Die Integration der Patientenperspektive im Bereich seltener Erkrankungen aus Sicht der Gesundheitsökonomie

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Für meine Familie

Zusammenfassung

Bemühungen zur Integration der Patientenperspektive im Gesundheitswesen haben in Anbetracht des Spannungsfeldes zwischen medizinischer Kompetenzhoheit und der Rolle des Betroffenen als Koproduzent seiner Gesundheit eine Vorgeschichte, die so alt erscheint, wie die Medizin selbst. Jüngst wird die Integration der Patientenperspektive in Deutschland dem Jahr 2003 zugeordnet, in dem zum ersten Mal Informations-, Aufklärungs- und Integrationspflichten gegenüber Patienten gesetzlich vorgegeben wurden. So unterstützt die politische Verankerung der Patientenintegration die Effektivität des Gesundheitssystems im Sinne einer patientenorientierten Versorgung. Der Begriff der seltenen Erkrankungen subsumiert eine Vielzahl an Erkrankungen. Ausschlaggebend ist hier das Kriterium der teils landesspezifisch definierten Prävalenz. In der Europäischen Union spricht man von einer seltenen Erkrankung ab weniger als fünf Betroffenen je 10.000 Einwohner. In Deutschland sind demnach circa vier Millionen Menschen betroffen. Diese leiden meist unter chronischen Leiden mit genetischem Ursprung und schwerwiegendem Verlauf, deren Symptome und alltägliche Herausforderungen je nach Subpopulation variieren. Aus diesen Gründen wurden politische Maßnahmen implementiert, wie beispielsweise der Deutsche Nationale Aktionsplan für Menschen mit Seltenen Erkrankungen oder gesonderte Zulassungsverfahren für medizinische Interventionen, mit dem Ziel, der Unterdeckung wissenschaftlich belegter Versorgungsbedarfe entgegen zu wirken. Neue Versorgungsstrukturen bergen die Chance unter Berücksichtigung knapper Ressourcen eine besonders bedarfsgerechte Versorgung mit Hilfe der Integration der Patientenperspektive zu entwerfen. Gerade hier gilt es die Berücksichtigung der Patientenperspektive sowie die Verwendung angemessener Methoden wissenschaftlich zu begleiten und zu unterstützen. Das Ziel der vorliegenden Arbeit ist daher, aktuelle Entwicklungen zu untersuchen und fundierte, praxisorientierte Methoden der direkten und systematischen Integration von Patientenperspektiven aus Sicht der Gesundheitsökonomie exemplarisch für den Bereich der seltenen Erkrankungen aufzuzeigen.

Diese kumulative Doktorarbeit umfasst neun Module. Modul 1 zeigt zunächst aktuelle Entwicklungen und methodische Alternativen der Integration der Patientenperspektive anhand des frühen Nutzenbewertungsverfahrens bei Arzneimitteln für seltene Erkrankungen. Im Anschluss werden Potentiale der Anwendung verschiedener Methoden der direkten und systematischen Integration der Patientenperspektive aus Sicht der drei gesundheitsökonomischen Ebenen, Mikro-, Meso- und Makroebene, vertiefend dargestellt. So zeigt Modul 2 zunächst auf Mikroebene die Bedeutung verschiedener Informationszugangswege für Betroffene seltener Erkrankungen und dass als erste Anlaufstelle die Internetinformation genutzt wird. Hier wird deutlich, dass die Berücksichtigung des in Modul 3 aufgezeigten Qualitätskriterienkata-

loges zur Einschätzung der Informationsqualität bei dürftiger Informationsbasis im Kontext seltener Erkrankungen als besonders relevant einzustufen ist. Im folgenden Schritt tritt die Interaktion mit dem Arzt in den Vordergrund. Mit Hilfe des Konzeptes der partizipativen Entscheidungsfindung können die durch Betroffene gesammelten Informationen im Versorgungskontext miteinfließen (Modul 4). Auf Mesoebene erweist sich das Analytic Hierarchy Process Konzept als besonders geeignet, um patientengetragene, transparente Entscheidungen im Versorgungskontext zu integrieren (Modul 5, 7). Bei der Wahl des Verfahrens ist insbesondere die Schwere der Krankheitslast zu berücksichtigen, da bei einem chronischen und schwerwiegenden Verlauf der seltenen Erkrankung die Zumutbarkeit des Verfahrens relevant ist (Modul 6). Auf Makroebene bestätigt sich am Beispiel eines Informationstelefons zu seltenen Erkrankungen der Nutzen qualitativer Verfahren zur Integration der Patientenperspektive bei der Konzeptionierung neuer Versorgungsstrukturen (Modul 8). Modul 9 zeigt wie quantitative Präferenzmessmethoden und qualitative Methoden ineinandergreifen können, um innovative Versorgungsstrukturen nahe am Bedarf der Betroffenen zu etablieren.

Zusammenfassend lässt sich somit feststellen, dass bei der Integration der Patientenperspektive im Bereich der seltenen Erkrankungen gerade Patientenpräferenzen sowie die Patientenzufriedenheit bereits jetzt deutlicher Berücksichtigung finden könnten. Forschungsbemühungen können den politischen Verankerungsprozess weiter unterstützen. Bei der Zusammenfassung aufgezeigter Methoden als Teil von Methodenkatalogen gilt es, auch auf weitere Erhebungsmöglichkeiten und deren Vor- und Nachteile zu achten sowie prävalenzabhängiger Empfehlungen für den sinnvollen und zielorientierten Einsatz im Bereich seltener Erkrankungen zu etablieren. Die indikationsübergreifende Aktualität der Thematik der Integration der Patientenperspektive zeigt sich bei der Entwicklung und Implementierung neuer Versorgungsstrukturen unter Berücksichtigung steigender Finanzierungsbedarfe unter der Prämisse konstanter Beitragssätze. Im Rahmen einer wissenschaftlichen Begleitung und gesundheitsökonomischen Evaluation scheint es demnach von höchster Relevanz stets zu hinterfragen, ob die zielgerichtete Versorgungsstrukturausrichtung am Bedarf, der direkt am Patienten erhobenen wird, die Chance birgt, das Gesundheitssystem noch effizienter zu gestalten.

Schlagwörter: *Patientenperspektive; Seltene Erkrankungen; Gesundheitsökonomie; Versorgungsforschung;*

Abstract

Efforts to integrate patient perspectives into health care have a long history, seemingly as old as medicine itself, and include striking a balance between medical sovereignty and patients as co-producers of their own health. In Germany, a law was passed in 2003, requiring for the first time the integration of patient perspectives, including patient information, medical enlightenment and integration requirements. In this regard, the political anchorage of integrating the patient's perspective seeks to endorse the affectivity of health care systems in the sense of patient-centred care. The terminology of rare diseases summarizes a variety of diseases. The decisive criterion is the prevalence rate, partly defined at a country level according to a set prevalence standard. In the European Union, a disease is defined as rare when it affects less than five in 10,000 people. Therefore, in Germany, approximately four million people are affected by a rare disease. Those affected predominately suffer from chronic and severe diseases with a genetic origin, whose symptoms and daily challenges vary depending on the subpopulation. Thus, policy measures have been implemented; for example, the German National Action Plan for Rare Diseases, or specific approval procedures for medical interventions, which aim to counteract the deficit in scientifically revealed health care service needs. For this very reason, new health care structures provide the opportunity to conceptualize a particularly needs-oriented health care system with the help of patient integration. As such, the integration of patient perspectives and the utilization of appropriate methods need to be scientifically monitored and endorsed. Therefore, the aim of the underlying thesis is to examine recent developments and to point out profound, practice-oriented methods for the direct and systematic integration of patient perspectives from the perspective of health economics exemplary in the field of rare diseases.

This cumulative doctoral thesis comprises nine modules. Module 1 highlights the recent developments and methodological alternatives regarding the integration of patient perspectives based on the example of the early benefit assessment process for pharmaceuticals used in the treatment of rare diseases. Further, the potential of different methodologies for the direct and systematic integration of patient perspectives are outlined in-depth from the standpoint of the three health economic levels, micro, meso, and macro level. In this regard, Module 2 presents the different information-access points for people affected by rare diseases, with information from the Internet as the first point of contact. It is at this point that the rendered quality criteria catalogue for the assessment of information quality, presented in Module 3, proves to be of particular relevance in the context of rare diseases. In the next step interactions with physicians come to the fore. With the help of the shared decision-making concept, the information collected from patients can be fed into the context of health care services (Module 4). At a

meso level, the concept of the analytic hierarchy process shows to be particularly suitable for the direct integration of patient-supported transparent decisions (Modules 5, 7). When choosing a methodology, it is of particular importance to consider the severity of the disease, as in the case of a chronic and severe course of the rare disease the reasonableness of the approach is of relevance (Module 6). At a macro level, the example of a helpline for rare diseases validates the benefits of qualitative methods for the integration of patient perspectives into the development of innovative health care concepts (Module 8). Module 9 demonstrates how quantitative preference measurement methods and qualitative methodologies can engage with each other to establish innovative health care structures that are close to the needs of patients.

In conclusion, it can be determined, that patient preferences and patient satisfaction as part of the integration of patient perspectives within the field of rare diseases could be integrated already clearer. Comprising the shown methods during the development of best practice handbooks, further survey methods and their pros and cons shall be examined, as well as prevalence-related recommendations for reasonable and targeted application in the field of rare diseases. The actuality of the topic indications of patient perspectives integration across various indications can be observed in the development of innovative health care structures, such as for example the latest online health coaches or health apps, while also considering the increasing financial requirements under the premise of retaining constant health insurance contribution rates. Within the scope of scientific monitoring and health economic evaluation, it therefore seems to be of highest relevance to always challenge whether the targeted health care structure alignment with the needs directly expressed by patients bears the chance to organize the health care system even more efficiently.

Key words: *Patient Perspective; Rare Diseases; Health Economics; Health Services Research;*

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1 Motivation und Zielsetzung

Ursprung und Entwicklung des Forschungsfeldes

Die Integration von Patientenperspektiven lässt sich mit dem Ursprung des Forschungsfelds der Patientenermächtigung (engl. patient empowerment) in der Geschichte der Medizin weit zurückverfolgen. Dieses ist auf die historisch gewachsene Hypothese zurückzuführen, dass das Kräfteverhältnis in der Medizin zwischen Arzt und Patient ein unausgewogenes sei. Zunächst gilt der Arzt wie im antiken Ägypten (4.000 bis 1.000 vor Christus) als Heiler, dessen Fähigkeiten unerklärlich erscheinen, woraus eine starke Dominanz gegenüber dem Patienten begründet wird. Im antiken Griechenland (600 bis 100 vor Christus), im Zeitalter des Hippokratischen Eids, geht man von einer Angleichung der Kräfteverhältnisse aus [1]. Die anschließende Paternalisierung innerhalb der Medizin wird auf eine Überinterpretation der im Eid hinterlegten Schutzbefohlenheit im Sinne der kleinkindlichen Bevormundung zurückgeführt [2]. So gilt es lange Zeit als fraglich, ob eine Aufklärung von Patienten überhaupt zweckmäßig ist. Erst im Anschluss an die Nürnberger Prozesse in den 1960er Jahren findet der Begriff des „informierten Einverständnisses“ Einzug und in diesem Sinne die informierte Entscheidungsfindung. Heute ist es Teil der ärztlichen Berufsordnung, dass Patienten zu ihren Behandlungsmöglichkeiten aufgeklärt werden müssen [3]. In den USA gibt die amerikanische Krankenhausgesellschaft der 1970er die „Patient Bill of Rights“ heraus [4]. In den 1980er Jahren folgt der Phase der medizinischen Innovationen eine Phase der Rechtstreitigkeiten zu den Folgen unerwünschter Wirkungen. In Folge dessen verabschiedet die Europäische Wirtschaftsgemeinschaft im Jahre 1965 die Richtlinie 65/65/EWG zur Angleichung der Rechts- und Verwaltungsvorschriften über Arzneispezialitäten im Sinne der Stärkung der Patientenposition. Nun müssen für Arzneimittel zum ersten Mal vor der Einführung Zulassungen inklusive eines Nachweises zur therapeutischen Wirksamkeit vorliegen [5]. In Deutschland findet die Umsetzung erst mit dem Arzneimittelgesetz (1976) und der Einführung eines Instituts für Arzneimittelzulassungen (1975) innerhalb des Bundesgesundheitsamts statt [6]. Hiermit ist die Grundlage für die Berücksichtigung patientenrelevanter Endpunkte bei der Bewertung medizinischer Interventionen gelegt. In den 1990er Jahren schließlich, verknüpfen sich die Forschungsfelder des „Informed Consent“ und „Shared-Decision Making“ im Sinne der partizipativen Entscheidungsfindung und werden zunächst in den USA verortet [7]. Mit dem Gesetz zur Modernisierung der gesetzlichen Krankenversicherung (GKV-Modernisierungsgesetz - GMG) [8] wird nicht nur eine ordnungspolitische Öffnung des Gesundheitssystems initiiert,

sondern auch Patientenbeauftragte installiert, erstmals ein Patientenbeauftragter der Regierung benannt und die Beteiligung von Patienten in Form von Patientenvertretern im Gemeinsamen Bundesauschuss ermöglicht [9]. Mit dem Patientenrechtsgesetz (2013) [10] wird in einem weiteren Schritt die Beteiligung von Patienten in der Selbstverwaltung und insbesondere im Arzt-Patienten-Verhältnis auf Mikroebene gestärkt. In diesem Sinne wurde auch in Deutschland der Einzug der Patientenpartizipation verankert. Im Wettbewerb versuchen „Gesundheitsunternehmen" verstärkt Patienten und Betroffene für sich zu gewinnen, weshalb nun auch der Begriff der Patientenzufriedenheit zusehends an Bedeutung gewinnt. Aus unternehmerischer Sicht sind Patienten und Betroffene die letztendlichen Endnutzer von medizinischen Technologien und können zum Verständnis der tatsächlichen Belastungen von Krankheit sowie dem tatsächlich empfundenen Mehrwert, der in diesem Kontext angewandten Verfahren oder Prozesse beitragen [11]. Diese Entwicklungen werden durch die zunehmende Bereitstellung laienorientierter bzw. leicht zugänglicher medizinischer Informationen noch weiter unterstützt. Forschungsergebnisse untermauern den initiierten Trend und zeigen, dass die zunehmende Einbindung von Patienten bzw. Betroffenen zu einer Verbesserung medizinischer Endpunkte sowie zu einer Erhöhung der Zufriedenheit mit dem Gesundheitssystem führen können [12]. So kann bereits in der Basisversorgung aufgezeigt werden, welche Aspekte der Versorgung für Betroffene wichtig sind [13]. Entsprechend dreht sich die gesundheitsökonomische Diskussion um die methodisch fundierte und zusehends direkte Einbindung von Patienten bei der Entwicklung von medizinischen Leistungen. So ist ein Beispiel der aktuellen gesundheitsökonomischen Diskussion die Berücksichtigung von Patientenpräferenzen bei der Kosten-Nutzen Bewertung [14, 15, 16].

Folglich zeigt sich die Integration der Patientenperspektive in der Gesundheitsökonomie insgesamt als ein weit zurückreichendes und breit gespanntes Forschungsfeld, welchem aufgrund neuster gesundheitspolitischer und gesundheitsökonomischer Entwicklungen gerade aktuell eine besondere Bedeutung beigemessen werden muss.

Der Kontext der seltenen Erkrankungen

Schätzungsweise leiden rund 4 Millionen Menschen in Deutschland an seltenen Erkrankungen. Weltweit sind circa 350 Millionen Menschen betroffen, darunter 29 Millionen Europäer. In Europa gilt eine Erkrankung ab einer Prävalenz von weniger als 5 Betroffenen je 10.000 Einwohner als selten [16]. Im internationalen Kontext variieren die Definitionen teilweise landesspezifisch. Aufgrund der Seltenheit und damit einhergehenden Besonderheit der Er-

krankungen im Versorgungsalltag werden sie im umgangssprachlichen Medizinjargon auch als „Kolibri-Erkrankungen“ bezeichnet. Zwischen 5.000 und 8.000 teils sehr heterogene Erkrankungen fallen unter diesen Begriff. Circa 80% der Erkrankungen sind genetischen Ursprungs. Ein klassisches Symptomprofil lässt sich nicht ableiten. Vielmehr zeigt sich die Heterogenität der unter dem Oberbegriff der seltenen Erkrankungen definitorisch zusammengefassten Krankheitsbilder. Oftmals treten bereits im Kindesalter die ersten Symptome auf. So eint diese Betroffenengruppe ein gemeinsames Profil an Herausforderungen. Diese gehen einher mit einer geringen prognostizierten Lebenserwartung, einer weitreichenden Beeinträchtigung der Lebensqualität, geringer wissenschaftlicher Evidenz, einem geringen allgemeinen Informationsstand, wenigen - teils weit entfernten - spezialisierten medizinischen Leistungserbringern und Zentren sowie mangelnden Therapieoptionen [18]. Dennoch kann ein vorschnelles „über einen Kamm scheren“ aller Krankheiten den Bedürfnissen der seltenen insbesondere auch der sehr seltenen Erkrankungen entgegenwirken. In diesem Sinne ist es auch hier im Bereich der seltenen Erkrankungen wichtig auf die Integration der Patientenperspektive zu achten.

Bisherigen Maßnahmen und Forschungsbedarf

Im Jahre 2014 haben das Bundesministerium für Gesundheit, das Bundesministerium für Bildung und Forschung und die Allianz Chronischer Seltener Erkrankungen (ACHSE) gemeinsam den Nationalen Aktionsplan für Menschen mit seltenen Erkrankungen auf den Weg gebracht [19]. Dieser basiert auf einem zuvor publizierten Forschungsbericht, welcher im Auftrag des Bundesministeriums für Gesundheit durch die Forschungsstelle für Gesundheitsökonomie der Leibniz Universität Hannover erstellt wurde. Dieser befasst sich umfassend mit den Herausforderungen, dem resultierenden Versorgungsbedarf sowie abgeleiteten Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit seltenen Erkrankungen in Deutschland [18]. Im Rahmen des Forschungsberichtes wird darauf hingewiesen, dass die Beteiligung der Patientenperspektive ein wichtiger Bestandteil der Etablierung neuer Versorgungsstrukturen ist. So zeigt „Kapitel 3.6 Handlungsfeld Patientenorientierung“ die Integration von Patientenperspektiven auf indirektem Wege über Selbsthilfeorganisationen hin [19]. Der Schlussbericht zur Evaluation der Umsetzung des Nationalen Aktionsplans weist auf das divergierende Verständnis der Integration der Patientenperspektive bei der Umsetzung von Maßnahmen des Aktionsplans hin. Ähnlich wie auch auf gesundheitspolitischer Ebene wurde dies zunächst als Einbezug der Selbsthilfe interpretiert. Aus diesem Grund wird auf das große Potential des direkten Einbezuges von Patienten und deren Angehörige verwiesen, da diese

zur eigenen seltenen Erkrankung einen großen Erfahrungs- und Wissensschatz angesammelt haben. Hieraus ergibt sich auch der Vorschlag der Entwicklung eines Good Practice Guides mit Positivbeispielen [20].

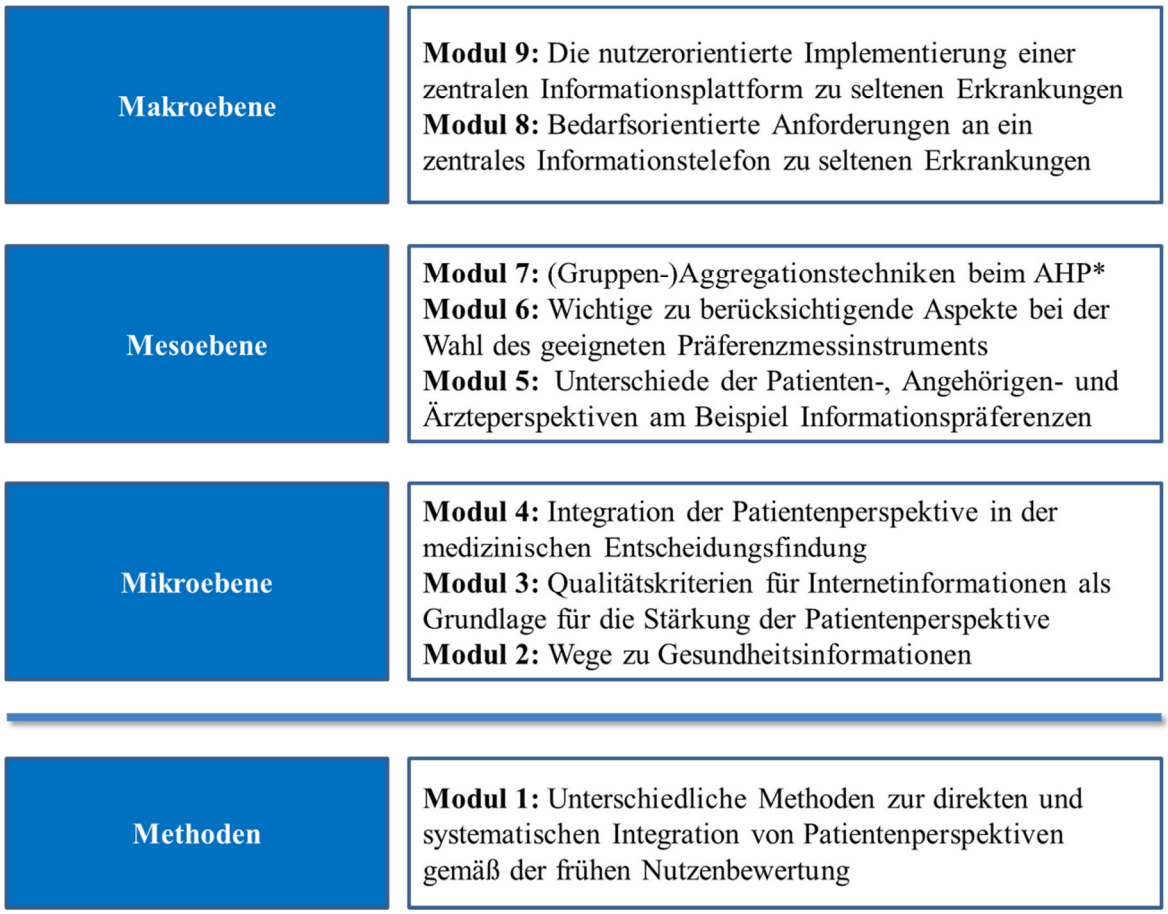

Abbildung 1 Übersicht der Module der kumulativen Doktorarbeit gemäß der Kernaspekte der einzelnen Publikationen (*AHP: Analytic Hierarchy Process)

In diesem Sinne zeigt die vorliegende kumulative Doktorarbeit verschiedene Beispiele der direkten Integration der Patientenperspektive aus gesundheitsökonomischer Sicht. Es können verschiedene Methoden der Integration von Patientenperspektiven differenziert werden. Beispielsweise können Betroffene als Teil von Komitees aktiv an den Entscheidungsprozessen von gesundheitsökonomischen Bewertungsinstituten mitwirken. Auch Patienten und Patientenvertreter werden vielerorts dazu eingeladen, Stellungnahmen abzugeben. Insbesondere die Entwicklung direkter und systematischer Verfahren der Patientenintegration bedarf einer wissenschaftlichen Begleitung. Qualitative und quantitative Verfahren können ergänzend ineinander greifen, um ganzheitliche Entscheidungen zu unterstützen, die sowohl auf Mikro- als auch auf Makroeben tragbar sind. Eine Übersicht verschiedener methodisch fundierter direkter Integrationsmöglichkeiten zeigt das Beispiel der frühen Nutzenbewertung im Bereich der

seltenen Erkrankungen (siehe Kapitel 2.1, Aktuelle methodische Entwicklungen). Mit ihr können Patienten bzw. Betroffene aus gesundheitsökonomischer Sicht auf verschiedenen Ebenen des Gesundheitssystems als Experten ihrer eigenen Gesundheit in die gesundheitsökonomische Entscheidungsfindung einbezogen werden. Auf mikroökonomischer Ebene im Kontakt mit Leistungserbringern wie Ärzten, bzw. unter Einbezug anderer Informationsquellen, können Patienten beispielsweise im Rahmen eines gemeinsamen und informierten Entscheidungsfindungsprozesses (siehe Kapitel 2.2, Die Integration der Patientenperspektive auf Mikroebene) einbezogen werden. Auf Mesoebene bringen sich Institutionen ein, welche Empfehlungen zur Implementierung von Gesundheitsleistungen abgeben. Beispielhaft kann die Implementierung eines webbasierten Gesundheitsportals für seltene Erkrankungen genannt werden (siehe Kapitel 2.3, Die Integration der Patientenperspektive auf Mesoebene). Hieraus lassen sich wiederum Handlungsbedarfe für die gesundheitsökonomische Makroebene im Sinne der Gesundheitspolitik bzw. gesamtgesellschaftlicher Versorgungsangebote ableiten (siehe Kapitel 2.4, Die Integration der Patientenperspektive auf Makroebene).

Ziel der vorliegenden kumulativen Dissertation ist es somit, die aktuellen Entwicklungen im Bereich der Integration der Patientenperspektive für seltene Erkrankungen aufzuarbeiten und praxisnahe und fundierte Methoden der Integration von Patientenperspektiven und deren Möglichkeiten exemplarisch im gesundheitsökonomischen Kontext aufzuzeigen.

2 Beitrag der vorliegenden kumulativen Dissertationsarbeit

2.1 Aktuelle methodische Entwicklungen

Gerade wegen des gesundheitspolitischen Rahmens zur Integration der Patientenperspektive gibt es im gesundheitsökonomischen Kontext weitreichende Diskussionen dazu, ob diese in der praktischen Anwendung bereits in hinreichendem Maße Berücksichtigung findet.

Beispielhaft kann hier die frühe Nutzenbewertung für den Arzneimittelmarkt angeführt werden. So ist die Einbindung des Patienten im Rahmen der Nutzenbewertung von Arzneimitteln gesetzlich gemäß §35b Abs. 1 Satz 4 SGB V definiert *„ […] [4]Beim Patienten-Nutzen sollen insbesondere die Verbesserung des Gesundheitszustandes, eine Verkürzung der Krankheitsdauer, eine Verlängerung der Lebensdauer, eine Verringerung der Nebenwirkungen sowie eine Verbesserung der Lebensqualität, bei der wirtschaftlichen Bewertung auch die Angemes-*

senheit und Zumutbarkeit einer Kostenübernahme durch die Versichertengemeinschaft, angemessen berücksichtigt werden. […] " Doch obwohl der Patient als Nutzentragender im Zentrum der Legaldefinition steht, stellt die direkte und transparente Beteiligung gemäß §35b Abs. 1 Satz 6 SGB V auf Sachverständige der medizinischen, pharmazeutischen und gesundheitsökonomischen Praxis und Wissenschaft sowie Patientenvertreter ab. Inwiefern die Definition des Patienten-Nutzens zu einer direkten und systematischen Integration von Patienten als beste Informationsquelle des eigenen Nutzens führt, ist somit Bestandteil einer umfassenderen gesundheitsökonomischen Diskussion, welche beispielsweise dann zu Tage tritt, wenn es um die Weiterentwicklung der Maßgaben der frühen Nutzenbewertung und Kosten-Nutzen-Bewertung der IQWiG Methodenpapiere geht [14, 15, 16].

