Agency	National	UK	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency#:~:text=The%20Medicines%20and%20Healthcare%20products%20Regulatory%20Agency%20regulates%20medicines%2C%20medical.of%20Health%20and%20Social%20Care.	28/08/2023
HTA bodies				
EunetHTA	EU	EU	https://www.eunethta.eu/	/
Austrian Institute for Health Technology Assessment (AIHTA)	National	Austria	https://aihta.at/page/homepage/en	19/06/2023
Belgian Health Care Knowledge Centre (KCE)	National	Belgium	https://kce.fgov.be/	19/06/2023
National Health Insurance Fund	National	Bulgaria	https://www.nhif.bg/en	03/07/2023
Ministry of health Cyprus	National	Cyprus	https://www.moh.gov.cy/moh/moh.nsf/index_en/index_en	/
Croatian Institute of public health	National	Croatia	https://www.hzjz.hr/en/	05/07/2023
CzechHTA	National	Czech Republic	https://czechhta.cz/en/health-technology-assessment/	29/08/2023
Danish health and medicine authority (DHMA)	National	Denmark	https://www.sundhedsstyrelsen.dk/en/english	03/07/2023
Health insurance fund	National	Estonia	https://www.tervisekassa.ee/en	04/07/2023
Haute Autorité de santé (HAS) (CEESP)	National	France	https://www.has-sante.fr/jcms/pprd_2986129/en/home	22/06/2023
Finnish Coordinating Center for Health Technology Assessment (FINCCHTA)	National	Finland	https://www.inahta.org/members/fincchta/	03/07/2023
IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)	National	Germany	https://www.iqwig.de/en/	21/06/2023
National Evaluation Center of Quality and Technology in S.A.- EKAPTY	National	Greece	https://www.ekapty.gr/en/	04/07/2023
Ministry of Human Capacities	National	Hungary	https://2015-2019.kormany.hu/en/ministry-of-human-resources	04/07/2023

Unità di Valutazione Technology Assessment (UVTA/AOP)	National	Italy	https://www.aopd.veneto.it/	05/07/2023
Health information and quality authority	National	Ireland	https://www.hiqa.ie/	18/07/2023
National health service of Latvia (NHS)	National	Latvia	https://www.vmnvd.gov.lv/en	04/07/2023
State Health Care Accreditation Agency (VASPVT)	National	Lithuania	https://vaspvt.lrv.lt/?lang=en	29/08/2023
CEM (La Cellule d'expertise médicale)	National	Luxembourg	https://cem.gouvernement.lu/fr.html	29/08/2023
Ministry for health - government of Malta	National	Malta	https://healthservices.gov.mt/en/pharmaceutical/Pages/home.aspx	18/07/2023
National Health Care Institute (ZIN)	National	Netherlands	https://www.zorginstituutnederland.nl/	21/06/2023
Norwegian Knowledge Centre for the Health Services (NOKC)	National	Norway	http://www.adhophta.eu/partner/norwegian-knowledge-center-health-services-nokc	23/06/2023
Agency for Health Technology Assessment and Tariff System (AOTMiT)	National	Poland	https://www.aotm.gov.pl/en/	23/06/2023
INFARMED National Health Technology Assessment System	National	Portugal	https://www.infarmed.pt/	05/07/2023
National Health Insurance House (CNAS)	National	Romania	http://www.casan.ro/	05/07/2023
National institute for Value and Technologies in Healthcare	National	Slovakia	https://niho.sk/en/	18/07/2023
National Institute of public health (NIJZ)	National	Slovenia	https://eurohealthnet-magazine.eu/slovenia-the-national-institute-of-public-health-nijz/?gclid=Cj0KCQjwho-IBhC_ARIsAMpgModY3wCEgmf6YmSoJvy_dDmhM-4RALw_-hygzsGmQzRFolGxwIaltQ0aApqKEALw_wcB	04/07/2023
Agencia de Evaluación de Tecnologías Sanitarias (AETS) + agency for health quality and assessment, RedETS/ISCIII or ICP	National	Spain	https://www.isciii.es/QuienesSomos/CentrosPropios/AETS/Paginas/default.aspx	22/06/2023
SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services)	National	Sweden	https://www.sbu.se/en/	22/06/2023



NICE (National Institute for Health and Care Excellence)	National	UK	https://www.nice.org.uk/	23/06/2023
Payer				
Association of Austrian Social Insurance	National	Austria	https://www.sozialversicherung.at/cdscontent/?contentid=10007.821628&portal=support	06/07/2023
RIZIV-INAMI (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering - Institut national d'assurance maladie-invalidité)	National	Belgium	https://www.riziv.fgov.be/nl/Paginas/default.aspx	05/07/2023
Croatian Health Insurance Fund	National	Croatia	https://hzzo.hr/	05/07/2023
The National Institute of Health Insurance Fund Management	National	Hungary	https://www.neak.gov.hu/oldal/nyelvi-oldal/angol	04/07/2023
ACSS IP (Administração Central do Sistema de Saúde, I.P.)	National	Portugal	https://www.acss.min-saude.pt/?lang=en	05/07/2023
NHS (National Health Service)	National	UK	https://www.nhs.uk/	05/07/2023

Appendix 1.2. OVERVIEW LITERATURE

Stakeholder type	Date of publication	Website search string	Rare disease definition	Other relevant information
Patient organisations				
EURORDIS	Not specified	Homepage > information & support > What is a rare disease?	The European Union considers a disease as rare when it affects less than 1 in 2 000 citizens. Rare diseases are characterized by a wide diversity of symptoms and signs that vary not only from disease to disease but also from patient-to-patient suffering from the same disease. Typically disabling, the quality of life of a person living with a rare disease is affected by the lack or loss of autonomy due to the chronic, progressive, degenerative, and frequently life-threatening aspects of the disease.	Due to the low prevalence of each disease, medical expertise is rare, knowledge is scarce, care offerings inadequate and research limited.
ProRare	Not specified	Homepage > over zeldzame ziekten	A disease is classified as rare in the European Union if it affects less than 1 in 2 000 people.	
RaDiOrg (Rare Diseases Organisation Belgium)	Not specified	Homepage > zeldzame ziekten > zeldzame ziekten	A disease is rare when it occurs in less than 1 in 2 000 inhabitants. Rare diseases tend to be severe and complex. A lot of rare diseases are life-threatening or chronically debilitating.	
Bulgarian National Alliance of People with Rare Diseases	Not specified	Homepage > Rare diseases	Rare diseases are diseases that affect less than 1 in 2 000 people. In most cases, their cause is genetic, they are often chronic and life-threatening.	(i) No accurate diagnosis; (ii) Lack of quality information and knowledge on the disease; (iii) Lack of proper medical care and; (iv) no equal access to treatment
Cyprus Alliance For Rare Disorders	Not specified	Homepage > rare diseases	in Cyprus, Europe and internationally, diseases with a prevalence equal to or less than 5 in 10 000 people are called. They concern 6 000-8 000 different diseases or syndromes characterized by low frequency in the population and great to enormous heterogeneity in their clinical outcome.	



Rare Diseases Croatia	Not specified	Homepage > rare diseases	By definition, rare diseases are those diseases that occur in less than 5 individuals per 10 000 inhabitants . From the medical side, these are most often chronic, degenerative and fatal diseases, due to which the quality of life of the patients is significantly reduced, especially since they are dependent on other people's help.	(i) Late diagnosis (ii) Lack of effective drugs (iii) lack of access to treatments because therapies are often unevenly available in EU countries, due to delays in P&R decisions; (iv) Lack of knowledge on the disease
Rare Diseases Czech Republic	Not specified	Homepage > rare diseases > what is a rare disease?	Rare diseases are clinically heterogeneous, mainly hereditary multisystem diseases with a very low incidence (prevalence) in the population, which have an impact on the patient's quality of life and social inclusion, or they threaten his life. A disease is defined as rare within the EU if it affects less than 5 people out of every 10 000.	
Rare Diseases Denmark	Not specified	Homepage > knowledge > rare diseases	In Denmark, a disease is called rare when 1-2 people out of 10 000 have it. The rare diseases are mainly congenital and genetically determined, as well as serious. The diseases cannot be cured and are very different.	
/ (Estonia)	/	/	Website not found/website did not work	
Alliance Maladie Rares	Not specified	Homepage > Nos combats > Définition et chiffres clés	A disease is called rare when less than one person is affected in 2 000, i.e. for France less than 30 000 people for a given disease. This definition is based on the prevalence established by the 1999 European Orphan Drug Regulation. Rare diseases are often severe and disabling for two thirds of the diseases. They are life-threatening for almost half of patients.	
Harvinaiset-Verkosto - Finnish Network for Rare Diseases	Not specified	Homepage	Rare diseases are usually defined based on the prevalence of the disease in a certain population . In Finland, the European definition is used, according to which a disease is rare if it occurs in no more than five people out of 10 000.	

ACHSE (Allianz Chronischer Seltener Erkrankungen)	Not specified	Homepage > ACHSE > Erkrankungen	Seltene	In Europe, a disease is considered rare if no more than 5 in 10 000 people have the specific syndrome. Many of these diseases are life-threatening or debilitating. Most are chronic: they cannot be cured and patients are permanently dependent on medical treatment.
"95" - Rare Alliance Greece	Not specified	Homepage		In Europe, a condition is considered rare when it affects less than 1 in 2 000 people . Many of them are complex, chronic and degenerative, thus causing serious disabilities.
Rare Diseases Hungary – HUFERDIS	Not specified	Homepage > diseases	about rare	A rare disease covers a disease that affects a small number of people compared to the average population. In Europe, a disease is considered rare if it affects more than 1 in 2 000 people. In many cases, life-threatening or chronic degenerative diseases with a high level of complexity.
Einstök Börn - Support Group for Children with Rare Disorders	/	/		No definition
Uniamo - Italian Federation of Rare Diseases	/	Homepage > Rare diseases > Rare diseases: what they are		At European level, a disease is defined as rare if it has a prevalence of less than 5 cases per 10,000 people.
Rare Diseases Ireland	/	/		No definition
Latvian Alliance for Rare Diseases	/	/		Website not found/website did not work
/ (Liechtenstein)	/	/		Website not found/website did not work
Rare Diseases Lithuania	/	/		No definition



ALAN – Maladies Rares Luxembourg	Not specified	Homepage > rare diseases > what is a rare disease	In the European Union, a disease is classified as “rare” if it affects less than 1 in 2 000 people. Rare diseases are often chronic and progressive, so symptoms can evolve over time.
National Alliance For Rare Diseases Support	/	/	No definition
VSOP (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties op het gebied van aangeboren en erfelijke aandoeningen)	Not specified	Homepage > Voor wie > problematiek van zeldzaam	According to the European definition, a rare condition is a life-threatening or chronically debilitating disease that occurs no more frequently than in 1 per 2 000 people. In the Netherlands, it is up to 8 000 people per rare condition.
Frambu - Resource Centre For Rare Disorders	Not specified	Homepage > Theme > What is a rare diagnosis?	A rare condition is defined as a health condition with a low prevalence, i.e., with an indicative incidence of fewer than 5 in 10 000
Polish National Forum on the treatment of Orphan Diseases	/	/	No definition
Fedra - Federação de Doenças Raras de Portugal	Not specified	Homepage > zeldzame ziekten	In the European Union, rare diseases are diseases with a prevalence of less than 5 in 10 000 people, taking into account the total population of the EU. These diseases can almost always be characterized as: *Serious chronic diseases, degenerative and usually life-threatening; * disabling diseases, where quality of life is compromised due to lack of autonomy; * Diseases in which the level of pain and suffering of the individual and his family is high; * Diseases for which there is no effective cure, but whose symptoms can be treated to improve quality of life and life expectancy.

Romanian Alliance for Rare Diseases	National Rare Diseases	Not specified	Homepage > 'about us' > BR policies > National plan for rare diseases	A rare disease is a disease that affects less than 5 in 10 000 people in the European Union.	
Slovak Alliance of Rare Diseases		Not specified	Homepage > rare diseases > general information	Rare diseases include diseases that affect no more than 1 person out of 2 000, or 500 people per 1 million inhabitants. Rare diseases have a serious chronic, progressive, degenerative, and often life-threatening nature.	(i) Lack of scientific knowledge, (ii) Delayed diagnosis trained specialists, but also poor health care and treatment, or little quality information contributes to the late recognition of the diagnosis and the development of complications and disability.
Viljem Association for Children with Rare Diseases	Julijan for Rare Diseases	Not specified	Homepage > What about rare diseases?	By definition, a rare disease affects no more than 5 people per 10 000 inhabitants.	(i) inaccessibility to proper diagnosis; (ii) lack of quality information about the disease; (iii) lack of scientific knowledge; (iv) problems with access to treatment
FEDER - Federación Española De Enfermedades Raras		Not specified	Homepage > Rare diseases > learn more about RE	Rare diseases or infrequent diseases are those that have a low prevalence in the population. To be considered rare, each specific disease can only affect a limited number of people. Specifically, when it affects less than 5 per 10 000 inhabitants.	
Rare Sweden	Diseases	Not specified	Homepage > about us > About the national association of rare diagnoses > what is a rare disease?	Rare diagnosis (rare health condition) means a disease, injury, disorder or change in body function, with a low prevalence (proportion of the population that has the condition). The National Board of Health and Welfare states as guidance that occurrence in fewer than 5 out of 10 000 inhabitants can be considered low prevalence.	
Rare Disease UK		Not specified	Homepage > What's a rare disease	The European Union defines a disease or condition as rare if it affects fewer than 1 in 2 000 people within the general population. Often rare diseases are chronic and life-threatening.	

Pharmaceutical industry/ Trade organizations



EFPIA (European Federation of Pharmaceutical Industries and Associations)	14/06/2019	Homepage > search on 'rare disease' > blog article 'Rare & childhood diseases: addressing unmet need'	While each individual rare disease affects less than one in 2 000 people, there are more than 6 000 conditions classified as "rare" diseases.
IFPMA (International Federation of Pharmaceutical Manufacturers & Associations)	Not specified	Homepage > areas of work > advancing sustainable health systems > rare diseases OR Homepage > news & resources > publications > rare diseases: shaping a future with no-one left behind	Rare diseases are a group of conditions which affect very small numbers of people. Definitions vary, although generally a disease is considered rare if it affects fewer than 1-5 individuals per 10 000 in the general population. Rare diseases pose a unique challenge to patients, their families, societies, healthcare professionals, and healthcare systems. They require 'orphan drugs', or drugs that are uniquely developed to target rare conditions. people are affected by rare diseases worldwide
FCIO (Fachverband der chemischen Industrie Österreichs)	/	/	No definition
Pharma.BE	Not specified	Homepage > expertise > zeldzame ziekten en wees-geneesmiddelen > weesgeneesmiddelen, een uitdaging voor de innoverende bedrijven	According to a European definition, a disease is considered rare when it affects less than one person in 2 000. In Belgium this means a maximum of 5 500 patients per disease.
ARPharM (Association of the Research-Based Pharmaceutical Manufacturers in Bulgaria)	/	/	No definition
KEFEA (The Cyprus Association of Research and Development Pharmaceutical Companies)	/	/	No definition

iFI (Innovative Pharmaceutical Initiative)	/	/	No definition	
AIFP (Asociace inovativního farmaceutického průmyslu)	28/2/2023	/	No definition	Rare diseases have one limitation - due to the small number of patients, it is often difficult to obtain definitive data on the efficacy and safety of treatments at the time of registration of new drugs. Therefore, it is necessary to develop a system for obtaining valid data beyond registration clinical trials.
LIF (The Danish Association of the Pharmaceutical Industry)	/	/	No definition	
APME (The Association of Pharmaceutical Manufacturers in Estonia)	/	/	No definition	
Leem (Les Entreprises du médicament)	24/02/2022	Homepage > innovatie & gezondheid > ziekten > zeldzame ziekten	Ziekten die minder dan één op de 2 000 personen treffen.	Challenges: Adapting the regulatory system to the specificity of rare diseases; (i) Ensure patient access to innovative medicines, (ii) build an integrated, interconnected and international database, (iii) Develop an incentive system for industrial R&D
PIF (Pharma Industry Finland)	/	/	No definition	
VFA (Association of Research-Based Pharmaceutical Companies)	21/02/2023	Homepage > english > 'selected vfa articles in english language > 'drugs for rare diseases examples and numbers'	In the EU, a disease is called "rare" if no more than 5 out of 10 000 EU citizens (in other words: one out of 2 000 EU citizens) suffer from it.	
sFEE (Hellenic Association of Pharmaceutical Companies)	/	/	No definition	



AIPM (The Association of Innovative Pharmaceutical Manufacturers)	/	/	No definition	
Frumtök	/	/	No definition	
Farmaindustria	Not specified	Homepage > English content > position paper about rare diseases	A rare disease is a disease with an incidence of fewer than 5 cases per 10 000 persons.	
IPHA (Irish Pharmaceutical Healthcare Association)	28/02/2019	Homepage > search on 'rare' > 2e result: Rare Disease Patients Can Access Just One-Third of Medicines Available in Rest of Europe,	Rare diseases are among the hardest medical conditions to treat. Though they affect fewer than one in 2 000 people, three-quarters of rare diseases are found in children and the mortality rate is very high. There are between 7 000 and 8 000 recognised rare diseases.	
SIFFA (Association of International Research-based Pharmaceuticals Manufacturers)	/	/	No definition	
/ (Liechtenstein)	/	/	Website not found/website did not work	
IFPA (The Innovative Pharmaceutical Industry Association)	/	/	No definition	
IML (Innovative Medicines for Luxembourg)	Not specified	Homepage > search on 'orphan' -> Newsletter on orphan drugs	According to the definition adopted by the European Community, a RD is a condition with a very low prevalence of less than 1 in 2 000 people. It represents about 30 000 people in Luxembourg. These are very different diseases genetic, chronic and progressive, but they are linked by the same difficulties.	(i) lack of therapies, (ii) lack of info, knowledge and specific expertise
PRIMA (Pharmaceutical Research Based Industry Malta Association)	/	/	No definition	



Vereniging innovatieve geneesmiddelen	/	/	No definition	
LMI (Legemiddelindustriforening)	/	/	No definition	
Infarma	/	/	No definition	
Apifarma	/	/	No definition	
ARPIM (The Romanian Association of International Medicines Producers)	Not specified	Homepage > search on 'rare' > 'Bolile rare – o prioritate pentru cercetătorii în medicină'	In the countries of the European Union, any disease that affects less than 5 people out of 10 000 is considered a rare disease.	
Association of Innovative Pharmaceutical Industry (AIFP)	Not specified	Homepage > Media and the public > page 2 > 'Changes for people with rare diseases: we have 5 good news!'	A uniform definition of a drug for rare diseases has existed in Europe. It is regulated by the European legislation 141/1999 on medicines for rare diseases.	
Forum of International Research and Development Pharmaceutical Companies, EIG (Forum)	Not specified	Homepage > news > #wewontrest until we make treatment for rare diseases less rare	Rare diseases are often genetic in origin, mostly emerging in childhood and result in a severe burden of illness.	(i) lack of validated biomarkers and end-points, (ii) poor diagnostics (iii) and limited clinical expertise
Farmaindustria	/	/	No definition	
LIF (Läkemedelsindustriförening)	/	/	No definition	
ABPI (Association of the British Pharmaceutical Industry)	24/02/2023	Homepage > our focus > content hubs > rare disease > awareness challenge	Whilst the definition of a rare disease is one which affects less than 1 in 2 000 people, collectively there are between 6 000 – 8 000 individual rare diseases	

Regulators



EMA (European Medicines Agency)	Not specified	Home > Human Regulatory > Overview > Orphan designation	EU definition: it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence of the condition in the EU must not be more than 5 in 10 000.
European Commission	Not specified	Home > Research and Innovation > Research by area > Health > Rare diseases	In Europe, a rare disease is one that affects no more than 1 person in 2 000.
AGES (Österreichische Agentur für Gesundheit und Ernährungssicherheit)	/	/	No definition
FAHMP (FAGG) (Federal Agency for Medicines and Health Products)	19/01/2023	Homepage > menselijk gebruik > geneesmiddelen > weesgeneesmiddelen	A medicine is designated as an "orphan medicine" if it is used to treat a life-threatening or seriously debilitating disease that affects no more than 5 in 10 000 people in the European Union.
BDA (Bulgarian Development Agency)	/	/	No definition
Ministry of health - Pharmaceutical services	/	/	No definition
HALMED (Agency for Medicinal Products and Medical Devices)	3/03/2014	Homepage > news and educations > news > 'International rare diseases day – 12 new orphan medicines authorised in the EU over the past year	Rare diseases are defined as potentially fatal conditions or disease leading to a chronic weakness, which is a condition that does not affect more than 5 in 10 000 people. It is estimated that 30 million people in the EU suffers from a rare disease.
State institute of drug control	/	/	No definition
Danish Medicines Agency	/	/	No definition
State agency of medicines	/	/	No definition

ANSM (Agence nationale de sécurité du médicament et des produits de santé)	Not specified	Homepage > glossaire > 'M'	Orphan medicinal products are intended for the treatment, prevention or diagnosis of rare, serious or life-threatening diseases, the prevalence of which does not exceed 5 cases per 10 000 people in the European Union.
FIMEA (Finnish Medicines Agency)	Not specified	Homepage > market authorisations > marketing applications > orphan drugs	Pursuant to the Regulation, the European Medicines Agency grants orphan drug designations upon application for preparations that will be developed into drugs for treating rare diseases. Preconditions for obtaining an orphan drug designation is that the incidence of the disease treated with the drug does not exceed 5 out of 10 000 EU citizens, the disease is life-threatening or chronically disabling and there is no good therapy available. (i) small research subject populations. (ii) carrying out clinical trials that comply with good clinical practice might be difficult when the trial is carried out in several centres that treat only a few patients. The EMA has created guideline presenting possible approaches for obtaining reliable information in clinical trials with small populations.
Federal institute for drugs and medical devices	Not specified	Homepage > medicinal products > medicines for rare diseases	The requirement for an orphan designation (OD) is that the disease for which the medicinal product is to be developed does not affect more than 5 out of 10 000 people in the EU.
National organisation of medicines	/	/	No definition
National institute of pharmacy and nutrition	/	/	No definition
Icelandic Medicines Agency	/	/	No definition
AIFA (Agenzia italiana del farmaco)	Not specified	Home > translate page to english > Access to medicinal products > Orphan Medicinal Products	Orphan medicines are used for the diagnosis, prevention and treatment of rare diseases. In Europe, a disease is considered rare when it affects no more than 5 people per 10 000 inhabitants.
HPRA (Health Products Regulatory Authority)	/	/	No definition



State medicines agency of Not specified	Homepage > search on 'Rare disease' > blog article 'Rare & childhood diseases: addressing unmet need' > Medicinal products available for compassionate use OR homepage > industry > marketing authorisation holders > pre-authorisation > medicinal products available for compassionate use	Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000 for treatment of rare diseases for which there are no satisfactory diagnostic, preventative and treatment methods approved within the Community or, if such exist, the medicinal product may provide substantial benefit to the people affected by this disease: affecting not more than five in 10 thousand persons in the Community
Office of health/Department of pharmaceuticals /	/	No definition
State Medicines Control Agency (VVKT) /	/	Website not found/website did not work
Ministry of Health Not specified	Home > search on "Rare disease" > Plan National Maladies Rares Luxembourg 2018-2022	Any disease affecting fewer than 1 in 2 000 people and no readily available treatment is known is considered a rare disease.
Malta Medicines Authority Not specified	Home > Activities > Registration > Orphan Medicinal Products	Rare diseases are life-threatening or chronically debilitating conditions that affect no more than 5 in 10 000 people in the EU.
CBG – MEB (College ter Beoordeling van Geneesmiddelen) /	/	No definition
Norway Medicines Agency /	/	No definition
Office for registration of Medicinal products, medical devices and biocidal products /	/	No definition

Servico nacional de Saúde	Not specified	Homepage > search on rare disease > "Dia Mundial das Doenças Raras"	Rare diseases are chronic diseases that are mostly debilitating and often fatal early on
National Authority of Medicines and medical devices	/	/	No definition
SUKL (SIDC, State Institute for Drug Control)	28/02/2012	Search on 'orphan disease' > translate the page in google chrome > select the third article with title: "In the treatment of rare diseases, the so-called orphan drugs"	They are following the general EU definition which states that rare diseases are defined as diseases that affect less than 5 out of 10 000 patients. (Diseases that affect less than 5 out of 10 000 patients are referred to as rare diseases in the professional literature.)
JAZMP (Javna agencija Republike Slovenije za zdravila in medicinske pripomočke)	/	/	No definition
AEMPS (Agencia Española de Medicamentos y Productos Sanitarios)	23/02/2017	Homepage > search on 'rare disease' > eerste zoekresultaat: Editan una guía para ayudar a los investigadores en el desarrollo de medicamentos huérfanos para enfermedades raras	Orphan drugs are drugs intended to treat rare diseases (affecting fewer than 5 in 10 000 inhabitants).
Swedish Medicinal Products Agency	/	/	No definition
Medicines & Healthcare products Regulatory Agency	Not specified	Homepage > search for rare disease > England rare disease action plan 2023 > documents: England rare disease action plan 2023: main report > introduction	A rare disease affects fewer than 1 in 2 000 people within the general population. Rare diseases can be both life-limiting and life-threatening, and disproportionately affect children.
HTA bodies			
EunetHTA	/	/	No definition



Austrian Institute for Health Technology Assessment (AIHTA)	/	/	No definition
Belgian Health Care Knowledge Centre (KCE)	Not specified	Homepage > search on 'rare disease'	EU definition in report
National Health Insurance Fund	/	/	No definition
Ministry of health Cyprus	/	/	Website not found/website did not work
Croatian Institute of public health	/	/	No definition
CzechHTA	/	/	No definition
Danish health and medicine authority (DHMA)	/	/	No definition
Health insurance fund	/	/	No definition
Haute Autorité de santé (HAS) (CEESP)	/	/	No definition
Finnish Coordinating Center for Health Technology Assessment (FINCCHTA)	/	/	No definition
IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)	10/10/2014	Homepage > search on 'rare disease' > Rare diseases: no reason for lower demands for studies (press release)	In the European Union rare diseases are classified as rare if they occur in not more than 5 per 10 000 inhabitants.

National Evaluation Center of Quality and Technology in S.A.-EKAPTY	/	/	No definition
Ministry of Human Capacities	/	/	No definition
/ (Iceland)	/	/	Website not found/website did not work
Unità di Valutazione Technology Assessment (UVTA/AOP)	Not specified	Home > News Archive > The states General on Rare Diseases in Padua	They also follow the EU guidelines (Regulation 141/2000) stating that "A pathology is rare when it affects fewer than 5 inhabitants out of 10 000."
Health information and quality authority	/	/	No definition
National health service of Latvia (NHS)	/	/	No definition
/ (Liechtenstein)	/	/	Website not found/website did not work
State Health Care Accreditation Agency (VASPVT)	/	/	No definition
CEM (La Cellule d'expertise médicale)	/	/	No definition
Ministry for health - government of Malta	/	/	No definition
National Health Care Institute (ZIN)	Not specified	Homepage > zoek op 'zeldzame ziekte' > Beoordeling van weesgeneesmiddelen (over ons > werkwijzen en procedures > adviseren over en verduidelijken van het basispakket zorg > beoordeling van geneesmiddelen)	Orphan drugs are medicines for rare, often serious conditions. These conditions are usually progressive in nature and can be severely disabling or life-threatening.