Entsprechend werden in Modul 1 *„Patient-reported data informing early benefit assessment of rare diseases in Germany: A systematic review",* 81 Prozesse der frühen Nutzenbewertung zu seltenen Erkrankungen untersucht, um die direkte und systematische Integration der Patientenperspektive im aktuellen Stand zu evaluieren. Grundsätzlich können qualitative und quantitative Methoden zur Integration der Patientenperspektive unterschieden werden. In Modul 1 wird das Konzept der patient reported outcomes (PRO) herangezogen, welches von Patienten berichtete Endpunkte unter einem Begriff zusammenfasst. Lediglich 16% der Hersteller von pharmazeutischen Produkten zur Behandlung von seltenen Erkrankungen reichten keinen direkt von Patienten berichteten Endpunkt ein. Mit 75% werden am häufigsten PRO Daten zur gesundheitsbezogenen Lebensqualität von pharmazeutischen Unternehmen eingereicht. Hierauf folgen klinische PRO Daten, welche in 48% der Fälle als solche eingereicht werden. Hierunter fallen beispielhaft Schmerzskalen oder eigens berichtete Morbiditätsendpunkte. Durch den Gemeinsamen Bundesausschuss (GBA) werden diese in 72% bzw. 46% der Fälle berücksichtigt, wobei diese Zahlen aufgrund der teils divergierenden Definition der Endpunkt-Kategorien durch Unternehmen und GBA einen Trend darstellen. Daten zu Patientenzufriedenheit (2%) und Patientenpräferenzen (1%) werden selten systematisch erhoben und dargestellt. Vom GBA werde diese innerhalb der Gesamtschau nicht berücksichtigt. Methodisch werden Befragungen und Fokusgruppen herangezogen. Eine Berücksichtigung der im breiteren gesundheitsökonomischen Kontext umfangreich diskutierten qualitativen und quantitativen Methoden kann in diesem Bereich bislang nicht beobachtet werden. Entsprechend zeigt sich die Notwendigkeit einer weiteren methodischen Auseinandersetzung unter Würdigung des Versorgungskontextes sowie einer Anreizsystematik.

2.2 Die Integration der Patientenperspektive auf Mikroebene

Werden nun in die Betrachtung des Versorgungssystems die zuvor beschriebenen drei Level (Mikro – Meso – Makro) einbezogen, so beschreibt die Erste, die Mikroebene, die Ebene der individuellen Interaktion. Der eingangs aufgezeigte Rückblick auf die Historie der Integration der Patentenperspektive zeigt in diesem Kontext insbesondere die Vorreiterrolle des Arztes als primäre Informationsquelle für Gesundheitsinformationen und Erkrankungen. Neben dem traditionellen Weg der Informationsgewinnung mit Hilfe des Arztes als medizinischen Experten eröffnen sich im Zeitalter der interaktiven und kollaborativ ausgerichteten, webbasierten 2.0 Medien noch weitere Möglichkeiten, um medizinische Informationen auf Mikroebene zu erschließen. In diesem Sinne können sowohl Diagnose-Tools genutzt als auch Tipps zum Gesundheits- und Krankheitsmanagement abgerufen werden. Risiken entstehen, sobald Informationen qualitativ fraglich sind und schlimmsten Falls zu einem Gesundheitsrisiko werden können.

Entsprechend erscheint es für eine effektive Gestaltung der Versorgung auf Mikroeben umso wichtiger die Patientenpfade zu kennen. Aus diesem Grund untersucht Modul 2 *„Use and importance of different information sources among patients with rare diseases and their relatives over time: a qualitative study“,* welche Informationsquellen neben der traditionellen Arztkonsultation im Verlaufe von seltenen Erkrankungen genutzt werden. Die Untersuchung basiert auf 68 qualitativen Interviews, 55 Patienten- und 13 Angehörigeninterviews, welche mit Hilfe eines halbstrukturierten Interviewleitfadens durchgeführt und gemäß der qualitativen Inhaltsanalyse nach Mayring ausgewertet wurden. Es stellte sich heraus, dass aktuell vor allem das Internet die wichtigste Informationsquelle für Gesundheitsinformationen zu seltenen Erkrankungen darstellt. Insbesondere zu Beginn der Erkrankung sind Online-Suchen die bevorzugte Strategie, auch wenn der Umgang mit den gewonnenen Informationen teilweise als schwierig eingestuft wird. Im Verlaufe der Erkrankung gewinnt der persönliche Kontakt, insbesondere mit Selbsthilfegruppen und medizinischen Fachexperten, an Bedeutung. In diesem Stadium bedienen Onlineinformationen manchmal den Informationsbedarf nicht in ausreichendem Umfang und können durch die Informationsquelle Arzt und Selbsthilfe komplementiert werden. Insgesamt werden so meist verschiedene Informationsquellen angesteuert. Die Wahl des Informationszugangs ist auch eng mit dem Umfang des bisher gesammelten Wissens und der Krankheitsphase verknüpft. So zeigt sich, dass die Integration der Patientensicht schon in einem frühen Stadium des Verlaufs einer seltenen Erkrankung von hoher Relevanz ist. Bereits vor dem Erstkontakt mit dem Versorgungssystem gilt es Gesundheitsinfor-

mationen so bereitzustellen, dass das Versorgungssystem passend angesteuert werden kann und mitgebrachte Informationen mit der Expertise der Fachexperten gut verzahnt werden können. So trägt auch eine intensivere Integration der Patientenperspektive auf Mikroebene im Felde der modernen Informationsbereitstellung bereits zur effektiven Gesundheitsversorgung bei.

Für eine effektive Information von Patienten auf Mikroebene ist auch ihre Qualität und leichte Zugänglichkeit ausschlaggebend. Gerade qualitativ ungeprüfte medizinische Informationen können aufgrund fehlleitender medizinischer Informationen ein Gesundheitsrisiko bergen. So beschäftigt sich Modul 3 *„Adopting Quality Criteria for Websites Providing Medical Information About Rare Diseases“* mit geeigneten Kriterien zur Auswahl von Informationsquellen im Internet. Es wird ein Kriterienkatalog für die Auswahl qualitativ hochwertiger webbasierter Informationsangebote zu seltenen Erkrankungen erstellt. Grundlage ist eine komprehensive Internetrecherche. So wurden relevante Zertifikate und Qualitätsempfehlungen identifiziert. Im folgenden Schritt wurden alle Qualitätskriterien der Zertifizierungsprogramme und –Kataloge untersucht, extrahiert und inhaltlich analysiert. Eine interdisziplinäre Expertengruppe validierte die relevanten Kriterien. Hieraus konnten 13 Qualitätskriterien für Internetseiten zu seltenen Erkrankungen entwickelt werden. So trägt die Einschätzung der Qualität der dargestellten Informationen mit Hilfe des Kriterienkataloges dazu bei, dass Betroffene und Angehörige auch bereits vor der direkten Kontaktaufnahme mit dem Versorgungssystem die Zuverlässigkeit von Informationen zu seltenen Erkrankungen einschätzen können. Gerade im Bereich seltener Erkrankungen sind medizinische Informationen nur spärlich verfügbar oder basieren teils lediglich auf Erfahrungsberichten. Erste Anlaufstellen sowie spezialisierte Zentren sind oft weit entfernt, sodass die Informationssuche über das Internet sehr wahrscheinlich angesteuert wird. Gerade hier ist es wichtig Kriterien zur Verfügung zu stellen, die es Betroffenen und Angehörigen möglich machen, die Qualität der Informationen richtig einzuschätzen.

Steuert der Betroffene nun den klassischen Weg der Versorgung mit dem Kontakt zum Arzt an, stellt sich die Frage, wie zuvor gesammelte Informationen gewinnbringend in die Interaktion einfließen können. Modul 4 *„Integrating patient perspectives in medical decision-making: a qualitative interview study examining potentials within the information exchange process of rare diseases in practice“* geht im Sinne des Patientenrechtegesetztes [10] auf den verbesserten Einbezug von Patienten auf Mikroebene im Versorgungssystem ein und zeigt die Chancen der Stärkung des Konzeptes der partizipativen Entscheidungsfindung für den Be-

reich der seltenen Erkrankungen. Neben der ausführlichen Information des Betroffenen steht auch die gemeinsame Auswahl der für den individuellen Patienten besten Behandlungsoption im Vordergrund. Die empirische Evidenz basiert auf 101 Interviews die zwischen März und September 2014 basierend auf einem qualitativen halb-strukturierten Interviewleitfaden in Deutschland durchgeführt wurden. In diesem Zusammenhang wurden 55 Patienten und 13 Angehörige interviewt. Die gewonnenen Erkenntnisse konnten mit den Ergebnissen aus 33 Ärzteinterviews trianguliert werden. Von den vier Grundpfeilern der partizipativen Entscheidungsfindung zeigte sich, dass die Entscheidungssituation an sich, trotz steigender Relevanz des Entscheidungsprozesses, kaum als partizipativ beschrieben wird. Stattdessen wird am häufigsten eine informierte bzw. nachgelagert eine paternalistische Entscheidungssituation geschildert. Die Stärkung der Patientenintegration birgt gerade da ihre Potentiale, wo ein unstimmiges Vertrauensverhältnis beschrieben wird. Dieses wird nicht nur von einer starken Abhängigkeit gegenüber dem Arzt charakterisiert, sondern auch durch die rasche Stigmatisierung der Patienten als Simulanten, die mit dem langwierigen Diagnoseweg und dem schwierigen chronischen Verlauf Hand in Hand gehen. Aufgrund des hohen Engagements und der besonderen Rolle als „Patienten-Experten“ zeichnet sich gerade hier ein besonders hohes Potential ab. So kann die Verquickung von Patientenwissen und Arztexpertise zu einem umfangreichen Bild der gesundheitlichen Situation führen und somit den Weg zur passenden Versorgung ebnen. An dieser Stelle gilt es die gesammelten Informationen in den Versorgungsprozess einzubinden. So kann eine intensivere Integration von Patienten im Arzt-Patienten Kontext auf Mikroebene zu einem stringenteren Diagnoseweg und einem verbesserten Krankheits- bzw. Gesundheitsmanagement beitragen.

2.3 Die Integration der Patientenperspektive auf Mesoebene

Neben der Mikroebene werden im folgenden Schritt Möglichkeiten und wichtige Aspekte der Integration der Patientenperspektive auf Mesoebene dargestellt. Innerhalb der Mesoebene werden somit institutionaliserte Versorgungsleistungen betrachtet, deren operative Ausgestaltung unter Einbezug der Patientenperspektive der angesprochenen Gruppierung ideal an den Bedürfnissen ausgerichtet werden kann.

In diesem Zusammenhang beschreibt Modul 5 *„Shaping an Effective Health Information Website on Rare Diseases Using a Group Decision-Making Tool: Inclusion of the Perspectives of Patients, Their Family Members, and Physicians“* beispielhaft, wie die konkrete Prä-

sentation des Informationsangebotes einer Informationswebsite zu seltenen Erkrankungen unter Einbezug der Patienten- und Angehörigenbedarfe anzuordnen ist. Auf diese Art und Weise können Betroffene effektiv bei ihrem Gesundheitsmanagement unterstützt werden. Gleichzeitig werden auch Unterschiede zu den Sichtweisen der untersuchten Ärzteschaft berücksichtigt. Methodisch wird der Analytic Hierarchy Process herangezogen, dessen Verwendungsmöglichkeiten aktuell im gesundheitsökonomischen Kontext als Entscheidungsfindungs- bzw. Präferenzmessmethode rege diskutiert werden. Insbesondere im Kontext seltener Erkrankungen bietet die Methode den Vorteil, kleine Populationen ohne spezifische Einschränkungen zur Stichprobengröße berücksichtigen zu können. Zudem kann die Stichprobe einerseits im Sinne der Definition der seltenen Erkrankungen als Überbegriff rechnerisch zusammengefasst werden. Andererseits können auch einzelne Krankheitsbilder im Sinne von Subgruppenanalysen bei Bedarf untersucht werden. Die Attribute wurden im Rahmen einer systematischen Internetsuche identifiziert und durch eine qualitative Interviewstudie verifiziert. Die so festgestellten Informationsbedarfe beinhalteten auf übergeordneter Ebene „Informationen zu medizinischen Sachverhalten“, „Forschung“, „sozialen Hilfsangeboten“ und „aktuellen Veranstaltungen“. Als Subattribute werden „Diagnose“, „Therapie“, „Krankheitsbild“, „aktuelle Studien“, „Studienergebnisse“, „Register“, „psychosoziale Beratung“, „Selbsthilfe“ sowie „sozialrechtliche Tipps“ betrachtet. Insgesamt konnten 176 Fragebögen aufgrund des Konsistenzniveaus von 0,2 in die Analyse eingeschlossen werden. So flossen 120 Patienten-, 24 Angehörigen- und 32 Ärztefragebögen in die Auswertung ein. Insbesondere Informationen zu „aktuellen Ereignissen“ und „sozialen Hilfsangeboten“ wurden als besonders wichtig eingestuft, gefolgt von „Forschung“ und als Schlusslicht „medizinischen Sachverhalten“. In der Gesamtschau der Subkategorien waren „psychosoziale Beratungen“ für Patienten, „Register“ für Angehörige und „sozialrechtliche Angelegenheiten“ für Ärzte die wichtigsten Informationsbedarfe. Demzufolge zeigte sich ein sehr heterogenes Bild der Informationspräferenzen. Die Ergebnisse zeigen eine prägnante Informationshierarchie, die bei der Anordnung des Informationsangebotes transparent und direkt übertragen werden kann. Auf Grundlage dieser Ergebnisse kann empfohlen werden die Informationsangebote entsprechend der aufgezeigten Präferenzen anzuordnen und spezifische Informationsangebote gemäß der divergierenden Bedürfnisse der drei betrachteten Interessensgruppen anzubieten. So zeigt sich der Analytic Hierarchy Process aufgrund der simplen Übertragbarkeit in die Praxis als hilfreiches Tool zur Integration der Patientenperspektive auf Mesoebene.

Neben dem Analytic Hierarchy Process wurden noch weitere Methoden zur Integration der Patientenperspektive bei der Gestaltung des Informationsangebots zu seltenen Erkrankungen

in die Betrachtung einbezogen. Entsprechend vergleicht Modul 6 *„Measuring patients' priorities using the Analytic Hierarchy Process in comparison with Best-Worst-Scaling and rating cards: methodological aspects and ranking tasks"* die Ergebnisse von drei verschiedenen Hierarchisierungsverfahren zur Integration der Präferenzen von Betroffenen. So werden der Analytic Hierarchy Process, das Best-Worst-Scaling und ein Rankingverfahren unter Verwendung eines Kartensets miteinander verglichen. Die Stichprobe umfasste 39 Patienten mit seltenen Erkrankungen. Es stellte sich heraus, dass das in Modul 4 gewählte Konsistenzniveau von 0,2 verglichen mit dem Konsistenzniveau von 0,1 keine signifikanten Unterschiede in den Ergebnissen aufweist, jedoch durch den niedrigeren Schwellwert weniger Fragebögen ausgeschlossen werden müssen und dementsprechend mehr Patientenfragebögen Berücksichtigung finden können. Es konnten moderate bis hohe Korrelationen zwischen den Ranking-Ergebnissen der beiden Verfahren Best-Worst-Scaling und Analytic Hierarchy Process ermittelt werden. Eine weitere Untersuchung der Ergebnisse der Ranking-Methode entfiel, da diese als Hilfestellung beim Ausfüllen der Analytic Hierarchy Process Fragebögen verwendet wurden und somit eine positive Korrelation unterstellt werden kann. Insgesamt verifizieren diese Resultate die Validität des Analytic Hierarchy Process. Jedoch sollte bei der Auswahl des Verfahrens aufgrund der Komplexität des Analytic Hierarchy Process der Nutzen der Analyse sowie die Krankheitslast der teils schweren chronischen Erkrankungen gegeneinander abgewogen werden. Gerade wenn beispielsweise eine Erkrankung des Nervensystems lange Konzentrationsintervalle schwierig macht, können simplere Verfahren wie das Best-Worst-Scaling oder das Ranking-Verfahren, bevorzugt eingesetzt werden. Im Zuge der Berücksichtigung der Patientenperspektive im Kontext der gesundheitsökonomischen Analyse ist die Abwägung der Komplexität der Verfahren mit der Krankheitslast der teils schwerwiegenden chronischen Erkrankungen somit ein wichtiger zu berücksichtigender Aspekt bei der Methodenentwicklung, -Bewertung und –Auswahl.

Gerade bei der Weiterentwicklung methodischer Ansätze ist eine kontinuierliche wissenschaftliche Begleitung notwendig. Modul 7 *„Comparison of different approaches applied in Analytic Hierarchy Process – an example of information needs of patients with rare diseases"* beschäftigt sich in diesem Sinne mit der Evaluation verschiedener Ansätze zur Aggregation der gewichteten Präferenzen von Betroffenen seltener Erkrankungen. 51 Patienten und Angehörige nahmen an der Untersuchung teil. 40 Teilnehmer nahmen an den Einzelbefragungen teil und 11 partizipierten an der Gruppenbefragung. Insgesamt konnten 31 Einzelfragebögen berücksichtigt werden. Die Teilnehmer der Gruppenbefragung wurden in 3 Kleingruppen eingeteilt, sodass 3 Gruppenentscheidungen in die Analyse einflossen. Interessant ist hierbei vor

allem der Einfluss der Entscheidungsdynamik. Im Gruppenentscheidungsprozess wurden Zwischenergebnisse zur Diskussion gestellt. Teilnehmer können so maßgeblich auf die Gruppenentscheidung Einfluss nehmen. Es liegt nahe, dass solche Methoden gerade dann von Vorteil sind, wenn eine Gruppenentscheidung herbeigeführt werden soll, die von den Betroffenen auf Basis dieser Diskussion getragen werden kann. Sind jedoch individuelle Meinungen und Werte maßgeblich, so spiegeln Einzelfragebögen diese wieder. Entsprechend zeigen die Resultate der Studie, dass die Ergebnisse der Gruppenfragebögen signifikant näher beieinander liegen, als die der Einzelfragebögen. Gerade diese Erkenntnisse können gewinnbringend bei der Etablierung von bedarfsgerechten und nachhaltig getragenen Versorgungsstrukturen auf Mesoebene eingesetzt werden.

2.4 Die Integration der Patientenperspektive auf Makroebene

Bewegt man sich nun im Rahmen des Versorgungskontextes von der Mesoebene eine Ebene höher, so wird die oberste Ebene, die Makroebene erreicht. Diese ist als gesamtgesellschaftliche Ebene des Gesundheitswesens definiert und tangiert somit Versorgungsangebote auf einem übergreifenden nationalen Level.

Auch auf Makroebene bieten sich verschiedene wissenschaftlich fundierte und systematische Ansätze zur direkten und transparenten Einbindung von Patientenperspektiven. Auch hier können neben quantitativen Methoden qualitative Verfahren herangezogen werden. Dies bietet sich vor allem dann an, wenn neue bisher unbeobachtete Forschungsgegenstände in ihrer Ganzheitlichkeit erfasst werden sollen, ohne die Restriktion bisheriger Annahmen, die womöglich aus der Analyse quantitativer Daten oder retrospektiver Literaturrecherchen resultieren könnten. In diesem Zusammenhang tragen die offenen oder semi-offenen Befragungsmethoden der qualitativen Forschung zur Reduktion eines solchen möglichen Bias bei, da sie darauf abzielen, die freie Narration der Befragten ohne vorgefertigte Antwortmöglichkeiten abzurufen. So kann die Forschungsfrage in seiner ganzen Breite erhoben werden. Modul 8 *„Telephone health services in the field of rare diseases: A qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany“* legt einen solchen Ansatz auf Makroebene dar. Entsprechend wird beleuchtet, welche Attribute den Nutzern einer nationalen telefonischen Beratungsstelle zu seltenen Erkrankungen wichtig sind. Die Fragestellung wurde im Rahmen einer Interviewstudie basierend auf einem halbstrukturierten Interviewleitfaden untersucht. In diesem Zuge wurden 107 Betroffene, deren

Angehörige und medizinische Experten befragt. Die Ergebnisse zeigen, dass den Befragten vor allem die professionelle Besetzung, der persönliche Kontakt, eine gute Erreichbarkeit und geringe technische Hürden wichtig sind. Die wichtigsten Inhalte der Beratung sind medizinische und psychosoziale Themen, die Lotsenfunktion durch das Informationschaos und Verweise an Anlaufstellen und Experten. Vor allem medizinisches Fachpersonal unterstrich die Wichtigkeit medizinischer Themen, insbesondere bei Fragestellungen zur Differentialdiagnostik und der Benennung passender Ansprechpartner bei Überweisungsnotwendigkeit. So zeigt die Interviewstudie ganz klare Eckpfeiler für die Etablierung einer zentralen telefonischen Beratungsstelle auf. Desto mehr es gelingt, diese Bedarfe bei der Einführung zu bedienen, desto mehr werden die Nutzer mit der Versorgungsstruktur zufrieden sein, diese nutzen und schlussendlich davon profitieren. Im übertragenen Sinne lässt sich dies auch auf andere innovative Versorgungsstrukturen im Gesundheitswesen anwenden und zeigt die Vorteile einer frühzeitigen und systematischen Involvierung von Betroffenen auf.

Andererseits können auch quantitative Methoden sehr hilfreich bei der transparenten Einbindung der Patientenperspektive auf Makroebene sein. Diese bieten sich vor allem dann an, wenn der Forschungsgegenstand bzw. die –fragestellung als solches bereits abgesteckt ist bzw. eine Theorie bereits besteht, welche validiert werden soll. Qualitative und quantitative Auswertungsmethoden können dann besonders passend ineinandergreifen, wenn die qualitativ entwickelte Theorie darauf aufbauend in ihrer Ausprägung quantitativ untersucht werden kann. Ein Beispiel für die Verquickung der methodischen Ansätze im Versorgungskontext auf Makroebene bietet Modul 9 *„Conceptualization and Implementation of the Central Information Portal on Rare Diseases (ZIPSE)“*. Hier werden die Ergebnisse der Module 2, 3 und 5 in einem gestuften Ansatz miteinander verbunden und letztendlich im spezifischen Versorgungskontext, der Etablierung eines zentralen Internetportales zu seltenen Erkrankungen in Deutschland für den Nutzer getestet. Im Zuge von insgesamt 108 qualitativen Interviews mit Patienten, Verwandten und Gesundheitsexperten wurde der grundsätzliche Bedarf an Informationen zu seltenen Erkrankungen, wie beispielsweise Informationen zu „Symptomen“, „Therapie“, „Forschung“ und „Beratungsangeboten“ zunächst in seiner Breite erhoben. Nicht nur qualitative Auswertungen sondern auch die zuvor angeführten quantitative Präferenzmessinstrumente konnten dann darauf aufbauend zur passenden Positionierung der Informationsangebote gemäß ihrer Wichtigkeit genutzt werden. Die passenden Informationsangebote wurden anhand der entwickelten 13 Qualitätskriterien überprüft und eingeschlossen. 19 potentielle Nutzer testeten die Website im Hinblick auf die Verständlichkeit der Anweisungen und Kurzinformationen sowie ihrer einfachen Handhabung. Entsprechend der Rückmeldungen

wurde die visuelle Darstellung der Ergebnisse noch einmal weiter an die Bedarfe der Nutzer angepasst. So zeigt sich an dieser Stelle auch noch einmal die Wichtigkeit der Patientenzufriedenheitserhebung im Zuge der Etablierung und nachhaltigen Weiterentwicklung neuer Versorgungsstrukturen. Aufgrund des direkten Einbezugs der Betroffenen sowie medizinischer Experten während der Etablierung des Internetangebots, konnte ein nutzerorientiertes und bedarfsgerechtes Informationsangebot für den übergreifenden Versorgungskontext seltener Erkrankungen in Deutschland geschaffen werden.

3 Zusammenfassung der Ergebnisse und Ausblick auf den weiteren Forschungsbedarf

Die Integration der Patientenperspektive ist ein historisch weit zurückreichendes Forschungsfeld, welches auf dem Informationsgefälle zwischen Arzt und Patient beruht. Gerade aufgrund aktueller Forschungsbemühungen und politischer Verankerungsprozesse hat die Integration der Patientenperspektive der letzten Jahrzehnte erneut an Aktualität gewonnen. Bisherige Bemühungen zur Stärkung der Integration der Patientenperspektive zeigen auf, dass Patienten zunächst allgemein auf Mikroebene in der Arzt-Patienten Interaktion gestärkt wurden. Auch auf Meso- und Makroebene wurde die Patientenperspektive durch die Gesetzgebung verankert, beispielsweise durch die Integration von Patientenvertretern im Gemeinsamen Bundesauschuss. Ferner wird im Rahmen der Umsetzung des Nationalen Aktionsplans für seltene Erkrankungen zunächst hauptsächlich von einer Integration der Patientensicht über die Selbsthilfe ausgegangen. Gerade diese Bemühungen ebnen den Weg zur Stärkung der direkten Integration der Patientenperspektive. So eröffnet sich ein Gesundheitssystem übergreifendes Forschungsfeld, welches eine Vielzahl an potentiellen Methoden und verschiedene Ebenen des Gesundheitssystems vereint.

Modul 1 zeigt Methoden auf, die bereits in einem spezifischen Bereich des Versorgungssystems zur direkten Integration der Patientenperspektive einfließen und gibt somit einen Einblick zum Status Quo in diesem Bereich. So zeigt das Beispiel der frühen Nutzenbewertung von Arzneimitteln für seltene Leiden, dass die Patientenperspektive in Form von patientenberichteten Endpunkten auch hier zusehends Berücksichtigung findet. Methoden der gesundheitsbezogenen Lebensqualitätsmessung werden aktuell am häufigsten verwendet. Es folgen klinische patientenberichtete Endpunkte, die ebenso an Bedeutung gewinnen und beispielsweise Schmerzen direkt am Betroffenen erheben. Vor allem die Bereiche der Patientenzufrie-

denheit und der Patientenpräferenzen zeigen an dieser Stelle großes Potential. So können diese einerseits im Rahmen des Bewertungsprozesses zusehends Berücksichtigung finden. Andererseits können sowohl im qualitativen als auch im quantitativen Bereich methodische Vorgaben noch präziser definiert werden.