Norwegian Knowledge Centre for the Health Services (NOKC)	/	/	No definition
Agency for Health Technology Assessment and Tariff System (AOTMiT)	/	/	No definition
INFARMED National Health Technology Assessment System	/	/	No definition
National Insurance House (CNAS)	/	/	No definition
National institute for Value and Technologies in Healthcare	/	/	No definition
National Institute of public health (NIJZ)	Not specified	/	No definition
Agencia de Evaluación de Tecnologías Sanitarias (AETS) + agency for health quality and assessment, RedETS/ISCIII or ICP	14/08/2018	Homepage > qué hacemos > áreas de investigación > enfermedades raras > publicaciones > SpainUDP: The Spanish Undiagnosed Rare Diseases Program	Rare diseases (RD) constitute a very heterogeneous group of clinical entities defined by low prevalence, high rates of mortality and long-term disability.
SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services)	22/10/2019	Homepage > search on 'rare disease' > experiences of rare inherited disorders in adults	In Sweden a disorder is considered rare if less than 100 in one million inhabitants have the disorder or condition and it causes a disability. For most people with a rare diagnosis, the disorder affects quality of life and daily activities like work, studies and hobbies.
NICE (National Institute for Health and Care Excellence)	/	/	No definition
Payer			

Association of Austrian Social Insurance	/	/	No definition
RIZIV-INAMI (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering - Institut national d'assurance maladie-invalidité)	Not specified	Home > zoekfunctie > 'zeldzame ziekte' > 'Het statuut van persoon met chronische aandoening verbetert de toegang tot de zorgen' > 'U lijdt aan een zeldzame ziekte of weesziekte en heeft grote uitgaven voor geneeskundige verzorging? Bezorg dan een medisch getuigschrift aan uw ziekenfonds'	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.
Croatian Health Insurance Fund	/	/	No definition
The National Institute of Health Insurance Fund Management	/	/	No definition
ACSS IP (Administração Central do Sistema de Saúde, I.P.)	/	/	No definition
NHS (National Health Service)	/	/	No definition



APPENDIX 2. RAPID REVIEW

Appendix 2.1. SEARCH STRING

Database	Search string	Results
PubMed	("Rare Diseases"[Mesh]) OR ("Rare disease"[Title/Abstract]) OR ("Rare disease"[Tiab:~10]) OR ("Rare diseases"[Tiab:~10]) OR ("Orphan disease"[Title/Abstract]) OR ("Orphan disease"[Tiab:~10]) OR ("Orphan diseases"[Tiab:~10]) OR ("Rare disorder"[Title/Abstract]) OR ("Rare disorder"[Tiab:~10]) OR ("Rare disorders"[Tiab:~10]) OR ("Rare condition"[Title/Abstract]) OR ("Rare condition"[Tiab:~10]) OR ("Rare conditions"[Tiab:~10]) OR ("Orphan condition"[Title/Abstract]) OR ("Orphan conditions"[Tiab:~10]) OR ("Orphan condition"[Tiab:~10]) OR ("Orphan designation"[Title/Abstract]) OR ("Orphan designation"[Tiab:~10]) OR ("Orphan designations"[Tiab:~10]) OR ("Orphan disorder"[Tiab:~10]) OR ("orphan disorders"[Tiab:~10]) OR ("orphan disorder"[Tiab]) AND ("Surveys and Questionnaires"[Mesh]) OR ("survey"[Tiab]) OR ("questionnaire"[Tiab]) OR ("Self Report"[Mesh]) OR ("self report"[Tiab:~3]) OR ("self reports"[Tiab:~3]) OR ("Qualitative Research"[Mesh]) OR ("Qualitative research"[Tiab:~3]) OR ("Qualitative study"[Tiab:~3]) OR ("Qualitative studies"[Tiab:~3]) OR ("Quantitative research"[Tiab:~3]) OR ("Quantitative study"[Tiab:~3]) OR ("Quantitative studies"[Tiab:~3]) OR ("Interviews as Topic"[Mesh]) OR ("Interview"[Tiab]) OR ("Focus Groups"[Mesh]) OR ("Focus group"[Tiab]) OR ("Focus discussion"[Tiab]) OR ("Multi criteria decision analysis"[Tiab]) OR ("Multiple criteria decision analysis"[Tiab]) OR ("Multicriteria decision analysis"[Tiab]) OR ("Multi criteria decision making"[Tiab]) OR ("Multiple criteria decision making"[Tiab]) OR ("Multicriteria decision making"[Tiab]) OR ("Multi criteria decision tool"[Tiab]) OR ("MCDA"[Tiab]) OR ("Registries"[Mesh]) OR ("Registries"[Tiab]) OR ("Registry"[Tiab]) OR ("Register"[Tiab]) OR ("Workshop"[Tiab]) OR ("Expert panel"[Tiab:~7]) OR ("Expert panels"[Tiab:~7]) OR ("Stakeholder panel"[Tiab:~7]) OR ("Stakeholder panels"[Tiab:~7]) OR ("Forum"[Tiab]) OR ("Stakeholder consultation"[Tiab:~7]) OR ("Stakeholder consultations"[Tiab:~7]) OR ("Expert consultation"[Tiab:~7]) OR ("Expert consultations"[Tiab:~7]) OR ("Patient Participation"[Mesh]) OR ("Patient Participation"[Tiab:~7]) OR ("Patient involvement"[Tiab:~7]) OR ("Patient empowerment"[Tiab:~7]) OR ("Patient engagement"[Tiab:~7]) OR ("Patient activation"[Tiab:~7]) OR ("Social network"[Tiab]) OR ("Engagement method"[Tiab:~7]) OR ("Engagement methods"[Tiab:~7]) OR ("Needs Assessment"[Mesh]) OR ("Needs Assessment"[Tiab:~7]) OR ("assessing needs"[Tiab:~7]) OR ("Need determination"[Tiab:~7]) OR ("determining need"[Tiab:~7]) OR ("Needs determination"[Tiab:~7]) OR ("determining needs"[Tiab:~7]) OR ("Patient Outcome Assessment"[Mesh]) OR ("Patient Outcome Assessment"[Tiab:~7]) OR ("Patient Outcome Assessments"[Tiab:~7]) OR ("Epidemiologic Methods"[Mesh]) OR ("Epidemiologic Method"[Tiab]) OR ("Epidemiologic research"[Tiab:~7]) OR ("Epidemiological research"[Tiab:~7]) OR ("Health Services Research"[Mesh]) OR ("Health Services Research"[Tiab:~7]) OR ("Health Services Evaluation"[Tiab:~7]) OR ("Health Services Evaluations"[Tiab:~7]) OR ("Health care research"[Tiab:~7]) OR ("Healthcare research"[Tiab:~7]) OR ("Observational research"[Tiab:~7]) OR ("Observational studies"[Tiab:~7]) OR ("Observational study"[Tiab:~7]) OR ("Cohort research"[Tiab:~7]) OR ("Cohort study"[Tiab:~7]) OR ("Cohort studies"[Tiab:~7]) OR ("case-control study"[Tiab:~7]) OR ("case-control studies"[Tiab:~7]) OR ("healthcare evaluation"[Tiab:~7]) OR ("health care evaluation"[Tiab:~7]) OR ("health-care evaluation"[Tiab:~7]) OR ("visual analogue scale"[Tiab]) OR ("EQ-5D"[Tiab]) AND	1 289

(("Unmet need"[Tiab:~6]) OR ("Unmet needs"[Tiab:~6]) OR ("Unmet demand"[Tiab:~6]) OR ("Unmet demands"[Tiab:~6]) OR ("Societal need"[Tiab:~6]) OR ("Societal needs"[Tiab:~6]) OR ("Societal demand"[Tiab:~6]) OR ("Societal demands"[Tiab:~6]) OR ("Community need"[Tiab:~6]) OR ("Community needs"[Tiab:~6]) OR ("Community demand"[Tiab:~6]) OR ("Community demands"[Tiab:~6]) OR ("Health need"[Tiab:~6]) OR ("Health needs"[Tiab:~6]) OR ("Health demand"[Tiab:~6]) OR ("Health demands"[Tiab:~6]) OR ("Healthcare need"[Tiab:~6]) OR ("Healthcare needs"[Tiab:~6]) OR ("Healthcare demand"[Tiab:~6]) OR ("Healthcare demands"[Tiab:~6]) OR ("care need"[Tiab:~6]) OR ("care needs"[Tiab:~6]) OR ("care demand"[Tiab:~6]) OR ("care demands"[Tiab:~6]) OR ("Medical need"[Tiab:~6]) OR ("Medical needs"[Tiab:~6]) OR ("Medical demand"[Tiab:~6]) OR ("Medical demands"[Tiab:~6]) OR ("Therapeutic need"[Tiab:~6]) OR ("Therapeutic needs"[Tiab:~6]) OR ("Therapeutic demand"[Tiab:~6]) OR ("Therapeutic demands"[Tiab:~6]) OR ("Therapeutical need"[Tiab:~6]) OR ("Therapeutical needs"[Tiab:~6]) OR ("Therapeutical demand"[Tiab:~6]) OR ("Therapeutical demands"[Tiab:~6]) OR ("Pharmaceutic need"[Tiab:~6]) OR ("Pharmaceutic needs"[Tiab:~6]) OR ("Pharmaceutic demand"[Tiab:~6]) OR ("Pharmaceutic demands"[Tiab:~6]) OR ("Pharmaceutical need"[Tiab:~6]) OR ("Pharmaceutical needs"[Tiab:~6]) OR ("Pharmaceutical demand"[Tiab:~6]) OR ("Pharmaceutical demands"[Tiab:~6]) OR ("Patient need"[Tiab:~6]) OR ("Patient needs"[Tiab:~6]) OR ("Patient demand"[Tiab:~6]) OR ("Patient demands"[Tiab:~6]) OR ("Population need"[Tiab:~6]) OR ("Population needs"[Tiab:~6]) OR ("Population demand"[Tiab:~6]) OR ("Population demands"[Tiab:~6]) OR ("Therapy need"[Tiab:~6]) OR ("Therapy needs"[Tiab:~6]) OR ("Therapy demand"[Tiab:~6]) OR ("Therapy demands"[Tiab:~6]))

**Embase NOT
abstracts**

'rare disease'/exp OR (('rare' OR 'orphan') NEAR/11 ('disease*' OR 'disorder*' OR 'condition*' OR 'designation*')):ti,ab,kw
AND

1 929

'questionnaire'/exp OR 'questionnaire':ti,ab,kw OR 'survey':ti,ab,kw OR 'self report'/exp OR (self NEAR/4 report*):ti,ab,kw OR 'qualitative research'/exp OR (qualitative NEAR/4 research*):ti,ab,kw OR (qualitative NEAR/4 stud*):ti,ab,kw OR 'quantitative study'/exp OR (quantitative NEAR/4 stud*):ti,ab,kw OR (quantitative NEAR/4 research*):ti,ab,kw OR 'interview'/exp OR 'interview':ti,ab,kw OR 'focus group':ti,ab,kw OR 'focus discussion':ti,ab,kw OR 'multicriteria decision analysis'/exp OR 'multicriteria decision analys?s':ti,ab,kw OR 'multi criteria decision analys?s':ti,ab,kw OR 'multiple criteria decision analys?s':ti,ab,kw OR 'multi criteria decision making':ti,ab,kw OR 'multiple criteria decision making':ti,ab,kw OR 'multicriteria decision making':ti,ab,kw OR 'multi criteria decision tool':ti,ab,kw OR 'MCDA':ti,ab,kw OR 'register'/exp OR 'register':ti,ab,kw OR 'registr':ti,ab,kw OR 'workshop'/exp OR 'workshop':ti,ab,kw OR 'patient participation'/exp OR 'patient empowerment'/exp OR 'patient engagement'/exp OR 'social network'/exp OR 'needs assessment'/exp OR 'health services research'/exp OR (('Expert*' OR 'patient*' OR 'expert*' OR 'stakeholder*' OR 'social' OR 'societal') NEAR/7 ('panel*' OR 'forum*' OR 'consult*' OR 'participat*' OR 'involv*' OR 'engag*' OR 'network*' OR 'activ*')):ti,ab,kw OR 'needs assessment'/exp OR (('need*' OR 'patient NEAR/4 outcome') NEAR/7 ('assess*' OR 'determinat*')):ti,ab,kw OR (('engagement' OR 'epidemiologic*' OR 'health NEAR/4 service*' OR 'health care' OR 'healthcare' OR 'health-care' OR 'observational' OR 'cohort*' OR 'case-control*') NEAR/7 ('method*' OR 'research' OR 'evaluation*' OR 'stud*')):ti,ab,kw OR 'visual analogue scale':ti,ab,kw OR 'EQ-5D':ti,ab,kw

AND

'unmet medical need'/exp OR (('medical' OR 'unmet' OR 'societ*' OR 'communit*' OR 'health*' OR 'health-care' OR 'care' OR 'therapeutic*' OR 'Pharmaceutic*' OR 'patient*' OR 'population*') NEAR/7 ('need*' OR 'demand*')):ti,ab,kw

NOT

'conference abstract':it



Appendix 2.2. EXCLUDED ARTICLES BASED ON FULL-TEXT SCREENING

Nr.	Source	Reason
1	Autoimmune Bullous Disease Quality of Life (ABQoL) questionnaire: Validation of the translated Persian version in pemphigus vulgaris, <i>A. Teimourpour, K. Hedayat, F. Salarvand, N. Ghandi, M. Ghiasi, H. Mahmoudi, et al.</i>	Geographical region
2	Living through liminality? Situating the transitional experience of parents of children with mucopolysaccharidoses, <i>S. Somanadhan, A. Brinkley and P. J. Larkin</i>	Duplicate publishing
3	MDS-261 Systematic Literature Review (SLR) to Identify the Burden of Illness and Treatment Effectiveness in ESA-Refractory or Relapsed, Transfusion-Dependent, Low-Risk MDS, <i>S. G. P. Rhiannon I. Campden PhD</i>	Wrong article type, abstract
4	Exploring Informational Needs of Parents of Children with Intestinal Failure: <i>A Thematic Analysis</i> , <i>L. A. Ragan, L. Duffett-Leger, C. M. Laing and D. L. Boctor</i>	Wrong article type, master thesis
5	Understanding genetic learning needs of people affected by rare disease, <i>L. Quinn, K. Davis, A. Yee and H. Snyder</i>	No needs assessment
6	Translating rare-disease therapies into improved care for patients and families: What are the right outcomes, designs, and engagement approaches in health-systems research?, <i>B. K. Potter, S. D. Khangura, K. Tingley, P. Chakraborty and J. Little</i>	Clinical and drug-development focus
7	Characterizing physicians' information needs related to a gap in knowledge unmet by current evidence, <i>A. Ostroplets, R. Chen, L. Zhang and G. Hripcsak</i>	not rare disease specific
8	Unmet Needs of Children with Inherited Metabolic Disorders in the COVID-19 Pandemic, <i>Ezgi Özalp Akin, Fatma Tuba Eminoğlu, Neslihan Doğulu, Merve Koç Yekeduz, Ummuhan Öncül, Funda Akpınar, Gamze Hayran</i>	Focus on Covid-19
9	Addressing unmet needs in rare bleeding disorders: selected poster extracts of recent research in hemophilia A and von Willebrand disease presented at the 14th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) (Feb 3–5, 2021; virtual congress), <i>Geoffrey Allen, Ping Du, Kate Khair, Hye-Youn Lee, Margareth C. Ozelo, Françoise Truong Berthoz & Jerzy Windyga</i>	Clinical focus on phase I, II and III trials
10	A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research, <i>Rémy Choquet, Meriem Maaroufi, Albane de Carrara, Claude Messiaen, Emmanuel Luigi, Paul Landais</i>	No needs assessment
11	An ICET- A survey on hypoparathyroidism in patients with thalassaemia major and intermedia: a preliminary report, <i>Vincenzo De Sanctis Ashraf T Soliman, Duran Canatan, et. Al.</i>	Clinical focus, nothing about unmet needs
12	Revisiting the NIH Taskforce on the Research needs of Eosinophil-Associated Diseases (RE-TREAD), <i>Paneez Khoury, et. Al.</i>	The topics considered ranged from basic eosinophil biology to clinical trials.
13	Unmet therapeutic, educational and scientific needs in parathyroid disorders: Consensus Statement from the first European Society of Endocrinology Workshop (PARAT), <i>Jens Bollerslev^{1,2}, Camilla Schalin-Jäntti³, Lars Rejnmark⁴, Heide Siggekkow⁵, Hans Morreau⁶, Rajesh Thakker⁷, Antonio Sitges-Serra⁸, Filomena Cetani⁹ and Claudio Marcocci</i>	Not rare disease specific and clinical focus
14	Understanding the present and preparing for the future: Exploring the needs of diagnostic and elective genomic medicine patients, <i>Kelly M. East, et.al.</i>	Not rare disease specific

15	The risk of re-identification versus the need to identify individuals in rare disease research, Mats G Hansson, et.al.	No needs assessment
16	Use of Big Data to Aid Patient Recruitment for Clinical Trials Involving Biosimilars and Rare Diseases, Raymond A. Huml, et. Al.	No needs assessment
17	Challenges of developing and conducting clinical trials in rare disorders, L. Kempf, et.al.	Clinical trial focus
18	Patient and caregiver experiences with pantothenate kinase-associated neurodegeneration (PKAN): results from a patient community survey, T. Klopstock, S. Mercimek-Andrews, A. Jurecka, P. Wood, M. Cwyl, A. Klucken, et al.	Drug-development focus
19	Challenges, facilitators and barriers to the adoption and use of a web-based national IRD registry: lessons learned from the IRD-PT registry, J. P. Marques, S. Vaz-Pereira, J. Costa, A. Marta, J. Henriques and R. Silva	no need assessment
20	Content validity of visual analog scales to assess symptom severity of acute angioedema attacks in adults with hereditary angioedema: An interview study, C. V. McMillan, J. Speight, A. Relan, L. Bellizzi, G. Haase and M. Cicardi	validity of the VAS scale was questioned, no real need assessment
21	The initiation, design, and establishment of the Desmoid Tumor Research Foundation Patient Registry and Natural History Study, K. A. Mercier and D. M. Walsh	no active needs assessment but the rather a protocol paper
22	Physician Perceptions of the Clinical, Economic and Humanistic Burden of Disease and Unmet Needs in Myelofibrosis: Preliminary Findings from the MPN Landmark Survey in Indonesia, I. F. Pandji, M. S. Hardianti, A. D. Tubagus, R. Wibawa, L. Hogg, K. M. Tan, et al.	Wrong geographical scope
23	Unmet needs in countries participating in the undiagnosed diseases network international: an international survey considering national health care and economic indicators, S. Sciascia, D. Roccatello, M. Salvatore, C. Carta, L. L. Cellai, G. Ferrari, et al.	focus on governmental policy, no needs
24	Unmet needs in the management of immune-mediated thrombotic thrombocytopenic purpura and the potential role of caplacizumab in the UK—A modified-Delphi study, M. Scully, T. Dutt, W. Lester, E. Farrington, S. Lockwood, R. Perry, et al.	no need assessment but consensus on clinical practice
25	Adult growth hormone deficiency in CEE region: Heterogeneity of the patient pathway, I. Shimon, C. Badiu, A. Bossowski, M. Doknic, I. Dzivite-Krisane, V. Hana, et al.	No needs assessment
26	x-linked hypophosphatemia: the value of feedback focus groups to assess patient and caregiver needs, E. Wagner, A. Bertholet-Thomas, R. Mélanie, L. Laure, L. Sandrine, V. Emmanuelle, et al.	Wrong article type, abstract
27	A systematic literature review of evidence-based clinical practice for rare diseases: What are the perceived and real barriers for improving the evidence and how can they be overcome?, A. Rath, V. Salamon, S. Peixoto, V. Hivert, M. Laville, B. Segrestin, et al.	No needs assessment, clinical focus
28	Study design challenges and strategies in clinical trials for rare diseases: Lessons learned from pantothenate kinase-associated neurodegeneration, Aleksandar Videnovic, et.al.	No needs assessment, clinical focus



Appendix 2.3. DATA EXTRACTION FORM

Overarching topics	Identified parameters
Publication specifications	• Article title • Author name • Author stakeholder group • Industry funded (yes/no) • Publication type • Geographic region • Overarching geographic region • Year of publication
Methodological aspects	• Primary/meta research • Method category • Broad method category • Method details • Recruitment strategy • Measures/tools • Number of participants • Study participant details • Research stakeholder group • Study participant group
Disease specifications	• Disease category • Disease name • General disease category • ICD-11 code • Prevalence • Incidence
Methodological challenges	Challenges related to the study design • Estimation of patients' health status • Profile of the included participant (sample bias) • Challenges related to the method used • Limited clinical knowledge



- Duration of the study

Challenges related to recruitment and study sample

- Sample size
- Sample variability
- Generalisability/representativeness
- Underdiagnosis

Challenges related to the data source

- Limited (comparable) data sources and limited infrastructure
- Completeness of the data
- Validity of the data
- Challenges in healthcare systems regarding rare diseases

Other

- Limitations related to clinical trials
- Limitations related to differences in healthcare systems
- Other

NEED criteria - Patient needs

Health

- Physical
- Psychological
- Autonomy
- Mortality

Healthcare

- Treatment
- Patient experience with healthcare professional
- Information needs
- Accessibility to care
- Diagnosis

Social

- Social support
- Impact on work
- Financial consequences

NEED criteria – Societal needs

Health



	• Transmissibility • Burden of disease
	Healthcare
	• Economic burden
	Social
	• Environmental impact
NEED criteria – Future needs	Health
	• Future public health trends • Equity
Other	• Other • Author suggestions/recommendations • Reviewer comments

Appendix 2.4. SUMMARY TABLE – INCLUDED STUDIES

Appendix 2.4.1. Literature based studies

Author (year)	Geographical region	Disease	Study design		NEED criteria
			Method	Objectives	
Review					
Wehrli (2023) ¹	Unspecified	Osteogenesis imperfecta		QoL of paediatric and adult patients	• Equity • Psychological • Impact on education
Choon (2023) ²	Unspecified	Generalised pustular psoriasis	Systematic review	Health-related QoL	• Physical • Psychological • Effectiveness of treatment • Burden of treatment • Social support
Wechsler (2023) ³	Unspecified	hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis		Unmet needs and evidence gaps	• EQ-5D average score • Physical • Effectiveness of treatment • Diagnosis • Information needs
Fournier (2023) ⁴	Europe	Rare genetic skin diseases	Systematic review	Psychosocial implications	• Burden of disease • Physical • Psychological • Autonomy • Accessibility to treatment/care • Social support • Impact on education
Connolly (2023) ⁵	Australia	Sarcoma			• Burden of Disease
Howley (2023) ⁶	Europe	Congenital athymia			• Economic burden



						• Psychological • Patient experience with HCP • Information needs • Accessibility to care • Diagnosis
Applequist (2023)⁷	US	Orphan but non disease specific			Direct-to-Consumer recruitment methods	
Dabbous (2023)⁸	Inter-continental	Orphan but non disease specific	<i>Systematic literature review</i>		Valuation of treatments of RD	• Burden of Disease • Economic burden
McMullan (2022)⁹	Unspecified	Rare diseases			Needs of informal caregivers	• Burden of Disease • Economic burden
Sawad (2022)¹⁰	US	Arginase 1 deficiency (ARG1-D)	<i>Systematic review of case reports</i>		Unmet needs of patients	• Physical • Treatment • Diagnosis
Trieste (2022)¹¹	Europe	Rare and complex connective tissue and musculoskeletal diseases (rCTDs)			Assessing QoL	
Brandt (2022)¹²	Inter-continental	Spinal muscular atrophy	<i>Systematic review of quantitative and qualitative data</i>		Psychosocial situation, caregiver burden and family needs	• Burden of Disease • Economic burden • Patient experience with HCP • Information needs • Social support
Hassall (2022)¹³	Europe	Lysosomal storage disorders (LSDs)	<i>Systematic review and integrative sequential explanatory narrative synthesis</i>		Psychosocial impact of parenting a patient	• Burden of Disease • Economic burden • Treatment • Diagnosis
Camerini (2022)¹⁴	Europe	Acromegaly	<i>Systematic review</i>		Clinical powerful instruments in diagnosis and management	• Effectiveness of treatment • Burden of treatment

Bardon (2022)¹⁵	Inter-continental	Orphan but non disease specific	<i>Realist literature review of</i>	Development, evaluation and implementation of evidence-based group therapy	• Equity • Social support
De Heus (2021)¹⁶	Europe	Rare cancer	<i>Systematic review</i>	Unmet supportive care needs	• Burden of Disease • Diagnosis • Social support
Soeun (2021)¹⁷	US	Immunoglobulin nephropathy	A <i>Systematic literature review</i>	Epidemiology, HRQoL and economic burden	• Economic burden • Physical • Psychological • Treatment • Diagnosis
Seefried (2021)¹⁸	Unspecified	X-linked hypophosphataemia	<i>Systematic literature review</i>	Burden of disease	• Physical • Psychological • Autonomy • Treatment • Accessibility to care • Impact on work
Petros (2021)¹⁹	US	Adult-onset disease	Still's	Clinical manifestation, diagnosis, treatment, and unmet needs	• Mortality • Accessibility to care • Diagnosis • Social support
Monga (2020)²⁰	Inter-continental	Mantle cell lymphoma	<i>Systematic literature review</i>	Real-world clinical, economic and humanistic burden data	• Economic burden • Physical • Treatment • Diagnosis
Lanar (2020)²¹	Europe	Orphan but non disease specific		To identify all relevant PROMs	
Hill (2019)²²	Europe	Osteogenesis imperfecta	<i>Systematic review</i>	Experiences and psychosocial impact on families and caregivers	• Burden of disease • Economic burden • Psychological • Autonomy • Information needs



						• Accessibility to care
Mackay (2019)²³	Unspecified	Prader-Willi syndrome		Describing health and well-being		• Burden of Disease • Physical • Impact on work
Meyer (2019)²⁴	Unspecified	Idiopathic inflammatory myopathies	<i>Narrative review</i> <i>Systematic literature search</i>	Unmet needs in clinical practice guidelines		• Quality of care
Palikara (2018)²⁵	Unspecified	Williams syndrome		Educational needs		• Physical • Autonomy • Information needs • Impact on work
Wheeler (2017)²⁶	US	Angelman syndrome	<i>Targeted review</i> <i>literature</i>	AS phenotype, epidemiology, diagnostic processes, treatment and burden		• Burden of disease • Physical • Psychological • Treatment • Diagnosis • Social support
Yamaguchi (2017)²⁷	Asia	Inborn errors of metabolism		Difficulties in Daily Life and Associated Factors and QoL		• Burden of Disease • Physical • Psychological • Accessibility to care • Financial consequences
Pelentsov (2015)²⁸	Australia	Orphan but non disease specific	<i>Scoping review</i>	Supportive care needs of parents		• Burden of Disease • Economic burden • Information needs • Accessibility to care • Social support
Banerji (2013)²⁹	US	Hereditary angioedema	<i>Boolean search</i>	Burden of illness		• Burden of Disease • Economic burden • Physical • Psychological

					• Autonomy • Accessibility to care • Social support
Rajmil (2010)³⁰	Unspecified	Orphan but non disease specific	<i>Systematic review</i>	Available instruments of HRQoL	
Gaite (2008)³¹	Europe	Orphan but non disease specific		Needs assessment	• Burden of Disease • Economic burden • Patient experience with HCP • Information needs • Diagnosis • Social support

Appendix 2.4.2. Quantitative studies

Author (year)	Geographical region	Disease	Study desgin		NEED criteria
			Population	Validated tool	
Survey/Questionnaire					
Schut (2023) ³²	Europe	Desmoid- type fibromatosis (DTF)	• Patients/patient organisations/patient representatives	• SQ20 • EORTC QLQ-C30	• QoL • Experience with HCPs • Accessibility to care
Landlust (2023) ³³	Inter-continental	Phelan-McDermid syndrome (PMS)	• Caregiver/parents	• Genetic Syndrome Stressors Scale (GSSS)	• Burden of disease • Equity
Taruscio (2023) ³⁴	Inter-continental	Undiagnosed diseases	• Multistakeholder		• Patient experience with healthcare professionals • Information needs • Diagnosis



Goldfarb (2023)³⁵	US	Primary hyperoxaluria	• Patients and caregivers	• Kidney Disease Quality of Life (KDQOL-36™) • Wisconsin Stone Quality of Life (WISQOL)	• Treatment • Diagnosis •
Skrobanski (2023)³⁶	Europe	tuberous sclerosis complex	• Caregiver		
Moore (2023)³⁷	Inter-continental	Pelizaeus-Merzbacher Disease	• Caregiver/parent		• QoL • Treatment • Diagnosis
Stubbs (2023)³⁸	US	juvenile localized and systemic scleroderma	• Caregiver	• The Barriers to Care Scale (BACS)	• Treatment • Patient experience with HCP • Accessibility to care • Diagnosis
Acaster (2023)³⁹	US	Hereditary transthyretin amyloidosis	• Caregiver/parents	• EQ-5D-3L • Hospital anxiety and depression scale	• QoL
Tkachuk (2023)⁴⁰	Latin-America	neuromyelitis optica spectrum disorders	• Patients/patient organisations/patient representatives	• EDSS	• Accessibility to care • Diagnosis
Alesci (2023)⁴¹	Europe	Immune thrombocytopenia	• Patients/patient organisations/patient representatives	• FACIT-F • BDI • Epworth Sleepiness Scale • STOP-BANG	• QoL
Ballesteros-Sayas (2023)⁴²	Europe	Dravet syndrome	• Caregiver/parents		• Diagnosis • Accessibility to treatment/care • Impact on education • Financial consequences



Büttner (2023)⁴³	Europe	Hypoparathyroidism	• Patients/patient organisations/patient representatives	• HPQ-28	• QoL • Information needs • Impact on work
Kerr (2023)⁴⁴	US	complex vascular anomalies	• Patients/patient organisations/patient representatives	• PROMIS Global Health Measure • PCC-Ca-36	• QoL • Quality of care • Information needs • Accessibility to treatment/care • Social support
Chappell (2023)⁴⁵	Unspecified	mtDNA deletion syndromes	• Patient and caregivers	• MCN-PNS • ZBI-22	• Burden of disease • Economic burden • Quality of care • Information needs
Mahic (2023)⁴⁶	Europe	myasthenia gravis	• HCPs	• WPAI • MG-QoL-15r • EQ-5D-5L • VAS	• QoL • Effectiveness of treatment • Quality of care
Pivonello (2023)⁴⁷	Europe	Cushing's syndrome	• HCPs		• Effectiveness of treatment
Runacres (2023)⁴⁸	Australia	Motor neuron disease	• Patients	• ALSFRS-R • IPOS-Neuro questionnaire	• QoL
Van Roessel (2023)⁴⁹	Europe	hypothalamic dysfunction	• Patients/patient organisations/patient representatives		• QoL • Quality of care • Diagnosis • Information needs • Financial consequences



Weiss (2023)⁵⁰	Unspecified	antisynthetase syndrome	• Patients/patient organisations/patient representatives • HCP		• Diagnosis • Information needs • Impact on work
Schuster (2022)⁵¹	Europe	Duchenne Muscular Dystrophy	• Patients & caregivers	• PUL-PROM EQ-5D-3L	• QoL • Treatment •
Pélissier (2022)⁵²	Europe	Non-disease specific	• Patients & caregivers		• Diagnosis
Strzelczyk (2022)⁵³	Europe	Dravet syndrome	• Patients & caregivers		•
Gutenbrunner (2022)⁵⁴	Europe	Non-disease specific	• Patients/patient organisations/patient representatives	• ReGoS	• QoL • Experience with HCP • Accessibility to care
Gimenez-Lozano (2022)⁵⁵	Europe	Non-disease specific	• Patients & caregivers		• QoL • Treatment • Accessibility to care • Diagnosis
Valassi (2022)⁵⁶	Inter-continental	Cushing's syndrome	• Patients & caregivers		• QoL • Treatment • Experience with HCP •
Kramer-Golinkoff (2022)⁵⁷	US	Cystic fibrosis (CF)	• Patients & caregivers		• QoL • Treatment • Accessibility to care
Kontogeorgos (2022)⁵⁸	Europe	Hypoparathyroidism	• Patients/patient organisations/patient representatives	• SF-36 • EQ5D-VAS	• QoL • Accessibility to care



Bonnekoh (2022)⁶⁹	Europe	Urticarial vasculitis	Patients/patient organisations/patient representatives	Treatment
Johansen (2022)⁶⁰	Europe	Loeys-Dietz syndromes, vascular Ehlers-Danlos syndrome	Patients/patient organisations/patient representatives	- Standardized Nordic Questionnaire - FSS - HADS - QoL - Expérience with HCPs - Accessibility to care
Rihm (2022)⁶¹	Europe	Non-disease specific	Caregiver/parents	- DT-P - QoL - Treatment - Experience with HCPs
Scharping (2022)⁶²	Europe	Inherited metabolic diseases (IMDs)	Caregiver/parents	- PNS - Expérience with HCPs - Accessibility to care
Mancuso (2022)⁶³	Europe	Rare neurological diseases (RNDs)	HCP	- Accessibility to care - Diagnosis
Mahic (2022)⁶⁴	US	Myasthenia gravis	HCP	- QoL - Treatment - Diagnosis
Al Mukaddam (2022)⁶⁵	Inter-continental	Fibrodysplasia ossificans progressiva	Patients & caregivers	- QoL - Treatment - Accessibility to care
Mesa (2022)⁶⁶	US	Systemic mastocytosis (SM)	Patients/patient organisations/patient representatives	QoL
Mesa (2022)⁶⁷	US	Systemic mastocytosis (SM)	HCP	- QoL - Treatment
Auchus (2022)⁶⁸	Inter-continental	Congenital adrenal hyperplasia	HCP	- QoL - Treatment



Rispoli (2022)⁶⁹	Europe	Dystonia	Patients/patient organisations/patient representatives		- QoL - Experience with HCPs
Koto (2022)⁷⁰	Asia	Fabry disease	Patients/patient organisations/patient representatives	SF-8	- QoL - Diagnosis
Atila (2022)⁷¹	Europe	Central diabetes insipidus	Patients/patient organisations/patient representatives		- QoL - Quality of care
Bogart (2022)⁷²	US	Orphan but non disease specific	Patients & caregivers		- QoL - Quality of care - Diagnosis - Information needs - Accessibility to treatment/care - Social support - Financial consequences
Moretti (2021)⁷³	Europe	Non-disease specific	Patients & caregivers	Checklist For Children with Special Healthcare Needs	- QoL - Accessibility to care
Strober (2021)⁷⁴	NS	Generalized pustular psoriasis (GPP)	HCP		Treatment
Bryson (2021)⁷⁵	Inter-continental	Non-disease specific	Patients/patient organisations/patient representatives		- QoL - Experience with HCPs
Drabbe (2021)⁷⁶	Europe	Non-disease specific	Patients/patient organisations/patient representatives		- Experience with HCPs - Diagnosis
Lamy (2021)⁷⁷	Europe	Non-disease specific	Patients/patient organisations/patient representatives		- Experience with HCPs - Accessibility to care - Diagnosis



Rose (2021)⁷⁸	NS	relapsing polychondritis	Patients & HCP	- SF-36 - MFI	- QoL - Treatment - Experience with HCPs - Diagnosis
McMillan (2021)⁷⁹	NS	Spinal Muscular Atrophy (SMA)	Patients & caregivers	- EQ-5D-5L - CSI	- QoL
Mendivil (2021)⁸⁰	Inter-continental	hereditary angioedema	Patients/patient organisations/patient representatives	- AE-QoL - SF-12v2 - AECT - HADS - WPAI	- QoL - Treatment
Langhinrichsen-Rohling (2021)⁸¹	US	EhlersDanlos Syndrome (EDS)	Patients/patient organisations/patient representatives		- QoL - Experience with HCPs - Diagnosis
de Graaf (2021)⁸²	Europe	Non-disease specific	Patients/patient organisations/patient representatives	- CarerQoI-7D - WPAI 5-D-Itch scale	- QoL - Treatment - Experience with HCPs
Ruiz-Casas (2021)⁸³	Europe	progressive familial intrahepatic cholestasis	Caregiver & HCP	- PedsQL™ - FIM - VSS - GMFC-MLD - HRQOL - Family Functioning Summary Scores - Total Impact Score	



Ammann-Schnell (2021)⁸⁴	Europe	severe neurological disorders, including Pontocerebellar hypoplasia type 2 (PCH2) and metachromatic leukodystrophy (MLD)	Caregiver/parents		
Fasshauer (2021)⁸⁵	Europe	Primary immunodeficiencies	Patients/patient organisations/patient representatives		QoL
Eichler (2021)⁸⁶	Europe	Gastrointestinal stromal tumours	Patients/patient organisations/patient representatives	EORTC QLQ-C30	- QoL - Treatment
Depping (2021)⁸⁷	Europe	Non-disease specific	Patients/patient organisations/patient representatives	SCNS-SF34	- QoL - Experience with HCPs
Cheung (2021)⁸⁸	Inter-continental	X-linked hypophosphatemia	Patients & caregivers	XLH Burden of Disease	- QoL - Treatment - Experience with HCPs
Grant (2021)⁸⁹	US	mucopolysaccharidoses	Family members		
Webb (2021)⁹⁰	Inter-continental	Non-disease specific	Patients & HCP		Diagnosis
Sestini (2021)⁹¹	Europe	Inherited Metabolic Diseases	Patient & caregiver		- QoL - Experience with HCPs - Accessibility to care
Qi X (2021)⁹²	Asia	Gaucher Disease	Patient & caregiver	- PSQI - SG-36	- QoL - Experience with HCPs - Accessibility to care - Diagnosis



Abeni (2021)⁹³	Europe	Autosomal recessive congenital ichthyoses	• Patients/patient organisations/patient representatives •	• FDLQI • FBI tool	• Burden of disease • Economic burden
Bejarano (2021)⁹⁴	Unspecified	hATTR amyloidosis	• Patients/patient organisations/patient representatives	• IEXPAC questionnaire	• Quality of care • Impact on work
Molnár (2021)⁹⁵	Europe	Pompe disease	• Patients/patient organisations/patient representatives	• Fatigue Severity Score • R-PAct-Scale • Rotterdam and Bartel disability scale • EQ-5D • SG-36	• QoL • Information needs
Martins (2020)⁹⁶	Latin-Amerika	Phenylketonuria (PKU)	• Patients & caregivers		• QoL • Experience with HCPs • Diagnosis



Painous (2020)⁹⁷	Europe	Four different groups of rare MDs were studied: group 1 included dystonia, paroxysmal dyskinesia and neurodegeneration with brain iron accumulation (NBIA) (group 1-DYS); group 2, ataxias and hereditary spastic paraparesis (HSP) (group 2-ATX/ HSP); group 3, atypical parkinsonism such as progressive supranuclear palsy, multiple system atrophy and corticobasal degeneration (group 3-AP); group 4 included Huntington's disease (HD) and other choreas (group 4-C).	• HCPs	• Treatment • Accessibility to care • Diagnosis
Dermer (2020)⁹⁸	Canada	Genetically determined leukoencephalopathies	• Caregiver/parents	• Parenting Stress Index–4th Edition • Diagnosis
Izquierdo-Garcíaa (2020)⁹⁹	Europe	Hereditary fructose intolerance	• Patients & caregivers	• EQ-5D-Y • ED-5D • QoL • Experience with HCPs • Accessibility to care • Diagnosis
Bolte (2020)¹⁰⁰	Europe	Transthyretin familial amyloid polyneuropathy (ATTRFAP)	• Patients/patient organisations/patient representatives	• PROMIS-10 • WHODAS 2.0 • QoL • Accessibility to care

Xu (2021)¹⁰¹	Asia	Gaucher Disease	Caregiver	- SF- 36 - SAS - SDS - Multi-dimensional Scale of Perceived Social Support - HHI	
Boettcher (2020)¹⁰²	Europe	Non-disease specific	Caregiver/parents	- QoL - ULQIE - BSI - CHIP - OSSS-3 - FAM	
Fjermestad (2020)¹⁰³	Europe	neurofibromatosis 1 (NF1) and hereditary spastic paraparesis (HSP)	Patients/patient organisations/patient representatives		Experience with HCPs
Saglio (2020)¹⁰⁴	Europe	Narcolepsy and idiopathic hypersomnia	HCP		
Cook (2020)¹⁰⁵	Inter-continental	Pigmented villonodular synovitis	Patients/patient organisations/patient representatives		- QoL - Treatment - Experience with HCPs - Accessibility to care - Diagnosis
Dinur (2020)¹⁰⁶	Inter-continental	Gaucher disease	Patients/patient organisations/patient representatives	GD1-PROM	- QoL - Treatment
Kodra (2020)¹⁰⁷	Europe	Cri du Chat syndrome (CdC)	Patients & caregiver		- QoL - Treatment



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Kuman (2020)¹⁰⁸	Europe	homozygous familial hypercholesterolemia	• Patients/patient organisations/patient representatives	• SCL-90-R	• QoL	
Valero-Moreno (2020)¹⁰⁹	Unspecified	Primary ciliary dyskinesia	• Patients/patient organisations/patient representatives	• BIEPS-J • HADS-A	• QoL	
Khair (2019)¹¹⁰	Europe	Inherited bleeding disorders	• Caregiver/parents	• PNS-RD	• Experience with HCPs	
Lagaea (2019)¹¹¹	Europe	Dravet syndrome (DS)	• Patients/patient organisations/patient representatives		• QoL • Treatment • Accessibility to care •	
Efthymiadou (2019)¹¹²	Europe	Non-disease specific	• Patients/patient organisations/patient representatives		• Experience with HCPs	
Courbier (2019)¹¹³	Inter-continental	Non-disease specific	• Patients & caregivers		• Experience with HCPs	
Conner (2019)¹¹⁴	US	Mucopolysaccharidoses	• Caregiver/parents		• QoL • Treatment • Accessibility to care	
Nagamatsu (2019)¹¹⁵	Asia	malignant pleural mesothelioma (MPM)	• Patients/patient organisations/patient representatives		• QoL • Treatment • Experience with HCPs • Accessibility to care	
Morrison (2019)¹¹⁶	Europe	Mucopolysaccharidosis type VII	• Patients/patient organisations/patient representatives		• Burden of disease • QoL • Diagnosis • Social support • Impact on education	



Godoy Torres (2018)¹¹⁷	Latin-Amerika	Chronic kidney disease (CKD) in children	Caregiver/parents	- CBS - BDI - BAI	- QoL - Accessibility to care
Ebert (2018)¹¹⁸	Europe	anorectal malformations (ARM) and the exstrophy-epispadias complex (EEC)	Patients/patient organisations/patient representatives		QoL
Fischer (2020)¹¹⁹	Europe	spinal muscular atrophy	Patients/patient organisations/patient representatives	- SWLS - RSES - PANAS - USER-P - BPNSFS	- QoL - Treatment
Efthymiadou (2018)¹²⁰	Europe	Non-disease specific	Patients/patient organisations/patient representatives		- QoL
Pinto (2018)¹²¹	Europe	hemophilia (PWH)	Caregiver/parents	- Sociodemographic and Clinical Questionnaires - Physical Activity Questionnaire - A36 Hemophilia-QoL:15 - CHO-KLAT - HAL - PedHAL - PROMIS-Anxiety and Depression - IPQ-R	QoL
Majoer (2017)¹²²	Europe	Fibrous dysplasia (FD)	Patients/patient organisations/patient representatives	EQ-5D	- QoL



van Walsem (2017)¹²³	Europe	Huntington's disease	Patients/patient organisations/patient representatives	- EQ-5D-3L - NPCS - UHDS	- QoL - Treatment
Lakhani Jindal (2017)¹²⁴	Canada	Hereditary angioedema	Patients/patient organisations/patient representatives	SF-36v2	
Dzemali (2017)¹²⁵	Inter-continental	congenital hypogonadotropic hypogonadism (CHH)	Patients/patient organisations/patient representatives	- MMAS - SDS - IPQ-R	- QoL - Treatment - Experience with HCPs - Accessibility to care - Diagnosis
Wolin (2017)¹²⁶	US	Neuroendocrine Tumors	Patients/patient organisations/patient representatives		- QoL - Effectiveness of treatment - Quality of care - Diagnosis - Accessibility to treatment/care - Impact on work - Financial consequences
Angelis (2016)¹²⁷	Europe	Juvenile idiopathic arthritis (group of different rare disorders)	Patients & caregivers	- EQ-5D - Barthel Index	
Molster (2016)¹²⁸	Australia	Non-disease specific	Patients & caregivers		- Experience with HCPs - Accessibility to care - Diagnosis
Landfeldt (2016)¹²⁹	Europe	Duchenne muscular dystrophy (DMD)	Caregivers/parents		
Silibello (2016)¹³⁰	Europe	Non-disease specific	Caregivers		- QoL - Experience with HCPs
Pelentsov (2016)¹³¹	Australia	Non-disease specific	Caregivers/parents		Experience with HCPs



					• Accessibility to care
Pelentsov (2016)¹³²	Australia	Non-disease specific	• Caregivers/parents		
Siden (2015)¹³³	Canada	Non-disease specific	• Patients & caregivers		• QoL
Chevreur (2015)¹³⁴	Europe	Systemic sclerosis	• Patients & caregivers	• EQ-5D-5L	
Fang (2015)¹³⁵	Asia	Primary cutaneous amyloidosis	• Patients/patient organisations/patient representatives	• DLQI • SF-36 •	• QoL •
Garcia (2015)¹³⁶	Europe	Orphan but non disease specific	• Patients/patient organisations/patient representatives		• Diagnosis • Information needs • Social support • Financial consequences
Kocova (2014)¹³⁷	Europe	Spinal muscular atrophy	• Patients & caregivers	• PedsQL Neuromuscular Module Scales	• Experience with HCPs
Anderson (2013)¹³⁸	Australia	Non-disease specific	• Patients & caregivers	• HUI- II • IOF • RAHC-MOF	• QoL • Accessibility to care • Diagnosis
Guillevin (2013)¹³⁹	Europe	Pulmonary arterial hypertension	• Patients & caregivers		• Burden of disease • QoL • Information needs • Social support • Impact on work
Morad (2007)¹⁴⁰	Canada	ocular genetic eye disease	• Patients/patient organisations/patient representatives		• Experience with HCPs • Accessibility to care

Database analysis



Bell (2023) ¹⁴¹	US	Eosinophilic granulomatosis with polyangiitis	Patients/patient organisations/patient representatives	- Effectiveness of the treatment/care - Financial consequences
Benito-Lozano (2023) ¹⁴²	Europe	Orphan but non disease specific	Patients/patient organisations/patient representatives	- QoL - Diagnosis - Social support - Impact on education
Strobel (2022) ¹⁴³	Inter-continental	Rare Eosinophil-Driven Diseases		- QoL - Accessibility to care - Diagnosis
Tisdale (2021) ¹⁴⁴	US		Patients/patient organisations/patient representatives	- QoL - Accessibility to care - Diagnosis
Hilker (2021) ¹⁴⁵	Europe	Sarcoidosis or Boeck's disease		Experience with HCPs
Burke (2021) ¹⁴⁶	US	Hemophilia B	Patients/patient organisations/patient representatives	- QoL
Carbone (2020) ¹⁴⁷	Europe	Primary sclerosing cholangitis	Patients/patient organisations/patient representatives	Experience in HCPs
Feng (2019) ¹⁴⁸	Europe	Adrenoleukodystrophy]	Patients & caregivers	- Experience in HCPs - Accessibility to care - Diagnosis
Pujades-Rodriguez (2018) ¹⁴⁹	Unspecified	hypertrophic cardiomyopathy	Patients/patient organisations/patient representatives	- QoL - Mortality - Treatment

Registries



Palladini (2023)¹⁵⁰	Europe	light chain (AL) amyloidosis	Patients/patient organisations/patient representatives	- Treatment - Diagnosis
Senn (2023)¹⁵¹	Europe	Inclusion Body Myositis	Patients/patient organisations/patient representatives	- QOL - Quality of care
Van Geest (2023)¹⁵²	Unspecified	MCT8 Deficiency	Patients/patient organisations/patient representatives	- Quality of care - Diagnosis
Duffy (2021)¹⁵³	US	WAGR syndrome	Patients/patient organisations/patient representatives	- IWSA questionnaire - QoL
Duda (2020)¹⁵⁴	Europe	Hemophilia	Patients/patient organisations/patient representatives	
Kolbin (2020)¹⁵⁵	Europe	Spinal muscular atrophies	Patients/patient organisations/patient representatives	
Tilson (2013)¹⁵⁶	Europe	Cryopyrin-Associated Periodic Syndromes (CAPS)	Patients/patient organisations/patient representatives	
MCDA				
Gasol (2022)¹⁵⁷	Europe	Non-disease specific	Multistakeholder	Varia
Cross-sectional studies				
Burgevin (2022)¹⁵⁸	Europe	Silver-Russell syndrome	Patients/patient organisations/patient representatives	- QoL - Social support
Clairman (2021)¹⁵⁹	Unspecified	Juvenile dermatomyositis	Patients/patient organisations/patient representatives	
Witt (2019)¹⁶⁰	Europe	achondroplasia	Patients & HCP	QoL



- Patient experience with healthcare professionals
- Varia

Appendix 2.4.3. Qualitative studies

Author (year)	Geographical region	Disease	Study design		NEED criteria
			Population	Objective	
Focus group discussions					
Snijders (2023) ¹⁶¹	Europe	Autoimmune hepatitis	Multistakeholder		• Patient experience with healthcare professionals • Information needs
Witt (2023) ¹⁶²	Unspecified	Orphan but non disease specific	Multistakeholder	Obstacles and barriers in route to psychosocial care	• Equity • Patient experience with HCP • Information needs • Reviewer comments
Beirne (2023) ¹⁶³	Europe	Hyperemesis Gravidarum	Patients	Healthcare experience	• Psychological • Quality of care • Accessibility to treatment/care • Social support • Financial consequences
Dreyer (2022) ¹⁶⁴	US	Kallmann syndrome	Patients & caregivers	In person vs virtual focus groups	• Diagnosis • Social support
Pignolo (2022) ¹⁶⁵	Inter-continental	Fibrodysplasia ossificans progressive	Multistakeholder	Unmet needs	• Treatment • Patient experience with HCP • Information needs • Accessibility to care • Diagnosis



						• Social support
Petracca (2021)¹⁶⁶	Europe	Type A Hemophilia		Multistakeholder	Input for app / improvement	
Kleinendorst (2020)¹⁶⁷	Europe	16p11.2 deletion		Patients & caregivers	Impact on life and information provision	• Burden of disease • Economic burden • Psychological • Autonomy • Patient experience with HCP • Information needs • Social support
Aiyegbusi (2020)¹⁶⁸	Europe	Renal transplant recipients and primary sclerosing cholangitis patients		Patients & HCP	Impact of rare disease on patients	• Environmental impact • Future public health trends • Physical
Pak (2020)¹⁶⁹	Unspecified	Acromegaly		Patients	Patient perceptions of primary to tertiary care	• Quality of care • Information needs • Social support
O'Mahony (2018)¹⁷⁰	Global	Haemophilia		Multistakeholder	Patient impacts	• physical • accessibility to care
Ogunsanya (2018)¹⁷¹	US	Cutaneous erythematous lupus		Patient/patient organisation/representatives	QoL	• physical • psychological • treatment • information needs • social support
Swezey (2018)^{172s}	Unspecified	Osteogenesis imperfecta		Patients/patient organisation/representatives	Key health issues, gaps in knowledge, research priorities	• physical • psychological • mortality • treatment • patient experience with HCP • social support



De Freitas (2017) ¹⁷³	Inter-continental	Congenital Disorders of Glycosylation	Multistakeholder	Public and patient involvement in needs assessment	• Burden of Disease • Economic burden • Equity • Psychological • Patient experience with HCP • Accessibility to care • Diagnosis • Social support
Pelentsov (2016) ¹³¹	Australia	Orphan but non disease specific	Patients & caregivers	Supportive care needs	• Burden of Disease • Economic burden • Equity • Patient experience with HCP • Information needs • Diagnosis
Interviews					
Loesken (2023) ¹⁷⁴	Europe	Primary cholangitis	sclerosing	Patients/patient organisations/representatives	Patient perception • Burden of disease • Physical • Psychological • Patient experience with HCP • Information needs • Diagnosis • Social support
Respondek (2023) ¹⁷⁵	Global	Progressive supranuclear palsy	Multistakeholder	Patient experiences	• Burden of Disease • Psychological • Patient experience with HCP • Information needs • Diagnosis
Kleitsch (2023) ¹⁷⁶ klei	US	Dermatomyositis	Patients/patient organisations/representatives	Physical and emotional impact	• Physical • Psychological • Treatment • Social support



Raspa (2023) ¹⁷⁷	US	Severe immunodeficiency (SCID)	combines Parents & caregivers	Uncertainties experienced by patients	- Burden of Disease - Information needs - Accessibility to care - Diagnosis
Witt (2023) ¹⁷⁸	Unspecific	Orphan but non disease specific	Patients & caregivers	Experiences/needs with medical and psychosocial care	- Burden of Disease - Psychological - Autonomy - Quality of care - Diagnosis - Information needs - Social support - Impact on education
Potter (2023) ¹⁷⁹	Inter-continental	Men diagnosed with breast cancer (MBC)	Patients/patient organisations/representatives	Patient experiences	- Physical - Psychological - Autonomy - Treatment - Patient experience with HCP - Information needs - Social support
Bauskis (2022) ¹⁸⁰	Australia	Orphan but non disease specific	Parents & caregivers	Diagnostic odyssey	- Burden of Disease - Treatment - Patient experience with HCP - Social support
Ciesluk (2022) ¹⁸¹	US	Nuclear protein in testis (NUT) carcinoma	Patients & caregivers	Patient experiences	Burden of Disease
Olischläger (2022) ¹⁸²	Unspecific	Orphan but non disease specific	Patients & HCP	Patient experiences & needs	- Patient experience with HCP - Information needs - Accessibility to care
Randall (2022) ¹⁸³	US	Classic galactosemia	Patients & caregivers	Disease burden & daily challenges	- Burden of Disease - Physical - Psychological



						• Autonomy • Social support
Garcia-Diaz (2022) ¹⁸⁴	Europe	Lysosomal Diseases	Storage	Patients & HCP	Disease impact	• Burden of Disease • Physical • Psychological • Autonomy • Patient experience • Information needs • Accessibility to care • Diagnosis • Social support
Smits (2022) ¹⁸⁵	unspecific	Orphan but non disease	Caregiver		Needs	• Burden of Disease • Psychological • Patient experience with HCP • Information needs • Accessibility to care • Social support
Ashtari (2022) ¹⁸⁶	US	Ehlers-Danlos syndrome	/		Effectiveness of online peer support groups	• Psychological • Treatment • Information needs • Accessibility to care • Social support
Hill (2022) ¹⁸⁷	Unspecific	Osteogenesis imperfecta	Multistakeholder		Patient experiences and needs	• Burden of Disease • Physical • Psychological • Burden of treatment • Quality of care • Accessibility to treatment/care • Social support • Impact on work • Financial consequences



Simpson (2021)¹⁸⁸	Europe	Orphan but non disease specific	Patient & caregivers	Impact on patients and their carers	- Economic burden - Patient experience with HCP - Accessibility to care
Cardão (2021)¹⁸⁹	Europe	Congenital disorders of glycosylation	Parents & caregivers	Patient experience	- Burden of Disease - Economic burden
Skrobanski (2021)¹⁹⁰	Inter-continental	Aromatic l-amino acid decarboxylase (AADC) deficiency	Caregiver	Impact of caring for a patient	- Burden of Disease - Economic burden
Maxfield (2021)¹⁹¹	Unspecified	Disorder of the corpus callosum	/	Patient experience	- Quality of care - Social support - Impact on education - Impact on work
Strugnell (2020)¹⁹²	Australia	Rett syndrome	Patients & caregivers	Aspects of life that are satisfying or challenging	- Physical - Psychological - Autonomy - Patient experience with HCP - Social support
Hiltrop (2020)¹⁹³	Europe	Male breast cancer patients (MBCPs)	Patients/patient organisations/representatives	Return-to-work experiences	- Economic burden - Physical
Brod (2020)¹⁹⁴	US	Hypoparathyroidism	Patients & HCP	Patient experience	- Burden of Disease - Physical
Verrecchia (2020)¹⁹⁵	Europe	Alpha-mannosidosis	/	Caregiver's and physician's perspectives	- Quality of care - Diagnosis
Oladapo (2019)¹⁹⁶	Unspecified	Congenital (Hereditary) Thrombotic Thrombocytopenic Purpura	Patients/patient organisations/representatives	Patient experiences	- Physical - Psychological - Autonomy
Baumbusch (2019)¹⁹⁷	Canada	Orphan but non disease specific	Parents & caregivers	Parent experiences	- Economic burden - Equity - Psychological - Patient experience with HCP



					• Information needs • Social support
Wu (2019)¹⁹⁸	Asia	Epidermolysis bullosa	Caregiver	Family caregivers' experiences	• Burden of Disease
Mooney (2019)¹⁹⁹	Unspecified	Rare rheumatic condition	/	Impact on patients and informal carers	• Burden of Disease • Economic burden • Physical • Psychological
Babac (2018)²⁰⁰	Europe	Orphan but non disease specific	Multistakeholder	Patient, relatives and HCP needs	• Psychological • Information needs • Social support
Ruijun (2018)¹⁴⁸	Asia	Adrenoleukodystrophy	Caregiver/parents	Parents' experience	• Burden of Disease • Patient experience with HCP • Diagnosis
Adams (2018)²⁰¹	Europe	Lipodystrophy	Patients/patient organisations/representatives	Impact on body image	• Psychological • Diagnosis • Information needs • Social support
Sibeoni (2018)²⁰²	Europe	Neuroendocrine tumors	/	Patients and physicians perspectives	• Psychological
Beynon (2015)²⁰³	Europe	Primary cutaneous T-cell lymphoma	Patients/patient organisations/representatives	Patient experiences, attitudes and approaches to coping	• Physical • Psychological • Burden of treatment • Diagnosis • Social support • Financial consequences
Montali (2011)²⁰⁴	Unspecified	Primary biliary cirrhosis	/	Patient experiences	• Equity • Quality of care • Social support