Im nächsten Schritt rücken Umsetzungsmöglichkeiten auf den verschiedenen Ebenen des Versorgungssystems stärker in den Fokus. Betrachtet man zunächst die Mikroebene zeigen Module 2 bis 4 die besondere Relevanz von Gesundheitsinformationen im Kontext der zunehmenden Integration der Patientenperspektive. In Modul 2 stellt sich heraus, dass gerade zu Beginn einer seltenen Erkrankung, vor dem Hintergrund langer Diagnosewege und teils weit entfernter Zentren zu seltenen Erkrankungen, Internetinformationen besonders relevant sind. Gerade hier ist es wichtig, mit Hilfe eines gesicherten Kriterienkataloges die Qualität der Informationen zu seltenen Erkrankungen auch ohne die Einschätzungen des konsultierten Arztes richtig einzuschätzen (Modul 3). Wird dann der persönliche Kontakt zum Spezialisten aufgenommen, rückt das Arzt-Patienten-Verhältnis in den Fokus. Insbesondere dort, wo Informationen zu spezifischen seltenen Erfahrungen rar sind und die Erfahrungen der Patienten mit ihrer individuellen Erkrankung eine primäre Informationsquelle darstellen, ist es besonders bedeutsam die Perspektive von Patienten miteinzubinden. Modul 4 zeigt die besondere Relevanz des Konzeptes der partizipativen Entscheidungsfindung im Bereich seltener Erkrankungen und deren Potentiale für den Versorgungskontext. So kann das Modell aufgrund des verbesserten Informationsflusses und der Erhöhung der Therapietreue auch im Bereich der seltenen Erkrankungen zu einem geradlinigeren Therapie- und Diagnoseweg sowie einem effektiven Gesundheitsmanagement führen.

Eine Versorgungsebene höher, auf der Mesoebene, zeigt sich der Analytic Hierarchy Process hier als besonders geeignete Methode zur Integration der Patientenperspektive, um auf institutioneller Ebene längerfristig tragbare Strukturen zu etablieren. In diesem Sinne untersuchen Modul 5 bis 7 detailliert die Anwendung des Analytic Hierarchy Processs im Bereich der seltenen Erkrankungen. So können trotz geringer Populationsgrößen Patienten und Angehörige auf direktem und transparentem Weg integriert werden. Gerade wenn Entscheidungen zu operativen Umsetzungsschritten führen, ist eine transparente Darstellung des Entscheidungsweges zur Generierung tragbarer und somit nachhaltiger Lösungen für das Versorgungssystem unabdingbar. Die Forschungsergebnisse aus Modul 7 zeigen verschiedene Methoden der Aggregation der Einzelentscheidungen des Analytic Hierarchy Process. Bei der Methode der Gruppenaggregation liegen die Einzelentscheidungen näher beieinander. Dies spricht dafür,

dass aufgrund des Meinungsaustausches zu einer Gesamtlösung gefunden werden kann, die nicht so stark von den individuellen Meinungen abweicht und somit tragbarer ist. Dies scheint gerade dann von Vorteil, wenn es darum geht, stabile Versorgungssysteme auf Mesoebene zu operationalisieren. Zudem können Subgruppenanalysen durchgeführt werden, welche es ermöglichen, einzelne Erkrankungsgruppen aus dem Erkrankungspool zu extrahieren und bei signifikanten Abweichungen vom Gesamttrend in ihrer Besonderheit zu berücksichtigen. Hier zeigt Modul 5 am Beispiel der Informationsgestaltung auf einer Website zu seltenen Erkrankungen, wie simpel und transparent die Präferenzstruktur des Analytic Hierarchy Process eins zu eins in die Versorgungsstruktur übertragen werden kann. Gerade bei Methoden aus dem Kontext der gesundheitsökonomischen Diskussion, die auf den direkten Einbezug von Betroffenen abzielen, ist Modul 6 besonders relevant. Es weist darauf hin, dass der Analytic Hierarchy Process durchaus ein komplexes Instrument ist und vor allem bei schwerwiegenden chronischen Erkrankungen, abgewogen werden muss, ob eine solche Methode trotz der hohen Krankheitslast zumutbar und somit anwendbar ist.

Auf Makroebene hat sich auch der wertvolle Beitrag qualitativer Erhebungsmethoden gezeigt. Gerade bei innovativen Versorgungsformen oder beschränkten historischen Erfahrungswerten können qualitative Erhebungen, wie in Modul 8 dargestellt, dazu beitragen, Klarheit über die wichtigen Attribute des aktuellen Versorgungsbedarfs zu schaffen. Dies erscheint gerade bei der Gestaltung von innovativen Versorgungsstrukturen insbesondere im Hinblick auf die neuerdings diskutierte „App-Versorgung“ als besonders relevant. Quantitative Methoden können dann ergänzend hierzu das Ausmaß oder die Wichtigkeit der Attribute innerhalb der Population aufzeigen. So zeigt Modul 9, wie qualitative und quantitative Forschungsmethoden zur ganzheitlichen und vollumfänglichen Darstellung und Berücksichtigung des tatsächlichen Versorgungsbedarfes bei der Entwicklung von Versorgungsstrukturen exemplarisch im Bereich der seltenen Erkrankungen ineinandergreifen können.

Die aufgezeigten methodischen Ansätze knüpfen dort an, wo Best Practice Ansätze zur Integration der Patientenperspektive für den Bereich der seltenen Erkrankungen gefordert werden. Jedoch zeigt sich, dass dies lediglich ein erster Einblick zu einer kontinuierlich weiter zu entwickelnden Methodenübersicht ist. Gerade bei näherer Betrachtung zeigt sich, dass noch weitere Methoden wie beispielsweise Descrete Choice Experimente im Hinblick auf ihre Anwendbarkeit im Bereich seltener Erkrankungen untersucht werden können. So stellt sich heraus, dass bei der Übertragung der methodischen Möglichkeiten der gesundheitsökonomischen Diskussion in die praktische Anwendung im Bereich der frühen Nutzenbewertung eine große

Translationslücke entsteht. Hier gilt es zusehends „Gold Standards“ zu konkretisieren und in der praktischen Anwendung wissenschaftlich zu begleiten und weiter zu verfeinern. Auch muss die Frage nach weiteren Anreizen beantwortet werden, die zusehends eine direkte und systematische Integration der Patienten auch in der praktischen Anwendung verankern. Auf Mikroebene werden sicherlich im Rahmen der Informationsgestaltung noch weitere Zugangswege zu diskutieren sein. Gerade die Entwicklung von Apps eröffnet weitere Wege der Informationsgenerierung und –weiterleitung. In diesem Sinne zeigt sich auch die Notwendigkeit einer stetigen Weiterentwicklung von Qualitätskriterien im Gleichschritt mit technischen Neuerungen. Zudem ist zu evaluieren, wie und wo das Konzept der partizipativen Entscheidungsfindung weiter verankert wird und ob die angeführten Potentiale tatsächlich aus gesundheitsökonomischer Sicht nutzenstiftend umgesetzt werden können. Das Beispiel des Analytic Hierarchy Process zeigt nur eine Möglichkeit der Würdigung von Patientenpräferenzen im Rahmen der Entscheidungsfindung auf. Auch Verfahren wie das ConJoint Verfahren bzw. Descrete Choice Experimente können im Hinblick auf ihre Vor- und Nachteile bei der Anwendung im Bereich seltener Erkrankungen untersucht werden. Dies ist gerade dann eine Herausforderung, wenn es nicht zielführend ist seltene Erkrankungen als Ganzes zu untersuchen und stattdessen einzelne Erkrankungsbilder mit geringer Prävalenz in den Vordergrund zu rücken, die nur kleine Stichproben erlauben.

So zeigt sich am Beispiel der seltenen Erkrankungen, dass gerade bei innovativen Versorgungsformen, welche direkt am Patienten ansetzen, quantitative und qualitative Erhebungsmethoden zur direkten und transparenten Integration der Patientenperspektive bei der bedarfsgerechten Entwicklung ideal ineinandergreifen können. Gewinnen Betroffene bei der Entwicklung von Versorgungsstrukturen zusehends an Bedeutung, so erscheint es zielführend, diese auch im Folgeschritt bei der langfristigen und nachhaltigen Evaluierung der Konzepte, beispielsweise mit Hilfe eines Erfolgsmessinstruments wie dem Konzept der Patientenzufriedenheit, mit einzubeziehen. Letztendlich kann nur eine langfristig angelegte gesundheitsökonomische Evaluation der entwickelten Versorgungsstrukturen feststellen, ob die durch eine bedarfs- und nutzerorientierte Gestaltung des Gesundheitssystems im Sinne der direkten und systematischen Integration der Patientenperspektive Effizienzpotentiale tatsächlich umgesetzt werden können.

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Modul 1:

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Modul 1

Patient-reported data informing early benefit assessment of rare diseases in Germany: A systematic review

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Health Economics Review

RESEARCH Open Access

Patient-reported data informing early benefit assessment of rare diseases in Germany: A systematic review

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Abstract

Background: Since the implementation of the Regulation on Patient Integration (2003), the Act on the Reorganization of the Pharmaceutical Market (2011), and the Patient Rights Law (2013), the inclusion of patient perspectives has been further anchored in the German early benefit assessment process. During the assessment of rare disease interventions, patient perspectives are particularly important, as clinical studies are often designed acknowledging small samples and patients suffering from severe symptoms and the chronic course of the disease. Therefore, our research question is whether patient perspectives are considered as part of early benefit assessments for rare diseases. We also strive to examine how patient perspectives are methodologically elicited and presented.

Methods: Our empirical evidence comes from a systematic review of orphan drug value dossiers submitted to the German Federal Joint Committee as well as the corresponding evaluations conducted between January 1, 2011 and March 1, 2019 ($n = 81$). Data on patient perspective integration were extracted using the following patient-reported outcome subcategories: clinical patient-reported outcomes, health-related quality of life, patient preferences, and patient satisfaction.

Results: The analysis demonstrates the specific relevance of patient-reported outcomes raised as part of the medical data set and presented during the early benefit assessment process. They are predominantly presented in the form of health-related quality of life data ($n = 75\%$) and clinical outcomes ($n = 49\%$). Preferences ($n = 2\%$) and satisfaction ($n = 1\%$) are still rarely presented, although the heated methodological discussion in Germany would suggest otherwise. While various methodologies for the integration of clinical outcomes and quality of life data were found, presenting data on satisfaction and preferences still lacks methodological rigor. The German Federal Joint Committee has not yet integrated these data in their decision text. Clinical outcomes and quality of life have been included in 46% and 73% of the cases, respectively.

Conclusions: The underlying analysis demonstrates that there is still a relative high potential for the regular and systematic inclusion of patient perspectives within the early benefit assessment process for rare diseases. In particular, patient preferences and patient satisfaction are still rarely included suggesting the need for a clear-cut methodological foundation and incentives.

Keywords: Patient perspective, patient-reported outcomes, health economic evaluation, early benefit assessment, AMNOG, Germany

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Introduction

The relevance of patient perspective integration in health care

In Germany, the 2003 Patient Participation Regulation [1] as well as the 2013 Patient Rights Law [2] form the most important basis for the integration of patient perspectives within the health care system. The Patient Participation Regulation, which is linked to §140f of the German Social Insurance Code Book Volume V, regulates the mandatory involvement of patient organizations in health care decision making. Within the German Federal Joint Committee, patient organizations now have the right to advise and request, but not to vote. In 2013, patients' position was further strengthened in terms of involvement and rights [1, 2].

In the extant literature, patient-oriented health care systems are created to extend traditional health care models using patient empowerment. Therefore, important attributes of patient-oriented health care systems are identified as: high-quality information generation and transparency, patient perspective integration through customization and collaboration, as well as the integration of patient choice and responsibility. To these, predictive and preventive instruments can also be added [3]. Consequently, empirical health economics have turned towards the collection of evidence regarding patient views. Patients should be effectively integrated during the health technology assessment process, beginning with evidence generation and value measurement and concluding with recommendations and communication of results, e.g., in the context of health policy [4].

Patient perspectives can be integrated in different ways. While summarizing data contributed by patients or their representatives is most common, this approach must be differentiated from the studies carried out from the patient perspective but contributing data, for example, collected by physicians or other health care specialists [5]. As a methodologically-grounded approach, patient-reported outcomes (PRO) stand for the reports directly originating from patients [5, 6] without the involvement of a physician or other communicators [5]. For instance, Klose et al. [7] report that the terms of PRO and outcome sometimes diverge in their interpretation. Used as a medical term, an outcome indicates an end result or intervention consequence in terms of symptoms and functioning, as well as the health-related quality of life (HRQoL). However, as reported by the PRO Harmonization Group, the discussion expanded from only including HRQoL outcomes to considering any outcome based on data provided by the patient or the patient's proxy [8]. In this study, we follow the broader interpretation of the term PRO, as provided by the PRO Harmonization group.

Since the definition of subcategories also varies broadly, we follow the nomenclature of Klose et al. [7]. This meant that clinical PRO, HRQoL, patient satisfaction, patient experiences, and patient preferences are differentiated. Within our analysis, it seemed preferable to differentiate between the clinical PRO following the traditional medical interpretation and HRQoL due to differences in mortality, morbidity, and quality of life endpoints within the process of early benefit assessment [2]. Furthermore, patient experiences were not acknowledged separately, as they are predominantly reported in the context of patient satisfaction and patient preferences. Preferences describe whether one item is favored over another [9], meaning they withhold information regarding preferable treatment options from the affected individuals. "Preference" is often used as an umbrella term. As such, a preference measurement can result in either utility or value depending on the measurement approach [10]. There may be various reasons for the consideration of patient preferences in health care, such as improved therapy uptake or efficiency of health care interventions in practice, thus facilitating patient involvement and promoting shared decision-making in medicine. Medical decisions that are consistent with patient preferences may facilitate patient acceptance [9, 11, 12]. Therefore, patient satisfaction is also considered an important component of medical intervention assessments. However, it is a rather subjective assessment of the quality of care and is often used to incorporate the patient's perspective on the quality of care as part of medical evaluations [12]. Patient satisfaction has not yet been well defined but is generally considered to describe a subjective assessment of medical care by patients [13]. Further, the concept can contain various elements such as medical therapy, nonmedical aspects of treatment, as well as health care infrastructure [14].

In general, the PRO can be raised via qualitative, mixed, and quantitative methodologies. Within the field of clinical PROs and HRQoL generic and disease-specific instruments are differentiated by incorporating symptom-specific modules. Patient preferences can be analyzed using contingent evaluation approaches, self-explication approaches, analytic hierarchy process, conjoint analysis, standard gamble, time trade-off approaches, as well as rating scales. For the examination of patient satisfaction, various approaches exist, such as the Patient Satisfaction Questionnaire and European Project on Patient Evaluation of General Practice Care Questionnaire [7].

Patient perspectives in the field of rare diseases

The term "rare diseases" summarizes between 5000 and 8000 different diseases that are characterized by their severity, by their genetic origin and status as life threatening, or by the chronically debilitating course of the

disease. Within the European Union, a disease is called "rare" when fewer than 5 out of 10,000 people are affected. Despite major medical advances in general, a major unmet medical need has been identified within the field of rare disease, concerning diagnostic procedures and effective treatment strategies [15]. According to the German Health Ministry, in Germany alone approximately 4 million people are affected by rare diseases [16] and although this would seem to suggest that patient perspectives are particularly important within the field of rare diseases due to its heterogeneity. There is still a lack of research on the systematic inclusion of this field during health economic processes. As demonstrated by a review of 11 national strategies regarding patient engagement, the focus of political strategies rests with the involvement of patient organizations [17]. Admitting that traditional assessments fail to endorse medical technologies for rare diseases due to a lack of power, new endpoints have been explored with names such as Patient-Centered Outcome Measures [18].

Early benefit assessment for rare diseases in Germany

Since the Act on the Reorganization of the Pharmaceutical Market (AMNOG) within the statutory health insurance law issued in December 2010 came into effect in January 2011, all manufacturers need to provide evidence of the additional benefit of pharmaceutical products claimed over an appropriate comparator. The German Federal Joint Committee then decides whether and to what extent a drug can be granted an additional benefit and their decision forms the basis of price negotiations for the statutory health care setting [19]. Typically, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen - IQWiG) is engaged to conduct early benefit assessment, and reports that patient perspectives play a key role in their judgments. Patient perspectives are generated using a standardized questionnaire regarding what is important to patients in terms of disease and treatment strategies [20].

However, in cases of drugs used solely for the treatment of rare diseases (orphan drugs), an additional benefit is presumed by the European drug approval, authorized in accordance with EC regulation number 141/2000 on orphan drugs [21]. In such cases, evidence must only be provided concerning the extent of the additional benefit to standard therapy for patients [22]. Here, the IQWiG is not involved in the benefit assessment, but in the estimation of patient numbers (target group, incidence, prevalence, and trends) as well as treatment costs. Only when the overall annual treatment costs of an orphan drug exceed the limit of 50 million euros for the statutory health insurance must it pass through the common early benefit assessment process [23]. Finally, decision making is taken over by the Federal Joint Committee, who describe patient involvement as the inclusion of patient representatives and patient organizations during the process but provide no further description of the procedure.

Aims of the study

To address this gap, this article examines how the integration of patient perspectives in the assessment of benefits proceeds. To this end, we examine the development of a methodologically grounded and direct approach to patient perspective integration, using the concept of patient reported outcomes, and analyzing the data submitted during early benefit assessments for rare diseases in Germany.

Method

Data sources

Our empirical evidence comes from the database of the German Federal Joint Committee, withholding all procedures of early benefit assessment induced by §35a Volume V of the Social Code Book starting with the implementation of the AMNOG law [23]. All procedures with a starting date of between January 1, 2011 and March 1, 2019 were considered. In a second step, we filtered for procedures with an orphan drug status and only procedures marked "completed" were finally reviewed. Due to the exceeding of the 50-million-euro boundary or an extension of the area of application, newly developed active substances can be subject to multiple assessments.

The Federal Joint Committee makes available the following information on each procedure: the "dossier" submitted by the pharmaceutical company in accordance with the modular template, "benefit assessment," "comments procedure," and the "resolution" comprising "decisions" as well as the corresponding "rationales" [23]. Data were extracted from the dossier, in particular module 4, the benefit assessment, as well as the decision text developed by the Federal Joint Committee.

Strategy of analysis

To analyze the integration of patient perspectives within the data set, the PRO concept was used following the broad definition provided by Black (2003) [6] and Patrick et al. (2003) [5] linked with the nomenclature of Klose et al. (2016) [7]. Therefore, the following subcategories have been used during the underlying analysis:

- Patient-reported outcomes clinical data (clinical PROs)
- (Health-related) quality of life (HRQoL)
- Patient preferences
- Patient satisfaction.

We did not specifically analyze the presented data for adverse events as HRQoL registers adverse events as well and mortality captures the fatal adverse events. We particularly analyzed the data presented within the synopsis section of the dossiers, the benefit assessment, as well as the decision text. The respective text passages were screened particularly searching for terms such as "patient-reported outcomes," "quality of life", "patient preference" and "patient satisfaction". The identified sections were than extracted and transferred to a separate Excel sheet. Quantitative and qualitative data were reviewed equally. To provide a first impression on the relevance of the reported patient perspective within the early benefit assessment of rare diseases, we also examined the extent of the requested, and later granted, additional benefit as well as the methodologies actually considered by the GBA for each PRO data category.

Results

Characteristics of the data sample

Our final sample contained $n = 81$ value dossiers. The first dossier was submitted on September 15, 2011 and the last on September 15, 2018. The different disease groups are shown in Table 1. A total of 51% of the dossiers within the field of rare diseases addressed oncological indications, while metabolic diseases were the second most common, at 25%.

Benefit assessments were predominantly ($n = 71$, 88%) conducted by the Federal Joint Committee itself. The IQWiG was commissioned with the rare diseases benefit assessment in 12% ($n = 10$) of cases, mostly when drugs were cross-passing the sales limit of 50 million euros ($n = 7$). In some cases, the manufacturer applied for an additional application area ($n = 3$). It should be noted that, whereas all agents cross passing the 50 million euro limit were commissioned to the IQWiG, applications for additional application areas were also assessed by the GBA itself.

Table 2 shows the benefit scores that were applied for by the pharmaceutical companies during those processes, as well as the GBA score granted by the Federal Joint Committee. Applied and granted benefit scores matched in 19% of cases. No additional benefit was determined in 2% of cases as part of a reassessment after the trespassing of the 50 million Euro limit conducted by the IQWiG.

Analysis

Table 3 shows a summary of the analysis of patient-reported data during the early benefit assessment process for rare diseases.

PROs are mostly presented in the form of self-reported clinical outcomes data ($n = 39$, 48%) followed by data on HRQoL ($n = 61$, 75%). Data on patient preferences were included twice (2%) and on patient satisfaction only once (1%). In only 15% ($n = 12$) of cases, no data on PROs were submitted. Therefore, data on PROs were presented to a relatively high extent. In 85% of cases, PROs were presented from at least one PRO subcategory. The Federal Joint Committee considered clinical PRO data in 37 (46%) cases, whereas HRQoL data were included in 59 (73%) cases. Patient satisfaction and patient preferences were not included within the decision text. Another example, which was often considered as part of the GBA decision text ($n = 13$), was the EORTC (Core Quality of Life Questionnaire). The splitting of the questionnaire items into clinical PROs and QoL PROs could also be observed here.

Table 4 shows the overall number of assessment processes for each year since the implementation of the AMNOG law. In 2017, 16 processes were initiated. Twelve processes presented data on Clinical PROs, 13 processes withheld HRQoL data, and 1 process presented data on

Table 1 Disease groups covered by the rare diseases benefit assessment procedures

Disease groups	Number	Percentage
Diseases of the eyes	2	2%
Cardiovascular diseases	3	4%
Infectious diseases	1	1%
Diseases of the digestive system	4	5%
Diseases of the respiratory tract	2	2%
Diseases of the blood and the blood-forming tissues	2	2%
Diseases of the musculoskeletal system	2	2%
Diseases of the nervous system	3	4%
Oncological diseases	41	51%
Metabolic diseases	20	25%
Other	1	1%
Sum	=81	=100%

Table 2 Benefit score of the orphan drug benefit assessment processes

Data analysis	Number of events (n)	Percentage of overall data%	Number of events (n)	Percentage of overall data%
Benefit score	Applied		Granted	
Major	45	56%	10	12%
Considerable	21	26%	0	0%
Minor	4	5%	20	25%
Not quantifiable	11	14%	49	60%
No additional benefit	–	–	2	2%
Comparison				
Matching benefit scores	15	19%	–	–

In some cases, patient populations were separated. In these cases, we solely considered the highest attained score

preferences. Overall, the direct integration of patient perspectives in the form of PROs has gradually increased in its absolute number, with an increased number of induced processes since the implementation of the AMNOG law in 2011. Regarding the relative percentage of PROs in relation to the number of processes included within our analysis, no clear-cut trend is observable.

Analyzing the clinical PRO and HRQoL data, it was observable that the GBA split the surveys into symptom scales (clinical PRO data listed as part of the morbidity endpoints) and HRQoL scales. An example is the oncology specific EORTC QLQ-C30. In this context, the EQ-5D VAS scale has been categorized as part of the morbidity section. However, the EQ-5D Index has been appreciated as part of the HRQoL section. Moreover, further commonly acknowledged methodologies were the childhood health questionnaires and the Brief Pain Inventory (BPI) as well as the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F). On the other hand, commonly acknowledged HRQoL methodologies included disease-specific FACT-questionnaires, SF-questionnaires, and the Pediatric Quality of Life inventory (PedsQL).

The heatedly discussed categories “patient satisfaction” and “patient preferences” were rarely referred to, and when they were, it was in a qualitative manner [24–26]. Quantitative methods were not used. The dossier submitted for the agent Velmanase alfa (2018) offered “patient cases” in the form of short summaries, backing clinical PROs as well as the relevance of symptoms (preferences) and overall quality of life (not naming HRQoL in this case). There was no description of the detailed qualitative research strategy. Telotristatethyl (2017) provided “semi-structured telephone-interviews” on topics such as symptom description, preferences, and patient experiences. Some structural background data were provided, but again no description of the qualitative research strategy was included. In the case of Eftrenonacog alfa (2016), during a first phase, “focus groups” were cited as well as a “structured questioning” that also considered satisfaction. Results were presented in a qualitative manner but there was no solid description of the qualitative research strategy. Patient satisfaction and patient preferences were not included at all within the GBA decision body, thus providing no incentives for further data presentation. A detailed overview of the data can be found in Table 5.

Discussion

Summary of findings

The present study analyzes data on the direct involvement of the patient perspective, particularly in the form of PROs, which are submitted, evaluated, and considered during the early benefit assessment process for rare diseases in Germany. The results demonstrate that patient perspectives predominantly enter the process via clinical PROs and HRQoL. However, in comparison with clinical PRO and HRQoL, the categories “patient satisfaction” and “patient preferences” were rarely referred to, and if they were, it was in a qualitative manner that lacked a solid description of the methodological foundation within qualitative research. Nevertheless, we found that 16% of the orphan drug dossiers did not present any data on PROs.

Significance in the context of literature

To our knowledge, this study provides unique insights into the inclusion of patient perspectives within the early benefit analysis process, in particular using PROs as part of the early benefit assessment of orphan drugs.

Braithwaite et al. [27] highlight again the importance of PROs in the field of rare diseases since some of the methods used in this field of research permit smaller sample sizes. They also pinpoint the importance of primary outcome measures in general and that, in particular, traditional outcome measures have failed to demonstrate efficiency. While considerable progress has been made in the development of associated measures, it is still difficult to find tools for less common indications [27]. This may be one of the explanations for low acceptance and / or submission of PROs in the field of rare diseases.

Table 3 Submission and consideration of PROs as part of the early benefit assessment process of rare diseases

Category	Number of PRO data sets (n)	Percentage of events in relation to overall number of processes (%)
Industry – type of PRO data submitted (module 4)		
Clinical PROs	41	51%
HRQoL	61	75%
Preferences	2	2%
Satisfaction	1	1%
Industry - extent of PRO data submitted (module 4)		
No PRO data submitted	13	16%
Data on one PRO category	35	43%
Data on two PRO categories	31	38%
Data on three PRO categories	2	2%
Early benefit assessment – type of PRO data considered in synopsis		
Clinical PRO	39	48%
HRQoL	58	72%
Preferences	0	0%
Satisfaction	0	0%
Early benefit assessment – extent of PRO data submitted		
No PRO data considered	43	53%
One PRO category	63	78%
Two PRO categories	54	67%
Three PRO categories	2	2%
GBA decision – extent of PRO data considered in the decision		
No PRO data considered	31	38%
One PRO category	25	31%
Two PRO categories	25	31%
Three PRO categories	0	0%
GBA decision – type of PRO data considered in the decision		
Clinical PROs	39	48%
HRQoL	59	73%
Preferences	0	0%
Satisfaction	0	0%
Comparison between data submitted and data considered by the GBA		
Identical number of PRO categories[a]	42	50%
Diverging number of PRO categories[a]	29	40%
Clinical PROs - not considered by GBA	8	21%
Clinical PROs - added by GBA	6	15%
HRQoL - not considered by GBA	19	31%
HRQoL – added in GBA decision	2	3%
Preferences – not considered by GBA	2	100%
Satisfaction – not considered by GBA	1	100%

GBA German Federal Joint Committee, *HRQoL* Health Related Quality of Life, *PRO* Patient-reported Outcomes. [a]The number does not add up to n = 81 (all regarded processes) as some manufacturers did not provide PRO data

control Changes within the political framework can affect pharmaceutical companies' submission behavior. For example, before the introduction of the Patient Rights Law in 2013 [2], only three dossiers were submitted, while afterwards, the number of dossiers for orphan drugs increased to approximately 16 per year. However, the data cannot capture the possible impacts of changes in legislation since these events occur at a

Table 4 Development of PRO data submissions for rare diseases over time

Items	2018		2017		2016		2015		2014		2013		2012		2011	
Assessment processes	10		16		17		15		13		3		5		2	
Clinical PROs	4	40%	12	75%	11	65%	6	40%	4	31%	0	0%	0	0%	0	0%
HRQoL	6	60%	13	81%	13	76%	11	73%	10	77%	2	67%	4	80%	2	100%
Preferences	1	10%	1	6%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Satisfaction	0	0%	0	0%	1	6%	0	0%	0	0%	0	0%	0	0%	0	0%

small rate and could be falsified by the overall orphan drug submission rate.

Furthermore, the methodological developments within the health economic environment in Germany can also influence the development of data submission and its appraisal. In 2013, the IQWiG discussed changes to its methodology for the very first time. Institutes and industrial representatives argued for the direct, transparent, and systematic integration of patient perspectives, in particular patient preferences and the definition of the precise integration processes [24]. In 2015, another discussion of the IQWiG general methods paper was published. However, the focus of the discussion concerning patient perspectives integration was predominantly in relation to the reintegration of patient satisfaction as optional data [25]. Moreover, in 2017, the last recorded methodological discussion was published and, in this context, the systematic direct integration of patient perspectives was again demanded in several parts of the IQWiG methods paper, e.g., the clear-cut acknowledgement of patient preferences [26]. The first pilot projects concerning the measurement and inclusion of patient preferences in health economic evaluation were published in 2013 (Analytic Hierarchy Process (AHP) [28, 29] and 2014 (Conjoint Analysis) [30, 31]. Although the named projects and discussions seem to lay the basis for the methodologically grounded inclusion of patient perspectives, the first inclusions of patient preferences were recorded in 2017 and 2018 in the field of rare diseases. However, since many of the above-named quantitative methods are not appropriate in the field of rare diseases due to the limitation of small sample sizes (see also [18]) (an exception is the AHP [32, 33]), further specified requirements for qualitative data presentation are required, as well as incentives for their adaptation. The same arguments hold for patient satisfaction, which is referred to as additional submittable data but in its patient-centeredness is relevant by definition.

Clinical patient-reported outcomes and health related quality of life

Furthermore, in terms of particular relevance, it has been argued that the documentation of clinical PROs - for example, as part of the phenotype “pain” - offers the chance to better align treatment options and outcomes [34].

Casamayor et al. [35] analyzed whether PROs in oncology matter in health technology assessments conducted in Germany, France, and the UK, and found that an improvement in such outcomes did not increase the chance of a positive health technology assessment (HTA) recommendation. The authors also demonstrated that PROs assessing Quality of Life (51/57, 89.4%) and pain measures (18/57, 31.6%) are the most common. PROs were not mentioned at all in 35.1% of cases [35]. Although our analysis examines HRQoL measures and morbidity-focused clinical PROs, the tendencies of both research papers seem to be similar. An early stage analysis of the first 25 dossiers in Germany regarded independently of the targeted indication demonstrated that in the beginning HRQoL outcomes were not considered during the early benefit process for different reasons [36, 37]. In our analysis, we found that this category was the most acceptable for the Joint Federal Committee. However, the general position of the Federal Joint Committee on the importance of quality of life data has changed significantly in the last 10 years. Initially rated as supporting or complementary information, quality of life data is today accounted equivalent to endpoints of mortality and morbidity [38]. Nevertheless, there are methodological questions regarding measurement and distinction that are not yet clear.

Patient preferences

The proportion of dossiers including data on patient preferences was quite low. Obradovic and Rauland [39] state that approximately 25% of all dossiers published between 2011 and 2014 referred to some extent to patient preferences. However, the database used seems to be more broadly designed. In the case of the present study, we included data from the as by the pharmaceutical company submitted studies but this also prompts further research questions regarding the differences between the integration of patient perspectives in the field of rare diseases and other indications. Of course, many quantitative measurement methods such as choice experiments/conjoint analyses are hardly feasible in the field of rare diseases. Furthermore, their specific aim is to compare different treatment methods (trade-off), which are often not provided in the field of rare diseases.

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases

			Clinical data		Patient-reported outcome data				
	Substance	Group of disease	Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
1	Tisagenlecleucel (1st application area)	Oncologic diseases	Overall survival (OS)	Progression free survival (PFS), overall response rate (ORR)	n/a	FACT-Lym, SF-36, no usable data	n/a	n/a	non-quantifiable
2	Tisagenlecleucel (2nd application area)	Oncologic diseases	OS	Complete response/remission (CR), relapse free survival (RFS), MRD-negativ-status	EQ-5D VAS, no usable data	PedsQL (no useable data)	n/a	n/a	non-quantifiable
3	Gemtuzumab Ozogamicin	Oncologic diseases	OS	RFS, event-free survival (EFS), CR, rate of stem cell transplants	n/a	n/a	n/a	n/a	non-quantifiable
4	Velmanase alfa	Metabolic diseases	deaths, no events	Serum-Oligosaccharid-concentration, Bruininks-Oseretsky Test of Motor Proficiency (BOT-2), audiological performance with pure tone audiometry (dBHL), 3-min-stair-climbing-test, FVC, FEV, 6-min-walk-test	Childhood Health Assessment Questionnaire (CHAQ), EQ-5D-5 L Index	n/a	n/a	n/a	non-quantifiable
5	Darvadstrocel	Digestive disorders	n/a	Combined remission, clinical remission, Perianal Disease Activity Index (PDAI) (partially), no reoccurrence after clinical remission, time to clinical remission, Perianal Disease Activity Index (PDAI),	Perianal Disease Activity Index (PDAI) (partially)	Inflammatory Bowel Disease Questionnaire (IBDQ)	n/a	n/a	non-quantifiable
6	Burosumab	Metabolic diseases	None	Rachitis symptoms with Rickets Severity Scale (RSS), serumphosphat, anthropometric parameters, physical resilience (6MWT), motoric abilities (Bot-2-scale), function and pain (POSNA-PODCI), Rachitis symptoms (Radiographic Global Impression of Change (RGI-C)), pain intensity (Faces Pain Scale-Revised (FPS-R))	PROMIS (function, pain, fatigue)	SF-10 (no usable data)	n/a	n/a	non-quantifiable
7	Glycerolphenylbutyrat	Metabolic diseases	None	24-h-AUC-ammoniac-concentration in the blood	n/a	SF-36, SF-15, no usable data	n/a	n/a	non-quantifiable
8	Letermovir	Metabolic diseases	OS	Clinical relevant CMV-infection, CMV-organ disease, induction of a preemptive therapy, rehospitalization (general and after CMV-reactivation), Graft-versus-Host Disease, opportunistic bacterial, viral, and fungus infections	n/a	n/a	n/a	n/a	non-quantifiable
9	Allogenic, genetic modified T-cells	Oncologic diseases	OS, median survival, 1-year survival, 10-year survival	Immune reconstruction, acute and chronic GvHD (occurrence, time to progression)	n/a	n/a	n/a	n/a	non-quantifiable
10	Brentuximab Vedotin (new application area)	Oncologic diseases	OS	PFS, ORR, hospitalization, cutane symptomatic – symptomatic domain skindex, skin changes, mSWAT-Total-	EQ-5D VAS	FACT-G (quality of life), Skindex-29 (quality of life)	n/a	n/a	minor

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases *(Continued)*

	Substance	Group of disease	Clinical data		Patient-reported outcome data				
			Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
				Scores, complete remission (mSWAT)					
11	Niraparib	Oncologic diseases	OS	PFS	FOSI, no usable data	no usable data	n/a	n/a	non-quantifiable
12	Cenegermin	Diseases of the eye	mortalities	Recovery of the corneal epithelium (FDA-definition), improvement of the best corrected visual acuity, progression of the lesion depth up to cornea melting, or perforation, cornea infection	EQ-5D VAS	NEI VFQ-25-score	n/a	n/a	non-quantifiable
13	Telotristatethyl	Oncologic diseases	n/a	Stool frequency, abdominal pain, compulsory stool, nausea, adequate improvement of the gastrointestinal symptoms of the carzinoid-syndrom	EORTC QLQ-C30 – diarrhea, sleeplessness	disease related worrying (EORTC QLQ-GI.NET21)	n/a	n/a	non-quantifiable
14	Midostaurin	Oncologic diseases	OS, 5-year survival	Disease free survival, CR, rate of stem cell transplants	n/a	A: n/a / B: SF-12	n/a	n/a	considerable
15	Obinutuzumab (new application area)	Oncologic diseases	OS	PFS	n/a	FACT-Lym subscale, FACT-G	n/a	n/a	non-quantifiable
16	Avelumab	Oncologic diseases	OS	PFS	EQ-5D-VAS (health state), no usable data	FACT-M, no usable data	n/a	n/a	non-quantifiable
17	Elosulfase alfa (new benefit assessment)	Metabolic diseases	n/a	Change of walk distance, change of 3MSCT, anthropometry, respiratory functioning, wheelchair use, usage of walk aids, anthropometry, respiratory functioning	MPS Health Assessment Questionnaire (MPS HAQ)	n/a	n/a	n/a	minor
18	Daratumumab (new benefit assessment, > 50 mio € limit, new application area multiple myeloma after one pretherapy)	Oncologic diseases	OS	PFS	A: EQ-5D VAS (health state), EORTC QLQ-C30 (symptom scales), B: no relevant data	A: EORTC QLQ-C30 (health state, function scales) B: no relevant data	n/a	n/a	considerable
19	Carfilzomib (new benefit assessment, > 50 mio. € limit)	Metabolic diseases	OS	PFS	EORTC QLQ-C30 (symptom scales), EORTC QLQ-MY20 (time till first deterioration)	EORTC QLQ-C30 (function scale), EORTC QLQ-MY20 (time till deterioration)	n/a	n/a	non-quantifiable
20	Inotuzumab Ozogamicin	Oncologic diseases	OS	CR, MRD-negativity rate within patients with CR/Cri, HSZT rate	EORTC QLQ-C30 (symptom scale) (time till deterioration), no usable data, EQ-5D-VAS (health state) (time till deterioration)	EORTC QLQ-C30 (quality of life, time till deterioration), no usable data	n/a	n/a	minor
21	Nusinersen	Diseases of the nervous system	OS, 5 year survival	Disease free survival, rate of complete remission, rate of stem cell transplants	n/a	No data considered	n/a	n/a	considerable
22	Cerliponase alfa	Metabolic diseases	n/a	Proportion of responder (ML-scale), decrease of the ML−/HML-scale, time to stable decrease of ≥2 points or occurrence of value 0 on ML−/HML-scale, point value change on the ML −/HML-scale, response rate ML-scale,	n/a	PedsQL (Parent report for toddlers)	n/a	n/a	non-quantifiable

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases *(Continued)*

	Substance	Group of disease	Clinical data		Patient-reported outcome data				
			Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
				ML-scale, MLV-scale, MLVS-scale					
23	Blinatumomab (re-evaluation after expiry of the term)	Oncologic diseases	OS	CR/CRh/CRi rate, MRD-remission rate, rate of patients with post-baseline allo-HSZT	EORTC QLQ-C30 (symptom scale, time to decrease), no usable data, ALLSS (time till decrease), no usable data	EORTC QLQ-C30 (function scale, time till deterioration), no usable data	n/a	n/a	considerable
24	Ixazomib	Oncologic diseases	OS	PFS	BPI-SF, EQ-5D-VAS	EORTC QLQ-C30, EORTC QLQ-MY20	n/a	n/a	non-quantifiable
25	Obeticholsäure	Digestive disorders	deaths, one event	Proportion of patients with ALP < 1,67 x ULN, ALP < 1,67, Bilirubin = <ULN, ALP reduction = > 15%	Pruritus (5D und VAS)	PBC-40 (quality of life)	n/a	n/a	non-quantifiable
26	Venetoclax	Oncologic diseases	OS	PFS	EQ-5D VAS, MDASI	EORTC QLQ-C30	n/a	n/a	non-quantifiable
27	Olaratumab	Oncologic diseases	OS	PFS	n/a	n/a	n/a	n/a	considerable
28	Macitentan (new benefit assessment, > 50 mio € limit)	Cardiovascular diseases	n/a	n/a	n/a	n/a	n/a	n/a	not proven
29	Ibrutinib (new application area))	Oncologic diseases	OS	PFS	EORTC QLQ-C30 (symptom scales, time to improvement/deterioration), FACIT Fatigue (time to improvement/deterioration), EQ-5D-5 L VAS (health state, time to improvement/deterioration)	EORTC QLQ-C30 (function scales, time to improvement/deterioration)	n/a	n/a	considerable
30	Teduglutid (new application area)	Digestive disorders	n/a	pE volume reduction/change, total withdrawal of pE, pE reduction	n/a	n/a	n/a	n/a	non-quantifiable
31	Tasimelteon	Diseases of the nervous system	n/a	CGI-C (health state)	UQ-dTSD (Upper Quartile Daily Total Sleep Duration), dTSD (Daily Total Sleep Time)	n/a	n/a	n/a	non-quantifiable
32	Pitolisant	Diseases of the nervous system	n/a	Epworth Sleepiness Scale (ESS), response analysis ESS, daily kataplexie-rate	frequency and severity of narcolepsy-symptoms (sleep diary), EQ-5D VAS	n/a	n/a	n/a	non-quantifiable
33	Brentuximab Vedotin (new application area)	Oncologic diseases	OS	PFS, time to first occurrence of B-symptoms (TTBS), time till onset of an allogene transplantation (TTAllo)	EQ-5D VAS	No data available	n/a	n/a	non-quantifiable
34	Carfilzomib (new application area) [annulled]	Oncologic diseases	OS	PFS	EORTC QLQ-C30 (symptom scales)	EORTC QLQ-C30 (function scales), EORTC QLQ-MY20, FACT/GOG-Ntx	n/a	n/a	minor
35	Ibrutinib (new application area)	Oncologic diseases	n/a	n/a	n/a	n/a	n/a	n/a	not proven
36	Obinutuzumab (new application area)	Oncologic diseases	OS	PFS	EQ-5D VAS	FACT-LymS, FACT-G	n/a	n/a	non-quantifiable
37	Eftrenonacog alfa	Diseases of the	n/a	Annualized bleeding rate	EQ-5D-Y (VAS)	Haem-A-QoL, CHO-KLAT	n/a	n/a	non-

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases *(Continued)*

			Clinical data		Patient-reported outcome data				
	Substance	Group of disease	Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
		blood and blood-forming organs							quantifiable
38	Daratumumab [annulled]	Oncologic diseases	number of deceased, median overall survival in months	PFS	n/a	No usable data	n/a	n/a	non-quantifiable
39	Albutrepenonacog alfa	Diseases of the blood and blood-forming organs	n/a	Annualized bleeding rate	n/a	Haemo-QoL	n/a	n/a	non-quantifiable
40	Migalastat	Metabolic diseases	n/a	Cardiac endpoints, cerebrovascular endpoints, mGFRiohexol, and eGFRCKD-EPI	BPI-SF (pain scale)	SF-36v2	n/a	n/a	non-quantifiable
41	Ataluren (reevaluation after date of expiration)	Musculoskeletal diseases	n/a	Walk distance 6MWT, time till persisting deterioration (10%), changes in TFT, walk distances, NSAA score, time for four stairs (up and down)	n/a	PedsQL, PODCI (Pediatric Outcomes Data Collection Instrument)	n/a	n/a	minor
42	Afamelanotid	Metabolic diseases	n/a	Sunshine exposition	Pain scale during phototoxic episodes, photoic episodes (self-reported, patient diary)	DLQI changes (overall score)	n/a	n/a	non-quantifiable
43	Ibrutinib (new benefit assessment, > 50 mio € limit)	Oncologic diseases	OS	PFS	EQ-5D VAS	FACT-G, FACT-LymS	n/a	n/a	non-quantifiable
44	Blinatumomab [annulled]	Oncologic diseases	OS	CR/CRh, MRD-response, alloHSZT eligible patients with transplantation	n/a	n/a	n/a	n/a	non-quantifiable
45	Carfilzomib [annuled]	Oncologic diseases	OS	PFS	n/a	EORTC QLQ-C30 (health state/quality of life), EORTC QLQ-MY20 (disease symptoms)	n/a	n/a	non-quantifiable
46	Ivacaftor (new application area)	Metabolic diseases	n/a	BMI change, BMI z-score change, pulmonary exacerbation, lung functioning, response analysis lung functioning	n/a	CFQ-R	n/a	n/a	minor
47	Isavuconazol	Infectious diseases	OS	Clinical response according to the data review committee	n/a	n/a	n/a	n/a	non-quantifiable
48	Asfotase alfa	Metabolic diseases	OS	Survival without invasive ventilation, anthropometric data, motoric functioning,	Pain/disability (POSNA PODCI), Pain (BPI-SF), Lower Extremity Functional Scale (LEFS)	n/a	n/a	n/a	non-quantifiable
49	Idebenon	Diseases of the eye	n/a	Changes in visual acuity, protan- and tritan-color-perception	n/a	No usable data	n/a	n/a	non-quantifiable
50	Panobinostat	Oncologic	OS	PFS	n/a	EORTC-OQL-C30, QLQ-MY-20,	n/a	n/a	non-

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases *(Continued)*

	Substance	Group of disease	Clinical data		Patient-reported outcome data				
			Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
		diseases				FACT/GOG-NTX, no valid results			quantifiable
51	Pomalidomid (new benefit assessment, > 50 mio € limit)	Oncologic diseases	OS	PFS	EORTC QLQ-C30 (time till deterioration of symptoms), EORTC QLQ-MY20 (time till deterioration of symptoms)EORTC QLQ-C30	EORTC QLQ-C30 (time till deterioration), EORTC QLQ-MY20 (time till deterioration)	n/a	n/a	considerable
52	Sebelipase alfa	Metabolic diseases	number of survivals	Age related weight, normalization of ALT-values, LDL-C concentration	FACIT-Fatigue	Chronic Liver Disease Questionnaires (CLDQ), PedsQL	n/a	n/a	non-quantifiable
53	Lenvatinib	Oncologic diseases	OS	PFS	n/a	n/a	n/a	n/a	non-quantifiable
54	Olaparib [annulled]	Oncologic diseases	OS	PFS	n/a	Functional Assessment of Cancer Therapy-Ovarian (FACT-O)	n/a	n/a	non-quantifiable
55	Eliglustat	Metabolic diseases	n/a	Change of spleen volume in percent, morbidity	Brief Pain Inventory (BPI), Fatigue Severity Scale (FSS)Fatigue (Fatigue Severity Scale, FSS)	SF-36	n/a	n/a	non-quantifiable
56	Nintedanib (new application area)	Respiratory diseases	time till death, time till respiratory induced death	Time till first acute exacerbation, time till first adjusted acute exacerbation, annual decrease of FVC	n/a	SGRQ-(≤ −4 point)-Responder, SGRQ-changes, SGRQ-I-score (no usable data), SOBQ-score (no significant data), CASA-Q-score cough-score (no significant data)	n/a	n/a	minor
57	Ramucirumab [annulled]	Oncologic diseases	OS	PFS	EORTC QLQ-C30 (symptoms, responder analysis symptoms), EQ-5D VAS (health state)	EORTC QLQ-C30 (health related quality of life, responder analysis)	n/a	n/a	minor
58	Pasireotid (new application area)	Metabolic diseases	n/a	Biochemical controls (GH + IGF-1, GH, reduction of tumor volume (25%), improvements of symptoms	n/a	AcroQoL, no significant data	n/a	n/a	minor
59	Ataluren [annulled]	Musculoskeletal diseases	n/a	Walk distance (6MWT, MW (m)), standing up from the back position, 10 m walk, climbing 4 stairs, descending 4 stairs	n/a	Pediatric Quality of Life Inventory (PedsQL)	n/a	n/a	minor
60	Ibrutinib [annulled]	Oncologic diseases	OS	Overall response rate (IRC-assessment), PFS	n/a	No usable data	n/a	n/a	non-quantifiable
61	Alipogentiparvovec	Metabolic diseases	n/a	n/a	n/a	n/a	n/a	n/a	non-quantifiable
62	Teduglutid	Digestive disorders	n/a	Response, withdrawal of pE, shortening of pE	n/a	SBS-QoL	n/a	n/a	minor
63	Ivacaftor (new application area)	Metabolic diseases	n/a	Change of FEV, change of BMI after 8 weeks, pulmonale eyazerbation	n/a	CFQ-R (respiratory system)	n/a	n/a	minor
64	Obinutuzumab	Oncologic diseases	OS	IRC-indicated PFS	n/a	EORTC QLQ-C30 (no significant results)	n/a	n/a	non-quantifiable

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases *(Continued)*

			Clinical data		Patient-reported outcome data				
	Substance	Group of disease	Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
65	Cabozantinib	Oncologic diseases	OS	n/a	MDASI-THY (symptom scale)	MDASI-THY (quality of life)	n/a	n/a	minor
66	Siltuximab	Oncologic diseases	OS	Tumor response (CR and PR), fading symptoms, cancellation of corticosteroid-treatment, failure of treatment	MCD-SS (symptoms), FACIT-F-(questionnaire) (Fatigue)	SF-36, Physical Component Score (PCS), Mental Component Score (MCS)	n/a	n/a	non-quantifiable
67	Elosulfase alfa [annulled]	Metabolic diseases	n/a	Walk distance changes, changes in 3MSCT	MPS Health Assessment Questionnaire (MPS HAQ)	n/a	n/a	n/a	minor
68	Cholsäure	Metabolic diseases	n/a	n/a	n/a	n/a	n/a	n/a	non-quantifiable
69	Ruxolitinib (new benefit assessment, > 50 mio € limit)	Oncologic diseases	OS	Milt volume reduction, MFSAF v2.0	MFSAF v2.1, EORTC QLQ-C30 (no usable data)	EORTC QLQ-C30 (quality of life)	n/a	n/a	considerable
70	Riociguat	Cardiovascular diseases	OS	Changes in six-minutes-walk-distance (6MWD), changes in WHO−/NYHA-functioning classes, clinical deterioration, changes in dyspnea and fatigue (borg-scale)	n/a	EQ-5d-Index, LPH-questionnaire	n/a	n/a	minor
71	Macitentan [aufgehoben]	Cardiovascular diseases	Death till EOS	Reaching first morbidity or mortality event (EOT), changes in the 6-min-walk-distance, hospitalization, changes in the Borg-dyspnea-index, improvement of the WHO/NYHA-class	n/a	SF-36	n/a	n/a	minor
72	Pomalidomid [annulled]	Oncologic diseases	OS	PFS	n/a	EORTC QLQ-C30 (No significant results in 13 of 15 subscales, physical functioning and nausea improvement), EORTC QLQ-MY20, EQ-5D (no significant results)	n/a	n/a	considerable
73	Ponatinib	Oncologic diseases	death cases, OS	Hematologic response (HR), zytogenic response (CCyR), PFS, molecular response	n/a	n/a	n/a	n/a	non-quantifiable
74	Bosutinib	Oncologic diseases	OS	Zytogenic response (CyR), molecular response, hematologic response, PFS	n/a	EQ-5D (no usable data), Fact-Leu (no usable data)	n/a	n/a	non-quantifiable
75	Brentuximab Vedotin	Oncologic diseases	OS	PFS, event-free survival, objective response rate, complete remission, decline B-symptoms, stem cell transplant rate	n/a	n/a	n/a	n/a	non-quantifiable
76	Decitabin	Oncologic diseases	OS	CR	n/a	EORTC QLQ-C30 (no valid data), EORTC QLQ-C30 (no valid data)	n/a	n/a	minor
77	Ruxolitinib [annulled]	Oncologic diseases	OS	Spleen volume reduction (MFSAF) version 2.0	EORTC QLQ-C30 (fatigue)	EORTC QLQ-C30 (quality of life), EORTC QLQ-C30, FACT-Lym (no valid data)	n/a	n/a	minor

Table 5 Clinical and patient-reported outcomes data considered by the German Federal Joint Committee for rare diseases *(Continued)*

			Clinical data		Patient-reported outcome data				
	Substance	Group of disease	Mortality	Morbidity	Clinical PROs	HRQoL	Preferences	Satisfaction	Benefit score
78	Ivacaftor	Metabolic diseases	n/a	FEV (1%), BMI (inkl. Z-Wert), pulmonary exacerbation (PE)	CFQ-R (respiratory system, child and parents), EQ-5D	n/a	n/a	n/a	considerable
79	Pasireotid	Metabolic diseases	n/a	Proportion of responders, proportion of reducers, mUFC-basic value, blood pressure, LDL-cholesterol, weight	Beck-Depressions-Inventar	Cushing's Quality of Life Questionnaires Questionnaire (CushingQoL)	n/a	n/a	minor
80	Tafamidis Meglumin	Other diseases	n/a	Neuropathy Impairment scale of the lower limb (NIS-LL), NIS-LL responder	n/a	Norfolk QOL-DN	n/a	n/a	minor
81	Pirfenidon	Respiratory diseases	n/a	n/a	n/a	n/a	n/a	n/a	non-quantifiable

Data source: German Federal Joint Committee (GBA), GBA decisions, table of study results according to the presented endpoints

Although we controlled for incentives to render data on patient perspectives in a direct and systematic way considering PROs, it must also be stated that there are some factors outside the set framework that may also influence the presentation of data. For example, the benefit score and associated documents form the basis for price negotiation in Germany [40, 41].