Henderson (2009) ²⁰⁵	US	Niemann-Pick disease	Patients & caregivers	Psychosocial aspects of patients	- Burden of Disease - Physical - Psychological - Information needs - Social support
Griffiths (2007) ²⁰⁶	Europe	Rarer cancers	Patients/patient representatives	organisations/patient	- Burden of Disease - Physical - Psychological - Quality of care - Accessibility of treatment/care - Social support
Lowton (2006) ²⁰⁷	Europe	Cystic fibrosis	Patients/patient organisations/representatives	Patient experiences	- Economic burden - Patient experience with healthcare professionals - Information needs
Report					
Mease (2023) ²⁰⁸	Unspecified	Orphan but non disease specific	/	Patient experiences	- Physical - Psychological - Effectiveness of treatment - Diagnosis - Impact on work
Gross (2017) ²⁰⁹	Inter-continental	Disease(s)-specific	/	Unmet needs	- Diagnosis - Accessibility to treatment/care - Social support - Impact on education
Mixed qualitative methods					
Foster (2023) ²¹⁰	US	Orphan but non disease specific	Multistakeholder	Self-efficacy managing by parent	- Burden of Disease - Treatment



Hartford (2023) ²¹¹	US	Generalized myasthenia gravis	Patients & HCP	Patient experience	- Physical - Effectiveness of treatment - Burden of treatment
Bingaman (2023) ²¹²	Inter-continental	GM1-gangliosidosis	Parents & caregivers	Disease burden	- Burden of Disease - Economic burden - Autonomy - Treatment - Social support
Martin-gomez (2023) ²¹³	Europe	NKX2-1-related disorders	Patients & caregivers	Preferences and information needs of patients and caregivers	/
Golden (2023) ²¹⁴	US	Niemann-Pick disease type C	Patients & caregivers	Patient experience	- Burden of Disease - Physical - Psychological - Autonomy - Patient experience with HCP - Diagnosis - Social support
Engler (2022) ²¹⁵	Europe	Life-limiting illness	Multistakeholder	Needs for palliative care	Accessibility to care
Teare (2022) ²¹⁶	Europe	Central diabetes insipidus	Patients & HCP	Challenges and improvement needs	- Economic burden - Treatment - Patient experience with HCP - Diagnosis - Social support
Hanbury (2021) ²¹⁷	Europe	Aromatic l-amino acid decarboxylase	Multistakeholder	Needs	Physical
Jimenez-Moreno (2021) ²¹⁸	Inter-continental	Neuromuscular diseases	Patients & caregivers	Patient preferences	- Physical - Psychological - Treatment - Impact on work



Güeita-Rodriguez (2020) ²¹⁹	Europe	Rett syndrome	Parents & caregivers	Access to health and social care resources	- Economic burden - Treatment - Patient experience with healthcare professionals - Information needs - Accessibility to care - Diagnosis - Social support
Khanna (2019) ²²⁰	Inter-continental	Systemic sclerosis	/	Patient perception of disease burden	- Diagnosis - Social support
Both (2018) ²²¹	Europe	Tuberous complex sclerosis	Patients & caregivers	Concerns and care needs of young adults	- Economic burden - Physical - Psychological - Autonomy - Information needs - Accessibility to care - Social support
Litzkendorf (2018) ²²²	Europe	Orphan but non disease specific	Multistakeholder	To develop an information portal on RD	Information needs
Simoes (2017) ²²³	Europe	/	Patients/patient organisations/representatives	Patient expectations	- Patient experience with HCP - Information needs
Pauer (2016) ²²⁴	Europe	Orphan but non disease specific	Patients & caregivers	Patient information needs	Information needs



Appendix 2.4.4. Mixed-method studies

Author (year)	Geographical region	Disease	Study design			NEED criteria
			Methods	Population	Objective	
Kocher (2023)225	Europe	Systemic sclerosis	Survey Interviews Focus discussion	Patients/ organisations / representatives group	Patient Patient To describe the current state of chronic illness care and HRQoL from the patient perspective	QoL Patient experience with healthcare professionals Information needs
Hoenig (2023)226	Europe	Non-tuberculous mycobacteria (NTM)	Survey Interviews	Patients/ organisations / representatives	Patient Patient Eliciting Patient Insights on the Burden of Nontuberculous Mycobacterial Lung Disease	QoL Treatment Patient experience with healthcare professionals Diagnosis
Antoniadu (2023)227	Europe	Orphan but non-disease specific	Survey Interviews	Multistakeholder	To identify the parameters that matter for patients, professionals and policymakers in the context of rare diseases	QoL Accessibility to care Social support
Hughes (2023)228	US	generalized myasthenia gravis	Survey Interviews	Patients and Caregivers	To characterize how SDOH barriers impact individuals from diverse racial, ethnic, educational, and socioeconomic backgrounds living with gMG	QoL Information needs Accessibility to treatment/care Social support Financial consequences
Müller (2023)229	Unspecified	tuberous sclerosis complex	Survey Interviews	Patients	To understand the impact of tuberous sclerosis complex through the development and validation of the TSC-PROM	



Marinello (2022)230	Europe	Rare and complex rheumatic tissue diseases (rCTDs)	Survey Focus group	Patients/ organisations / representatives	Patient Patient	Exploring patient's experience and unmet needs on pregnancy and family planning in rare and complex connective tissue diseases	QoL Patient experience with healthcare professionals Information needs
McMullan (2022)9	Europe	Orphan but non-disease specific	Survey Focus group			To gain an understanding of carer reported experiences derived specifically from persons caring for someone with a rare disease	Burden of disease Economic burden Information needs Social support Varia
Spencer-Tansley (2022)231	Europe	Orphan but non-disease specific	Survey Interviews	Patients and caregivers		To explore the impact on mental health of living with a rare condition, and experiences of health service support	QoL Patient experience with healthcare professionals Accessibility to care Social support Varia
Marcinkowska (2022)232	Europe	Tuberous Sclerosis Complex	Survey Interviews	Patient and caregiver		Identifying the needs and difficulties of patients with Tuberous Sclerosis Complex	QoL Impact on education
Yang (2022)233	US	Neurofibromatosis Type1 (NF1) and Plexiform Neurofibroma (PN)	Survey Interviews	Patients and caregivers		To gain understanding in the burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN)	Burden of disease Economic burden QoL
Godfrey (2021)234	US	Cystic fibrosis	Survey Focus group	Patients, HCP and caregivers		To determine the educational needs and preferences	Social support



Long (2021)235	Australia	Mitochondrial Respiratory Chain Disorders (MRCDs)	Survey Focus group	Patients and caregivers	Identifying the perspectives of people and parents of children concerning disease management after diagnosis	Patient experience with healthcare professionals Information needs Accessibility to care Social support
Depping (2021)236	Europe	neurofibromatosis type 1; primary sclerosing cholangitis; pulmonary arterial hypertension; and Marfan syndrome	Survey Focus group	Patients/patient organisations/patient representatives	The development of a self-care intervention for patients with rare diseases	QoL Accessibility to care Social support
Applebaum (2020)237	US	Erdheim–Chester disease	Survey Interviews	Caregivers and parents	Understanding the burden of caregivers	Burden of disease Economic burden
McMullan (2020)238	Europe	Orphan but non disease specific	Survey Interviews	Patients/patient organisations/patient representatives	Identifying which improvements are required to further support people living with a rare disease	Burden of disease Information needs Social support
Porter (2020)239	US	Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome)	Survey Focus group	Patient and caregivers	Identifying the unmet treatment needs	Burden of disease QoL Treatment Information needs Accessibility to care Social support Varia



Inhestern (2020)240	Europe	Orphan but non disease specific			Developing best practice recommendations on management concepts in healthcare for rare diseases	
Ragusa (2020)241	Europe	Prader-willi	Survey Interviews	Patients and caregivers	Gaining insights in the needs of patients and caregivers	Burden of disease Diagnosis
Kocher (2019)242	Europe	Systemic sclerosis	Survey Interviews	Patient, HCP and caregivers	Gaining insights into the chronic illness care and disease management	Patient experience with healthcare professionals
Noël (2019)243	Europe	Fabry Disease	Survey Interviews	Patients/patient organisations/patient representatives	Identification of treatment needs and expectations	Varia
Svernling (2019)244	Europe	Locked-in syndrome	Database analysis Interviews	Patients/patient organisations/patient representatives	Assessment of the QoL	QoL Patient experience with healthcare professionals Social support
Erbis (2018)245	Europe	Autoinflammatory diseases	Survey Focus group	Patients and caregivers	Evaluating the patient perspective of the unmet needs in AID	Burden of disease Economic burden QoL Information needs Accessibility to care Diagnosis Social support
Hiremath (2018)246	US	Eosinophilic gastrointestinal disorders (EGID)	Survey Focus group	Patients and caregivers	Identification of the unmet medical needs and barriers in patients with EGID	QoL Patient experience with healthcare provider Accessibility to care Social support Varia



Tejada-Ortigosa (2017)247	Europe	Rare metabolic diseases	Survey Interviews	Patients and caregivers	Identification of the health and socio-educational needs	Burden of disease Economic burden QoL Patient experience with healthcare provider Accessibility to care Diagnosis Social support Varia
Kasparian (2015)248	Australia	Von Hippel–Lindau disease	Survey Interviews	Patients and caregivers	Eliciting the experiences and unmet medical needs of patients their families and caregivers	Burden of disease QoL Patient experience with healthcare provider Information needs Diagnosis Social support
Van Groenendaal (2015)249	Europe	Alstrom syndrome	Survey Interviews	Patients and caregivers	Analyzing the effectiveness of the MDC	Patient experience with healthcare provider
Behan (2016)250	Europe	Primary ciliary dyskinesia	Survey Interviews	Patients/patient organisations/patient representatives	To investigate the patients' perspectives on diagnosis between	Diagnosis Information needs Social support
Dwyer (2014)251	Europe	Congenital hypogonadotropic hypogonadism	Survey Focus group	Patients/patient organisations/patient representatives	Identifying the unmet health needs of patients	QoL Patient experience with healthcare provider Information needs Social support



Appendix 2.5. OVERVIEW OF TOPICS STUDIED PER TYPE OF METHOD

Method	Summary of studied topics	Reference(s)
Literature review	• societal preferences related to attributes characterizing orphan drugs • history of needs assessment that exists in rare diseases • results of studies of rare needs • implications for the future • research areas that are still open in this field • epidemiology • HRQoL • economic burden of illness • specific areas of the disease phenotype (motor, communication, behavior, sleep) • diagnostic processes • treatment • burden	8, 17, 26, 31
Disease database	Real-world burden databases • socioeconomic aspects (population-based) • incidence • survival rate • cause of mortality of patients Electronic databases of helplines • needs of users contacting a helpline (e.g. NORBS helpline users). Here, the “need” was the reasons for addressing the helpline. Database of medical centres/ Electronic health records (HER)/ medical records • physical examination • admission signs and symptoms • medical history • comorbidities • demographics • skin involvement • laboratory results	146, 147 252 149, 150, 253



- antibiotic treatment
- extent and number of surgical interventions
- intensive care treatment
- all people diagnosed with a particular disease matched by age, sex and general practice with ten randomly selected people without the disease.
- identification of people diagnosed with a particular rare disease (e.g. HCM) and matching them by age, sex and general practice with randomly selected people without the disease.
- patient demographics
- clinical characteristics at diagnosis
- treatments (at first and second line)
- survival outcomes (overall survival (OS))
- time on treatment (ToT) (analysed by treatment initiation period)
- cardiac stage
- hematologic responses

Databases set up during prospective studies

- **Real-world evidence** on chain (AL) amyloidosis, a retrospective, observational study was set up to collect real-world evidence for the management of systemic AL amyloidosis in patients who initiated first-line treatment. Aside from patient demographic and clinical characteristics at diagnosis, treatments (at first and second line), and survival outcomes (overall survival (OS); time on treatment (ToT)) analyzed by treatment initiation period, cardiac stage, and hematologic responses were collected. Landmark analyses on time to event endpoints for hematologic responses were performed .

150

Disease registries

- quantify the number of rare disease patients
- incidence
- survival rate
- cause of mortality (e.g. patients with primary sclerosing cholangitis)
- clinical burden
- humanistic burden
- economic burden (e.g., severe hemophilia B in the United States)

144, 146, 147

Other databases (e.g. health care service databases)



- prevalence
- interest
- unmet needs
- direct medical costs
- diagnostic journey for some patients
- direct medical costs
- total cost of care
- the average cost per patient (PP)
- per patient per year (PPPY) cost and the average cost of age-matched patients without the rare disease (control population)

144, 145

Interviews

Interviews with patients

- patients' perspectives and experiences
- patients' experiences with online support groups, telephone health services and the diagnostic process
- current disease management demands
- patients' main concerns about disease management
- the well-being of affected children
- the impact on family life
- how patients perceive their illness and associated symptoms
- how patients cope with these challenges
- how patient perceptions and management strategies evolve over time.
- return-to-work (RTW) experiences
- physical and emotional impact

174, 186, 189, 193

Interviews with caregivers (consistent with the Center for Drug Evaluation and Research (CDER) (FDA) guidance)

- need for support to understand what to expect over their child's lifespan
- how to manage uncertainty
- burden of living with the disease (e.g. Classic Galactosemia)
- caregiver burden
- symptoms with greatest impact
- meaningful but unmet treatment needs.

177, 183, 239

Interviews with HCPs



	- the impact of the diagnostic process and search for adequate treatment on RTW in patients with a rare cancer - presence/absence of supportive care and its impact on RTW, - the specific influence of legislation regarding sick leave and work disability (WVP and WIA, respectively) on rare cancer patients' RTW and work retention	182
Focus group discussions	- impact of living with a rare disease on daily life - psychological and familial functioning to examining experiences with healthcare and information provision - impact of living with a child diagnosed with the rare disease (both on daily life and on psychological and familial functioning) - experience with and perspectives on healthcare and information provision about the rare disease	167
Surveys	- patient characteristics - sociodemographics - health conditions - diagnostic experiences - healthcare service utilization - emotional and social impact - financial aspects - EuroQoL health-related QoL questionnaire EQ-5D-3L or EQ-5D-5L or other specific scales. - the prevalence of patients with a particular rare disease treated at a particular institute. - experience of diagnosis - health related function of the patient - impact on family - use of health services - use of support services - economic impact - emotional and social impact - date of diagnosis - roles and plans for the future - general experiences and functional impairment - associated diseases - date of diseases onset - current treatment and greatest challenges in everyday life - comorbidity	35, 37, 39, 54, 55, 59, 64, 69, 77, 79, 82, 85, 92, 100, 103, 107, 111-113, 115, 118, 127, 134, 138, 212, 231, 237, 247, 248, 254



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- heritability
 - fertility
 - tiredness
 - ability to participate in sports
 - ability to work
 - ability to take part in social activities
 - daily medicine intake
 - sleep quality
 - physical discomfort
 - disease-related subjects “keep them up at night”
 - most important sources of scientific information on their disease
 - health service experiences
 - presence of any formal or informal care
 - symptoms
 - impact of the diseases on working hours and conditions loss and social burden (temporary and permanent sick leave or early retirement)
 - disease-related expenses
 - resources not available in the healthcare system and not affordable for the household budget
 - the emotional and social impact
 - health care resource utilisation (HRU)
 - work productivity
 - medical support in everyday life
 - which professional soft skills their treating physicians’ should have, such as medical expertise, paying attention to patients’ concerns, having empathy, taking enough time, collaboration with other disciplines or the self-help groups as well as having been treating patients with a particular disease before
 - need for rehabilitative measures
 - depression
 - anxiety
 - beliefs about and experiences of the disease
 - perceptions of personal susceptibility to tumours
 - perceived impact of the disease on one’s physical health
 - perceived impact of the disease on emotional well-being
 - perceived impact of the disease on interpersonal relationships
 - perceived impact of the disease on finance
 - perceived impact of the disease on career opportunities
 - perceived impact of the disease on sense of self
 - family dynamics and communication about the disease
-



-
- information and supportive care needs
 - health service utilization
 - social support
 - sleep quality
 - care burden
 - self-reported health (using validated surveys like SF-36)
 - For instance surveys on rare metabolic diseases may also include topics on special food. This particular survey organised the topics in 3 sections:
 - a) Health order: neonatal screening, treatments used, medication and special food, other benefits, health, economic cost and access to these resources, with variables of disability, dependency, financial aid, health care, lack of coverage, scientific knowledge of the disease, support from associations and research;
 - b) Educational order: type of education, educational support and home care, associated health personnel, harassment;
 - c) Psychosocial order: quality of life of pediatric patients and their caregivers, types of primary caregivers, psychological support, family situation, work life and other variables related to care needs.
 - Some surveys are organised in particular parts, e.g. first a part related to costs and another part related to HRQoL (cost-of-illness survey). When costs are measured, the following aspects are considered:
 - direct health care resources,
 - non-health care resources (formal or informal care),
 - productivity losses (i.e. indirect costs)
 - One study divided these costs in 4 categories: direct healthcare costs (all costs directly linked to the diagnosis and treatment of the disease), direct non-healthcare formal costs (related to professional caregivers, social services, and transport), direct non-healthcare informal costs (informal care by a relative or friend), and indirect costs (loss of productivity linked to work absence and early retirement).
 - Specific types of surveys exist to measure particular parameters, such as treatment practices across a large range of diseases using a point-in-time survey (e.g. in the delphi Real-World Disease Specific Program used in a study on Myasthenia gravis)
 - Some surveys focus on data sharing and data protection in research and healthcare settings
Surveys may also focus on patient empowerment
 - degree of knowledge patient associations about screening systems and their needs regarding screening, with topics such as does screening exist in your country, is screening done systematically, who supports its costs and what are your organisation's views on screening.
 - Some of such qualitative surveys are designed as 'requests to physicians' surveys.
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- Surveys could also be designed as preference surveys, inquiring about most important symptoms and treatment characteristics.
 - presenting symptoms,
 - path to diagnosis,
 - identity and impact of most bothersome symptoms
 - most pressing needs that future treatment should address
 - most bothersome symptoms
 - expected outcomes that they would like to see from disease treatment.
 - rate symptom severity on a scale of 1 to 10, where 1 was used to represent the least bothersome and 10 the most bothersome.
 - Some surveys were specifically developed to assess the needs of patients during the corona pandemic, whereby 37 items
 - demographic characteristics
 - dystonia-related features
 - neurological service provision
 - therapeutic relationship with the neurologist
 - perceptions related to virus infection
 - perceptions about healthcare-related needs
 - work-related questions
 - requesting information
 - seeking support during the pandemic
 - Some surveys are focused on particular care needs, where the following aspects for part of the questionnaire:
 - the satisfaction with receiving care
 - experiences and needs of providing daily care
 - the impacts of disease on relationships
 - the emotional and psychological burdens of disease,
 - parents' overall satisfaction with the support received
 - The aim was to find out more about equity in care, practical care needs and about relationships and emotions.
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Appendix 2.6. SPECIFIC SCALES/ VALIDATED INSTRUMENTS FOR RARE DISEASE

Rare disease	Specific scale/validated instruments
Hereditary transthyretin amyloidosis	Hospital anxiety and depression scale (HADS) ³⁹
Fibrodysplasia ossificans progressiva (FOP)	Patient-Reported Mobility Assessment (PRMA) and the FOP Physical Function Questionnaire (FOP-PFQ), Zarit Burden Interview (ZBI) with caregiver ⁶⁵
Rare chronic neurological disease in childhood	Paediatric Quality of Life Inventory (PedsQL™) Version 2.0 Family Impact Module (FIM), Viking Speech Scale (VSS) and the Gross Motor Function Classification-MLD (GMFC-MLD) ⁸⁴
Rare disease	World Health Organisation's framework for International Classification of Functioning and Health (ICF) to support the development of a new survey tool. ⁷ Other validated tools such as the Health Utilities Index Mark II (HUI- II) (assessing health functioning); the Impact on Family scale (IOF); and the Royal Alexandra Hospital for Children Measure of Function (RAHC MOF) (psychometrically validated tools)
Juvenile idiopathic arthritis	Barthel Index ¹²⁷
Erdheim–Chester disease	16-item Covinsky Family Impact Survey, Caregiver Burden Inventory (CBI) and the Caregiver Reaction Assessment (CRA), Cancer Survivors' Partners Unmet Needs (CaSPUN) assessment, McGill Quality of Life Questionnaire-Revised (MQOL-R) and the Hospital Anxiety and Depression Scale (HADS) ²³⁷
Osteogenesis imperfecta	Patient's musculoskeletal function was evaluated using the 36-Item Short Form (SF-36, adult version) ²⁵⁵
Myasthenia gravis (MG)	Particular patient reported outcome (PRO) instruments are used, required or optional, to avoid overburdening all participants. Core PRO instruments: EQ-5D-5L, EQ-5D-5L bolt-on items. There are a number of additional single-question dimensions to the EQ- 5D- 5L that are relevant to common health and/or HRQoL problems in MG, namely vision, breathing problems, tiredness, sleep, social relationships and self-confidence, Myasthenia Gravis Activities of Daily Living, Myasthenia Gravis Quality Of Life 15-item revised scale, Hospital Anxiety and Depression Scale, Health Utilities Index III, COVID-19 survey. Opt-in PRO instruments: The Patient- Reported Outcomes Measurement Information System (PROMIS) Dyspnoea Characteristics, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue measure, PROMIS Sleep Disturbance short form 6a ²⁵⁶
Rare diseases requiring mechanical entilation²¹²	The Ulm Quality of Life Inventory for Parents (ULQIE) (for QoL), The Brief Symptom Inventory (BSI) (for mental health), The Coping Health Inventory for Parents (CHIP) (for coping), The Oslo-Social Support Scale (OSSS-3) (for social support), The German version of the Family Assessment Measure (FAM) (for family functioning) ²¹²
Familial amyloid polyneuropathy (FAP)	PROMIS-10 und WHODAS 2.0 to assess disability ¹⁰⁰
NUT Carcinoma	a PRO tool based on patient input and qualitative interviews in NUT carcinoma patients and their caregivers. The tool is based on the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) with additional items selected from the EORTC Item Library and newly created items based on patient experience data ¹⁸¹

Rare diseases	Depression Patient Health Questionnaire (PHQ99–11) and anxiety Generalized Anxiety Disorder Scale-7 (GAD-7 12 13) ⁸⁷ , patients' physical disability (using the Barthel Index [BI] score). ⁶¹ An overview of diverse PROMs in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) evaluations of orphan drug designations was made ¹⁸⁸
Rare chronic diseases	German short version of the Supportive Care Needs Survey (SCNS-SF34) to assess psychosocial support needs ¹⁸⁵
Genetically Determined Leukoencephalopathies	Parenting Stress Index–4th Edition (PSI-4) evaluates the magnitude of stress in a parent-child system for children aged 1 month to 12 years ⁹⁸
Type 1 Gaucher disease	GD1-PROM was developed by Shire/Takeda based on the input of adult patients with GD and of worldwide physicians managing patients with GD, sent via mobile SMS notice to 405 adult patients (age ≥ 18 years) with GD ¹⁰⁶
Women with congenital hypogonadotropic hypogonadism	The Morisky Medication Adherence Scale (MMAS) is an 8-item instrument that assesses medication taking behaviour to determine low, medium or high adherence. ^{29, 68, 178} The Zung Self-Rating Depression Scale (SDS) is a widely used, validated 20-item instrument quantifying the severity of affective, somatic, psychomotor and psychological depressive symptoms. ^{34, 180} The Illness Perception Questionnaire – Revised (IPQ-R) includes 38 statements to assess emotional and cognitive representations of illness. ^{34, 125, 180}
Sarcoma patients	European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), added with 11 single items concerning symptoms from the EORTC item library. ⁸⁶
Autoinflammatory diseases	DISABKIDS-questionnaire, a validated, generic instrument for children and adolescents with chronic disease and their parents. ²⁴⁵
Primary cutaneous amyloidosis (PCA)	SF-36 dermatology life quality index (DLQI) to quantify the burden of PCA on the health-related QoL in Chinese PCA patients, Dermatology life quality index (DLQI), a simple, practical and self-administered questionnaire designed to assess limitations caused by the impact of skin disease, covering six domains, namely symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment; Short form 36 health survey (SF-36) is a 36-item general health status instrument often used in clinical trials and health services research. This is a self-administered questionnaire that contains 36 questions. The questions are summarized into eight scales: Physical Function (PF), Role Limitations-Physical (RP), Vitality (VT), General Health Perceptions (GH), Bodily Pain (BP), Social Function (SF), and Role Limitations: Emotional (RE) and Mental Health (MH). ¹³⁵
Hereditary angioedema	36-item Short-Form Health Survey (SF-36v2) ¹²⁴
Child with a bleeding disorder	Validated Parental Needs Scale for Rare Diseases (PNS-RD) 13 to measure the overall support needs of parents caring for a child with a bleeding disorder. ¹¹⁰
Systemic sclerosis (SSc)	PACIC scale and quality of life measured by the Systemic Sclerosis Quality of Life Questionnaire (SScQoL) ²²⁵
Spinal Muscular Atrophy	PedsQL Neuromuscular Module Scales comprise parallel child self-report and parent proxy-report formats for children aged 2-18 years. Parents and children completed the questionnaires separately. ¹³⁷ Another study made use of the following instruments ⁷⁹ : the EQ-5D-5L and Caregiver Strain Index (CSI).