Besides, the methodological foundation for patient preferences has also been developed in an international context and substantial literature has been published. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) developed a good research practice checklist for conjoint-analysis in health.

The checklist included 10 items covering the research question, levels and attributes, task development, the design of the experiment, preference elicitation, design of instruments, data-collection, analyzing statistical data, results and conclusions as well as study presentation standards. Even though, not endorsing a specific methodological approach, the checklist can serve as a good foundation for further discussions of good research practice for the application of conjoint-analysis methods in health care studies [42]. Besides, further research efforts give in depth advice concerning specific elements of the research process, for example the experimental design [43]. Several studies review the usage of different methodologies raising patient preferences systematically for different indications such as for example diabetes [44, 45]. Further, CONSORT guidelines advise on the reporting of PRO data in general [46]. This study contributed to the existing literature by outlining the methodology of PRO data inclusion within the field of rare diseases in Germany.

Limitations

In terms of limitations, data on clinical PROs could only be identified as such as long as they were highlighted as a self-reported measure or indicated to be a patient-reported measure. When no particular definition was provided, we assumed that the endpoint was physician-reported. We assume that almost all endpoints were specifically marked as patient-reported, as dossier providers have often argued that clinical PROs are particularly relevant to the patient and should therefore be specifically considered during the valuation and decision-making process. Furthermore, PROs are clearly defined as self-reported. However, in the case of clinical PROs, the reporting system was sometimes not indicated. In these cases, we searched for the primary classification of the symptoms scale.

In addition, pharmaceutical companies present their HRQoL data as a whole data subset. However, the Federal Joint Committee separates parts of the questionnaires selectively regarding mortality endpoints and HRQoL endpoints. Therefore, the data reveal a splitting of the datasets rendered by the pharmaceutical company. Endpoints were not shifted as this would not reflect the actual status quo of the data presented but would, rather, lead eventually to a presentation bias. However, it needs to be highlighted as a specific procedure presented by the German Federal Joint Committee and considered when selecting the appropriate data presentation technique.

Finally, it needs to be highlighted that some dossiers can fail due to formal reasons, for example not the appropriate comparator, a study population narrower than label etc. Therefore, the impact of PROs on the final decision is not always directly derivable.

Conclusions

The underlying evaluation demonstrates that although the political basis has been strengthened and the presented concepts have been broadly laid out as part of the health economic discussion in the context of benefit analysis and cost-benefit analysis, there remains a broad potential for the development of the practical framework regarding the systematic inclusion of patient perspectives, especially in referring to patient preferences and patient satisfaction, particularly considering the example of early benefit assessments for rare diseases in Germany. In this regard, it is interesting that patient preferences are presented in a qualitative manner. The broadly discussed and exemplified (by the IQWiG) quantitative methods have not been demonstrated in the field of rare diseases to date. While methodological standards for qualitative reporting have not yet been adopted, they must be appreciated with the same thoroughness as within quantitative research settings. An according clarification of the standard guidelines needs to be demanded. Moving even one step ahead, potentials of the integration of qualitative and quantitative research may be discussed, appreciated, and scientifically monitored in this specific context. Furthermore, the interim radiation of patient satisfaction has been commented on with vehement protest. In practice, however, it is only presented in 2% of cases in the field of rare diseases, even though this topic seems highly relevant due to the predominantly chronic and severe course of diseases. Neither of the PRO categories are enlisted within the GBA decision text. Acknowledged clinical PROs are often raised by the BPI-SF (pain scale) and FACIT-F (fatigue index). On the other hand, FACT-questionnaires, SF-questionnaires, and PedsQL are often GBA-appreciated HRQoL PROs. It is noteworthy that HRQoL questionnaires are in many cases split with regard to morbidity and HRQoL items, as datasets produced by one questionnaire are submitted cohesively. In this regard, the EQ-5D VAS is often appreciated as a morbidity endpoint by the GBA and therefore, in this context, it is

categorized as a clinical PRO, whereas the EQ-5D-Index is categorized as a HRQoL. Another commonly accepted example is the oncology indication specific EORTC QLQ-C30. This may lead to irritation, hindering the preparation of PRO data inclusion by pharmaceutical companies. Therefore, potential implications should be clarified.

Furthermore, the extent of PRO data presentation withholds considerable potentials. It is questionable whether morbidity-oriented clinical PROs should only be included in every second dossier, when it is highly relevant to the patient and to treatment success. Patient satisfaction and patient preferences follow by the same token. Appreciating the central role of patient perspectives within early benefit assessments and the according legal framework, the GBA decision text should particularly appreciate the consideration of patient perspectives, flagging incentives for more extensive consideration. Considering the growing financial pressure on health care systems, strengthening direct patient perspective involvement by further integrating PROs holds an immense opportunity to align health care with actual patient needs and therefore to contribute to an effective and needs-oriented health care system development.

Abbreviations

AMNOG: Arzneimittelmarktneuordnungsgesetz - Act on the Reorganization of the Pharmaceutical Market; GBA: Gemeinsamer Bundesauschuss – Federal Joint Committee; HRQoL: Health Related Quality of life; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen – Institute for Quality and Efficiency in Health Care; PRO: Patient reported outcomes

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Authors' contributions

AB conducted the data analysis and drafted the manuscript. JMS and KD revised the document for important intellectual content. All authors have read and approved the final manuscript.

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Not applicable.

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The authors declare that they have no competing interests. AB is employed by the AOK Bayern.

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Publisher's Note

Modul 2

Use and importance of different information sources among patients with rare diseases and their relatives over time: a qualitative study

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Use and importance of different information sources among patients with rare diseases and their relatives over time: a qualitative study

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Abstract

Background: Finding reliable information on one of more than 7000 rare diseases is a major challenge for those affected. Since rare diseases are defined only by the prevalence criterion, a multitude of heterogeneous diseases are included. Common to all, however, are difficulties regarding information access. Even though various quantitative studies have analyzed the use of different information sources for specific rare diseases, little is known about the use of information sources for different rare diseases, how users rate these information sources based on their experiences, and how the use and importance of these information sources change over time.

Methods: Fifty-five patients with a variety of rare diseases and 13 close relatives participated in qualitative interviews. For these interviews, a semi-structured guideline was developed, piloted, and revised. Data analysis involved a qualitative content analysis developed by Philipp Mayring.

Results: The participants considered internet as the most important and widespread information source, especially for early information. Although patients have difficulty dealing with information obtained online, they consider online searching a quick and practical option to gather information. During the course of the disease, personal contact partners, especially self-help associations and specialized doctors, become more important. This is also because information provided online is sometimes insufficiently detailed to answer their information needs, which can be complemented by information from doctors and self-help.

(Continued on next page)

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(Continued from previous page)
Conclusions: People rarely use just one type of source, but rather refer to different sources and informants. The source used depends on the type of information sought as well as other person-related factors such as preexisting knowledge and the disease stage. To improve people's information searching and connect them with medical specialists in rare diseases, a central information portal on rare diseases might be a suitable access point to provide free and quality assured information for patients, caregivers, and physicians. This would allow not only patients but also doctors to find quality assured information on symptoms and therapies as well as patient associations and specialized doctors.

Keywords: Rare diseases, Information sources, Informants, Health information seeking, Qualitative research, Content analysis, Self-help, Online information, Written information

Background

In recent years, rare diseases have become an important issue. Although a uniform definition is still pending, rare diseases are globally characterized only by their low prevalence. In Europe, "rare diseases" is the umbrella term for diseases that affect less than or equal to 1 in 2.000 people. Although rare diseases can differ greatly in type, symptoms, and causes, affected people usually face similar challenges. These include insufficient information. On the one hand, this is because many rare diseases are so rare, that only little information exists. Beyond that, information is often widely dispersed and difficult to find in the vastness of the internet or literature, so that access is limited [1].

However, it is undisputed that information plays an important role in coping with illness [2–8]. Based on Antonovsky's concept of sense of coherence, perceiving the world as comprehensible, manageable, and meaningful enables an individual to cope with critical life events [9]. In this context, information can make a decisive contribution in helping individuals develop their sense of coherence [10]. Understanding an illness's causes, symptoms, and impact seems to be a precondition for dealing with the disease in everyday life and can increase people's quality of life. Accordingly, not being provided adequate information about the disease and its implications can lead to feelings of resignation and fear among patients and their families [5–8]. Moreover, information is an important prerequisite to know where help can be found and pave the way to specialized centers and providers [3]. Both, again, impact patients' health situations. However, the information needs of individuals with rare diseases and their relatives include not only medical knowledge regarding diagnosis, therapy, progress, and prognosis but also information on various other aspects of the disease. These include practical information for everyday life, psychological counselling and social law aspects [3, 11]. Therefore, knowing how patients as well as their family members, who can also be strongly affected by their relatives' disease, search for information is an important issue. To shape the information gathering process as well as possible and thus meet the patients' information needs optimally, knowledge is needed on how searching is done, what sources are used, and what relevance different sources have. Moreover, how the use and relevance of different sources change over time should be investigated.

Information searching patterns from patients suffering from chronic but not rare diseases have been extensively analyzed. Numerous studies revealed different sources of information, which are of importance to different groups of patients, but mostly cancer patients [12–18]. These range from physicians, who are often rated as one of the most favored and trusted sources [13, 17, 18], to information brochures, the internet, as well as non-medical professionals, such as pharmacists and nurses [14–16]. Other generally used sources of information include books, newsletters, and mass media sources. For patients with common diseases, family members and friends were also used to gather disease related information [14, 16]. Moreover, some factors have been identified that affect people's search for information. Female patients were reported to inform themselves more often and to use more sources than male patients. Additionally, younger patients and those with a higher education showed more frequent information seeking behavior than older patients and people with a lower educational background [15]. Regarding phase of illness, it was found that shortly after their diagnosis people favored written information while at a later stage relatives and friends become increasingly important [16].

Because of the specific characteristics of rare diseases, such as unpredictable courses, limited available knowledge, lack of exposure in the media, etc., it can be assumed that information seeking behaviors by people with rare diseases are not completely similar to those of patients with common diseases [19]. However, still little is known about how people affected by a rare disease and their families search for information. Previous studies may be outdated, have relied on few single sources,

focused on specific information needs only, and did not focus on rare diseases in general [19–24]. Teixeira et al. [22] conducted a questionnaire survey of 1019 patients with a rare blood disorder, which showed that medical specialists are of particularly great importance when it comes to sources that were widely used for information gathering. In this study, respondents who reported feeling sufficiently informed about genetic testing and its implications for their health mostly reported having received this information from medical specialists before family doctors and support groups. Even though medical specialists were also the source they most trusted, they would like to get more information from their family doctor. Furthermore, among patients who did not feel sufficiently informed, the majority answered that they would like to gain information from their family doctor. Additionally, non-medical sources, such as patient associations, websites, nurses, and printed information were of importance to the respondents. After medical specialists, patient associations were the most trusted information source. Due to the high level of knowledge possessed by patient associations, these are often called patient experts [25].

General practitioners also proved to be one source of information patients would like to receive significantly more information from, according to a study by Matti et al. [21]. They identified preferred sources of information based on responses from 30 patients with multiple sclerosis (MS) and found that there was a discrepancy between the amount of information people actually receive and the amount they would like to obtain. Moreover, eye specialists and neurologists were identified as sources they would like to receive more information from. Regarding MS patient associations and MS specialist nurses, patients reported an almost ideal amount of information that was being provided.

An older study from Lanigan and Layton [20] on 108 patients with a rare skin disorder drew similar conclusions. The results from their questionnaire survey also illustrate that medical specialists were the most used and preferred information source, followed by general practitioners. However, it must be considered that this study occurred before the arrival of the internet, so that its relevance for today's conditions is limited. Wibberly et al. [23] studied 16 patients with a rare lung disorder and identified various information sources by means of face-to-face interviews. These include primary healthcare physicians, patient information leaflets, as well as the World Wide Web, nurse specialists, and patient support groups. The most valuable information sources were medical specialists in rare lung diseases, nurse specialists, as well as patient support groups.

Carpenter et al. [19] also confirmed that physicians and the internet were the most used and credible sources for patients with vasculitis to obtain information on medication, followed by pharmacists, and other affected people. Based on an online survey of 232 patients, they also found that family and friends are not relevant sources of information, presumably because they do not hold much information on rare diseases. Additionally, gender differences were found. While male patients, unlike female patients, rated their spouses or partners, as well as nurses as fairly credible sources, female patients preferred medication package inserts and the internet as sources of information.

Molster et al. [24] conducted an online survey of 810 patients with different rare diseases and found that the most sought and preferred sources of information were medical specialists and patient organizations followed by friends and family members. Regarding non-personal sources, respondents stated that they prefer to be referred to an information website or social media. Other preferred types of information sources included printed media, such as leaflets and brochures, as well as journal articles.

To summarize, family doctors and medical specialists, the internet, and support groups are of great importance for patients with rare diseases when searching for information on their disease. However, limited studies have investigated the use and perceived credibility of information sources over time and if so, their reasons for it. Since existing studies are based mostly on quantitative methods, further qualitative research is needed to analyze how people with rare diseases assess different sources and on what experiences. Due to its open approach, qualitative research can achieve a deeper understanding of peoples' attitudes and causes. The aim of this study, therefore, was to obtain a holistic picture of the information sources used by patients with various rare diseases and their relatives; specifically, what relevance they attach to different sources and how this relevance changes during the course of the disease.

Methods

Due to the lack of substantial data on information sources in the field of rare diseases, the authors decided on a qualitative study design. Thus, it is possible to explore under-researched areas with maximum openness and reveal all aspects of importance for patients and their families concerning finding information. To detect patients' experiences regarding information acquisition and information sources used, semi-structured interviews were conducted. Therefore, we developed an interview guideline, stimulating people to tell us about their medical history and the way they searched for information (Table 1). Since the research team included young associates with mostly theoretical knowledge in qualitative research, this was done in close cooperation with an

Table 1 Semi-structured interview guide

Set	Principal questions
Experiences with the disease (from patients who consciously experienced their diagnosis)	Please remember the beginning of your disease. What changes did you notice?
	How did diagnosis proceed?
	What happened after diagnosis?
	When imagining yourself in that position again, how did you feel?
Experiences with the disease (from patients who did not consciously experience their diagnosis)	Please tell me about your disease and how life has changed due to it.
	How does your disease affect your everyday life?
	Some people want to learn more about the diseases that they live with. How about you?
Information seeking and information needs	How was that, striving to find information about your disease?
	Do you remember any events that you associate with increased demand for information?
	Please tell me about situations in which it was easy to gather information.
	Please tell me about situations in which it was difficult to gather information.
	Which moments do you consider important in searching for information?
Type of access	Please imagine the many possibilities of modern and classic media to communicate. Please recall your own situation. Which media did you use when searching for information?
	Which medium would you prefer for accessing information?
Completion	Are there any other topics that you would like to talk about?

external specialist at Hanover Medical School, who has long-time expertise in qualitative health research. The specialist conducted a workshop during which they shared the knowledge and skills required for planning, conducting, and analyzing qualitative interviews. In addition, extensive literature studies were carried out. Afterwards, the authors developed a first draft of the interview guideline and discussed it jointly with the specialist. A concerted version was then presented at a research workshop held at Hanover Medical School with several internal and external qualitative researchers, during which revisions were made to generate the final version. Individual sources of information and their usefulness could be derived from this. After pretesting the interview guideline with three patients with rare diseases, we observed that patients diagnosed before or shortly after birth found it difficult to answer the opening questions and narrate their diagnostic paths. An alternative conversation starter was then added, to ensure that it was suitable for such patients too.

To select a heterogeneous and balanced sample, several medical experts from the project consortium divided the total of rare diseases into eleven different groups of diseases in accordance with the affected organ systems. It was planned to conduct six interviews in each group as well as ten interviews with patients, who had to wait for at least 10 years until they received a correct diagnosis. Thus, a total sample of 76 patients was planned to be recruited. Nevertheless, upon saturation of interview data, a smaller sample would suffice. Participants were recruited consecutively over several months by a physician and GCP trained study investigator Freiburg Center for Rare Diseases (FZSE) at the University Medical Center Freiburg, University of Freiburg, Germany. Patients with rare skin diseases and their relatives were reached out directly through FZSE via personal approach during patient visits (gatekeeper sampling) and board notices (sampling by self-activation). To recruit other groups of rare diseases, more centers for rare diseases belonging to the consortium of rare diseases (AG-ZSE) were included as well as patient organizations.

Care was taken to establish a consolidated interview atmosphere with the participants. Therefore, researches allocated enough time and visited patients and close relatives at home whenever requested. Telephonic interviews were conducted only if participants requested for it. After making small talk, we explained our research project in detail and answered any questions. We emphasized that all data would be kept strictly confidential and that anonymity would be ensured, so that retroactive conclusions concerning the participants would not be possible.

The interviews were analyzed following the structured content analysis method by Philipp Mayring [26]. Each audio recording was verbally transcribed and read into MAXQDA analysis software. Subsequently, two researchers worked through the first three interviews and marked all relevant text passages. To develop an extensive system of categories (Table 2), a deductive-inductive

Table 2 Coding tree

Core categories	Sub categories
Print media	Books
	Brochures/leaflets
Television	
Helpline	
Internet	Non-specified
	Patient organization
	Medical facility
	Encyclopedia
	Social media
	Scientific database
	Email/newsletter
Personal contacts	Center for rare disease/specialized clinic
	Primary care doctor
	Pediatrician
	Specialized doctor in outpatient practice
	Parents
	Social worker
	Patient organization
	Other affected persons
	Congress

procedure was used. Several categories could be derived from the theoretical framework based on previous research on information sources for rare diseases, including medical specialists, patient organizations, and primary care doctors. These were completed by inductive categories if they appeared from the text. This procedure was followed by a critical examination and, if necessary, modification of the original categories. Afterwards, the marked text excerpts were analyzed with regard to the research question. After assessing the interview transcripts, the researchers conducted three focus groups with participants of the interviews and one focus group with patient representatives and members of the Alliance of Chronic Rare Diseases in order to discuss and validate the findings.

Extracted citations were translated by an external translation service, approved by a native speaker and then included in the paper. The following will accompany direct interview quotations: Gender ("M" for male, "F" for female), a consecutive number, age, and status as either a patient ("P") or relative ("R").

Results

We interviewed a total of 55 patients and 13 close relatives between March and December 2014 (Table 3). There were almost twice as many women ($N = 45$) as men ($N = 23$). Participants' mean age was 50.5 years. The interviews lasted 10–143 min, with 68 min on average.

Based on the evaluation of the interviews, a multitude of different information sources used by patients and their relatives for gathering information on rare diseases was revealed. The authors disclosed four main themes that were of importance in nearly all interviews. These main themes include the "internet as the first source of information" (theme 1), which describes the relevance of online searches for those affected. The second theme highlights the role of patient organizations and other patients in the information retrieval process, which allow for communication at peer level. Doctors and their perception as a source of information by persons affected is illustrated in theme 3. Lastly, theme 4 deals with written information.

The internet as the first source of information on rare diseases

Many of those interviewed reported in detail about their struggle to receive a correct diagnosis. Often this meant a long-lasting and emotionally charged odyssey. The need for information, once a diagnosis has been made, was accordingly high. In this context, for almost all the respondents, the internet and especially search engines such as Google were one of the first sources to search for information on their own or their relatives' disease. According to the interviewees, this allowed them quick and uncomplicated access to information. In this context, different approaches to how to proceed when searching online for information were identified. Most of the participants simply googled their disease and clicked in a more or less unstructured or unskilled manner through the provided information websites, while others advanced more systematically. In many cases, it was possible to establish a connection between people's searching approach and their prior knowledge. Patients or family members, who work in the health sector and are familiar with medical terms, demonstrated a more targeted and satisfied approach to research online than those without medical backgrounds. Moreover, people who are familiar with online searches reported fewer difficulties.

> *"It was when everything was new. We took in all the information we could."* (M47, 59 years, P).

> *"Well, the information is primarily shared over the internet."* (F14, 57 years, P).

> *"(…) I enter it into the internet and then find the information. It would now be the easiest and*

Table 3 Participant characteristics

Patients		
Age	Gender	Group of rare disease
23	female	Genetic skin disease
32	male	Cystic fibrosis and pulmonary disease
32	male	Immunodeficiency
39	male	Skeletal dysplasia
66	male	Genetic skin disease
85	female	Connective tissue disease
70	male	Connective tissue disease
72	male	Genetic kidney disease
47	male	Congenital metabolic disease
50	female	Immunodeficiency
53	female	Genetic skin disease
58	female	Genetic disease of the digestive tract
54	female	Cystic fibrosis and pulmonary disease
57	female	Immunodeficiency
44	female	Neuromuscular disease
43	female	Cystic fibrosis and pulmonary disease
47	female	Neuromuscular disease
71	male	Neuromuscular disease
44	female	Genetic skin disease
53	female	Connective tissue disease
72	male	Genetic skin disease
48	female	Immunodeficiency
54	female	Genetic skin disease
58	female	Congenital metabolic disease
72	female	Immunodeficiency
48	female	Genetic kidney disease
47	female	Congenital blood formation disease
44	female	Skeletal dysplasia
27	female	Congenital blood formation disease
36	female	Genetic kidney disease
40	female	Congenital metabolic disease
61	female	Neuromuscular disease
48	male	Congenital blood formation disease
44	female	Genetic eye disease
52	female	Genetic eye disease
46	male	Cystic fibrosis and pulmonary disease
60	male	Neuromuscular disease
62	female	Neuromuscular disease
48	female	Genetic eye disease
61	female	Connective tissue disease
66	female	Congenital metabolic disease
18	female	Congenital blood formation disease
64	female	Congenital metabolic disease
37	male	Cystic fibrosis and pulmonary disease
49	female	Congenital metabolic disease
59	male	Genetic kidney disease
70	male	Connective tissue disease
45	female	Genetic kidney disease
51	female	Genetic kidney disease
62	female	Genetic eye disease
39	female	Neuromuscular disease
51	male	Immunodeficiency
40	male	Skeletal dysplasia
74	male	Cystic fibrosis and pulmonary disease
69	female	Immunodeficiency
Relatives		
Age	Gender	Group of rare disease
44	male	Neuromuscular disease
48	male	Skeletal dysplasia
28	female	Genetic skin disease
46	female	Genetic skin disease
60	female	Skeletal dysplasia
50	male	Neuromuscular disease
43	female	Skeletal dysplasia
46	male	Congenital metabolic disease
40	female	Genetic skin disease
49	female	Cystic fibrosis and pulmonary disease
45	female	Genetic skin disease
32	female	Genetic disease of the digestive tract
41	male	Skeletal dysplasia

quickest way for me." (F17, 47 years, P).

"Well, when I am looking for something like this, I will look at Wikipedia first, because I think it's great and well-structured. Yes, then I do not know anymore. Then you land somewhere at large. What just/whichever link appeals to one, but I cannot recite it now." (F67, 45 years, R).

Even though, the internet was perceived as providing easy and quick possibilities for information seeking, most respondents did not report satisfaction with the search results at the beginning of their research. Dissatisfaction, for example, arose when only little information was available. This was particularly the case when people were affected by very rare diseases with only a few sufferers or few research efforts. Otherwise, finding a multitude of information was also challenging for

searchers. Interviewees, who told us that there was a wide range of information, often felt they are not enough of an expert to manage these amounts of data. Moreover, people suffering from diseases that proceed differently in each individual case recounted problems comprehending what information is correct for specific cases. Younger persons and people who use the internet on a regular basis reported fewer difficulties with large quantities of information than those who are unskilled in online searches and of older age. Moreover, it could be seen that people reported fewer difficulties as the disease progressed and their expertise grew.

> *"I also think that it is better, I think it sucks when there are several million websites when you look up cancer or the like. I also think that if someone gets diagnosed with cancer, he immediately wants to know what impact it will have. If there are then a thousand websites, you will go completely crazy."* (F17, 47 years, P).

Another challenge reported in connection with online searches was that of dealing with information that is perceived as frightening. Many interviewees told us that when they started searching, they found information on the internet that was shocking, for example regarding life expectancy, severe courses of disease, etc. This information was so dreadful that some of our interviewees did not continue their online research. In this regard, some patients criticized being left alone with their findings and worries and wished for greater support from their doctors. Being alone with this information, in their opinion, could incite panic or despair. The results suggest that when people start searching they do not have enough expertise or support by others to put information into its proper context and assess it correctly. Our interviewees, in this connection, expressed the need for a closer support, especially by their doctors.

> *"Well, I was only on Wikipedia. What I read there shocked me, because it sounded extremely bad. After that, I never went onto the internet again."* (M60, 46 years, R).

> *"You stand there alone, and that is, that is the problem, when you stand alone with your illness. Err. Meanwhile you think about it and say: Mhh. And now?"* (M38, 60 years, P).

Furthermore, peoples' perceptions of the utility and credibility of the information found online varied greatly. This became obvious in regard to who is behind the information (website), what information is communicated, and how. Since most patients and their relatives barely know about their own or their relatives' disease shortly after diagnosis, the assessment is based partially on who is the websites' operator rather than on the contents of the information itself. Many of our interviewees first encountered Wikipedia when they started searching online. Some of them rejected this website, since the information offered there was too generic for them. Others criticized Wikipedia because it does not control its information, which can be changed arbitrarily by anyone at any time. In contrast, other patients and family members expressed positive views about it. From their point of view, especially in the beginning, Wikipedia is a good source of information to get an idea of the disease, its causes, symptoms, and progression. It was also highlighted that this information, compared with others, was clearly structured as well as quickly and freely available. Looking back, some people who now have an extensive knowledge on their disease rated the quality of the information offered there as good or high.

> *"(…) and then, after the appearance, one decides what is serious, yes, who is behind it, (…) are the err, here mmhhh Alliance of the chronic/well, the ACHSE associated, NAMSE associated, yes."* (F35, 44 years, P).

> *"Yes, I had, of course, I have. I then do not want useless information, because of my job I also have reasonable/ well, I would never at Wikipedia, we already had it."* (F19, 44 years, P).

> *"I just entered it and then usually ended up at Wiki. Wikipedia. It was the most reliable for me."* (F14, 57 years, P).

Medical databases on the internet, such as PubMed, were hardly used. Often only interviewees with medical backgrounds reported knowing these sources of information. This was described as an advantage in relation to other patients who do not have medical backgrounds, due to its high quality and current information.

> *"I therefore rather checked at PubMed or so, but it was of my advantage, because I have been active in the field myself."* (M65, 40 years, R).

Patient organizations and other affected persons – information sharing at peer level

In many cases searching the internet for information helped patients or their family members to contact patient organizations at an early stage. No interviewee reported being informed by their doctor about this way to receive support and information. Almost all our respondents who used a patient association

website valued their supply of information highly. One person, however, criticized that their information was not comprehensive and current enough regarding new developments and findings. Another patient, who visited a website that was not specialized on one disease but a group of diseases also reported lower satisfaction, since there was detailed information only on the more common rare diseases. Other interviewees praised their relevant and helpful information. In particular, concerning information on issues in everyday life, such as finding medical specialists near to home, dealing with the disease in family and working environments, etc., self-help organization websites provided crucial hints. One person especially emphasized that his patient association helps to make the latest findings accessible to the general public by translating English scientific articles into German and displaying them on the website. Thus, patient organization websites contribute to knowledge transfer and access. For many of our respondents, patient association websites provided the most reliable and high-quality information, so that after identification, no further websites were used.

"Well the main information, the thing that helped with our progress the most, was the support group. The exchange actually starts there, when you join in on the conversation at eye level (…). " (M58, 48 years, R).

"It strengthens one, when you sometimes think you are insane. (LAUGHS) Yes, because everything changes and one thinks, yes why am I feeling so bad, why am I always tired and hurting? But when you have the opportunity to exchange stories err, then you can put your mind at rest, because you learn that, ok, it is normal." (F31, 36 years, P).

"No. I never looked it up, because I have to say, up to three years ago we regularly participated at the annual meeting of the support group or the regional meeting in LOCATION and therefore the information actually was sufficient." (F51, 62 years, P).

Interviewees particularly valued the close personal contacts made with those committed to self-help. When a rare disease leads to similar and severe progressions and is accompanied by comparable restrictions and challenges as those of affected individuals, patient organizations play a key role in information gathering. While there is sometimes too little time for patients in the medical setting, in the self-help field patients with rare diseases and their relatives often feel that people take a lot time for their issues and needs. It was often reported that the personal contact resulted in a close and strong contact between existing members of the patient organization and the interviewees for years. Furthermore, people see information from patient organizations as an opportunity to gain practical knowledge that goes beyond the perfunctory information they receive from the internet. Since rare diseases often show an individual progression, online information is perceived as too generic, while self-help contacts meet the demands for more specific information.

"I then called the chairman myself and he immediately took an hour of his time and answered everything, the questions, that I already had and more (…). " (M64, 46 years, R).

"And those are the information, which the doctor does not give you, how I deal with everyday life, when I need what." (F22, 72 years, P).

I: "How do you judge the quality of the information?"
P: "That however is good, well only the information about the support group, nothing else."
I: "And the information, that you found on other sites in the internet?"
P: "No. It was too general, unmeaningly." (F10, 50 years, P).

Nevertheless, some patients feel no need for personal exchange or even reject the principle of self-help. This is based mainly on the assumption that it only serves the purpose of commiserating with each other. This can be noticed, in particular, among people who have trusting relationships with persons outside patient organizations, such as medical specialists in hospitals, who are available to answer any questions. However, individuals who are reserved about the idea of self-help due to this assumption often have no practical experience with self-help at all. Others see no additional benefits since disease progression differs too greatly from one person to the next. Moreover, people with a mild disease course sometimes do not make contact with patient organizations, since their need for information and exchange is low. They reported being able to cope with their situation and pointed out that they get along. Furthermore, meeting with patients with serious disease progression is perceived as discouraging.

"Whining does not help; therefore, I do not sit down and moan. I do, however, understand the people that complain in the support group. Yes, I do not know if it helps them." (F39, 62 years, P).

Physicians, basic health care provider and highly specialized experts

During their medical care process, patients and their families often met many different physicians. Although some patients reported receiving a quick diagnosis and were referred to specialized care from the very beginning, such as patients with cystic fibrosis, which can be easily diagnosed shortly after birth, many respondents first consulted their family doctor when searching for a diagnosis and did not attend a medical specialist until a later stage. Even in the further course of treatment, not only medical specialists, but also primary care doctors play an important role due to community care provision. The experiences with doctors outlined by the patients and their families are, however, very heterogeneous.

> *"I was lucky to be under the care of a very experienced orthopedist from an early stage on (…). "* (M04, 39 years, P).

> *"Yes, I was not amused about it, but also not depressed. Every time I was told that it was not it, we somehow made new attempts to get a diagnosis. I have also been to a lot of so-called experts on muscles."* (M18, 71 years, P).

Preference for commitment and support instead of knowledge transfer from general practitioners

Many of the participants, who first contacted their general practitioner (GP), feel dissatisfied regarding information provided by their doctor. Many of our interviewees criticized that their doctor gave too little or even no information on their disease. Especially when patients received their diagnosis they complained about too little and barely patient friendly information. Even though patients and their relatives understand that doctors, who do not deal with rare diseases on a regular basis, cannot hold information about all rare diseases, they would wish for more transparent dealing with that lack of knowledge.

> *"I have to say that, when it comes all doctors, (…) you cannot expect anything else from them, they did not identify it, do not know this disease, that is to say, if you go there, here, my hemogram is not in order, standard things get asked (…). A good doctor can recognize that a level is out of the norm, but that was of course also a little stupid, sort of, that he did not think to look into the other direction too."* (M34, 48 years, P).

> *"Yes, and there I was the one time, err, with my telephone and thought, yes, maybe the doctor will say something about it, but no, it was done for her! She had the diagnosis and it was over. I am supposed to look for someone, who mhm, yes look for a doctor."* (F28, 47 years, P).

Patients expressed frustration and resignation with general practitioners who refused to seek assistance for their limited knowledge. Particularly, shortly after receiving a diagnosis, when specialized centers for rare diseases or contact partners had not yet been found patients felt left alone and helpless.

Nevertheless, other patients reported high satisfaction with information transmission from family doctors. In many cases, this contentedness resulted less from an immediate and comprehensive offer of information on the GPs' part, but more from the commitment to learn more about their patients' conditions and go in search themselves. However, even if the GP did not acquire the knowledge by himself but through the patients or their relative, this was highly valued. From the interviews, it was found that in such cases GPs often became trusted informants, near to their homes, who played an important role in patient's health care provision.

Specialists and centers for rare diseases – trusted and current disease-related information

For almost all interviewees involved in specialized care, such as at centers for rare diseases or university hospitals, the doctors working in these institutions are an important information source regarding medical issues. Besides patient organizations, medical specialists in these centers were often described as key informants on disease specific information. After diagnosis, as well as in the course of the disease when the state of health deteriorates noticeably or treatment becomes necessary, the need for information sharing with specialized doctors arises. Many of our interview partners reported very high information quality and valued the fact that specialized carers are available for all kind of questions. The currency of the information was furthermore praised. Because of their proximity to research efforts and other experts, medical specialists have up-to-date knowledge that they pass on to their patients, which is highly respected. One interviewee, however, complained that he would have to claim medical specialists' information instead of doctors transmitting their knowledge by themselves.

> *"For me, it is enough to have the feedback from the very knowledgeable skin clinic."* (F01, 23 years, P).

> *"Professor PERSON always tried to share his knowledge and his research with his patients."* (F40, 48 years, P).

Of particular importance is also the fact that patients and their families normally have fixed individual

contacts in the centers for rare diseases, who are entirely familiar with their disease history and symptoms. In this context, people also positively highlighted not needing to repeatedly explain their condition, which was felt as a relief. Some people also discussed longstanding and trusting physician-patient relationships arising from that, allowing for low-threshold contact, as well as quick and personal answers to all medical concerns. From the interviews, it became clear that patients and their families also see medical specialists and centers for rare diseases as a (good) complement to the range of information offered from their patient's association. While those hold relevant and most trusted information on most issues beside medical issues, medical specialists are especially important regarding detailed aspects concerning therapy, diagnosis, etc.

Printed information – high quality, but not up to date information and sparsely used

Even though many of the patients and their relatives in our interview sample received information to a large extent from the internet or personal contacts, others, however, reported the wish for printed information. On the one hand, this is because people appreciated the possibility of holding something in their hands, where they can look things up again, when they feel like it. This was especially emphasized at earlier stages of disease progression.

> *"(…) I would rather need it in writing, to refer back to again."* (F31, 36 years, P).

Shortly after diagnosis, for example, information brochures are perceived as helpful sources, since they provide comprehensive and often comprehensible information. Moreover, people reported that brochures are well suited for bringing them on the day of doctors' appointments to give them a review of their disease. At later stages, however, brochures do not cover people's needs for more specific and detailed information.

> *"Well I also (…) got the booklet, how do I deal with it myself and where can I get help from. Very good information, yes."* (F43, 18 years, P).

> *"Here you go. My husband has brought me informative literature, because I knew that he (doctor) did not know it. I pushed it into his hands and told him to read about it."* (F31, 36 years, P).

Some of the interviewees found it helpful to read magazines offered by patients' associations. Additionally, for those who did not actively participate in regional meetings or did not look for personal exchange, this type of information provision was important. In this connection, patients especially highlighted experience reports from other affected patients and families as valuable information.

> *"The most important source of information was simply/ the newspaper of Glandula. Publicly displaying the personal experience reports that people wrote there, the stories of what they have been through, when they got diagnosed. That is what I realized and what I took in."* (M47, 59 years, P).

Additionally, specialist books were used for information gathering, but some of the interviewees put them aside, discouraged by the medical terminology. Especially in the time shortly after diagnosis, they exceeded the capabilities of patients and relatives. People also complained that books would often not be up to date, a fact that can be important when considering that specialist books often refer to medical issues such as therapeutic options, which could be subject to frequent amendment.

> *"(…) and that is anyway the medical terminology and how can you as a layman go and change it for yourself, or read it, it will not do, it does not work."* (F17, 47 years, P).

> *"As mentioned before, books, they definitely are not; they definitely do not have the latest insights."* (M55, 74 years, P).

Discussion

Different sources for different needs

Patients affected by a rare disease as well as their relatives use a variety of different sources to keep themselves informed. In accordance with previous quantitative studies of specific rare diseases, among others, especially the internet, patient associations as well as specialist doctors play an important role when gathering information [6, 20–23]. However, to date, the types of information sources used by patients with various rare diseases and their families, how they assess these information sources, and how their value changes over time have remained unclear.

From our interviews, it was shown that initially after diagnosis, when the need for information is very high, only few patients obtained detailed and profound information from their doctors. This is in line with a study by Molster et al. [24] who reported that almost three-quarters of the surveyed patients with a rare disease received little to no information at the time of diagnosis. A systematic review investigating experiences of patients

with rare diseases found that more than half of the included studies reported lack of knowledge among health professionals about patients' rare diagnosis [8]. Most patients and relatives therefore searched online for further information and were confronted with a flood of information. To assess the quality and relevance of such information and deal with frightening information is a difficult task for laypersons. Therefore, this first step of information search is often a frustrating and intimidating experience. Contact with other affected persons can help patients and relatives to find their way through the thicket of information by placing them into a proper context and thus, gain a deeper understanding of the disease. Additionally, doctors can contribute to successful information acquisition if they face the challenges that people with rare diseases bring to their care provision openly. This includes that doctors show willingness to become acquainted with their patients' diseases and do not leave them alone with information acquisition, especially in the initial time after diagnosis. This is underpinned by various studies [5, 11, 27–29]. Lack of involvement is common among health professionals when they lack experience in their patients' diagnosis [27]. Particularly, when medical professionals withdraw in such cases, it can lead to feelings of resignation and insecurity [5]. Efforts to mitigate their lack of knowledge, on the other hand, are highly valued by patients with rare diseases [11].

We were also able to show that the use of different sources is not stable, but can change over time. While, for example, people regarded the internet as an uncertain source of information due to information overload in the beginning, at a later stage their perception changed as they learned a more targeted approach to search and carefully choose which websites to use. Thus, our results indicate that the importance of different sources varies depending on, among other things, the state of disease progression and the state of knowledge.

Great potential for patient associations

The interviews have shown that patient organizations play a major role in people's information acquisition. Previous studies of different rare diseases have confirmed the importance of patient organizations and knowledge sharing with other people experiencing the same condition [11, 19, 21–25]. As a contact partner at peer level, they can help people to cope with their disease by offering comprehensive and comprehensible information as well as guide their way to specialized care by helping patients and families to find competent caregivers from the very beginning. This way, time-wasting detours in information searches can be avoided. As described by the interviewees, patient associations can close the gap of information offered by medical specialists in rare diseases, by not only providing medical information, but information relevant to everyday life. Huyard [11] reported a similar finding among patients with one of the six rare diseases and their parents. They sought answers to questions regarding living with the disease in daily life, such as how to lead a happy life, from other affected persons [11]. Therefore, information from patient organizations should be regarded as an important supplement for information offered by patients' caregivers. However, despite very positive self-help growth, its potentials do not seem to have been completely realized. Nowadays, there are approximately 60, 000 self-help organizations with a health-related focus in Germany, but only a small number of those deal with rare diseases [30].

Although possibilities for participation have increased over the past decade, in the future self-help associations should be even more integrated to improve patients' health care. As we have shown, no patient or relative from our interview study was made aware of the possibility of contacting a patient organization by their doctor. Under the term of "self-help friendliness" different attempts to institutionalize relationships between carers from the in- and outpatient sector and self-help associations in Germany have been made [31]. In this context, a set of commitments has been agreed to sustainably integrate self-help on a collective level into health services [32]. In the stationary sector, for example, different quality criteria have been defined to ensure a close connection between hospitals and self-help. So far, however, few care facilities have joined these voluntary collaborations. In the future, carers in the field of rare diseases should also endeavor to collaborate with patient associations. Besides opening their medical care provision to knowledge and experiences from patient organizations, they could also strengthen contacts between their patients and self-help groups and thereby support their patients' coping processes.

However, to permanently secure patient organizations' work, sufficient funding is required. Even though, the funds approved by statutory health insurance recently increased due to the Prevention Act (PrävG) adopted in 2015 [33], it is still unknown whether patient organizations have sufficient financial resources to sustain their important work. Especially, for self-help in the field of rare diseases, which is often characterized by local groups with a limited number of members and low public visibility, sustainable funding to maintain their services seems to be endangered; hence, further research is needed. Moreover, still little is known about the economic potential of self-help groups. The study shows that patient organizations play a major role for patients to find highly specialized care units. This is also interesting from an economic point of view. Patient organizations do not only provide

information very efficiently at low cost but also provide a communication platform for patients to exchange their worries, fears, experiences, and observations. Until now, the role of patient organizations has not been assessed from a health economic point of view and, therefore, should be studied in the future.

Online sources for quick and easy information gathering and recommendation for a central information portal on rare diseases

Besides the great potential for self-help associations, it has been demonstrated that online information is currently of crucial importance for patients and their families to gather information. It especially enables newly-diagnosed patients to search for information quickly and easily. Additionally, in more advanced stages of the disease, people rely on online information in case they need information on current developments. Dissatisfaction, however, arose due to the unfiltered flood as well as the unknown quality of the information.

Therefore, new approaches for optimizing and developing user oriented information systems are preferable. For this reason, efforts have been made to establish and implement an information portal on rare diseases (ZIPSE) [34], where patients, their relatives, as well as medical professionals can access clearly presented and high-quality information from a central web based point. Since information provides the basis for coping with the disease and receiving specialized care [2–8], such a portal can help to improve patients' health situation sustainably. Besides increasing their quality of life, reduced doctor-hopping and targeted therapy can help to use limited financial resources more adequately. This also allows doctors, who cannot hold information on all 7000 rare diseases, to obtain information, for example, on treatment options, medication, or specialized medical colleagues when necessary. This could also help on the caregivers' part to make their patients' healthcare more efficient and compensate for the uneven level of information, which was often criticized in the interviews. Physicians should be conscious of their important role in people's health care and endeavor to better inform themselves on their patients' diseases, and give them specific assistance regarding which websites to use and where self-help contact partners can be found.

Strengths and limitations

The purpose of this study was to gain insights into how people affected by rare diseases experienced their search for information, which sources of information they used, and how they assess different sources. We conducted interviews with an extensive sample of patients, with a variety of rare diseases, and their relatives, revealing a wide range of attitudes and opinions. Unfortunately, not all aspects that have been mentioned in the interviews could be reproduced in detail in this manuscript due to lack of space. Rather, the main themes were presented as comprehensively as possible. Therefore, supplementary observations regarding information sources and their potentials should be a topic for further publications.

It must be noted that our sample included individuals who had been living with the rare disease for many years and whose information needs may not be as high as those who have been recently diagnosed. Hence, recall bias cannot be completely ruled out. Nevertheless, living with symptoms, finding a correct diagnosis, and searching for information on the disease represent phases of great significance for patients and their relatives; thus, a sufficient ability to recall could be assumed.

Due to the qualitative approach of this interview study, it is not possible to generalize the findings to patients with rare diseases and their relatives as a population. It must be kept in mind that findings from a qualitative survey must be embedded in their spatial and temporal context [26]. However, that does not mean that they are not transferable to other people and situations. The creation context, however, must be considered when applying the findings to a new context.

Moreover, it was not possible to conduct theoretical sampling due to limited access to patients and their families as well as time restrictions. Sample recruitment was carried out by the Freiburg Center for Rare Diseases (FZSE) at the University Medical Center of Freiburg, University of Freiburg, Germany. As this center specializes particularly in the treatment of people with rare skin disorders, it was difficult to gain access to patients with other rare diseases. Nevertheless, by covering most of the planned six interviews in each group and reaching a saturation point at a later stage of the interview process, a heterogeneous and balanced sample can be assumed.

It should be mentioned that the interviews were obtained from a study of the conceptualization and implementation of a central information portal on rare diseases. This study identified the information needs of people living with rare diseases, their families, and of health professionals to integrate them into the information portal. Nevertheless, the researchers evaluated the interviews regarding important information sources in an unbiased way and with maximum openness.

Conclusions

In our study, various information sources, such as the internet, self-help organizations, and doctors, have been confirmed as important access channels for people living with a rare disease and their families. Due to the qualitative approach, reliable statements on the reasons why, and how important they are to patients and their families have been made for the first time. Moreover, it was

possible to show how the importance of different sources changes over time.

For physicians, especially those who do not deal with rare diseases daily, this does not mean they must hold information on all 7000 rare diseases, but they do need to know where to get quality assured information when necessary. For them as well as patients and their families, a central information portal, such as ZIPSE, might be an option. Interested people can find here bundled high quality information on a large number of rare diseases, which makes searching for information easier. It can also raise awareness of services from patient organizations that are of particular importance for patients and their families as they help to bring them together with specialized partners and address their need for practical everyday information as well as share experiences.

Abbreviations

AG-ZSE: Consortium of rare diseases; F: Female; FZSE: Freiburg Center for Rare Diseases; GCP: Good Clinical Practice; GP: General practitioner; M: Male; P: Patient; PrävG: Prevention act; R: Relative; ZIPSE: Central Information Portal on Rare Diseases

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Authors' contributions

SL conducted interviews and analyzed and interpreted the data. MF, TH and JMS contributed to the methodological conception of the interview study. AB and DR conducted interviews and contributed to the interpretation of the results. FS recruited patients and relatives for participating in our study and contributed in conceiving the manuscript. SL drafted the manuscript and all authors were involved in its review and revision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to data privacy but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study received ethical approval from the research committee of the University of Freiburg in February 2014 (ref: 53/14).
Written informed consent was obtained from all individual participants included in this study.

Consent for publication

We have obtained consent to publish from the participant to report individual patient data.

Competing interests

The authors declare that they have no conflicts of interest.

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Publisher's Note

Modul 3

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Original Paper

Adopting Quality Criteria for Websites Providing Medical Information About Rare Diseases

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Abstract

Background: The European Union considers diseases to be rare when they affect less than 5 in 10,000 people. It is estimated that there are between 5000 and 8000 different rare diseases. Consistent with this diversity, the quality of information available on the Web varies considerably. Thus, quality criteria for websites about rare diseases are needed.

Objective: The objective of this study was to generate a catalog of quality criteria suitable for rare diseases.

Methods: First, relevant certificates and quality recommendations for health information websites were identified through a comprehensive Web search. Second, all considered quality criteria of each certification program and catalog were examined, extracted into an overview table, and analyzed by thematic content. Finally, an interdisciplinary expert group verified the relevant quality criteria.

Results: We identified 9 quality certificates and criteria catalogs for health information websites with 304 single criteria items. Through this, we aggregated 163 various quality criteria, each assigned to one of the following categories: thematic, technical, service, content, and legal. Finally, a consensus about 13 quality criteria for websites offering medical information on rare diseases was determined. Of these categories, 4 (data protection concept, imprint, creation and updating date, and possibility to contact the website provider) were identified as being the most important for publishing medical information about rare diseases.

Conclusions: The large number of different quality criteria appearing within a relatively small number of criteria catalogs shows that the opinion of what is important in the quality of health information differs. In addition, to define useful quality criteria for websites about rare diseases, which are an essential source of information for many patients, a trade-off is necessary between the high standard of quality criteria for health information websites in general and the limited provision of information about some rare diseases. Finally, transparently presented quality assessments can help people to find reliable information and to assess its quality.

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KEYWORDS

rare diseases; self-help groups; Internet; health information exchange; quality indicators

Introduction

The European Union considers diseases to be rare when they affect no more than 5 in 10,000 people. It is estimated that there are between 5000 and 8000 different rare diseases, affecting nearly 30 million people in the European Union and 4 million people in Germany alone [1,2]. Consistent with this diversity, the quality of information available on the Web varies considerably. People searching the Web often find it very difficult to find the right information and to assess its quality [3,4]. With Orphanet [5], an information platform exists, which holds comprehensive and quality-tested information. However, the target group it addresses is potentially specialists rather than patients [6,7]. In keeping with the European Council's recommendations, Germany has published a National Action Plan for Rare Diseases in August 2013, which will guide and structure actions in the context of rare diseases within their health and social systems [8]. It includes 52 policy proposals. The national project ZIPSE (German: Zentrales Informationsportal über seltene Erkrankungen; English: Central Information Portal about Rare Diseases), initiated by the Federal Ministry of Health, deals with the realization of the plan's topics 37 to 39, which cover the subject of a central information portal [9]. Hereby, the health and well-being of people with rare diseases should be improved.

The aim of the ZIPSE project is to conceptualize and implement a central information portal about rare diseases in Germany. A centralized access point for quality-tested information appears to be very helpful for people with a rare disease, their relatives, and medical experts [9]. The portal itself does not contain primary information but refers to existing quality-assured information sources. The aim is the provision of an intelligent user guide to relevant and appropriate sources of information [10]. Web-based information and websites about rare diseases will be linked in the information portal. More precisely, a variety of quality-tested websites about rare diseases will be offered to all users. Furthermore, users will be able to search for disease-specific websites and to filter them by quality criteria. Therefore, a method to distinguish high- and low-quality websites needs to be established [10,11]. A number of quality certificates for websites dealing with medical information already exist. Websites with such a certificate demonstrate quality-tested content [3]. It can be hypothesized that existing quality certificates for websites with health information (eg, Health On the Net Foundation Code of Conduct, HONcode; DISCERN; and Stiftung Gesundheit) are rarely used by websites about rare diseases. It can be assumed that patient organizations often provide well-researched and reliable information about rare diseases, but they have limited resources in terms of time and money to present themselves as professionally as other information providers on the Web to fulfill the requirements of existing quality certificates. Furthermore, the providers' motivation to present themselves professionally is unknown. The quality control process of certificates such as HONcode can be costly and require significant effort owing to stringent requirements. Verifying websites providing medical information about rare diseases using quality criteria can help increase acceptance and signal trustworthiness to patients, relatives, and medical experts. Most existing quality certificates focused on medical information pursue different goals and contain a wide range of different types of quality criteria. Hence, specific quality criteria for websites about rare diseases are needed. The objective of this study was to generate a catalog of quality criteria suitable for rare diseases. Implementing these quality criteria will improve the evaluation and assessment of information about rare diseases for patients, health professionals, and other users of the information portal.

Methods

The method we adopted can be regarded as a process divided into 3 steps, as shown in the flowchart in Figure 1.

In step 1, a comprehensive Web search was performed to identify quality certificates and criteria catalogs for websites containing medical or health information. Although we focused on programs and catalogs active in Germany because of its implementation of the information portal about rare diseases, we considered several international sources as well. Quality certificates and criteria catalogs were only included if the quality criteria were published transparently. Furthermore, to be included the certificates and catalogs had to focus on Web-based resources containing medical or health information. Certificates, catalogs, and recommendations were therefore excluded if, for example, they focused only on printed medical information. Additionally, websites about rare diseases were analyzed to identify their quality criteria and their use of quality certificates. These criteria were added if they were not already identified through the Web search. Finally, all identified references were again checked for suitability.

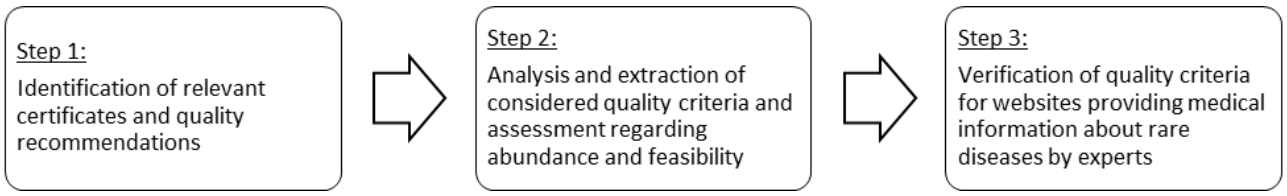
In step 2, the unique criteria of each certification program and catalog were examined, extracted into an overview table, and analyzed by thematic content. Thematic correlations between the criteria were pooled together with an inductive design into major categories. Experts on rare diseases were consulted on the construction of the major categories. Finally, each criterion was assigned to one of the following major categories: thematic, technical, service, content, and legal. Where feasible, the categories were broken down further into groups of criteria. Additionally, experts on rare diseases provided opinions and general information about the importance of each criterion and critical aspects of quality criteria for information about rare diseases. If a criterion was already present in the map, it was not reentered but marked as being part of another criteria catalog. In order to evaluate the importance of a single criterion, its repeated occurrence among different criteria catalogs was examined. Criteria appearing in several catalogs were considered more important, whereas those that were part of a single catalog alone were considered less important. Thus, a hierarchy of the quality criteria appearing in the identified catalogs was

constructed, ordered from the criteria appearing the most number of times to those appearing just once.