Fabry disease	Tentative Fabry disease-specific QOL scale—the Adult Fabry Disease QOL scale (AFQOL) ⁷⁰
Phelan-McDermid syndrome (PMS)	Genetic Syndrome Stressors Scale (GSSS) ³³
Gaucher disease patients	Medical Outcome Study Short Form- 36 (SF-36), Zung's Self- Rating Anxiety Scale (SAS), Zung's Self- Rating Depression Scale (SDS), the Multi- dimensional Scale of Perceived Social Support (MSPSS), the Herth Hope Index (HHI). The 36-Item Short-Form Health Survey Questionnaire (SF- 36) is a set of generic, coherent, and easily administered instruments for evaluating health- related quality of life year. Zung's Self-Rating Anxiety Scale (SAS) is a self-administered instrument for measuring levels of anxiety in respondents who answered the questions according to last week's experience. Zung's Self-Rating Depression Scale (SDS) is a norm-referenced instrument to the potential presence of depressive disorders in adults. MSPSS (includes 12 items that cover three dimensions ("family," "friends," and "significant"). The HHI contains three subscales involving 12 items: temporality and future, positive readiness and expectancy, and interconnectedness; 12 items measure various dimensions of hope using a 4-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree). ¹⁰¹ Another study ⁹² assessed the sleep quality by the Pittsburgh Sleep Quality Index [PSQI]), and used the Short Form Health Survey (SF-36). ⁹²
Achondroplasia	Generic Peds QL 4.0™ as self-reports for children aged 8–14 years and parent-reports for children aged 4–14 years. The present study is part of the Achondroplasia Personal Life Scale Experience Scale study that focused on developing a questionnaire to assess quality of life and functioning in children and adolescents with achondroplasia based on the International Classification of Functioning, Disability, and Health. They measured parental quality of life using the Short-Form-8 questionnaire (SF-8), which is a short form of the SF-36, an internationally used generic quality of life instrument. ¹⁶⁰
Huntington's disease	HRQoL questionnaire EuroQoL, EQ-5D-3L, Needs and Provision Complexity Scale (NPCS), functional ability was determined using the Unified Huntington's Disease Rating Scale (UHDRS) Functional assessment scales ¹²³
Alstrom syndrome	Health Utilities Index scales (HUI) that uses the factors of vision, hearing, speech, walking, dexterity, happiness, cognition, and pain in the measure related to good health to assess Quality of Life ²⁴⁹

Polyneuropathy Organomegaly Endocrinopathy Monoclonal gammopathy Skin changes (POEMS) syndrome	Hospital Anxiety and Depression Scale; World Health Organisation Quality of Life Scale (brief); Brief Illness Perception Questionnaire. Hospital anxiety and depression scale (HADS) The HADS is a well-validated questionnaire that assesses symptoms of anxiety and depression, and was designed for use in general medical populations. There are 14 items; each item is scored on a 0–4 Likert scale. There are 7 items relating to anxiety and 7 items relating to depression. The scores for the anxiety items and the depression items are summed separately to provide two domain scores. These scores relate to one of four categories: 0–7 (normal), 8–10 (mild), 11–14 (moderate), 15–21 (severe). World Health Organisation quality of Life-BREF assessment (WHOQOL-BREF) The WHOQOL-BREF is a cross-cultural self-report quality of life assessment. It consists of 26 items based on four domains: physical health, psychological, social relationships, and environment. The mean score from the items in each domain is used to calculate the domain score. The higher the domain score the higher the individual's perception of quality of life for that domain. Brief illness perception questionnaires (BIPQ) The BIPQ assesses cognitive illness representations including the timeline of an illness, personal control over an illness, treatment control, and illness identity. It also assesses emotional representations, illness comprehensibility and causal representations of illness. Assessment of causal representations is an open-ended item adapted from the Illness Perception Questionnaire-Revised (IPQ-R), in which individuals can provide a qualitative free text response. An increase in the item scores represents an increase in the measured domain. ²⁵⁷
Charcot-Marie-Tooth (CMT) disease	EuroQol 5 Dimensions 5 Levels (EQ-5D-5L), PROMIS™ Sleep Disturbance 8a, Falls Efficacy Scale – International (FES-I), Falls Efficacy Scale – International (FES-I) Lower Extremity Function Scale (LEFS), Quick Disabilities of Arm, Shoulder & Hand (QuickDASH) ²⁵⁸
Juvenile localized and systemic scleroderma	Barriers to Care Scale (BACS) adapted ³⁸
Dravet syndrome	HRQoL in paediatric and adolescent patients was respectively assessed by the Kiddy KINDL in those aged 4–6 years old and by the Kid KINDL in those aged 7–17 years old. Both instruments measured HRQoL based on physical, emotional, self-esteem, relationships with family, relationships with friends and schooling sub-domains. In the 12-week-diary, caregivers chronicled their child's. In addition, Composite symptom scores (CS1-2-3) can be assigned ⁵³ day-to-day experiences with DS, including their daily seizure count.
Desmoid-type fibromatosis	EORTC (QLQC30), DTF- specific HRQoL (DTF- QoL) and healthcare utilisation ³²
Non-Ambulatory Patients with Duchenne Muscular Dystrophy	PUL-PROM was used to evaluate patients' upper limb functioning and was compared to data collected on non-ambulatory stage and quality of life ⁵¹
Urea Cycle Disorders	Parental Needs Survey (PNS) ⁶²
Relapsing polychondritis	Four patient-reported outcomes scales, namely PtGA, 36-item Short Form Health Survey (SF-36), Brief Illness Perception Questionnaire (BIPQ) and Multidimensional Fatigue Inventory (MFI) ⁷⁸
Rare diseases – caregivers	Distress (Distress Thermometer for Parents; scale 0–10) psychosocial information needs (self-developed items; scale 0–100), and caregiver-reported HRQoL of the children with RDs (DISABKIDS Chronic Generic Measure, short-form; scale 0–100) ²²²



Hemophilia¹²¹	Functionality (HAL/PedHAL), QoL (A36 Hemofilia-QoL/CHO-KLAT), anxiety and depression (PROMIS), and illness perceptions (IPQ-R) ¹²¹
Rare disorders with delayed psychomotor/intellectual development¹³³	Data related to psychomotor/intellectual development were asked to the parents according the last specialistic evaluation performed. A normal neurological development is defined as an Intelligence Quotient (IQ) level above 85. IQ scores of 70–84 indicate borderline intellectual functioning while values below 70 identify intellectual disability. Specifically, an IQ level between 51 and 69 defined a mild intellectual disability while an IQ between 36 and 50 or below 35 identify a moderate and severe-profound intellectual disability respectively.
Systemic mastocytosis⁶⁶	The online TouchStone SM Patient Survey is composed of 100 questions and included three validated instruments: the Indolent Systemic Mastocytosis Symptom Assessment Form (ISMSAF), the 12-item Short-Form Health Survey (SF-12), and the Work Productivity and Activity Impairment (WPAI) Questionnaire. The ISM- SAF is a reliable and valid, 12- item questionnaire that assesses relevant SM- specific symptoms identified by patients with ISM and SSM. Reported severity of bone pain, abdominal pain, nausea, spots on skin, itching, flushing, fatigue, dizziness, brain fog, headache and diarrhea generates a total symptom score (TSS) that carries prognostic significance. The SF-12, WPAI, and ISM- SAF were combined with investigator developed questions that were adapted from items used in a previous cross- sectional study of patients with myeloproliferative neoplasms regarding symptoms and the type and frequency of health care use (27 questions); the impact of SM on daily functioning, emotional well- being, and quality of life (32 questions); and patient demographics (10 questions). The online TouchStone HCP Survey contained 51 items, required approximately 15–20 minutes to complete, and was organized into four key domains: provider characteristics, disease assessment, patient burden, and current management. Provider characteristics (11 items) covered practice setting, practice characteristics, and information about how HCPs diagnose SM, including KIT D816V mutation testing and time to diagnosis. Disease assessment (15 items) captured the assessment of symptoms HCPs commonly encountered in practice and asked HCPs which guidelines they referenced for the treatment of patients with SM. Patient burden (14 items) used scaled responses (ranging from not at all to a great deal) to collect HCP perceptions of the impact of SM symptoms on their patients' activities of daily living and potential limitations. Finally, current management (11 items) assessed how HCPs were treating patients with SM and queried their satisfaction with overall treatment and management options. For instance, HCPs were asked to estimate the time spent with each patient in the clinic, the percentage of patients with ISM who were treated aggressively (and how aggressive treatment was defined), and how both over- the- counter and prescribed medications were used to manage patient symptoms. HCPs were also asked to assess treatment side effects on their patients' QoL, to designate the first and second most important treatment goals for ISM and advanced SM.⁶⁷

**Hereditary angioedema⁸⁰**

Instruments used to measure patient-reported outcomes included the Angioedema Quality of Life questionnaire (AE-QoL), 12-Item Short-Form Health Survey (SF-12v2), Angioedema Control Test (AECT), Hospital Anxiety and Depression Scale (HADS), and Work Productivity and Impairment questionnaire (WPAI). Data were analyzed with descriptive statistics.⁸⁰ In another study, the SF-36v2 is used, which is a generic health questionnaire measuring eight health domains including physical functioning (PF), limitations in daily role functioning due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), limitations in daily role functioning due to emotional problems (RE), mental health (MH) as well as an item asking respondents about health change over the past year.¹²⁴

Rare disorders in children⁷³

96 published instruments of HRQOL for children and adolescents, 30 generic and 66 specifics measures



Appendix 2.7. PROPOSED NEW INDICATORS AND RESPECTIVE SUGGESTIONS FOR PATIENT QUESTIONNAIRE

Proposed indicators vs initial indicator	Indicator	Proposed measurement method	Proposed question for patient questionnaire
Proposed	Unpredictability	Patient survey + interview	On a scale from 1 to 5, how would you rate the predictability of your condition, considering the possibility of sudden changes, unclear signs of improvement or worsening, and difficulty in planning ahead?
Proposed	Self-esteem BEFORE vs TODAY	Patient survey + interview	Inspiration in publication by Donnellan et. Al. ²⁵⁹
Proposed	Reproductive health need	Patient survey + interview	- Do you want kids or more kids someday? (Yes – no – I am not sure how I feel about having (more) kids right now) - Has your disease influenced this decision?
Initial	Effectiveness of the treatment	Patient survey	Question already included in the questionnaire: "Do you think the treatment you have received for your melanoma is working?"
Proposed	Treatment adherence	Patient survey + interview	How would you describe your treatment adherence?
Proposed	Availability of diagnostic methods	Expert opinion	
Proposed	Waiting time	Patient survey + interview	- How satisfied are you with the waiting time you experience in between visits to your specialist? - How satisfied were you with the waiting time you experienced during your recent visits to your specialist? (very satisfied – satisfied – not satisfied – no satisfied at all – no opinion)
Proposed	Travel distance	Patient survey + interview	- How do you travel to your health-care facility? By foot – By bike – by car – with public transport - How much time, on average, does it take for you to complete this journey? - Do you perceive the travel distance from your home to the health-care facility as burdensome?
Proposed	Availability of research and information	Expert opinion	
Proposed	Existence of clinical practice guidelines	Expert opinion	
Initial	Impact on work	Patient survey	- Has your disease influenced your job choice? - Has your disease impacted the intensity (number of working hours, responsibilities) of your job?
Proposed	Stigmatization	Patient survey + interview	- Do you experience any of type of stigmatization, i.e. expectations of prejudice, stereotyping, and discrimination, because of your disease?

Proposed	Social connection needs	Patient survey + interview	- Has your disease influenced your personal relationships (with your partner, family, children, etc.)? - Do you feel you need additional support in your romantic relationship, parenting, or relationships with siblings?
Initial	Costs related to work absenteeism, presenteeism, early labour force exits of patients	Database analysis + patient survey	- How many working days in total have you been absent from work (absenteeism) for the past 12 months due to health problems? If you are unable to indicate this number of days correctly, please give an estimate. - On average, how many days per month do you experience reduced productivity (presenteeism) due to health issues? - Have you exited the labor force early due to health problems? If yes, how many years or months, on average, did you exited the labor force early due to health problems?



APPENDIX 3. STAKEHOLDER WORKSHOPS

Appendix 3.1. APPENDIX 3.1. SURVEY

Appendix 3.1.1. Appendix 3.1.1. Workshop 1

Introduction

Dear participant,

Thank you for taking part in the first workshop organized by the Belgian Healthcare Knowledge Centre (KCE) and KU Leuven as part of a study titled: “applicability of the NEED framework to assess patient and societal needs in patients suffering from rare diseases.” This study is being conducted in the context of the NEED (Needs Examination, Evaluation and Dissemination) project.

The main aims of this project are to:

1. Understand your perspective on the proposed need criteria and the associated measurement methods and its applicability to rare diseases
2. Assess how the evidence on rare diseases collected according to the NEED framework can be used by decision-makers (is there an added value compared to the current approach?)
3. Assess whether/how the framework and/or procedures need to be adapted to be applicable to rare diseases

In preparation of the first workshop, concerning the first aim of this project, you are kindly invited to participate in this online survey.

What is asked from me and how long does it take to complete the survey?

We would like to have your input and opinion about the following aspects:

- In part 1, we would like to collect some background information about yourself: your name and organization (optional) and which stakeholder group you represent
- In part 2, we would like to ask your personal opinion on: each criterion and subcriterion of the NEED framework, whether it fits for needs assessment in rare diseases and whether there is a need to add or adapt certain (sub-)criteria for this specific context. Besides that, we would like your personal opinion on the proposed methodology to collect evidence for each criterion in case of rare diseases.

This survey will take approximately 20 minutes to complete.

Informed consent

To participate in this survey, you must provide your informed consent. Therefore, it is important that you understand and agree with the statements below:

- I have had the opportunity to read the information sheet of the study which aims to determine the applicability of the framework, i.e. the criteria and methods, to assess patient and societal needs in patients suffering from rare diseases;



- I have had the opportunity to ask questions or discuss any concerns regarding the information of this study;
- I was given sufficient time to decide whether I was willing to participate in this study;
- I am aware that participation in this study is completely voluntary;
- I am aware that this questionnaire has been prepared in collaboration with the Belgian Healthcare Knowledge Centre (KCE), as stated in the information sheet;
- I am aware that I can withdraw from this study at any time;
- I understand that the data resulting from this research will be kept for a maximum of 25 years after the end of the research;
- I understand that my data may be used for future research;
- I am aware that the results of this research will be published in scientific journals and disseminated through presentations at conferences or meetings. I understand that these results are based on the analysis of anonymous data and cannot identify me in any way.
- I understand that my data will be processed in accordance with the European General Data Protection Regulation (GDPR).

Do you agree with the above statements?

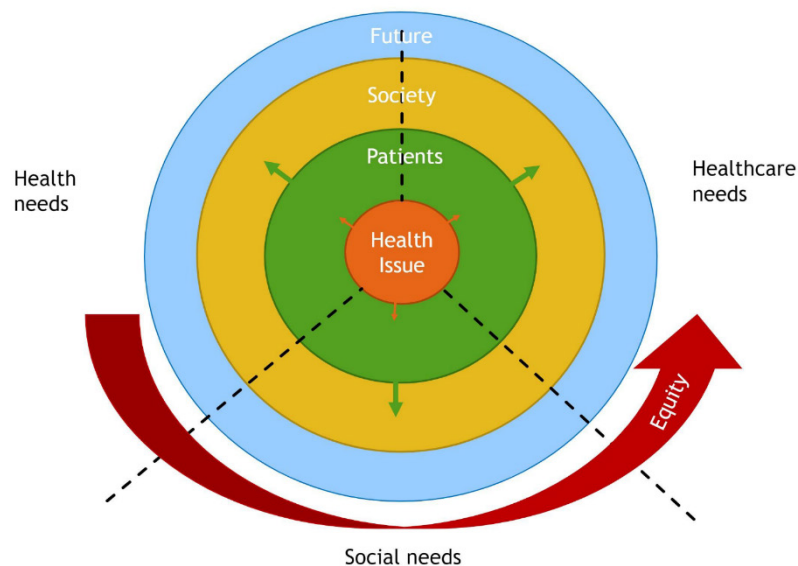
- I agree to all the statements and confirm my participation
- I do not agree to all the statements and do not confirm my participation

in case something is unclear, or you would like additional information, please feel free to contact Zilke Claessens (zilke.claessens@kuleuven.be)

Background information

What is the NEED framework and criteria?

The KCE NEED ('Need Examination, Evaluation and Dissemination') project aims to develop a NEED framework (conceptual approach) to collect evidence for particular health issues or conditions on unmet health-related needs. Health-related needs can include "health needs", "healthcare needs" and "social needs" ("non-health(care) needs"). The evidence will be collected from a patient, societal and future generations perspective, in a database accessible to all relevant stakeholders.



The NEED framework consists of three main dimension levels, being **impact on patients**, **impact on society** and **future impact**. Every dimension consists of explicit health-related need criteria to collect evidence on the health issue. These criteria are factors that are most responsible for the high burden of the health issue and that are linked to the impact of a health issue on the patients and on the broader society, both in the present and in the future. Every criterion consists of at least one but more often several sub-criteria.

- (Sub-)criteria linked to the dimension **impact on patients** can be found here ([flowchart](#))
- (Sub-)criteria linked to the dimension **impact on society** can be found here ([flowchart](#))
- (Sub-)criteria linked to the dimension **future impact** can be found here ([flowchart](#))

The evidence on unmet health-related needs will be collected based on the criteria, making use of particular methods. Several types of methods are used in the NEED project, such as qualitative methods (interviews, expert panels), quantitative methods (patient surveys), database sources (BeBoD, Farmanet,...) or literature reviews.

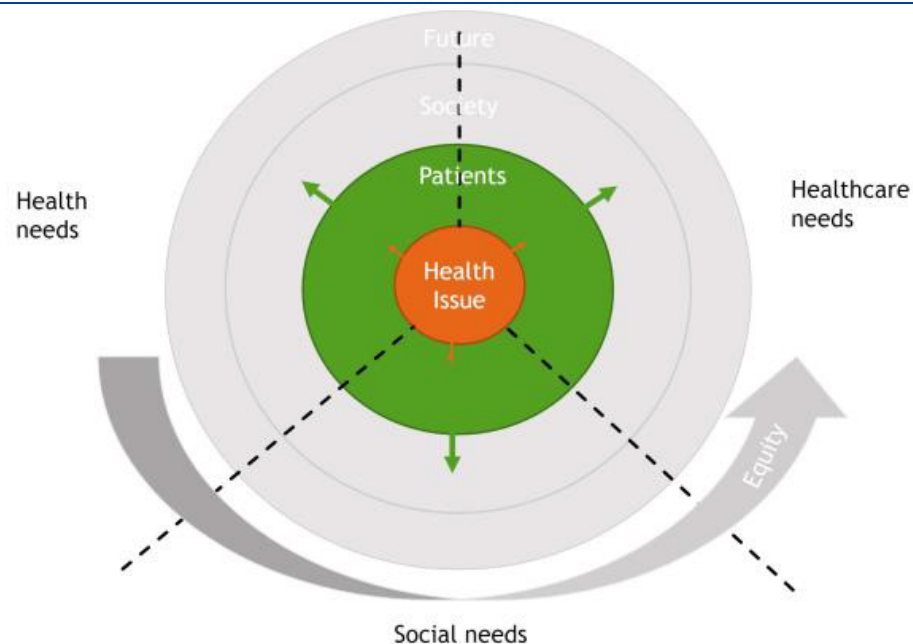
In case something is unclear, or you would like additional information, please feel free to contact Zilke Claessens (zilke.claessens@kuleuven.be)

Your answers are saved automatically by clicking on the blue arrow at the bottom of the page and submitted automatically when closing your browser

Important: when a word is underlined with a dotted line, you can hover over the word with your mouse to get additional information or definitions.



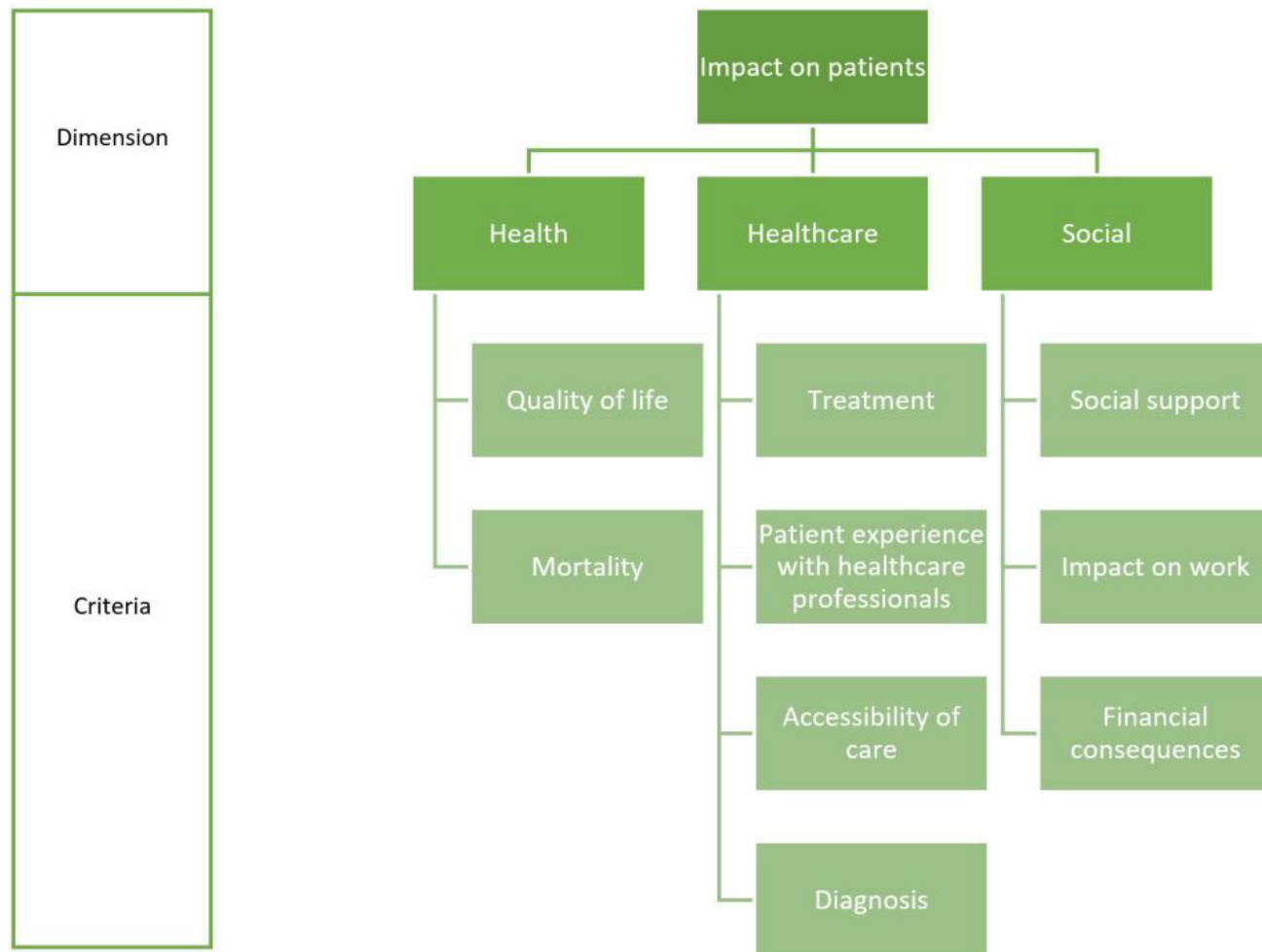
Question	Answer(s)	Remark
Part 1: General information		
Name	Open answer field	Optional
Organisation	Open answer field	Optional
Which stakeholder category do you represent?	○ Regulator ○ Policymaker ○ HTA body/payer ○ Pharmaceutical industry/ trade organization ○ Research organization ○ Healthcare professional ○ Patient organization ○ Other: (open answer field)	
Part 2: considerations for the application of the NEED framework and its criteria in the context of rare diseases – IMPACT ON PATIENTS		
As mentioned before, the NEEDs framework consists of three dimensions from which a health issue can be approached: the impact it has on the patients, the society and the future. Each of these dimensions consists of specific criteria that can characterize the needs and can be used to measure them. The criteria are also distributed over 3 levels: criteria generating health needs, criteria generating healthcare needs and criteria generating social needs.		



The patient needs criteria are initially measured at the individual patient level and then aggregated over the entire patient population, by taking into account a measure of disease frequency (i.e. prevalence or incidence).

For the first cluster of questions, we will be focusing on the dimension: **impact on patients**. We kindly invite you to take a look at the different criteria within this first dimension, layed out in the flow chart below. At a later point in this survey we will further zoom in the sub-criteria and the methods used to measure them.

The **criteria** used to measure the **impact of a health issue on patients** are shown in the figure below:



Do you have any comments or suggestions related to the criteria of the dimension 'impact on patients' in the context of rare diseases?

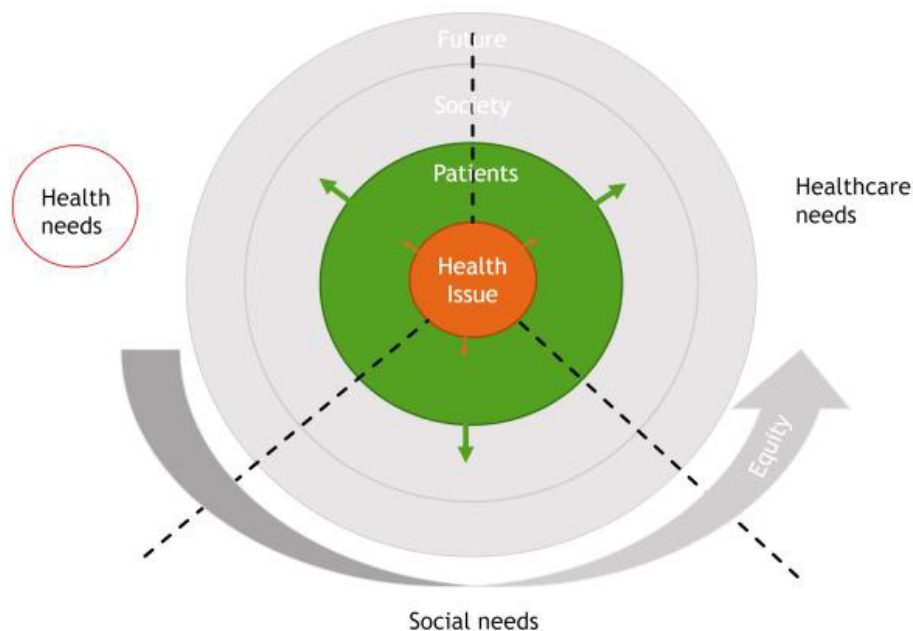
Open answer field



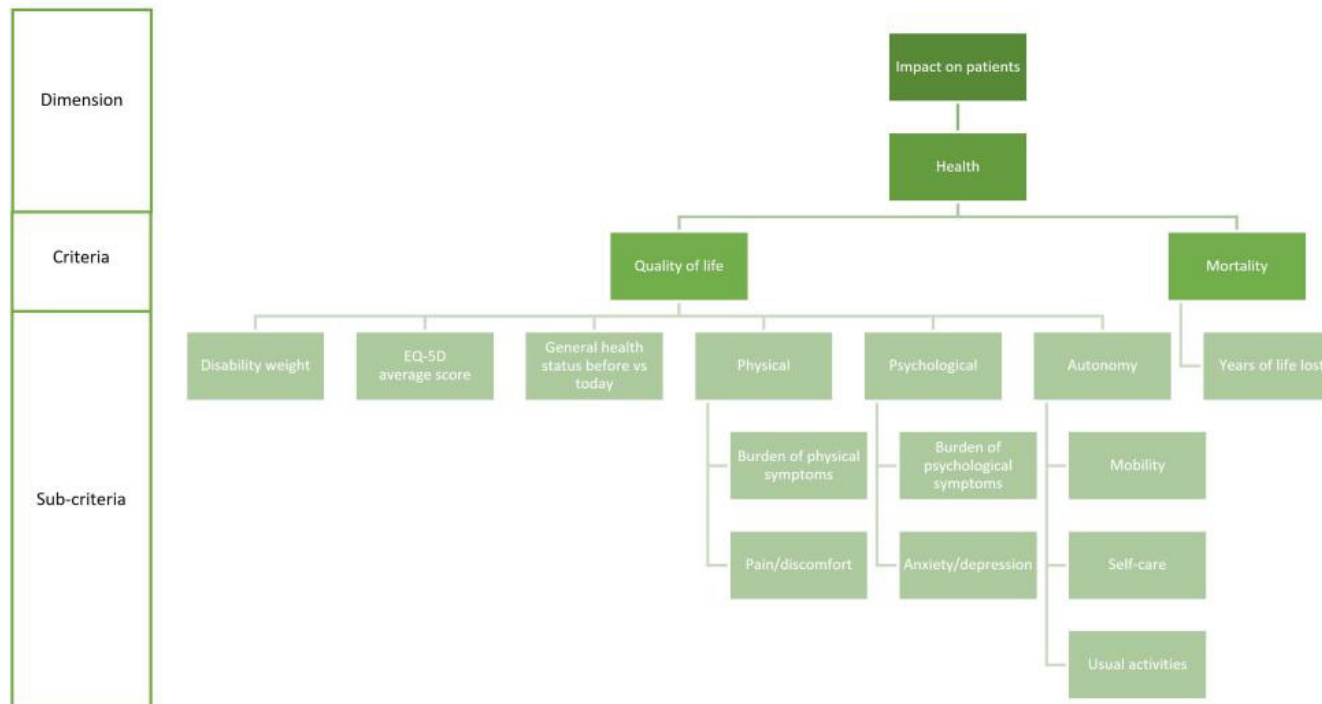
Do you believe that one or more criteria should be added, adapted or removed in the context of rare diseases?

- ☐ Yes, the criteria should be added/adapted/removed and the reasons why are the following:
(open answer field)
- ☐ No
- ☐ I do not know/ I am not competent to answer this question

we will now look further into the **subcriteria** associated with each criterion. We will first focus on the sub-criteria used to measure **patient HEALTH needs**.



for the following set of questions, we kindly invite you to take a look at the subcriteria, layed out in the flowchart below.
The **(sub-)criteria** are represented in the figure below:



Quality of life (QoL)

The first criterion, within the dimension 'impact on patients, generating health needs' is Quality of Life. The criterion 'Quality of Life' measures the extent to which a health issue impacts the general health, physical health, psychological health and autonomy of patients.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to Quality of Life in the context of rare diseases?

- Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following:
(open answer field)
- No
- I do not know/ I am not competent to answer this question



Survey: EQ-5D question on pain/discomfort before vs today	☐	☐	☐	☐	☐	☐	☐
Psychological health status							
Survey question for experienced burden of psychological symptoms related to the health issue	☐	☐	☐	☐	☐	☐	☐
Survey: EQ-5D question on anxiety/depression before vs. today	☐	☐	☐	☐	☐	☐	☐
Autonomy							
Survey: EQ-5D question on mobility self-care and usual activities before vs. today	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

Mortality



The second criterion, within the dimension 'impact on patients, generating health needs' is Mortality. The criterion "mortality" measures the impact a health issue has on the life expectancy of patients.

The only **sub-criterion** of mortality is 'Years of life lost'.

- Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to mortality in the context of rare diseases?
- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following:
(open answer field)
 - ☐ No
 - ☐ I do not know/ I am not competent to answer this question

- Do you have any additional concerns or suggestions related to this criterion or sub-criterion in relation to rare diseases?
- ☐ Yes: (open answer field)
 - ☐ No

In this table the sub-criterion of mortality is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

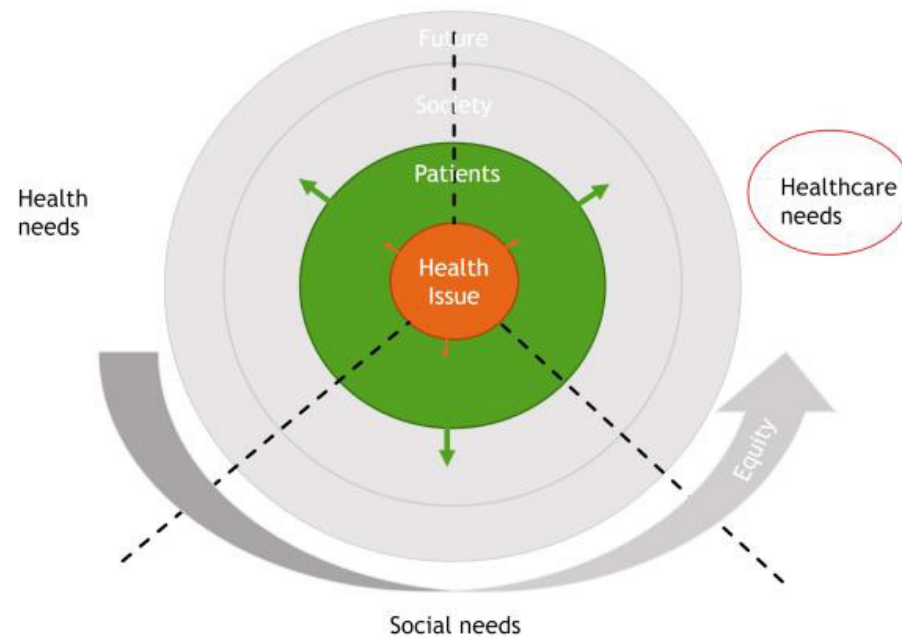
	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Years of life lost							
Belgian Burden of Disease Study (BeBoD)	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criterion that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

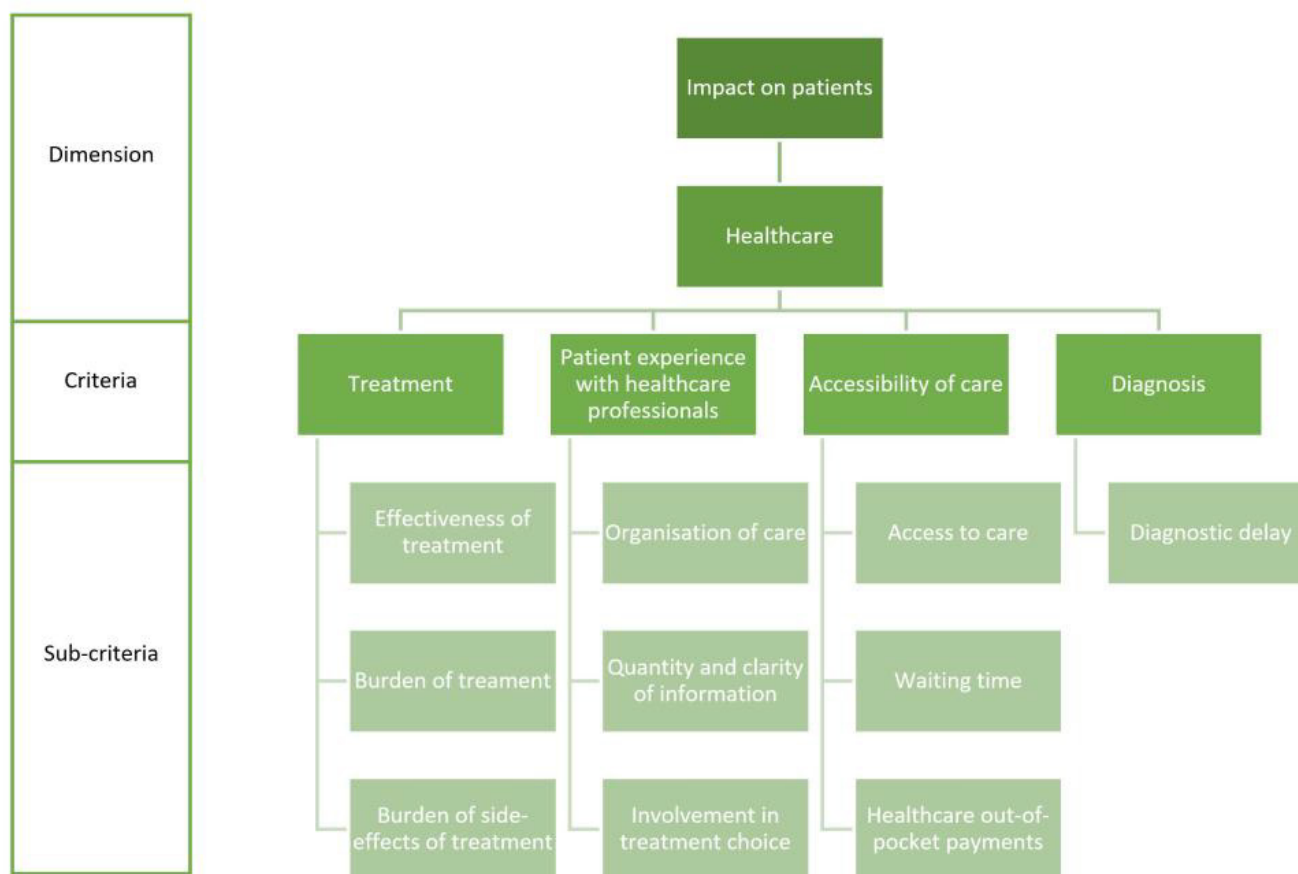
- For most sub-criteria, a literature review is performed alongside the other methods (e.g. survey). Do you agree with this? If not, please specify why.
- ☐ Yes
 - ☐ No (open answer field)
 - ☐ I do not know

Secondly, the focus is on the sub-criteria used to measure **patient HEALTHCARE needs**:



For the following set of questions, we kindly invite you to take a look at the sub-criteria within the **dimension impact on patients**, generating **healthcare needs**, presented in the flowchart below.

The (sub-)criteria are presented in the figure below:

**Treatment**

The first criterion, within the dimension 'impact on patients, generating healthcare needs' is Treatment. The criterion 'Treatment' measures the extent to which the currently available treatment(s) is/are effective and relieving for patients.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to treatment in the context of rare diseases?

- Yes, the sub-criteria that should be added/adapted/removed and the

(open answer field)

- No
- I do not know/ I am not competent to

do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- Yes (open answer field)
- No

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Effectiveness of each treatment							
Literature review	○	○	○	○	○	○	○
Experienced burden of each treatment							
Survey question	○	○	○	○	○	○	○
Experienced burden of side-effects of each treatment							
Survey question	○	○	○	○	○	○	○

Survey question	☐ ☐ ☐ ☐ ☐ ☐ ☐	
Involvement in treatment choice		
Survey question	☐ ☐ ☐ ☐ ☐ ☐ ☐	

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

Accessibility of care

The third criterion, within the dimension 'impact on patients, generating healthcare needs' is Accessibility of care. 'Accessibility of care' measures the ease with which patients accessed the care they needed, including waiting times and costs.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to patient experience with healthcare professionals in the context of rare diseases?

- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following:
(open answer field)
- ☐ No
- ☐ I do not know/ I am not competent to answer this question

Do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- ☐ Yes: open answer field
- ☐ No

In this table all the sub-criteria of patient experience with healthcare professionals are listed. Please indicate to what extent you agree with the proposed method(s) being used to measure the sub-criterion



	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Access to care							
Survey question	☐	☐	☐	☐	☐	☐	☐
Waiting time							
Survey question	☐	☐	☐	☐	☐	☐	☐
Healthcare out-of-pocket payments							
Different databases	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

open answer field

Diagnosis

The fourth criterion, within the dimension 'impact on patients, generating healthcare needs' is Diagnosis. The criterion 'Diagnosis' measures the extent to which the diagnosis of the health issue is timely.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to patient experience with healthcare professionals in the context of rare diseases?

- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following:
(open answer field)

- ☐ No
- ☐ I do not know/ I am not competent to answer this question

Do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- ☐ Yes: open answer field
- ☐ No

In this table the sub-criterion of diagnosis is represented. Please indicate to what extent you agree with the proposed method(s) being used to measure the sub-criterion

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Diagnostic delay							
Survey question	☐	☐	☐	☐	☐	☐	☐

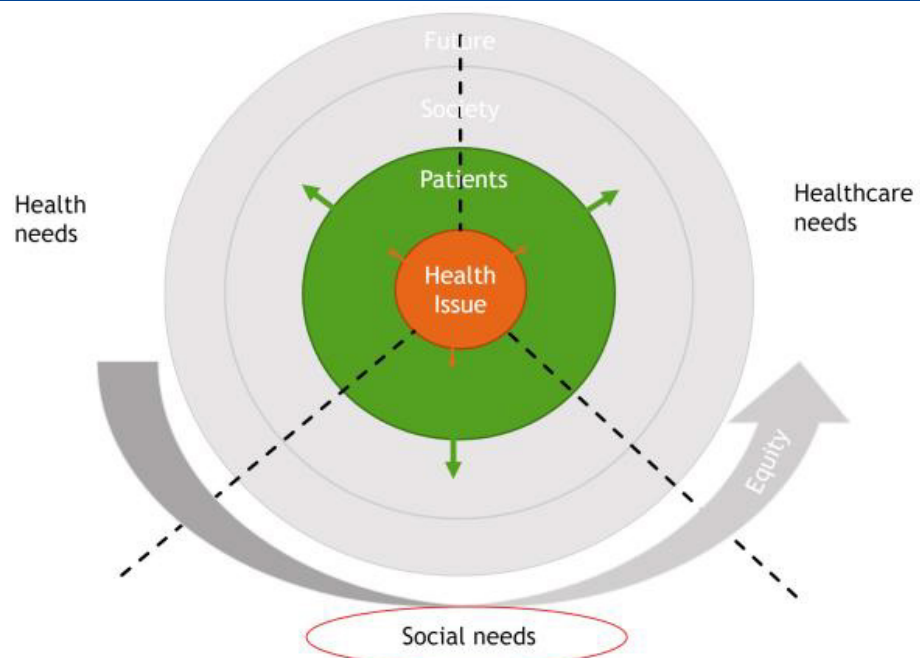
Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

open answer field

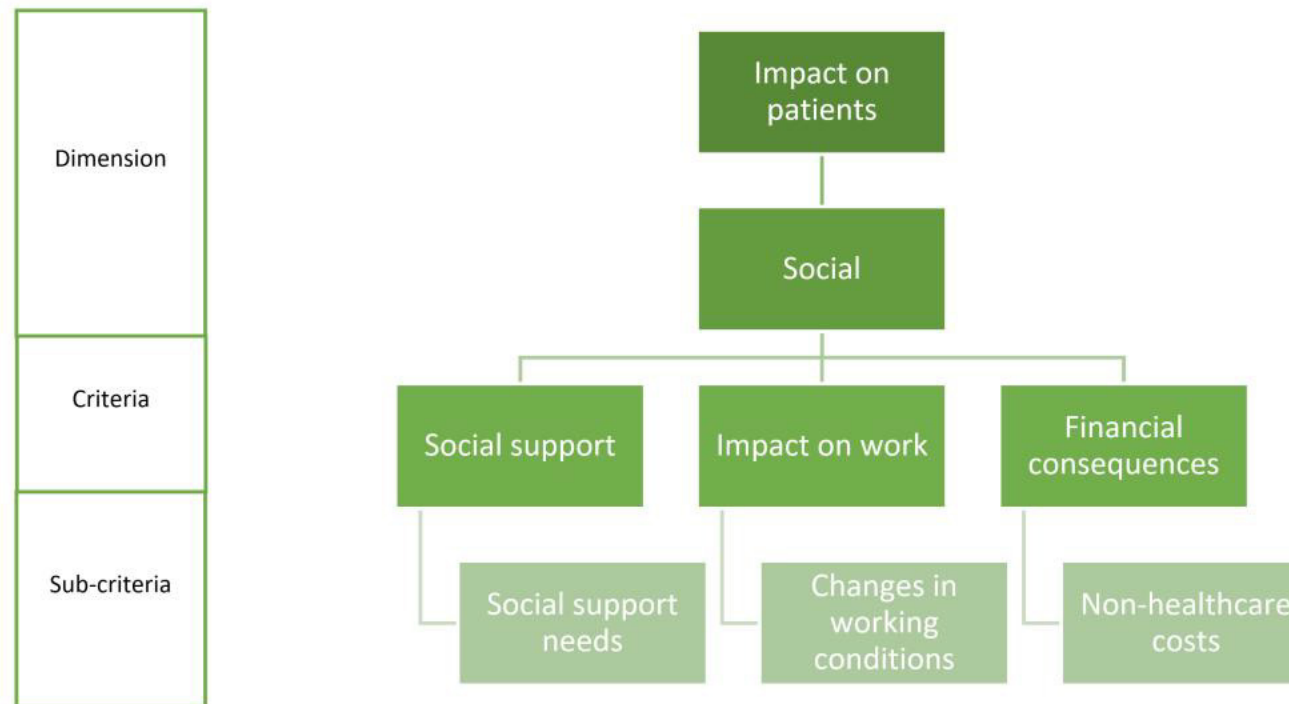
For most sub-criteria, a literature review is performed alongside the other methods (e.g. survey). Do you agree with this? If not, please specify why.

- ☐ Yes
- ☐ No (open answer field)
- ☐ I do not know

Thirdly, the focus is on the sub-criteria of the criteria used to measure **patient SOCIAL needs**:



For the following set of questions, we kindly invite you to take a look at the sub-criteria, layed out in the flowchart below:



Social support

The first criterion, within the dimension 'impact on patients, generating social needs' is Social support. The criterion 'social support' measures the needs related to social interactions with the community or family and building relationships.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to social support in the context of rare diseases?

- Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- No



- ☐ I do not know/ I am not competent to answer this question

Do you have any additional concerns or suggestions related to this criterion or sub-criterion in relation to rare diseases?

- ☐ Yes: (open answer field)
- ☐ no

In this table the sub-criterion of social support is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Social support							
Survey question	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

Impact on work

The second criterion, within the dimension 'impact on patients, generating social needs' is Impact on work. The criterion 'Impact on work' measures the impact of the health issue on patients' working conditions.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to impact on work in the context of rare diseases?

- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- ☐ No

- I do not know/ I am not competent to answer this question

Do you have any additional concerns or suggestions related to this criterion or sub-criterion in relation to rare diseases?

- Yes: (open answer field)
- no

In this table the sub-criterion of impact on work is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Changes in working conditions							
Survey question	○	○	○	○	○	○	○
Interview	○	○	○	○	○	○	○

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

Financial consequences

The third criterion, within the dimension 'impact on patients, generating social needs' is Financial consequences. The criterion 'Financial consequences' measures the additional costs for patients in accessing treatment and care for their health issue.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to financial consequences in the context of rare diseases?

- Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)



- ☐ No
- ☐ I do not know/ I am not competent to answer this question

Do you have any additional concerns or suggestions related to this criterion or sub-criterion in relation to rare diseases?

- ☐ Yes: (open answer field)
- ☐ no

In this table the sub-criterion of financial consequences is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Non-healthcare costs							
Interview	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

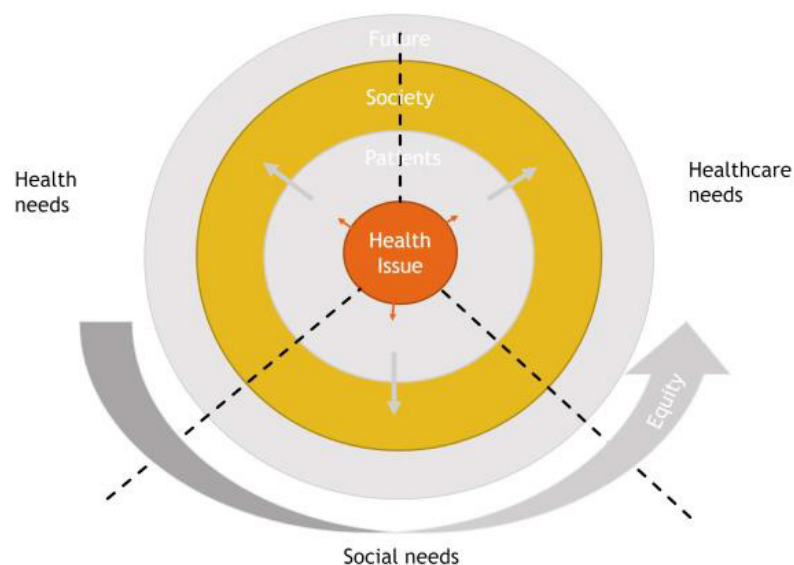
Open answer field

Do you have any other suggestions regarding certain **patient needs** criteria or **sub-criteria that should be added, removed or adapted** to make the framework fit for the assessment of needs in **rare diseases**?

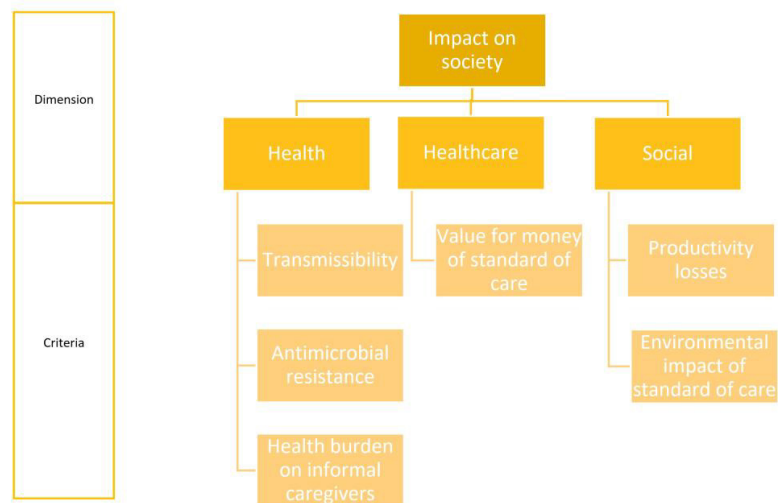
Open answer field

Part 2: considerations for the application of the NEED framework and its criteria in the context of rare diseases – IMPACT ON SOCIETY

Now, we will zoom in on the **second dimension** and its criteria: **impact on society**



The **criteria** used to measure the **impact of a health issue on society** are shown in the figure below:





We will now look further into the **subcriteria** associated with each criterion. We will first focus on the sub-criteria used to measure **societal HEALTH needs**.

Transmissibility

The first criterion, within the dimension 'impact on society, generating health needs' is Transmissibility. The criterion 'Transmissibility' measures the extent to which a health issue can be transmitted from one organism to another

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to transmissibility in the context of rare diseases?

- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- ☐ No
- ☐ I do not know/ I am not competent to answer

Do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- ☐ Yes: (open answer field)
- ☐ No

In this table, the sub-criterion of transmissibility is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Basic reproduction number							
Data from sciensano	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

Antimicrobial resistance

The second criterion, within the dimension 'impact on society, generating health needs' is Antimicrobial resistance. The criterion 'Antimicrobial resistance' measures the extent to which antibiotics and other antimicrobial medicines used to treat a health issue are ineffective or infections related to a health issue become increasingly difficult or impossible to treat due to drug resistance.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to antimicrobial resistance in the context of rare diseases?

- Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- No
- I do not know/ I am not competent to answer

Do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- Yes: (open answer field)
- No

In this table, the sub-criterion of transmissibility is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Existing antimicrobial resistance to treatments used							
Expert opinion	○	○	○	○	○	○	○
Volume of antibiotic delivered to treat the disease (proxy)							
The RIZIV-INAMI Pharmanet database	○	○	○	○	○	○	○

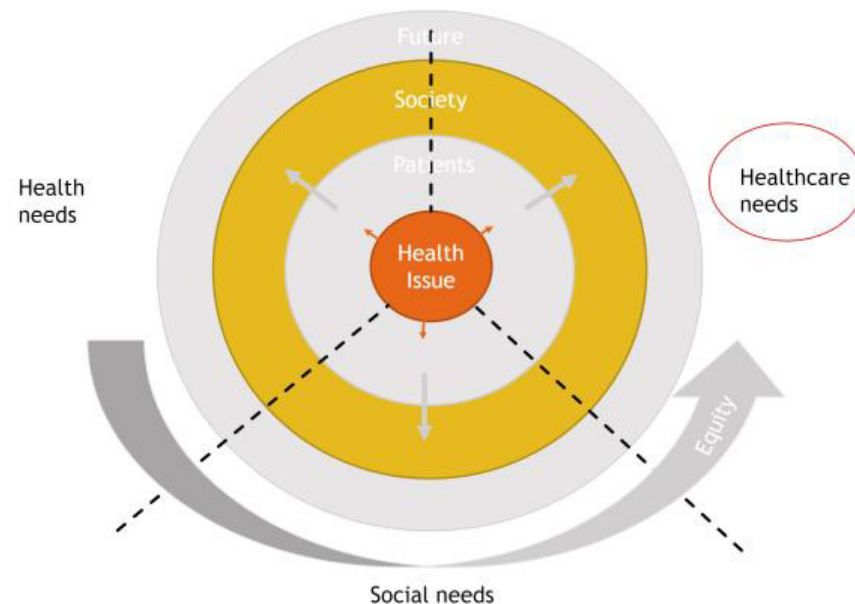
Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

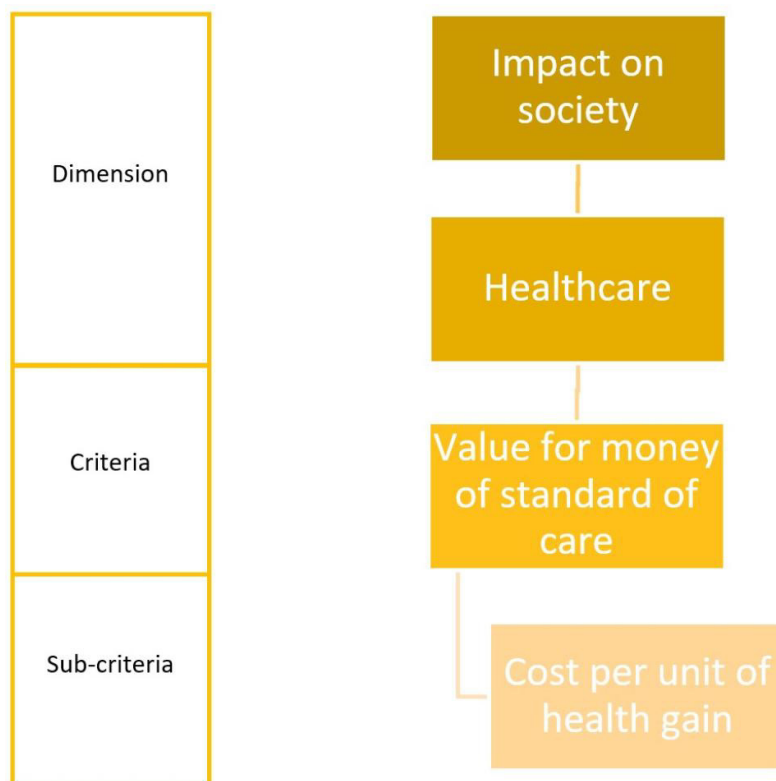
For most sub-criteria, a literature review is performed alongside the other methods (e.g. survey). Do you agree with this? If not, please specify why.

- ☐ Yes
- ☐ No: (open answer field)
- ☐ I do not know

Secondly, the focus is on the sub-criteria used to measure **societal HEALTHCARE needs**:



For the following set of questions, we kindly invite you to take a look at the sub-criteria, layed out in the flowchart below:

**Value for money of standard of care**

The only criterion, within the dimension 'impact on society, generating healthcare needs' is Value for money of standard of care. The criterion 'Value for money of standard of care' measures the health gain achieved for the level of healthcare spending associated with the standard of care for a health issue. It facilitates the identification of inefficiencies in the healthcare system.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to value for money of standard of care in the context of rare diseases?

- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- ☐ No
- ☐ I do not know/ I am not competent to answer

Do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- ☐ Yes: (open answer field)
- ☐ No

In this table, the sub-criterion of health burden is represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

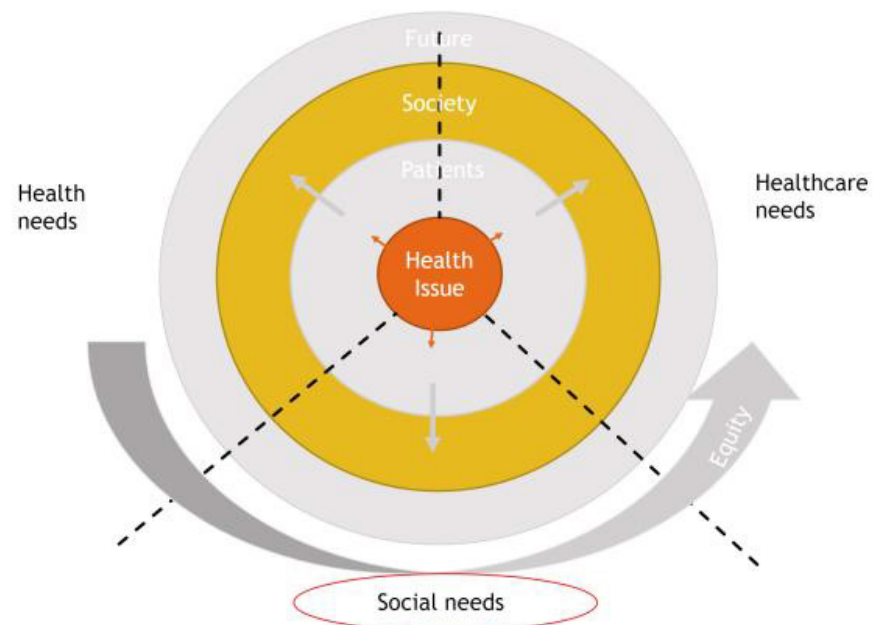
	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Healthcare costs per unit of health gain (disaggregated presentation of total healthcare expenditures and total health effects of standard of care)							
Different databases	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

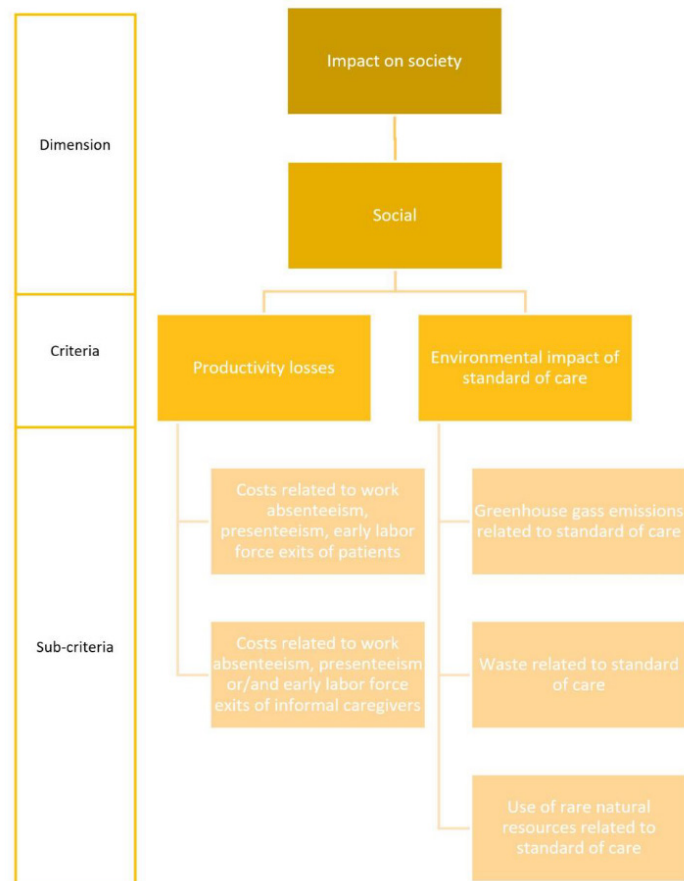
Open answer field



Thirdly, the focus is on the sub-criteria used to measure **SOCIAL needs of the society**:



For the following set of questions, we kindly invite you to take a look at the sub-criteria, layed out in the flowchart below:



Productivity losses

The first criterion, within the dimension 'impact on society, generating social needs' is Productivity losses. The criterion 'Productivity losses' measures the costs related to work absenteeism, presenteeism, early labor force exits of patients with the health issue and their caregivers.