In step 3, the most important criteria were selected by the project group as preliminary quality criteria. Next, a workshop was held with various experts on website quality and other publications with medical content, experts on health economics and medical informatics, as well as medical experts in the field of rare diseases. A total of 27 experts participated in the workshop—4 of them were professors and 12 graduate doctors. These experts were invited to participate in the group discussion about quality criteria for websites providing medical information about rare diseases. Participants did not receive incentives to attend the workshop and discussion. The relevance and applicability of each quality criterion were discussed, evaluated, and verified by the expert group. The discussion with medical experts as well as experts on the quality of medical information focused on choosing the criteria that should be mandatory for websites offering medical information on rare diseases. Input from medical experts was equally valuable as input from experts on quality of medical information. At the end of the discussion, the experts were expected to arrive at a consensus on the importance of the different quality criteria. Finally, it was decided which of the quality criteria should be mandatory for these websites to be listed on the information portal about rare diseases. Experts from the following institutions participated in the workshop and group discussion:

- German Action Forum Health Information System (afgis e.V.)
- German Alliance of Chronic Rare Diseases (ACHSE e.V.)
- Agency for Quality in Medicine (ÄZQ)
- Federal Ministry of Health Germany (BMG)
- Charité Universitätsmedizin Berlin
- Center for Health Economics Research Hannover (CHERH)
- German Cochrane Center (DCZ)
- Frankfurt Reference Center for Rare Diseases (FRZSE)
- Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz
- Institute for Quality and Efficiency in Health Care (IQWiG)
- Cancer Information Service Heidelberg (KID)
- Hannover Medical School (MHH)
- National Action League for People with Rare Diseases (NAMSE)
- Orphanet Germany
- Public Health Foundation
- Department of Dermatology, Medical Center University of Freiburg
- University Medical Center Hamburg-Eppendorf (UKE)
- Centre for Quality and Management in Healthcare, Medical Association of Lower Saxony (ZQ)

Figure 1. The three steps of the analyzing procedure.



Results

Identification of Relevant Certificates

A total of 9 quality certificates and criteria catalogs for websites containing medical or health information were identified. Of these certificates and catalogs, 2 were used internationally; 7 were verified only for German websites. The most common certificate for medical information websites was identified as HONcode [12]. Three further certificates verifying only German websites were identified: afgis Qualitätslogo [13], Stiftung Gesundheit [14], and Medisuch [15]. Additionally, several German, European, and international criteria catalogs were considered: afgis Checkliste für medizinische Websites [16], DISCERN [17], Gute Praxis Gesundheitsinformation [18], NAMSE Kriterien und Standards [19], and Patientenorientierte Krankheitsbeschreibung nach ACHSE-Kriterien [20]. Lastly, the results of a study identifying the most important quality criteria for medical information websites were analyzed [21]. All identified quality catalogs are described in Table 1. Furthermore, the development of quality criteria is an ongoing process, including more detailed quality assurance whereby recent quality catalogs take into account older catalogs and quality certificates. In summary, the identified quality catalogs, certificates, and recommendations show different thematic focuses on the criteria that are considered important to ensure a high quality of health information. Moreover, Table 1 shows that the process of determining the quality of information differs among the identified providers (self-reporting audits vs publicly available information).

Table 1. Quality catalogs and quality certificates.

Name	Description	Characteristics	Number of criteria (n=304)
NAMSE Kriterien und Standards[a] [19]	A discussion paper about quality criteria for enhancing patient information about rare diseases.	It contains requirements for the categories: creation process, results, implementation, and evaluation.	56
HONcode[b] [12]	As an international certificate, awarded by the Health On the Net Foundation located in Switzerland and established in 1995, it has held NGO[c] status at the United Nations since 2002. Since 1996, a free certificate for "trusted" sites with medical information was awarded. Since 2015, certification is provided as a paid service. The organization claims that about 8000 medical websites hold their certificate.	Its principles: Information must be authoritative—stating the qualifications of the author. Complementarity—information must supplement and help to support medical advice, not replace it. Privacy—compliance with confidentiality of personal data entered by a website visitor. Assignment—References to sources of information and dates must be present. Verifiability—treatments, products, and services must be supported by balanced, verifiable, scientific information. Transparency and contact information. Disclosure of funding—sponsorship, sponsors, and financial sources must be named. Advertising policy—separation of advertising and editorial content.	55
afgis-Qualitätslogo[d] [13]	The afgis Qualitätslogo is based on 10 quality categories for transparently provided information, whereby the verification is based on self-reporting audits.	It is based on 10 quality categories for transparently provided information: criteria for transparent information about providers, purpose and target group, authors and information sources, data release, timeliness, and planned maintenance of the information, possibility to give user-feedback, procedure of internal quality assurance, separation of advertisement and editorial contribution, financing and sponsoring, cooperation and networking, and data protection, data transmission, and use of data.	39
afgis Qualitätskriterien [16]	afgis Checkliste für medizinische Websites[e] is a guideline for providers that want to regenerate websites with medical information content.	It contains essential Web standards for the following categories: timeliness, data protection, design and navigation, medical information, legal aspects, service aspects, search engine, transparency, and access.	35
Gute Praxis Gesundheitsinformation[f] [18]	A catalog containing quality criteria for the development of health information with a requirement for evidence-based information.	It focuses on the development of health information with a requirement for evidence-based information, which is comprehensible given the expertise of the target group. Thus, the catalog contains different criteria for various target groups.	30

Name	Description	Characteristics	Number of criteria (n=304)
Stiftung Gesundheit[g] [14]	Awards a seal of approval after checking more than 100 issues, whereby the verification is based on information that is available on the website.	It awards a seal of approval after checking criteria out of the following categories: legal quality, publishing diligence, usability, and search engine optimization.	30
Patientenorientierte Krankheitsbeschreibung nach ACHSE-Kriterien[h][20]	Contains quality criteria grouped into 5 categories.	It contains quality criteria of the following categories: creation and formal aspects, medical-scientific data and information, disease management, establishment of contact and information about specialties of health professionals, and additional links and references.	28
DISCERN [17]	A tool to evaluate medical publications with a focus on patient information.	It focuses on the following: reliability of the publication and quality of information on treatment alternatives.	19
Medisuch [15]	Provides a certification process and is operated by the institute for quality and transparency of health information.	As a part of its certification process, information providers have to declare that the information provided on the website is not influenced by industrial offers.	12

[a] NAMSE Kriterien und Standards: NAMSE (National Action League for People with Rare Diseases) criteria and standards (in English).

[b] HONcode: Health On the Net Foundation Code of Conduct.

[c] NGO: nongovernmental organization.

[d] afgis Qualitätslogo: German Action Forum Health Information System (afgis) quality logo (in English).

[e] afgis Checkliste für medizinische Websites: afgis checklist for medical websites (in English).

[f] Gute Praxis Gesundheitsinformation: good practice health information (in English).

[g] Stiftung Gesundheit: Public Health Foundation (in English).

[h] Patientenorientierte Krankheitsbeschreibung nach ACHSE-Kriterien: patient-oriented description of disease by the criteria of ACHSE (German Alliance of Chronic Rare Diseases) (in English).

Analysis and Extraction of Quality Criteria

The number of criteria present in the quality certificates is listed in Table 1. The presented number can be higher (or lower) than the official numbers stated by the providers owing to a more detailed valuation of criteria by the project group. The number of criteria ranged from 12 to 56 in the catalogs analyzed. In total, we identified 304 single criteria items. Through this, we aggregated 163 different quality criteria into 5 major categories: thematic, technical, service, content, and legal. The thematic criteria category containing 90 criteria (90/163, 55.2%) was by far the largest, followed by the service category with 26 criteria (26/163, 16.0%), the technical category with 18 (18/163, 11.0%), the legal category with 15 (15/163, 9.2%), and the content category with 14 (14/163, 8.6%). The degree of detail varied among the different criteria catalogs, and while 66 criteria (66/163, 40.5%) were found in multiple catalogs, no criterion was found in all of the certificate definitions or criteria catalogs. The 2 most frequently occurring criteria appeared in 6 of the analyzed catalogs (6/9, 67%). Three criteria appeared in 5 (5/9, 56%) and 13 criteria in 4 of the catalogs (4/9, 44%), whereas 20 criteria appeared in 3 (3/9, 33%) and 28 criteria in 2 of the catalogs (2/9, 22%). The majority of 87 criteria were unique to a single catalog. With the exception of one catalog (Gute Praxis Gesundheitsinformation), each contains a criterion unique to itself. All identified quality criteria are presented in Multimedia Appendix 1. In summary, the number of criteria present in quality certificates and quality catalogs differs. Nevertheless, most catalogs contain a unique criterion not shown elsewhere. The number of quality criteria in each of the major categories varies widely.

Expert Verification

To assess the relevance of a quality criterion specific to websites offering medical information on rare diseases, different principles were applied. First, criteria appearing in many of the reviewed catalogs were considered more important to ensure a certain level of information quality. This resulted in initially selecting the two most abundant criteria (authors are mentioned and creation and updating dates of information are mentioned) as mandatory for websites to be listed in the information portal ZIPSE. Criteria appearing less often were only selected in consideration with their relevance and their applicability to rare diseases and the targeted websites. This relevance was assessed by checking several properties. If a criterion is applicable, it is to a certain extent defined by its feasibility. Criteria seemingly

important to the quality of general medical information may only be adapted to a limited extent. Finally, in the discussion workshop with 27 experts, quality criteria for websites offering medical information on rare diseases were defined. A consensus about the following 13 quality criteria for websites offering medical information on rare diseases was determined:

- Authoring information
- Mentioning of authors
- Mentioning of sources
- Mentioning of creation and update date
- Data security
- Declaration of evidence
- Marking of conflicts of interests
- Consideration of target group
- Evaluation of content
- Review of information
- Characteristics of the website (accessibility)
- Imprint
- Contact opportunity

A decision was made on the quality criteria that should be a mandatory requirement for websites about rare diseases for them to be listed in the information portal. As a legal requirement for all websites, an adequate *data protection concept* as well as an *imprint* is mandatory. Moreover, we identified the *creation and updating date* and the possibility to *contact the website provider* as very important categories for patients with a rare disease.

Discussion

Principal Findings

The literature review of quality catalogs, certificates, and recommendations for websites containing medical or health information showed different thematic focuses on criteria that are important for the quality of health information. Interestingly, the investigated certificates reveal a great variety of quality criteria used by the common certificates. There is also a wide range of quality criteria where the degree of detail varied among the different criteria catalogs. Furthermore, the process for determining the quality of websites differs among the identified providers (self-reporting audits, eg, [13] vs publicly available information, eg, [14]). The classification of the quality criteria into the major categories, thematic, technical, service, content, and legal, showed that the number of quality criteria in each category varies widely. The presence of a larger number of quality criteria in one category does not necessarily indicate a greater relevance of the category. It is rather an indication that this category can be investigated more thoroughly than categories with a smaller number of different criteria [12].

Defined quality criteria for websites about rare diseases were coordinated and verified by a multidisciplinary expert group to ensure the quality of the information provided. These quality criteria will be applied for registration of websites on the portal about rare diseases. Out of the 13 verified quality criteria for websites about rare diseases, 4 were identified to be mandatory for registration to the information portal. First, as a legal requirement for all websites an adequate *data protection concept* and an *imprint* are mandatory. Moreover, *creation and updating date* and *possibility to contact the website provider* were identified as very important categories for patients with a rare disease. The documentation of the creation and updating date of information is especially important owing to rapid advances in the development of information and to demonstrate the latest research findings [22]. The possibility to contact the website provider is also an important quality aspect for these websites. Particularly, if there is limited information elsewhere, patients, health professionals, and other users can offer the provider advice or suggestions for improvement or ask for more precise information about a rare disease [23]. These 4 categories are mandatory for registration to the information portal and for linking to medical information about rare diseases. Fulfillment of the remaining 9 categories is optional. Nonetheless, these categories are still important for quality-tested information about rare diseases. To achieve transparency, it would be beneficial to publish the degree to which the websites fulfill these categories. In particular, information on the characteristics of the website, such as its accessibility, is important for many patients [24]. Thus, the fulfillment of each single low-barrier criterion needs to be shown transparently.

Using quality criteria to verify websites providing medical information about rare diseases can help to improve their acceptance and signal trustworthiness to patients, relatives, and medical experts [3]. In further studies, all selected quality criteria will be transferred to a so-called self-disclosure questionnaire. These questions will then be used to assess the quality of rare disease websites. The results from the first evaluation of these can help to improve and adjust the quality assessment process of the information portal. Moreover, we can evaluate and test the assumptions made at the beginning:

- Do patient organizations provide well-researched and reliable information about rare diseases?
- Do they present themselves as professionally as other information providers on the Web to fulfill the requirements of existing quality certificates?
- Do websites with little content and a small editorial staff hold high-quality information?

A further problem for investigation is the availability of robust evidence of information on rare diseases. Providing evidence for the source of information is a requirement often sought to ensure a piece of information is well researched. However, with merely 5 in 10,000 people affected by rare diseases, it is almost impossible to collect sufficient data to statistically test a hypothesis. It could be argued that a single proven case is also a form of evidence, albeit a very thin one. However, as long as no other data exist, it is still the best evidence available [25]. There are also important implications for future research from analysis of those categories where we identified a lower number of different criteria. New detailed quality criteria on these categories may help improve the discussion on quality of websites providing medical information.

Limitations

Despite our focus on programs and catalogs active in Germany, we identified a large number and variety of different quality criteria. As with other quality catalogs, the defined criteria

cannot verify the thematic content of health information. These criteria simply verify factors influencing the thematic content, as well as the quality of the website itself. A more complex and expensive solution to verify the heterogeneous information about rare diseases would be for medical experts to verify and highlight single articles of listed websites about rare diseases in the information portal. The defined quality criteria for such websites were verified by the participants of a workshop. Although this workshop was held with 27 renowned and excellent experts on website quality and other publications with medical content, experts on health economics and medical informatics, as well as medical experts in the field of rare diseases, subjectivity in their decision-making process cannot be ruled out.

Conclusions

The relatively low intersection of criteria appearing in the different criteria catalogs shows that the opinion of what is important concerning quality of medical information differs. For the development of useful quality criteria for websites about rare diseases, a trade-off between the high standard of quality criteria for general health information and the provision of limited existing information about rare diseases, which is essential for many patients, appears unavoidable. Providing defined quality criteria for websites about rare diseases can help seekers to find reliable information and to assess its quality [3,4]. Accepted criteria for websites with information about rare diseases, which allow for a minimum of quality control while keeping the workload reasonable, have been defined. In summary, 13 categories with quality criteria were defined by a group consisting of medical experts as well as experts on the quality of medical information. Fulfillment of 4 of these categories (*data protection concept*, *imprint*, *creation and updating date*, and *possibility to contact the website provider*) was identified as being mandatory for registration to the information portal and for publishing medical information about rare diseases. With the help of these quality criteria, we can evaluate, for instance, the quality of information provided by rare disease self-help groups or other information providers.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Quality criteria for health information websites.

[PDF File (Adobe PDF File), 563KB - ijmr_v5i3e24_app1.pdf]

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Abbreviations

ACHSE: German Alliance of Chronic Rare Diseases
afgis: German Action Forum Health Information System
BMG: Federal Ministry of Health Germany
e.V: registered society
HONcode: Health On the Net Foundation Code of Conduct
NAMSE: National Action League for People with Rare Diseases
ZIPSE: Central Information Portal about Rare Diseases

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Modul 4

Integrating patient perspectives in medical decision-making: a qualitative interview study examining potentials within the rare disease information exchange process in practice

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Integrating patient perspectives in medical decision-making: a qualitative interview study examining potentials within the rare disease information exchange process in practice

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Abstract

Background: Many European countries have recently implemented national rare disease plans. Although the network is strengthening, especially on the macro and meso levels, patients still go a long way through healthcare systems, with many health professionals involved and scarce evidence to gather. Specifically, patient involvement in the form of shared decision-making can offer further potential to increase healthcare systems' efficiency on a micro level. Therefore, we examine the implementation of the shared decision-making concept thus far, and explore whether efficiency potentials exist—which are particularly relevant within the rare disease field—and how they can be triggered.

Methods: Our empirical evidence comes from 101 interviews conducted from March to September 2014 in Germany; 55 patients, 13 family members, and 33 health professionals participated in a qualitative interview study. Transcripts were analyzed using a directed qualitative content analysis.

Results: The interviews indicate that the decision-making process is increasingly relevant in practice. In comparison, however, the shared decision-making agreement itself was rarely reported. A majority of interactions are dominated by individual, informed decision-making, followed by paternalistic approaches. The patient-physician relationship was characterized by a distorted trust-building process, which is affected by not only dependencies due to the diseases' severity and chronic course, but an often-reported stigmatization of patients as stimulants. Moreover, participation was high due to a pronounced engagement of those affected, diminishing as patients' strength vanish during their odyssey through health care systems. The particular roles of "expert patients" or "lay experts" in the rare disease field were revealed, with further potential in integrating the gathered information.

Conclusions: The study reveals the named efficiency potentials, which are unique for rare diseases and make the further integration of shared decision-making very attractive, facilitating diagnostics and disease management. It is noteworthy that integrating shared decision-making in the rare disease field does not only require strengthening the position of patients but also that of physicians. Efforts can be made to further integrate the concept within political frameworks to trigger the identified potential and assess the health-economic impact.

Keywords: Shared decision-making, Rare diseases, Expert patient, Patient preferences, Patient centered care, Qualitative research

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Background

The relevance of shared decision-making and patient perspectives

Historically, a paternalistic decision model has been established within several healthcare systems [1, 2]. However, as healthcare systems shift toward patient-centered care, the patient's role has become increasingly prominent. Integrating concepts of evidence-based medicine and patient perspectives, such as the inclusion of patient preferences, has also become increasingly relevant [3, 4].

The concept of shared decision-making (SDM) was first mentioned as such in 1982 [5]. It has been positioned as a centerpiece between paternalistic models, in which physicians dominate the decision-making process, and an informed patient choice model, in which the physician provides information but the patient assumes a leading role [4, 6]. The most often-cited concept originates from the work of Charles et al. [6], who defined SDM as a collaborative process between patient and provider based on a discussion of options, evidence, and potential benefits and harms; this especially considers the patient's preferences and situations [6].

A review of literature published between 1996 and 2011 by Blanc et al. [7] identified 1285 out of 229,179 publications in 15 journals addressing the topic of SDM. In this context, it was identified that publications in medical journals increased exponentially during this period, which indicates the topic's growing relevance. However, the meaning of SDM is often assumed rather than interpreted through SDM testing models [8]. Other studies suggest that existing SDM models only partially reflect the factors that influence patient empowerment or the breadth of their further potential [9, 10]. Literature suggests that SDM concepts augment patients' satisfaction with the healthcare system, especially regarding the quality of care [12]. Further, this can also positively affect health outcomes. Patients' poor compliance and inappropriate use of medicines arise from poor communication, the patient's lack of understanding of how the drug is expected to work and its potential side effects, and a failure between the patient and physician to find a common ground or concordance [13, 14]. Desrroches et al. [4] suggest that SDM should be chosen as an ideal chronic disease strategy to improving compliance with medications and therapeutic processes, which is a major public health issue. This suggests a particular relevance regarding diseases with chronic life cycles.

Nevertheless, healthcare professionals consistently fail to facilitate patient involvement, and even fewer include patient preferences in care [15]. An appropriate level of SDM does occur in practice, although only in approximately 10% of cases [16], suggesting that although literature broadly covers the SDM process, further efforts are still necessary to expand its usage.

The rare disease context

Estimations reveal that approximately 350 million people are affected by rare diseases worldwide. Many rare diseases can be traced to a genetic origin, often linked to a chronic course of diseases as well as severe symptoms [17]. Although various different health conditions affecting different parts of the human body are subsumed under the term "rare diseases," these people share common difficulties [18].

Consequently, worldwide rare disease national plans have been implemented, with 20 implemented overall in Europe from 2004 to 2014. These policies focus on centers, networking, research, disease registries, coding, therapies, information provision, and patient organization [19]. In this regard, patients are solely and indirectly included through patient organizations. However, the German National Plan for cancerous diseases indicates that direct patient involvement is also strengthened through empathetic communication and including patients in decision-making, as noted in action field number 4 [20].

On the one hand, information needs and preferences have already been examined in the rare disease field [21–23]. However, concepts of shared decision-making have thus far only been evaluated in such contexts as diabetes [8], mental illnesses [9], coronary heart disease [24], and cancer screening programs [25]. Evaluations regarding rare diseases that include all people affected as well as physicians are still lacking.

On the other hand, physicians can provide extensive information on treatment options and managed care contracts in prominent disease areas, such as diabetes and cancer. However, information in the rare disease field is often scarce, and those affected often become "experts" of their own disease by capturing substantial information during their long odyssey through healthcare systems [26].

The study's aim

Triggering this information through effective information exchange strategies, such as shared decision-making, could contribute to the efficiency of, and overall satisfaction with, healthcare systems. Therefore, the purpose of the underlying study is to examine the implementation of the SDM concept in Germany. Further, the study explores whether efficiency potentials exist for the healthcare system within the rare disease field. The triangulation of patient interviews with family members' and physicians' opinions controls for the results' validity and practicability. The results also contribute to the framework of shared decision-making, as this framework identifies potentials resulting from the specifics of rare conditions.

Method

The study was based on Mayring's qualitative research methodology [27]. A qualitative setting was chosen as the goal to observe a holistic picture of SDM, rather than analyze by focusing on the research topic's provisional aspects [28]. The qualitative setting also allows participants to independently address important aspects. Therefore, the outcomes illustrate participants' current, actual experiences, and are not channeled by interviewers. The material was collected through semi-structured interviews and evaluated based on a qualitative content analysis in an inductive-deductive approach. The research items in this context are chosen from existing concepts, and all evolving topics in the evaluation process are assigned to the research items and the evolving subcategories [27].

This study's empirical evidence is derived from three data sets, offering information on three comparison groups. These sets were chosen by considering the information rendered on the research topic, and whether the sets contribute more to a rich description then one data set alone [29]. Further, comparisons within qualitative research add more to the full understanding of the issue than analyzing differences [30]. Hence, this study triangulates patients, or the directly involved; their relatives, or the indirectly involved; and physicians, as the counterparts within the decision-making process. Therefore, the comparison groups' different perspectives could be carved out.

Participant recruitment

Overall, a qualitative, non-random quota-sampling technique was used. In this context, the population is first determined regarding specific qualities, and certain quotas are then recruited from these subgroups [31].

Patients and family members were recruited by the Freiburg Centre for Rare Diseases at the Department of Dermatology of the University Medical Centre. As "rare diseases" summarizes many conditions with different appearances, the goal was equal coverage of the following disease areas ($n = 11$): skeletal dysplasia, neuromuscular disorders, immunodeficiencies, genetic eye disorders, genetic skin disorders, connective tissue disorders, genetic kidney diseases, cystic fibrosis and lung diseases, an inherent disturbance of hematopoiesis, inherent metabolic disturbances, and genetic diseases of the digestive tract. However, the interview results often indicated an overall complex, systematic involvement. We also strive for a balanced recruiting of female and male participants, as well as a participant from different age groups. We included at least nine patients with a long path to diagnosis, defined as lasting at least 10 years. The inclusion of relatives was necessary, as many rare diseases affect children, who are ineligible for interview, and participants needed to be at least 18 years old. Alternatively, a close relative was invited to answer the questions. Potential participants were chosen from the rare disease center's clinical register and were contacted as part of a clinical visit with visiting patients randomly chosen. Patients did not agree to participation in advance. Further, all participants who signed an informed consent agreement and were assigned to an interviewer remained in the study.

The interviewed physicians are part of the field of action of people affected by rare diseases defined as such by Meuser and Nagel [32]. Physicians as health experts serve to supply information from the operating contexts of those affected, covering the overall spectrum of the providing health care structure [32]. Therefore, physicians were selected in accordance with their profession, including general practitioners, specialists, and clinicians. Moreover, guides in the rare disease field were also questioned. The term "clinicians" in Germany represents medical experts working in hospitals, while "specialists" operate in private practice. Guides differ in their qualifications and are equally trained to direct patients suffering from rare diseases, but were only included in instances in which a medical background could be determined. The Centre of Quality and Management in Health Care, in the State Medical Chamber of Lower Saxony in Hannover, was responsible for recruiting medical professionals. All physicians were recruited within the geographic region of Lower Saxony, representing both urban and rural areas in Germany. As clinical guides occur less frequently, this entire subgroup was recruited from all regions in Germany. The following criteria were employed to create appropriate subgroups: residence, such as rural, urban, or metropolitan; single versus group practice; medical care level, such as basic, regular, specialist, and maximum; and level of the physician's medical experience, with hierarchy levels of assistant physician, senior physician, and chief physician. A physician's hierarchy level is referred to as an indicator of the experience of hospital physicians. Therefore, different modes of employment, called "hierarchy levels" in this case, were differentiated. In German hospitals, three different professional positions are common, beginning with the lowest level of "assistant physician," followed by "senior physician," and then the most experienced level of "chief physician". Therefore, the sample covers the heterogeneous area of healthcare provision relative to the research topic of interest, and thus, covers the field of action defined by Meuser and Nagel [32] regarding physicians as experts on rare diseases in Germany.

Data collection

Three different interviewers queried patients and family members between March and November 2014, while

two other interviewers met with physicians between April and October 2014.

Interviews were held face-to face (patients and relatives: 40; physicians: 26) and by telephone (patients and relatives: 29; physicians: 7). Not all interviews could be conducted face-to-face due to appointments on short notice, the need for extensive disproportionate travel, or participants' preference.

Interviews were conducted according to a semi-structured interview guide. The interview guide was developed during a mutual workshop of the research group led by an experienced external qualitative researcher. The qualitative researcher presented the relevant qualitative research guidelines. Afterwards, the research group presented the potential interview questions. During our mutual discussion, questions were adapted further, as the first draft included questions that did not induce narration appropriately. The second drafts of the question and sub-question sets containing further minor wording adaptions was sent to the research group via email to reach a final consensus on the question set. The interview flow was initiated through a narrative question requesting rare disease experiences from the onset. Sub-questions concerned the diagnosis, and therapy and disease management were only posed when questions were not autonomously addressed. This approach was chosen to identify emerging SDM aspects, rather than proffering the SDM concept for the participants. Thus, we strove to avoid overestimating SDM effects, which can occur due to expressive reporting, when directly inquiring about a concept. Further, requests were made as interviewers observed the necessity. Questions on information-gathering behavior and interchanges were subsequently posed.