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

Environmental impact of standard of care

The second criterion, within the dimension 'impact on society, generating social needs' is Environmental impact of standard of care. The criterion 'Environmental impact of standard of care' measures the impact of the management of a health issue on the natural environment.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to environmental impact of standard of care in the context of rare diseases?

- Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- No
- I do not know/ I am not competent to answer

Do you have any additional concerns or suggestions related to this criterion or sub-criteria in relation to rare diseases?

- Yes: (open answer field)
- No

In this table, the sub-criteria of environmental impact of standard of care are represented. Please indicate to what extent you agree with the proposed method being used to measure the sub-criterion.

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Greenhouse gas emissions related to the standard of care							
Literature review	○	○	○	○	○	○	○



Expert opinion	☐	☐	☐	☐	☐	☐	☐
Waste related to standard of care							
Literature review	☐	☐	☐	☐	☐	☐	☐
Expert opinion	☐	☐	☐	☐	☐	☐	☐
Use of rare natural resources related to standard of care							
Literature review	☐	☐	☐	☐	☐	☐	☐
Expert opinion	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

For most sub-criteria, a literature review is performed alongside the other methods (e.g. survey). Do you agree with this? If not, please specify why.

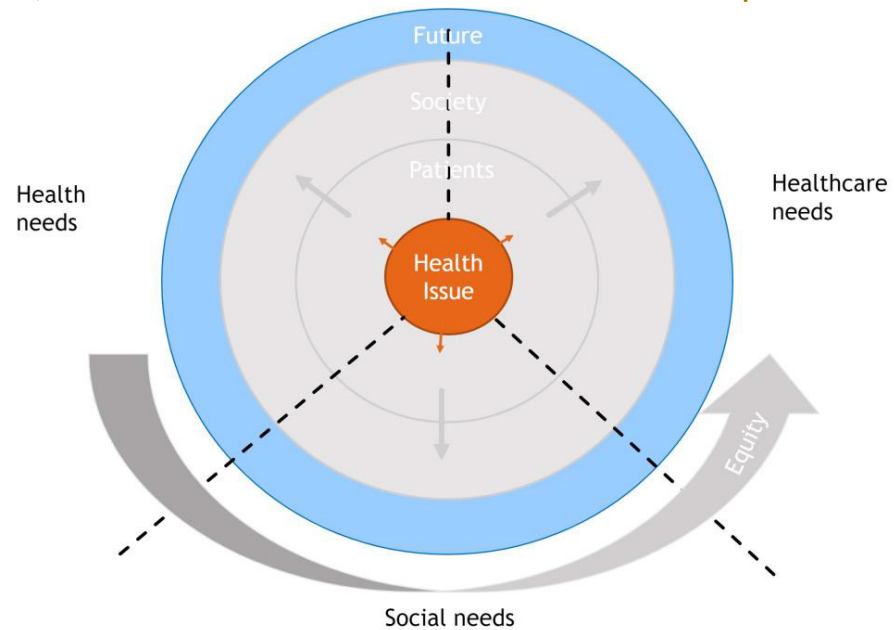
- ☐ Yes
- ☐ No: (open answer field)
- ☐ I do not know

Do you have any **other suggestions** regarding certain **social needs criteria** or **sub-criteria** that should be **added, removed or adapted** to make the framework fit for the assessment of needs in **rare diseases**?

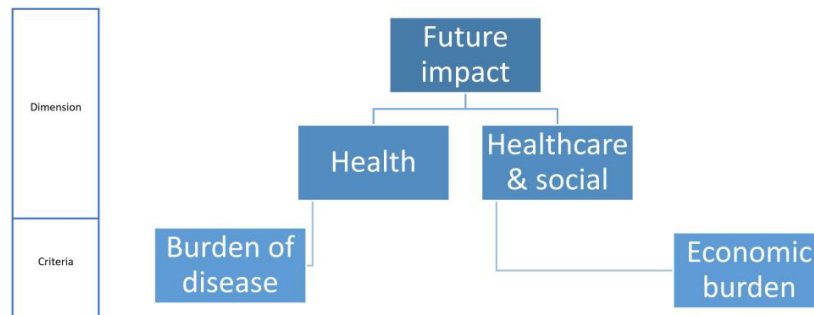
Open answer field

Part 2: Considerations for the application of the NEED framework and its criteria in the context of rare diseases – FUTURE IMPACT

Now, we will zoom in on the **third dimension** and its criteria: **future impact**



The criteria used to measure the **impact of a health issue on the future** are shown in the figure below:





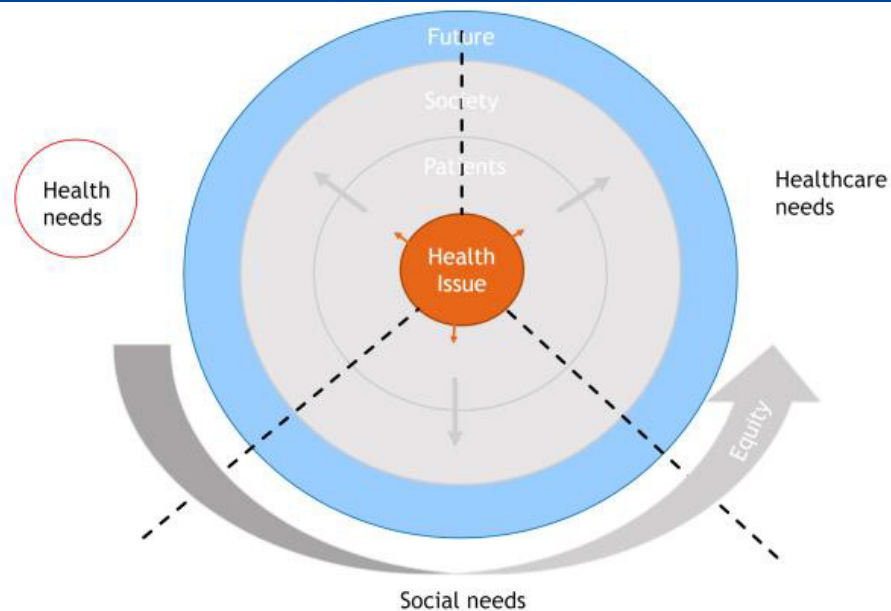
Do you have any comments related to the criteria of the dimension 'Future impact' in the context of rare diseases?

Open answer field

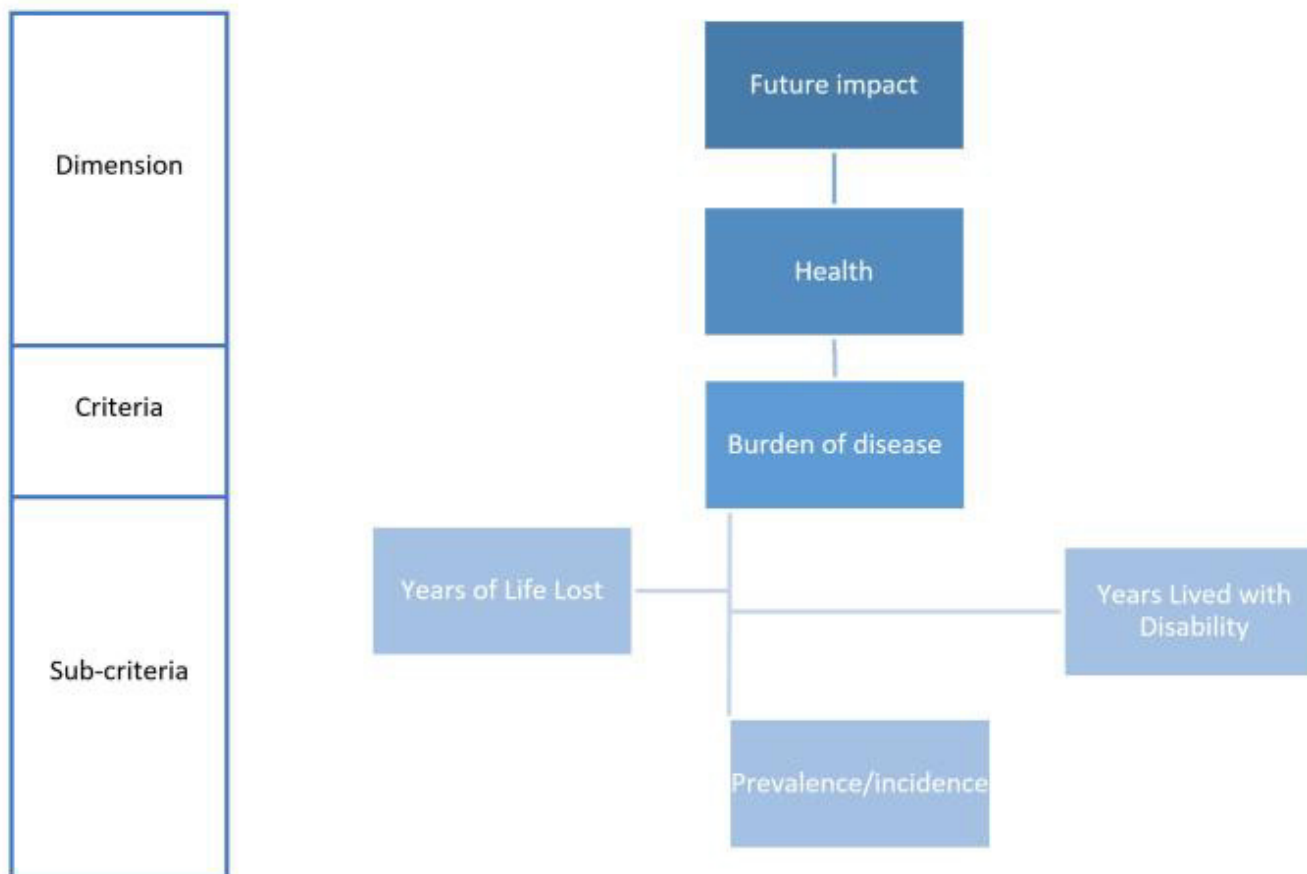
Do you believe that one or more criteria should be added, adapted or removed in the context of rare diseases?

- ☐ Yes, the criteria that should be added/adapted/removed and the reason why are the following: (open answer field)
- ☐ No
- ☐ I do not know/ I am not competent to answer this question

We will now look further into the **subcriteria** associated with each criterion. We will first focus on the sub-criteria used to measure **future HEALTH needs**.



For the following set of questions, we kindly invite you to take a look at the sub-criteria, layed out in the flowchart below:

**Burden of disease**

The only criterion, within the dimension 'future impact, generating health needs' is Burden of disease. The criterion 'Burden of disease' measures the future impact of a health issue on population's physical and psychological health.

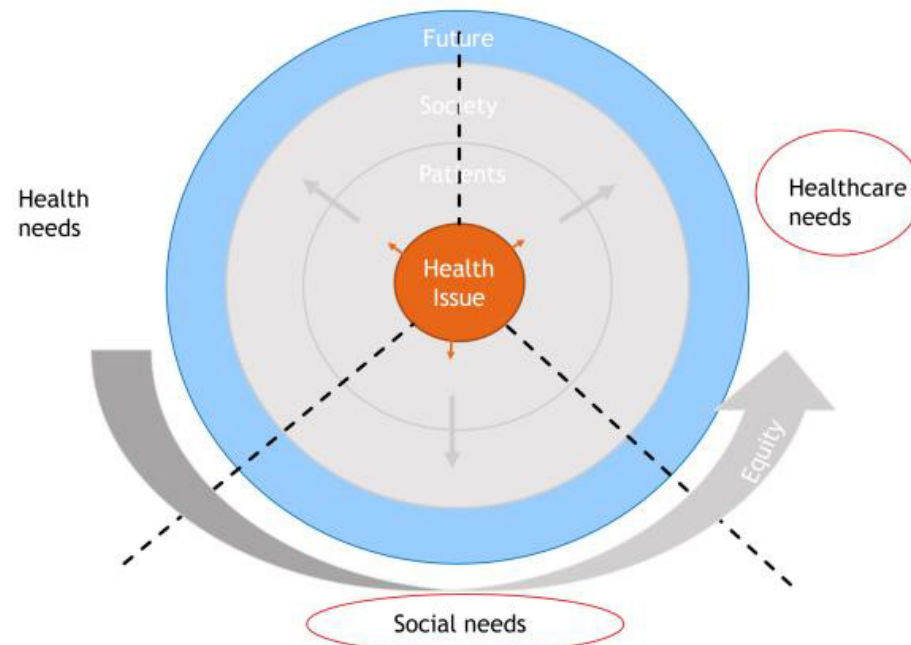
Do you have any suggestions, alternatives or challenges regarding the method(s) used to measure the sub-criteria that you want to share? (if you propose an alternative method, please provide also a reference)

Open answer field

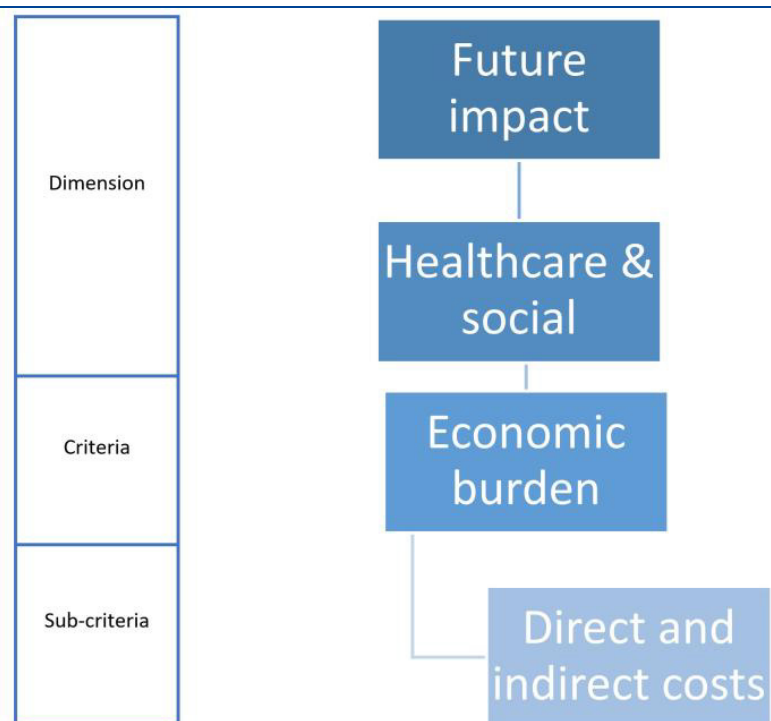
For most sub-criteria, a literature review is performed alongside the other methods (e.g. survey). Do you agree with this? If not, please specify why.

- ☐ Yes
- ☐ No: (open answer field)
- ☐ I do not know

Secondly, the focus is on the sub-criteria used to measure **future HEALTHCARE & SOCIAL needs**.



For the following set of questions, we kindly invite you to take a look at the sub-criteria, layed out in the flowchart below:

**Economic burden**

The only criterion, within the dimension 'Future impact, generating healthcare & social needs' is Economic burden. The criterion 'Economic burden' measures the future impact of a health issue on healthcare expenditures and on productivity, in monetary terms.

Do you believe that one or more sub-criteria should be added, adapted or removed to assess the needs related to economic burden in the context of rare diseases?

- ☐ Yes, the sub-criteria that should be added/adapted/removed and the reasons why are the following: (open answer field)
- ☐ No

- I do not know/ I am not competent to answer this question

Do you have any additional concerns or suggestions related to this criterion or sub-criterion in relation to rare diseases?

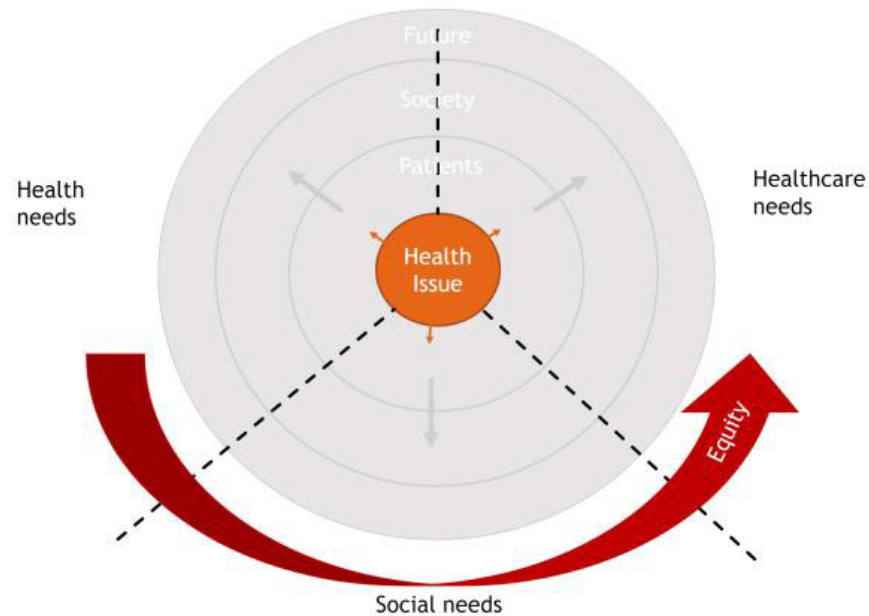
- Yes: (open answer field)
- No

Do you have any **other suggestions** regarding certain **future needs criteria** or **sub-criteria** that should be **added, removed or adapted** to make the framework fit for the assessment of needs in **rare diseases**?

Open answer field

Part 2: considerations for the application of the NEED framework and its criteria in the context of rare diseases – TRANSVERSAL

Across the 3 dimensions discussed before, there is also a **transversal criterion: equity**



**Transversal impact of a health issue on equity:**

A given health issue has an impact on equity from a patient and a society's perspective. Equity implies the absence of unfair and avoidable or remediable differences in health and healthcare among population groups defined socially, economically, demographically or geographically or by other dimensions of inequality.

When relevant, evidence for patient, societal or future needs criteria and sub-criteria will be presented by population subgroup.

In this table possible methods for measuring equity are listed. Please indicate to what extent you agree with the proposed method(s)

	Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree	I have insufficient knowledge
Equity							
Survey question	☐	☐	☐	☐	☐	☐	☐
Literature review	☐	☐	☐	☐	☐	☐	☐
Different databases	☐	☐	☐	☐	☐	☐	☐

Do you have any comments related to this transversal criterion or suggestions for other transversal criteria that need to be added to the framework in the context of rare diseases?

Open answer field

In case something is unclear, or you would like additional information, please feel free to contact Zilke Claessens (zilke.claessens@kuleuven.be)



Appendix 3.1.2. Workshop 2

Introduction

Dear participant,

Thank you for taking part in the **second stakeholder workshop** organised by the **Belgian Healthcare Knowledge Centre (KCE)** and **KU Leuven** regarding the NEED (Needs Examination, Evaluation and Dissemination) project: ***“Applicability of the NEED approach to assess patient and societal needs in patients suffering from rare diseases.”***

Your perspective and insights will help us refine the NEED assessment framework and adapt it to the context of rare diseases, in order to better identify and prioritize health conditions with likely high unmet needs. In order to do so, we need to **capture the diverse challenges and considerations related to rare disease** together with their impact on patients and society. Ultimately, identifying the highest unmet needs in the areas of prioritization may lead to better decision-making for these conditions, e.g., better research orientation, healthcare services organisation, and investment in research and development of treatment and technologies.

This survey aims to inform the **second stakeholder workshop** which will be held on **September 7th**.

The aim of this second workshop is **to understand your views on the 5-step implementation model for the evaluation of unmet needs proposed by the KCE** in the context of rare diseases (such as the [identification of priority topics](#) and the [prioritization of these topics](#)). The aim is also to **balance rare diseases against more common diseases** in the NEED approach.

The topic of ‘unmet patient and societal needs’ has been chosen as a priority area for the Belgian Presidency of the EU in 2024. Belgium aims to formulate Council conclusions by the end of its term. The findings of this research (including this survey and workshop) are intended to inform these council conclusions.

! Please note that the implementation model has recently been updated to include the evaluation of societal needs (7- to 5-step model) and that this survey contains the last available version.

Confidentiality of your data and informed consent

Confidentiality of the data

The data collected in this survey will be analysed and used to inform subsequent multistakeholder workshops. We present the aggregated data on the workshops in an anonymous way. However, we may contact you personally following the survey for further information.

This survey will take 10-15 minutes to complete.

Informed consent

To participate in this survey, you must provide your informed consent. Therefore, it is important that you understand and agree with the statements below.

- I have had the opportunity to read [the information sheet](#) of the study which aims to determine the applicability of the framework, i.e. the criteria and methods, to assess patient and societal needs in patients suffering from rare diseases;
- I have had the opportunity to ask questions or discuss any concerns regarding the information of this study;
- I was given sufficient time to decide whether I was willing to participate in this study;
- I am aware that participation in this study is completely voluntary;
- I am aware that this questionnaire has been prepared in collaboration with the Belgian Healthcare knowledge centre (KCE), as stated on the information sheet;
- I am aware that I can withdraw from this study at any time;



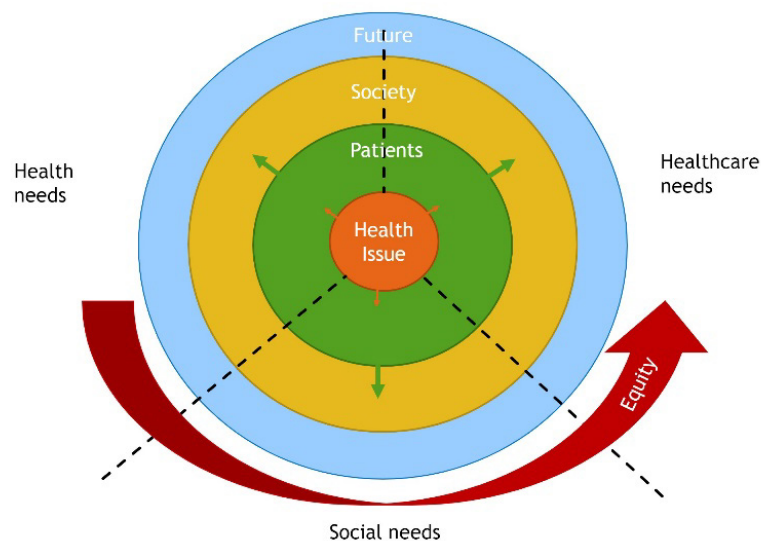
- I understand that the data resulting from this research will be kept for a maximum of 25 years after the end of the research;
- I understand that my data may be used for future research;
- I am aware that the results of this research will be published in scientific journals and disseminated through presentations at conferences or meetings. I understand that these results are based on the analysis of anonymous data and cannot identify me in any way.
- I understand that my data will be processed in accordance with the European General Data Protection Regulation (GDPR).

Do you agree with the above statement

- I agree to all the statements and confirm my participation
 - I do not agree to all the statements and do not confirm my participation
- ➔ Since you did not agree with the informed consent, it is not possible to participate in this study. However, we thank you for your interest.

Background information**1. What is the NEED assessment framework?**

The KCE NEED ('Needs Examination, Evaluation and Dissemination') project developed **conceptual approach called the NEED framework** (conceptual approach) to collect evidence for particular **health issues** or conditions on unmet health-related needs. Health-related needs can include "health needs", "healthcare needs", and "social needs" ("non-health(care) needs") (figure below). The evidence will be collected from three perspectives: patients, society, and **future generations**. The data will be summarised in a database accessible to all relevant stakeholders.

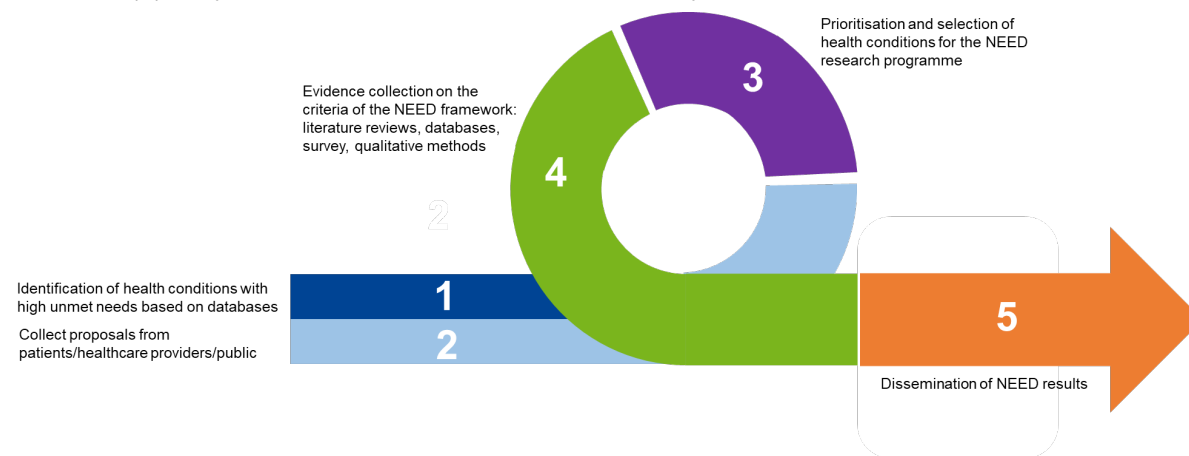


In the NEED framework, explicit **criteria** are used to collect evidence on the unmet needs related to a given health issue. These criteria are factors responsible for the burden of the health issue on patients as well as on the broader society, both in the present and in the future.

The NEED 5-step implementation model

Because it will be impossible to collect evidence for all health conditions at once, it will be necessary to identify and prioritize specific health conditions. Therefore, for the initial phase of the NEED project will involve a selection of topics based on a database search (step 1) and collection of proposals (step 2), followed by a prioritization process (step 3).

This 5-step implementation model is developed to (i) identify relevant topics (that is, diseases or health conditions that potentially have high unmet needs), (ii) select priority health conditions, (iii) apply the NEED assessment framework to identify unmet needs within each health condition, and (iv) disseminate the results.



2. What is asked of me?

This survey consists of the following 2 parts:

- PART 1: **background questions** about yourself such as your name and organization
- PART 2: questions regarding the 5- step **NEED implementation model**

3. What should I do if something is unclear, or if I would like additional information?

Please contact Zilke Claessens (zilke.claessens@kuleuven.be) if you are experiencing difficulties in completing the survey or would like any information regarding this survey.

Your answers are saved automatically by clicking on the blue arrow at the bottom of each page and submitted automatically when closing your browser.

Number	Question	Answer(s)	Remarks
General information			
Q 0.1	Name	Open answer field	Optional
Q 0.2	Organisation	Open answer field	Optional

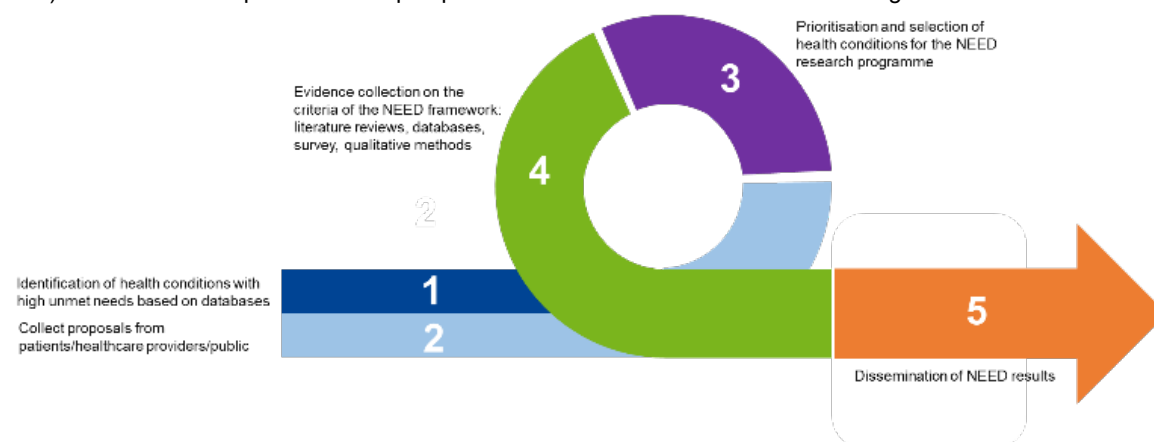


Q 0.3 Which stakeholder category do you belong to?

- Regulator
- Policy maker
- HTA body/ payer
- Pharmaceutical industry/ trade organisation
- Research organisation
- Healthcare professional
- Patient organisation
- Other (open answer field)

Your opinion regarding the proposed steps in the NEED 5-step implementation model

Please consider the figure below, which represents the process for how the KCE would like to organise the assessment of unmet needs in rare diseases. This implementation model contains 5 steps to identify patient, societal, and future needs and is the updated version of the previous 7-step model (published and explained in [KCE report 348](#) on page 170). The different steps of the 5-step implementation model are visualised in the figure below:



- **Step 1** involves the identification of health conditions with potential high unmet needs using existing databases.
- **Step 2** involves the call for proposals that will invite patients or patient organisations, healthcare providers, and the general public to highlight health conditions with potential high unmet needs.
- **Step 3** involves the prioritisation and selection of health conditions obtained from steps 1 and 2 for the NEED research program.
- **Step 4** involves the collection of evidence on the unmet needs criteria following the methods in the NEED assessment framework, such as literature reviews, database analysis, survey, and qualitative methods.
- **Step 5** involves the dissemination of the results on the NEED website and to the relevant stakeholders.

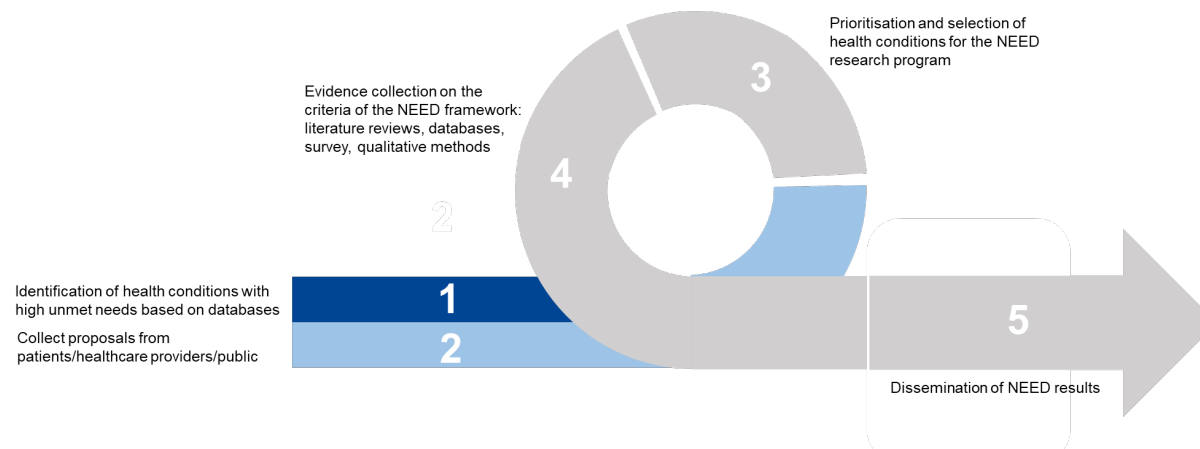
First, we will ask you about your general remarks regarding the model before to go more in detail over the different steps.

- Q 0.4 Do you have any general remarks regarding this 5-step implementation model and its applicability to rare diseases?
- Q 0.5 Do you think certain steps of this proposed process should be adapted or new ones added to make it applicable to the context of rare diseases?

- ☐ Yes; namely: [open answer field]
- ☐ No
- ☐ Yes; namely: [open answer field]
- ☐ No
- ☐ Don't know

Step 1: Identification of priority topics (i.e. health issues/conditions)

According to the 5-step implementation model, **Step 1** involves the identification of health conditions with potential high unmet needs using existing databases. In this step, **data from large databases** like the [Belgian Burden of Disease database](#) and the [Global Burden of Disease database](#) can be used. (KCE Report 348)



- Q 1.1 In general, how do you think priority topics with potential high unmet needs should be identified in rare diseases? [Open answer field] Optional
- Q 1.2 Do you believe that a combination of the proposed databases ([Belgian Burden of Disease database](#), the database from the [unmet medical needs program](#) and the [special solidarity fund](#) of the NIHD, [international horizon scanning initiative](#), and [the Global Burden of Disease database](#)) is a good data source to help identify priority topics for the NEED assessment in the context of rare diseases, besides the open call for proposals (step 2)?
- Q 1.3 What type of data/metrics are fit for the purpose of identifying/prioritizing rare diseases/conditions with potential high unmet health-related needs [open answer field]

- ☐ Yes
- ☐ No; please provide the reason [open answer field]
- ☐ Don't know



- | | | |
|-------|--|--|
| Q 1.4 | Do you believe that other rare disease-specific databases or sources should be used for the identification of priority topics? | <ul style="list-style-type: none">○ Yes; which existing databases or sources [open answer field]○ No○ Don't know |
|-------|--|--|

- | | | |
|-------|---|---------------------|
| Q 1.5 | Do you have any recommendations regarding the use of databases for the identification of priority topics in the context of rare diseases? | [open answer field] |
|-------|---|---------------------|

Step 2: call for proposals

In step 2, patients, patient organizations, healthcare professionals, and the general public can submit topic proposals (i.e. a topic referring to a rare disease or health condition).

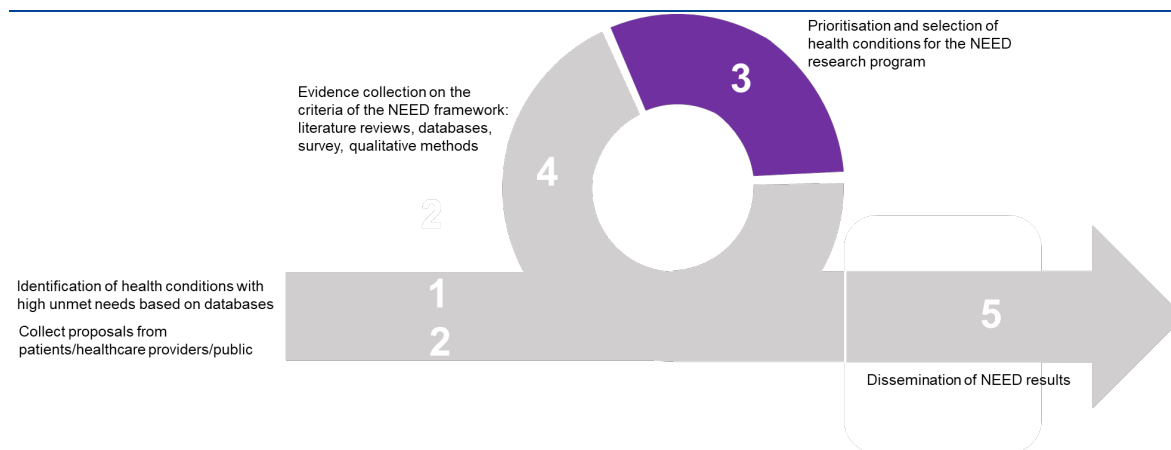
- | | | |
|-------|---|--|
| Q 2.1 | Do you believe that an open call for topics targeted towards patients, healthcare professionals, and the general public is a relevant methodology to identify priority topics with potential high unmet needs, in the context of rare diseases? | <ul style="list-style-type: none">○ Yes; because: [open answer field]
Are there any points of attention? [open answer field]○ No; why not? [open answer field]○ Don't know |
|-------|---|--|

- | | | |
|-------|---|---------------------|
| Q 2.2 | What is the minimal information that should be requested in the call for rare disease topic proposals to enable the prioritisation of topics with potentially high unmet needs (step 3) | [Open answer field] |
|-------|---|---------------------|

- | | | |
|-------|---|---|
| Q 2.3 | Should the information requested in the call for proposals be different for rare and common diseases? | <ul style="list-style-type: none">○ Yes; explain why and how the information must differ in your opinion: [open answer field]○ No; because: [open answer field]○ Don't know |
|-------|---|---|

Step 3: prioritization of topics with potentially high unmet needs

In step 3, priority topics will be selected, based on a set of pre-defined prioritisation criteria and an independent review of proposals (KCE Report 348).



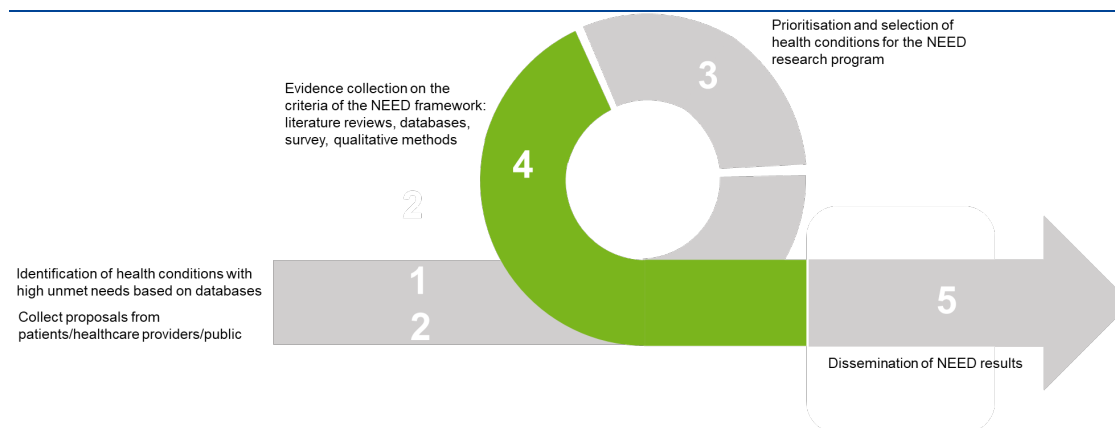
- Q 3.1 In your opinion, should priority topics for rare diseases be identified by means of [open answer field] the same procedures as for common diseases (i.e. based on explicit priority criteria) or should an alternative approach be taken?
- Q 3.2 Do you have other suggestions/remarks for the prioritisation of topics with high [open answer field] potential unmet needs in rare diseases?

Step 4: Evidence collection on the criteria of the NEED framework: literature reviews, databases, survey, qualitative methods

After the identification of topics (steps 1 and 2) and the prioritisation of topics (step 3), the KCE proposes **the 4th step**, which consists of the actual evidence collection on the health-related unmet needs for each selected health condition. The collection of unmet needs will follow the pre-defined criteria of the NEED framework.

The evidence collection performed in step 4 includes different methods that are criteria-specific (discussed in workshop 1):

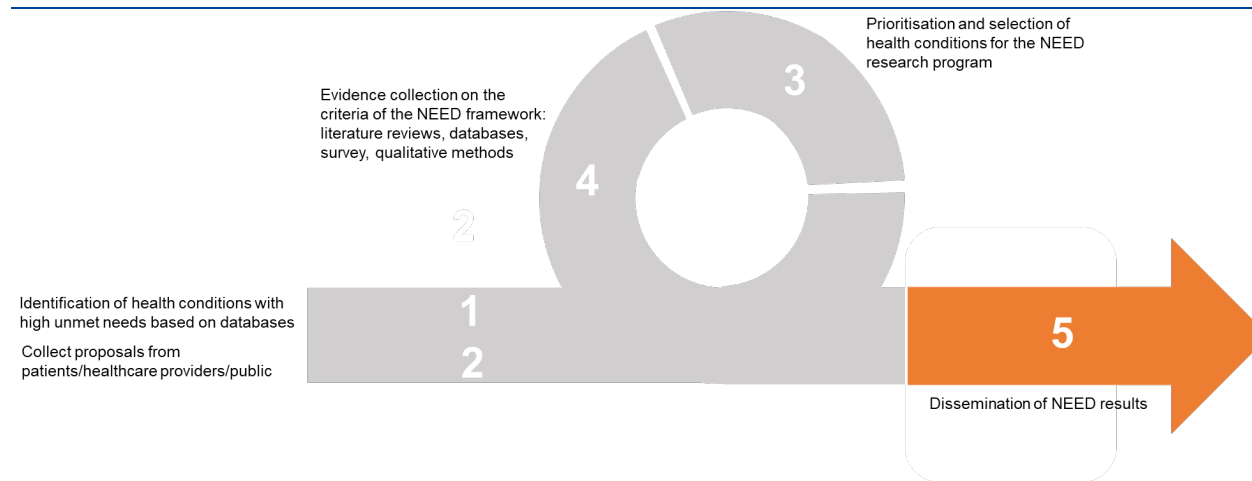
- **Literature reviews:** to (1) collect information to adapt the generic patient NEED survey and interview guide to the selected health condition and then (2) gather existing evidence on the unmet needs criteria.
- **Analysis of databases**
- **Implementation of adapted patient NEED survey** (developed by the KCE)
- **Implementation of a qualitative study:** among patients and experts, such as individual interviews and expert opinions



Q 4.1	Do you have any recommendations or alternative methods for the NEED survey in case the number of patients living with the rare disease is very low?	☐ Yes; I propose the following: [open answer field] ☐ No ☐ Don't know	
Q 4.2	Do you have any ethical concerns (e.g. anonymization) relating to the conduct of a survey among patients in the context of rare diseases?	☐ Yes; I have the following concern(s): [open answer field] ☐ No concerns specific to rare diseases ☐ Don't know	
Q 4.3	Do you have any other suggestions or remarks related to steps 4 of the implementation model?	[open answer field]	Optional

Step 5: dissemination of NEED results

The results of the NEED approach might be useful for diverse types of stakeholders, including but not limited to healthcare policymakers, RIZIV/INAMI, sickness funds, patient organisations, healthcare providers, the healthcare industry, research funding agencies, several regional organisations.



Q 5.1	In your opinion, which other decision-making processes regarding rare diseases might be informed by the results of the NEED assessment?	[open answer field]	Optional
Q 5.2	What suggestions, if any, do you have on the dissemination of the results of the NEED assessment to ensure visibility?	[open answer field]	Optional
Q 5.3	To which specific stakeholders or organizations do you think the evidence derived from the NEED assessment should become available?	[open answer field]	Optional
Q 5.4	How, if even, do you suggest to keep the NEED database up-to-date?	[open answer field]	Optional

*We thank you for your time spent taking this survey and look forward to the workshop on 07/09/2023. Your response has been recorded.
If you have questions or suggestions relating to the survey, workshop, or study, please contact us via zilke.claessens@kuleuven.be and we will get back to you as soon as possible.*



Appendix 3.2. WORKSHOP GUIDE

Appendix 3.2.1. Workshop 1

Questions	Sub-questions	Aim
Welcome and introduction		
1 General description of the NEED approach		To provide participants with a broad understanding of the research scope
2 Outline of the research objectives for workshop 1: <i>To assess the extent to which the NEED framework, along with its criteria and methods, is applicable to rare diseases</i>		To clarify the subject of this in-depth discussion
Dimension 1: Impact on patients – general		
3 With respect to this dimension, what is your opinion on the proposed criteria and sub- criteria?	• Why are the highlighted sub-criteria so important? • Why is it important to add the sub sub-criterion: prevention? • Why is it important to add the sub sub-criterion: impact on social life?	To obtain a general understanding of participants' perspectives regarding the overarching “ impact on patients ” dimension and its specific criteria and sub-criteria
Dimension 1: Impact on patients – criteria and sub-criteria related to HEALTH needs		
4 Do you have any recommendations on the sub-criteria included within this dimension?	• Why is it important to add the sub-criterion: fatigue or exhaustion? • Why is it important to add the sub-criterion: aesthetic concerns? • Do you think the sub-criterion “usual activities” should be removed? Why?	To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases
Dimension 1: Impact on patients – criteria and sub-criteria related to HEALTHCARE needs		

5 Do you have any recommendations on the sub-criteria included within this dimension?	- Why is it important to add the sub-criterion: existence of a treatment? - Why is it important to add the sub-criterion: treatment adherence? - Why is the criterion “patient experience with healthcare professionals” so important? - Why is it important to add the following sub-sub criteria: i) access to information, ii) access to diagnostic tests, iii) availability to disease experts? - Why is it important to add the follow sub sub-criteria: i) number of mis-diagnosed and ii) number of specialists visited?	To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases
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Dimension 1: impact on patients – criteria and sub-criteria related to SOCIAL needs

6 Do you have any recommendations on the sub-criteria included within this dimension?	- Why do you think the current criterion “impact on work” is to narrowly defined? - Why is it important to add the sub-criterion: re-integration after the disease?	To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases
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Dimension 2: Impact on society – general

7 With respect to this dimension, what is your opinion on the proposed criteria and sub- criteria?	- Why are the highlighted (!) sub-criteria so important? - Should the sub-criteria highlighted by a “?” be included within this domain? - Why is it important to add the sub-criterion: impact on patient organisations?	To obtain a general understanding of participants' perspectives regarding the overarching “ impact on society ” dimension and its specific criteria and sub-criteria
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- Why is it important to add the sub-criterion: **indirect costs for caregivers**?
- Why is it important to add the sub-criterion: **productivity gains**?

Dimension 2: Impact on society – criteria and sub-criteria related to HEALTH needs

- | | | | |
|---|---|---|--|
| 8 | Do you have any recommendations on the sub-criteria included within this dimension? | <ul style="list-style-type: none"> • What do you think of the criterion: transmissibility? • What do you think of the criterion: antimicrobial resistance? • Why is it important to add the sub-criterion: social impact on caregivers? | To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases |
|---|---|---|--|

Dimension 2: Impact on society – criteria and sub-criteria related to HEALTHCARE needs

- | | | |
|---|---|--|
| 9 | Do you have any recommendations on the sub-criteria included within this dimension? | To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases |
|---|---|--|

Dimension 2: Impact on society – criteria and sub-criteria related to SOCIAL needs

- | | | |
|----|---|--|
| 10 | Do you have any recommendations on the sub-criteria included within this dimension? | To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases |
|----|---|--|

Dimension 3: Impact on future generations – general

- | | | | |
|----|---|--|--|
| 11 | Do you have any recommendations on the sub-criteria included within this dimension? | <ul style="list-style-type: none"> • Why is it important to add the criterion: speed of innovation uptake? • Why is it important to add the criterion: impact on caregivers? | To assess the applicability of the criteria and sub-criteria within this dimension for rare diseases |
|----|---|--|--|

Methodological challenges

- | | | |
|----|---|---|
| 12 | Overview of the different databases that can be used to | To inform participants on the different databases and which database will be used to measure a certain criterion or sub-criterion |
|----|---|---|

identify rare health conditions with potential high unmet needs

- | | | |
|---|---|--|
| 13 What is your opinion on the use of databases in the context of rare diseases? | <ul style="list-style-type: none"> • What are or could be challenges related to this methodology? • What are or could be potential mitigation strategies? | To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases |
| 14 What is your opinion on the use of the BeBoD register in the context of rare diseases? | | To evaluate the adequacy of the BeBoD database to assess specific NEEDs criteria |

Methodological challenges – literature reviews

- | | | |
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| 15 Overview of the different criteria and sub-criteria that can be measured by conducting a literature review | | To inform participants on which criteria and sub-criteria can be measures by conducting a literature review |
| 16 What is your opinion on the use of literature reviews in the context of rare diseases? | <ul style="list-style-type: none"> • What are or could be challenges related to this methodology? • What are or could be potential mitigation strategies? | To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases |

Methodological challenges – qualitative methods

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| 17 Overview of the different criteria and sub-criteria that can be measured through qualitative methods | | To inform participants on which criteria and sub-criteria can be measures through qualitative research methods |
| 18 What is your opinion on the use of qualitative methods in the context of rare diseases? | <ul style="list-style-type: none"> • What are or could be challenges related to this methodology? • What are or could be potential mitigation strategies? | To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases |

Methodological challenges – surveys

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| 19 Overview of the different criteria and sub-criteria that can be measured through the NEED survey | To inform participants on which criteria and sub-criteria can be measures through qualitative research methods |
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20	What is your opinion on the use of qualitative methods in the context of rare diseases?	- What are or could be challenges related to this methodology? - What are or could be potential mitigation strategies?	To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases
21	What are possible actions that can be taken to "target the hard to reach" ?		To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases
22	What are possible actions that can be taken to generalize findings from a national to an international level ?		To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases
23	What is your opinion on the use of the EQ-5D in the context of rare diseases?	Are you aware of other questionnaires that are better suited to measure certain criteria or sub-criteria?	To evaluate the appropriateness of the proposed methods in the NEED framework to assess the NEEDs criteria in the context of rare diseases

Methodological challenges – multi methods

Overview of the different criteria and sub-criteria that can be measured using multiple methods

To inform participants on which criteria and sub-criteria can be measures using multiple methods

Closing remarks

Appendix 3.2.2. Workshop 2

Questions	Sub-questions	Aim
Welcome and introduction		
1	General description of the NEED approach	To provide participants with a broad understanding of the research scope
2	Recap of workshop 1: <i>NEED assessment framework and its</i>	To outline the scope and key findings from the previous workshop

applicability in the context of rare health conditions

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| 3 | Outline of the research objectives for workshop 2: <i>To evaluate the 5-step model for the identification of patients' needs as a whole and its applicability to rare diseases</i> | To clarify the subject of this in-depth discussion |
| 4 | Description of the 5-step model <ul style="list-style-type: none"> • Identification of health conditions with high unmet needs based on databases (step 1) • Open calls to collect proposals from patient organisations, HCPs* and the general public (step 2) • Prioritisation and selection of health conditions (step 3) • Evidence collection on the criteria of the NEED framework (step 4) • Dissemination of the NEED results (step 5) | To inform participants on the objectives of the individual phases within the NEEDs 5-step implementation model |

General remarks on the 5-step implementation model

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| 5 | Do you have any general remarks regarding this 5-step implementation model and its applicability to rare diseases? | To assess participants overall opinion on the 5-step model |
| 6 | Do you think certain steps of this proposed model should be adapted of added to make it applicable to the context of rare diseases? | To assess the applicability of the 5-step implementation model in the context of rare diseases |

Step 1: Identification of health conditions with high unmet needs based on databases

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| 7 | In general, how do you think priority topics with potential high unmet needs should be identified in rare diseases? | To identify methods that support the identification of rare health conditions |
| 8 | Do you have any recommendations regarding the use of databases for the identification of priority topics in the context of rare diseases? | To gather participants' perspectives regarding the potential (dis)advantages of using databases to identify rare health conditions |

Step 2: Open calls to collect proposals from patient organisations, HCPs and the general public



9	What is your opinion on the open call for topics to identify priority topics with potential high unmet needs, in the context of rare diseases?	Do you have any specific recommendations on how to perform the call for topics?	To gather participants' perspectives regarding the potential (dis)advantages of using open calls to identify rare health conditions
10	What platforms/channels do you suggest for the dissemination of the call for topics?		To identify platforms such that open calls can be broadly distributed
11	For common diseases, particular information items can be requested in the call for proposals, for instance the impact on quality of life, mortality, prevalence, inconveniences or availability of treatment?	What is the minimal information that should be requested in the call for rare disease topic proposals to enable the prioritization of topics?	To identify which information/topics should be requested in open calls
12	Should the information requested in the call for proposals be different for rare and common diseases?	How should information items differ in view of rare diseases?	To assess the differences in information requirements between common vs rare diseases
Step 3: Prioritisation and selection of health conditions for the NEED research program			
13	Outline of the KCE prioritisation process		
14	Should the prioritisation process be different or equal for common and rare health conditions?	- Why do you think that is important? - In what way do you think the prioritisation process must be different?	To assess whether common vs rare diseases require a different approach for prioritisation
15	Do you have any suggestions or remarks regarding the prioritisation criteria and its applicability in the context of rare diseases?		To assess the applicability of the current prioritisation criteria for rare diseases
Step 4: Evidence collection on the criteria of the NEED framework			
16	Do you have any recommendations or alternative methods for the NEED survey in case the number of patients living with the rare disease are very low?		To identify general recommendations on how to tackle the problem of low disease prevalence within the context of rare diseases
17	Do you have any recommendations or remarks on the proposal to broaden the data gathering to the European level in the context of rare health conditions?		To identify general recommendations on how to tackle the problem of low disease prevalence within the context of rare diseases



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| 18 | Do you have any ethical concerns relating to the conduct of a survey among patients in the context of rare diseases? | To identify general recommendations on how to tackle the problem of low disease prevalence within the context of rare diseases |
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Step 5: Dissemination of the NEED survey

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| 19 | What suggestions do you have on the dissemination of the results of the NEED assessment to ensure visibility? | To identify the future use and application of the results |
| 20 | Which other decision-making processes regarding rare diseases might be informed by the results of the NEED assessment? <ul style="list-style-type: none">• How can these processes be informed? | To identify the future use and application of the results |
| 21 | To which specific stakeholders or organisations do you think the evidence derived from the NEED assessment should become available | To identify the future use and application of the results |
| 22 | How do you suggest keeping the NEED database up to date? | To identify the future use and application of the results |

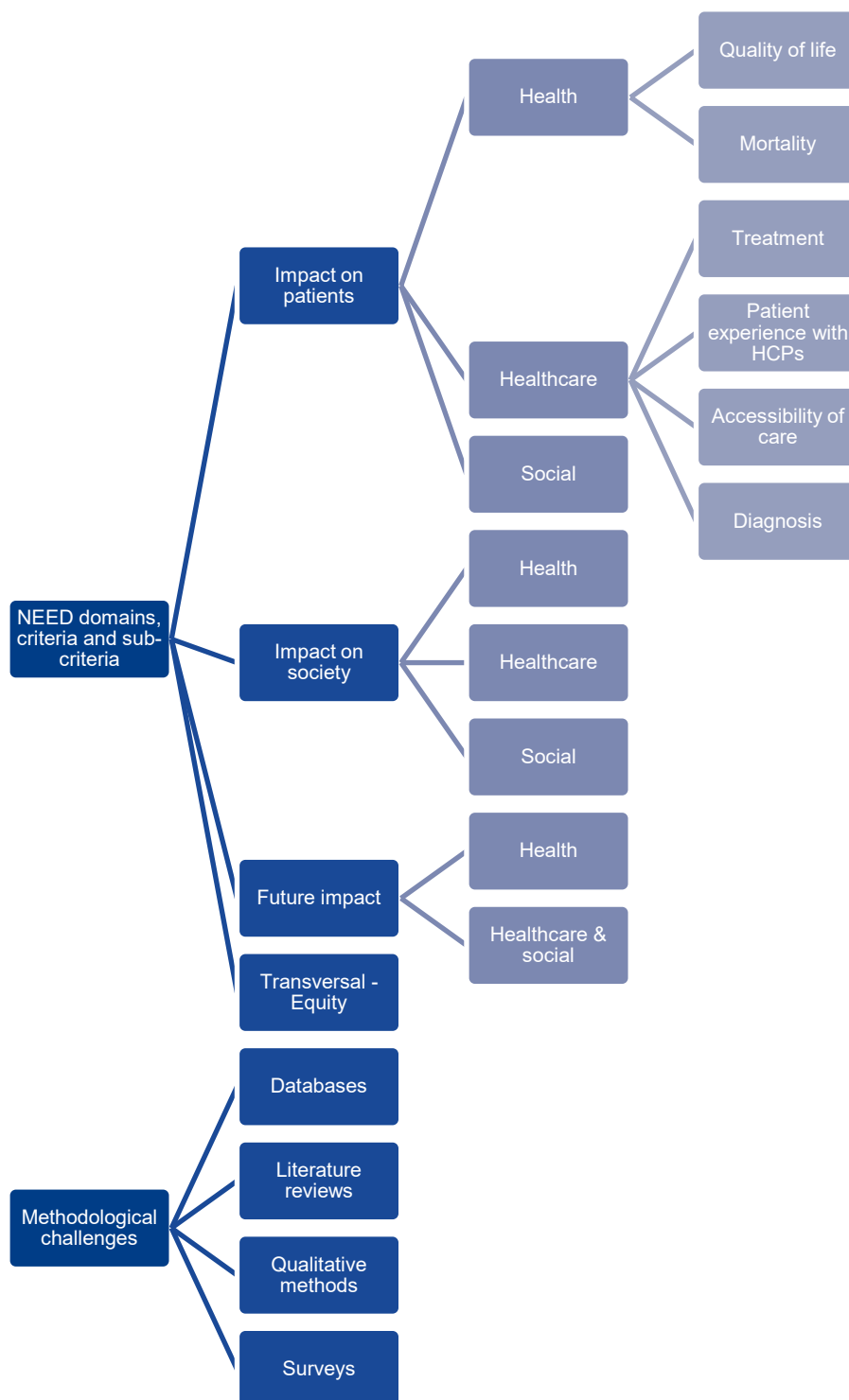
Closing remarks

**HCPs; healthcare professionals*



APPENDIX 3.3. CODE-TREE

APPENDIX 3.3.1 Stakeholder consultation 1



*Appendix 3.2.3. Stakeholder consultation 2*



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