The interview study was embedded into the creation of a national rare disease Internet platform in Germany (Zentrales Informationsportal über seltene Erkrankungen, or "ZIPSE"), which enables patients and family members to actively gather quality-assured evidence [33].

The interview guide was pretested with one patient and one family member, and was then adapted to include the perspectives of participants who have experienced their diseases since birth. The following interviews appropriately covered the different courses of rare diseases, and therefore, this study could optimally cover the different paths through the healthcare system and interactions with healthcare specialists could be ideally covered. The physician's interview guide was accordingly developed to align the guide's structure, and was pretested by interviewing one physician (female, 43 years). Piloting the interview guide demonstrated that relevant cases could be appropriately triggered based on the interview guide. Nevertheless, some adaptations were necessary, as the healthcare professionals offered different perspectives on the topic. The research group mutually reviewed both interview guides to align standardized procedures. We first conducted a trial run of an interview to practice the procedure and control for the fit of the posed interview questions. During the following interviews, participants' pathways through the healthcare system, also referring to interactions with the contacted medical professionals, diagnosis, and potential therapies, as well as the diverging information sources and/or information access points, were well described. Qualitative research also gives the option to further adapt the interview guide along the way. Therefore, we continuously checked for further adaptation needs. However, due to in-depth narration of interviewees and coverage of the addressed topics, no further adaptations were deemed necessary.

Data analysis

All participant interviews were audio recorded, and later transcribed with the aid of F4 transcription software (Version 6, Dr. Dresing & Pehl GmbH in Germany). A standardized interview protocol was also distributed to interviewers of patients and family members to document any special circumstances potentially relevant in interpreting the collected data. A standardized transcription booklet was developed for patients, relatives, and physicians, and was used as a transcription guideline. The transcription booklet offers a standardized definition of different transcription strategies and codes, where diverging options were possible. This defined the anonymization of participants and locations, as well as the handling of any incomprehensible audio sections.

All steps of a qualitative content analysis were then recognized [34]. Hence, transcripts were analyzed based on a directed qualitative content analysis [27]. An inductive-deductive approach was used. Predefined items were identified in a deductive first step using Charles et al.'s [6] predominately used definition of SDM. Therefore, the following items were noted: 1. The "patient-physician relationship," 2. "Participation," 3. "Information exchange," and 4. "Decision-making." Second, subcategories were developed, assigned and revised in a stepwise procedure following Mayring's [27] inductive category development process. Finally, two further researchers revised the evolving items to ensure both formative and summative reliability and any differences were addressed and included in the data analyses. Ultimately, the patients', family members', and physicians' results were triangulated. Evolving items from physicians' and relatives' interviews were matched with already identified items from patients' interviews, where appropriate. Otherwise, a new subcategory was deemed necessary. All quotations were reviewed by a native speaker.

Results

Appendix 1 displays detailed characteristics for the participating patients, family members, and physicians. Overall, 55 patients, 13 family members, and 33 physicians were interviewed as a part of the study, although at least one participant could not independently participate in the interview study due to the severity of their illness. The patients' median age was 52, family members was 44, and physicians was 48; 67% of patients, 61% of family members, and 30% of the physician subgroup were female. The diseases' severity were self-assessed, with 9% of patients rating their disease severity as mild, 47% as medium, and 38% as severe. 6% did not state any specifications.

The interview results were marked with a code consisting of an interview number and letter: "P" represents the patient, "A" represents an "acquaintance or family member," "GP represents the general practitioner," "CP" represents clinical physicians, and "EP" represents expert physicians. The following themes regarding experiences, decision-making processes, and information exchange procedures were identified in the rare disease field:

Item 1: the relationship between patient and physician

Nurturing trust-building processes

Patients report that trust is an important basis for effective communications about their disease. If a relationship of trust has not evolved, patients will prefer to make their decisions and search for the answers to their health questions on their own, often through the Internet (P37). Communication can lay the foundation for a trusting relationship. For example, one physician reported that she would not write reports, but trusted the patient's understanding of their rare disease (GP02).

Moreover, a trusting relationship is nurtured when physicians admit the limits of their knowledge of rare diseases and make the appropriate contacts to compensate for this gap (GP04, GP08). A trusting relationship is particularly strong when patients can obtain answers to current health questions—no matter how straightforward—and when physicians take the time to research and discuss these questions with their patients (P06).

Several aspects within the patient-physician interaction must be considered to avoid mistrust. Our patient respondents were disappointed with highly qualified physicians who lack information about rare diseases (P05, P08, P27). Patients also believed that physicians could hardly empathize with their conditions (P22), and searched for medical professionals who cared (P27). This, and the lack of a constant contact person, especially in outpatient care, led to high dissatisfaction and patient mistrust. Alternatively, patients positively perceived the existence of a permanent contact person (P01, P24). Further, a relationship of trust is undermined by misdiagnoses (P05, P17), as patients recognize that physicians experience difficulty in diagnosing rare diseases. Although they somewhat understand physicians' struggle, patients also reported the need to search for a physician capable of diagnosing their disease (P34). Moreover, disappointment occurs when treatment is denied as a result of a high-risk disease classification due to comorbidities or age (P06, P38). Family members also report that they need to verify physicians' information regarding treatment considerations, as therapy options are often scarce or newly developed, and they rather feel like "guinea pigs," which feeds their distrust (A09). It is also reported that no elucidation by the physician occurred, although the diagnoses were already established, which increased suspicion (A10). The next step may involve a further increase in mistrust if patients—or family members, in this case—do not acquiesce to the opinion offered during the medical consultation (A05).

Dependencies

On the one hand, rare diseases often exhibit a chronic course and the relationship between patients and physicians is often characterized by dependence, which also highlights the importance of a positively perceived relationship. On the other hand, negative perceptions can lead to a change of physician. Those affected can organize in patient networks or self-help groups, which help them feel supported; therefore, they become empowered and can assume more responsibility for their disease management (P30).

Family members also report that one must be "lucky" to find an appropriate physician (A04), or that one "relies on a physician for better or worse" (A02).

The psychosomatic corner

It was found that physicians complain about patients who return with the same problems. As rare diseases are difficult to diagnose, patients suffering from rare diseases on the long path toward diagnosis may be categorized as psychosomatics, simulants, or hypochondriacs, or suffering from psychological problems, which further undermines a positive patient-physician relationship (A06, P08, P16, P22, P27, P28, P39, P49, P52, P56). Consequently, patients do not believe they are taken seriously, which can also lead to them terminating their treatment (A06, P12). Physicians also reflected upon the difficulty in diagnosing rare diseases and the problem of over-reported symptoms due to Internet information (CP01, CP05, EP02); however, these areas of interest are not linked.

Other participants

Patients also consider the recommendations of others affected through rare disease self-help groups. Other

physicians are also predominantly involved, as diagnostic procedures may span a longer time period, and many different fields of expertise may be involved due to polysystemic patterns. Patients even noted that they are glad when physicians cooperate with the resulting "referral marathon" (P13).

However, many patients reported their struggles when shifting from one physician to the next. This is especially the case when crossing the boundary from the stationary to the ambulatory healthcare sector, in which patients are confronted with a loss of information or a lack of information transfer, as it is assumed that other physicians are responsible for communication, or that this communication has already occurred in other events (A07, A08, P05, P13, P14, P18, P24, P26, P27, P28).

The following Table 1 summarizes the findings for Item 1 and provides corresponding anchor examples:

Item 2: participation during the decision-making process

Physicians' commitment

Participation is perceived as minimal when no time seemingly exists to build an in-depth, trust-based patient-physician-relationship (P06). Patients were especially disappointed when physicians did not demonstrate engagement during the particularly long diagnosis process, with successive symptoms in the rare disease field (P19, P56). This was interpreted as a lack of effort to link symptoms in a networking approach (P06) and a lack of interest to further analyze the diagnosed disease (P50).

Alternatively, physicians expressed anger in not considering a rare disease (GP03). Further, a diagnosis is critical for patients, and especially when they experience a long path from their first symptoms to diagnosis. In this case, the patients strive to self-diagnose, for example, by making their own appointments for a verifying biopsy (P49). This importance is highlighted by their describing the difficulty in arguing for an understanding of their special physical needs due to their symptoms in front of family, friends, and colleagues with no diagnosis to build upon (P56).

Similarly, family members report that they even feel neglected by their pediatricians (A03). Patients' reports also reveal that physicians must invest substantial time to work up the course of rare diseases, as patients experience a long path to diagnosis (P07). Physician respondents reported that cases take several weeks to work up (GP01).

The physicians also stated that the diagnosis does include a naming of the disease, but no scope, leading to limited decision-making (GP07). In this regard, they would like to offer more, but are bound to offer less due to limited therapy options or missing curative therapies within the rare disease field (P14).

Patients' commitment

A particularly active form of engagement can be observed in family members, who described driving 500 km to search for a well-trained pediatric orthopedist or a specialized center for rare diseases (A01, A02, A06).

Physicians also highlight the particular engagement of family members, who urge proper diagnoses with the help of Internet information (A01, CP06, EP07). In this regard, physicians also emphasize the importance of engaged patients, as physicians need their participation to obtain anamnesis data they could not otherwise obtain (EP04).

Table 1 Anchor examples for the "relationship between the patient and physician"

Identified Items	Anchor Examples
Nurturing trust-building processes	*"[...] But [regarding] the counseling, people often ask, 'What do you say about that? What should I do? Should I really choose a hearth catheter, or should I drop it? What do you say about that?'" [Interviewer: 'Hm.'] "And when I say, 'Yes, go!' or when I say, 'No, don't go!'—" [Interviewer: Hm] "That's absolute. That's what I experience again and again. They confide very much in our opinion. And when we endorse something, then it's okay, and if we do not, then it's not." (Primary physician, female, 47 years old, GP03)* *"[...] As noted, one has no chance with physicians with such a disease. […] There are rare diseases, that's disastrous. And physicians get a chance, somehow, to search for anomalies, to get clues about which diseases can be considered. In my case, it was rather stupid, as liver values were so much in the foreground; however, one only needed to regard the thrombocyte values. I don't know how this can be done in an intelligent way, as based on this or that, it can be that. But private physicians in particular have a hard time identifying a proper diagnosis. And many people do not have the energy to transfer from one doctor to the next, as I do. Yes, that's what one does." (Patient, male, P34)*
Dependencies	*"[...] In the new city I live in, I have gone to hematologists, with whom I have not gotten along with at all, and the personal contact within the network has encouraged me to simply say, 'No, I have a chronic disease and I am relying on that physician; if I do not get along with him, I need to change the physician.'" (Patient, female, P30)*
The psychosomatic corner	*"[…] And many physicians are still of the opinion that if there are no identifiable causes, then it is psychological. Then there are many dystonia patients who need to fight [the opinion] that this is simply not psychological, but neurological." (Patient, female, P39)*
Other participants involved	*"I am lucky to have physicians who play along with this 'referral marathon.'" (Patient, female, P13)*

Alternatively, patients also describe a passive form of interaction, in that they trust physicians' expert knowledge and hope that they will share all relevant information. This subsequent form of interaction is a "supervisory" relationship (P55). Physicians also report that patients who are unwilling to cooperate (GP05) as well as those who are willing to co-operate especially experience high psychological strain, which they want to ameliorate or share (GP03).

The following Table 2 summarizes the findings for Item 2 and provides corresponding anchor examples:

Item 3: information exchange

Professional health knowledge on rare diseases

Patients appraise broad rare disease knowledge, which is interconnected with the trust-building process (P05). Patients also report satisfaction with a single contact point when expert information is attained (P02). However, patients must independently search for rare disease health experts, as health information on rare diseases is perceived as generally scarce (A08, A11, GP01, P17, P34, P38). Patients repeatedly reported that they are lucky to have found someone on short notice who can diagnose their disease (P47). Patients also felt uncomfortable when realizing that physicians need to research their sometimes incredibly rare disease (P49). Physicians noted that comprehensive guidelines augment this dilemma by making it difficult for patients to fall within general medical guidelines (EP03). Problems arise when a lack of information leads to misinformation that must be clarified by other health experts (P05). However, this process can be positively transformed by not only explaining the knowledge gap in rare diseases, but also transferring the case to experts on the disease (P55). Relative to health information needs, patients request information on innovative health procedures, for example (A08). When patient questions regarding their diagnosis remain unanswered, this feeds dissatisfaction and mistrust (P15, P16, P28). Patients are sometimes offered initial information, such as a diagnosis, and are subsequently asked to proceed by themselves to the next steps, such as finding information on the disease and searching for a proper physician (P08). However, physicians also highlighted the limitations of Internet information, and especially emphasized that physicians must take patients in hand when thoroughly structuring and sorting the gathered information (EP09). While physicians offer only indication names, self-help groups can render further in-depth information (A02). Moreover, patients acknowledge that it is impossible for physicians to grasp the entire spectrum of a rare disease's effects, which are often linked to genetic mutations (P49).

Health information scope: between feeding fear and effective health management

Patients reported ambiguity about the scope of health information communications; on the one hand, they demand more information on diagnoses and diseases' possible courses (P12, P24). On the other hand, some patients hold back information crucial for diagnosis due to a sense of shame (GP03). A diagnosis without further information exchange triggers a process of concern or dissatisfaction within patients (A10, P12, P24, P32). Some patients reported struggling with a language barrier resulting from the extensive usage of professional jargon, and needed more simplified information (P12). Patients reported feeling like "guinea pigs" when information was not rendered to a sufficient extent (P29). Presumably, patients' parents in particular tend to extensively worry. In this regard, information should be communicated by keeping the patient and family members grounded and explicitly integrating reassurance as an instrument (GP09). Other physicians complained

Table 2 Anchor examples of "participation during the decision-making process"

Identified Items	Anchor Examples
Physicians' commitment	*"Yes, […] I think that is the interesting part of the issue. Basically, the point is, they do not take into account this hypothesis. Simply, they always think about the obvious, at present, or what that could be. And basically, 'It is not even a complex disease, and […] not even complicated to diagnose,' [and they think,] 'Oh, I can also add something about the diagnosis later on.' But, one also needs to come up with it first. And there is the statement of the physician, whom I told that I suspected I have achalasia, and who then said, 'Oh, that's so rare; that's not what you have for sure.' They do not search for this." (Patient, female, P56)*
	"[...] And somehow, one has a contact person, and I have the feeling, and the neurologist says, 'It is good that you take Valaclicloviv, and I can also prescribe you physiotherapy. There is nothing more I can do.' And there is this [feeling that] I would like to do more." (Patient, female, P14)
Patients' commitment	*"So, in the run-up, a catastrophe [occurs] because one really has nobody [without a] diagnosis, [and it is] extremely difficult to somehow find the right doctor. Actually, there is, or there was at that point, as we started searching, […] no such centers for rare diseases that were developed during the last few years. And therefore, I should say, one naturally depends on the pediatrician in the first line, and one has to simply, that's what we felt, have luck to get to the right physician." (Family member, male, A06)*
	"[…] Shingles, send a picture, then you know what it is. But when it's something rare: no chance. But, you need to talk to the patient, you need anamnesis data." (EP04)

about a communication filter system, in that a questionnaire is first rendered, a doctor's assistant reviews the notes and the physician himself is finally consulted (EP02).

The "expert patient"

Patients described themselves as deliverers of information on rare diseases, and they close existing knowledge gaps through the use of Internet information, for example (A03, P21). Younger physicians (KA04, KA06) in particular wished to individually inform patients through, for example, web-based information sources, but were concerned with other physicians' negative reactions (P08, P30). In this regard, patients even described themselves as "good" patients when blindly trusting their physician (P12). Alternatively, physicians also reacted positively toward individuals' searches for health information through web-based sources (EP01, EP11, KA07). Although those affected are aware of the limited quality of Internet information, such as the broad spectrum of users in web-based forums (A13), physicians perceive themselves as necessary information filters (EP09). Moreover, some health professionals discourage patients to search for web-based health information, as it is difficult to properly classify such information, leading to increased concerns (EP03, KA01, KA05, KA09). Physicians were concerned that the false alarms caused by misconceptions from Internet information could hinder the resources within healthcare systems that different positions urgently require (GP04). Other physicians differentiated between handling anxious patients, and discouraged information searches, and other patients, who are allowed to search for Internet health information (EP11).

Patients described a knowledge-gathering process in which they "hop" from one physician to the next and gather information from a primary information access point: the self-help group (A01, A02). Further information sources with growing importance include the expert centers for rare diseases, developed at university clinics throughout Germany. Those affected describe the knowledge transportation process from the center to the local consultant, in which the consultant takes the leading role by communicating the next steps in the medical process (A13). Patients' high responsibility regarding their medical information and the search for physicians can be interpreted as a hurdle on the path to SDM. Further, patients may feel left to their own fate rather than achieving mutual health goals. As these centers increase in number, this step is also increasing in importance, and physicians discourage the use of forums due to the doubtful quality of their health information (GP03, EP03).

Information delivery is demanded at an earlier stage, in this case immediately at diagnosis (P31). In this regard, patients also remarked that they needed to urge physicians toward information generation, emphasized that these health experts are likely to forget that each patient must be informed from the onset, and demanded different scopes of information (P34).

Alternatively, patients also reported that those affected needed to inform physicians about their disease when they changed their permanent location and searched for a proper specialist (A06). Physicians complained that the reporting obligation does not exist due to a lack of obligatory transfers, resulting in the need to ask patients for their documents or call the prior provider (CP05, GP01).

Other patients noted that they communicated with physicians at the same level, avoiding unbalanced communication (P03). Patients suffering from rare diseases even urged physicians for a diagnosis, as their symptoms are often genetic. However, they were also thwarted by the physician, who stated, "How can you take upon yourself the right to intervene with the medical decision-making process? (P09)" Patients also tended to transfer on their own, by taking responsibility for their own disease management (P17).

Patients are called health "experts" on their own diseases, as they have unique knowledge on their symptoms and can gather information on their individual form of the disease (CP07). Similarly, family members are also called "lay experts," as they also extensively gather and exchange health information (GP09).

The following Table 3 summarizes the findings for Item 3 and provides corresponding anchor examples:

Item 4: decision-making and agreement

Paternalistic communication

Paternalistic decision-making is unavoidable, and especially in emergencies (P17); transfers are also suggested in a paternalistic way (P06). Further, patients under diagnosis may not be asked whether they wish to be informed (P11, P28), and physicians may define the specifics of therapeutic interventions, and especially dosages (P22). Patients and family members described physicians who wished to convince them of a specific therapy option, and urged them toward a specific outcome, such as surgery (A05, P21). However, patients searched for a second opinion in severe interventions, ruling out alternative therapy options. (P51).

Some patients reported perceiving a paternalistic communication as positive due to the perception of protection (A09).

One patient opposed shared decision-making as well as the associated discussions, and noted that he needs a paternalistic communication approach, as this offers him reassurance (P17). Patients sometimes even make demands of their physicians by telling them what to do

Table 3 Anchor examples for the "information exchange"

Identified Items	Anchor Examples
Professional health knowledge on rare diseases	*"[...] Yes, I think that if I had the right diagnosis—if I had MS, for example, which was never really excluded—but if I had this as a diagnosis, then I could have told every physician, 'Look, I've got MS.' Then, everybody would know what that is, everybody would know what kind of constraints I have, and one would eventually show a little consideration for me." (Patient, female, P16)*
Health information scope: Between feeding fear and effective health management	*"First, to protect the patient from himself, as the induced therapy wave or perhaps also false/ or diagnostic wave can also be harmful. But I also see it as a question of capacity of our health care system. That we are not able to smooth every false alarm induced by "chatrooms" through profound information coming from physicians." (GP04)*
The "expert patient"	*"Especially those exchange websites. [I1: Um]. That he comes to me, and then somehow has enormous expectations and wants to tell me how it needs to be done [or not done], that's difficult for me; but he can be right. Thus, I mean, who is the specialist for these diseases? Actually it's the person afflicted. 'Well, he's got the symptoms, he knows how it was diagnosed, and he also knows what works for him.' The real specialist on the disease is in general the sick person. When it comes to common diseases, we are also experts, because we experience them so often. When it comes to rare diseases—well, I think if the physicians were honest, they are sometimes just helpless, because, they just do not have it that often." (Physician, female, 42 years, KA07)*

(GP03). Family members also highlighted the importance of their expectations of physicians' alleviating their worries (A08), which physicians also expressed; the latter reported that family members tended to turn to physicians more quickly and frequently, and channeled parts of the responsibility toward their children (CP08). Physicians also highlighted their own responsibility when defining the diagnosis as a process of weighing the correct balance between clinical necessity and the willingness to be confronted with the disease, and especially in the case of parents (CP08).

Patients also described patients' suppression mechanisms in coping with their disease, which suggest the necessity of a watchful physician (P47). A paternalistic attitude is also associated with protection, and offers hope by guiding patients in steps through a previously unknown health condition (P09). Patients also expressed the need for a general physician to lead them through the course of the disease (P11). Specifically, elderly patients tended to fully rely on the physician's information, and reconciled themselves to their status rather than pushing for further health improvement (P48).

Informed (individual) decision-making

Informed decision-making is directly linked to the expert knowledge of many patients and family members, drawing many parallels. Patients reported that they feel as though they have no right to participate in the decision-making process in that the physicians focus on their diseases, but they would prefer to be holistically perceived as a person. Individual ideas are unwelcome, but perceived as questioning the physician's expertise or authority (A12, P16). Similarly, physicians noted that individual information searches may lead to conflicts within the decision-making process between patients' expectations and economic and medical action strategies (CP03, EP01).

However, patients reported that they solely discuss acute symptoms with their physicians. One case also noted that physicians were only consulted for general medical advice, as knowledge on this incredibly rare disease is so scarce that they preferred to consult other affected families (A12). Moreover, patients and family members also decide upon the point at which they consult a doctor, or whether they preferred to consider a second opinion (A12, GP04, GP05, GP06, EP07, GP09, CP02). Patients often manage their own basic daily care for these diseases, as well as preventive measures, such as sports and healthy nutrition (P54). Specifically, the patients themselves attend to their own daily chronic disease symptoms or discuss them in self-help groups (A03, P37).

However, some physicians also support patients' informed individual decision-making processes by welcoming their self-reliance (P11, GP03), and encourage laying out the patients' treatment choices (P10).

Some physicians report worry as a result of patients' individual decisions. For example, if the physician decides upon a therapy, the patient may refuse to take the prescribed medication. The patient may oppose it due a lack of readiness for a radical procedure and its associated side effects (P28). A similar pattern occurs when patients are not involved in the decision-making process, and consequently, patients or family members often switch to a physician who more highly appreciates their opinions (A01).

Further, patients often report a struggle with the physician, and especially when they feel something is wrong but the physician cannot determine a diagnosis (P17, P28) or patients would prefer a specific therapeutic service (P38). Conflict also occurs when the physician

urges health services that the patient opposes (P38). In contrast, physicians also struggle with patients who they describe as "overly engaged," in that some patients attempt to pin down a diagnosis the physician does not endorse (GP03, GP09). In this case, decision-making in the rare disease field can play a specific role when there is no initial decision to make due to missing therapy options (P26). Another physician also described his struggle with solely servicing patient wishes, although he prefers to retain primary control of diagnoses (GP09).

Shared decision-making

The SDM concept was rarely described across all interviews, suggesting that it has not yet integrated into common healthcare practice—or at least in the rare disease field.

One patient emphasized the trust-based relationship with her physician achieved through the SDM process. Although she initially denied therapy, the application of SDM nurtured a trustful relationship, in that she finally admitted that if the physician determines she needs therapy, she will cooperate (P28).

Similarly, physicians can offer different therapeutic options but leave the final treatment choice to the patient (P24).

On the one hand, another positive effect of shared decision-making is that it can lead to the patient's self-responsible understanding of their own disease and adherence to existing therapy options (P33). On the other hand, interviews confirm that although people affected with rare diseases depend on their physician's expert knowledge, ignoring patient preferences can still lead to a change in physician (A03). For example, decisions can be made during a consultation that the patient does not agree with (P38), the patient and physician can disagree with diagnostic procedures (P39), or a specific therapy may not be prescribed (P30, P34).

Physicians admit that shared decision-making's role is increasing, as patients want their own perspectives to be considered (EP04). Shared decisions' importance has also evolved, as diagnoses can be made after a longer period of subtle symptoms. In this case, the disease has already lead to irreversible, adverse effects that patients must cope with as they struggle with whether the physician should have intervened at an earlier point in time (P49). The physician's learning of the patient's perspective and their medical and family history can lead to a better understanding of the disease (P22, EP08).

The following Table 4 summarizes the findings for Item 4 and provides corresponding anchor examples:

Discussion

Summary of findings

The underlying interview study revealed that medical decision-making as a part of the patient-physician interaction is particularly relevant in the rare disease field due to a many medical contacts and a high dependency on the exchange and physicians' engagement in general. All parts of the SDM process, as systematically added to existing literature using Charles et al.'s [6] framework, were indicated as increasingly relevant within the rare disease field in practice. However, the status quo demonstrates that the SDM agreement itself was rarely depicted or respectively perceived. In summary, the patient-physician encounter was characterized by a balancing of trust and mistrust and high dependencies, including an often-reported stigmatization of patients as stimulants and many participants were involved. Commitment was high due to a pronounced engagement of those affected. Within the information communication

Table 4 Anchor examples for "decision-making and agreement"

Identified Items	Anchor Examples
Paternalistic communication	*"He knew [the disease], but I think […] he wanted to protect me. I had this feeling. He said, 'Okay, we will first look at this.' So first of all, [he] very slowly introduced the disease, and I had that feeling. And there was no malevolence, rather the contrary, he did know the disease very well, I have to admit. As I said, I cannot say 'I think,' but rather protection, so he rather wanted to protect the parents. No pessimism with such a disease and no giving up of hope, but rather, he said, 'Let's first of all wait and to the contrary care for it. First of all, you move on with your life as it is, you keep working and everything, not giving up anything.'" (Family member, female, A09)*
Informed (individual) decision-making	*"Therefore, I actually see my task in keeping the strings together during a transfer on my own, and I'd like to be invited to fill out one or another transfer form from somebody with a lot of knowledge. But to just nod something through in retrospect, that I have some reluctance with." (Physician, male, GP09)*
Shared decision-making	*"[…] It really helped me, and if I listened to my physician, I would have taken Hydrea since 2009. These are chemo tablets, which have a lot of side effects. Where one asks himself or herself, 'What is really the benefit? And what's actually the best way to go?' And that's what Professor [NAME] does and that's what he confirmed as unambiguous: that I can […] decide as a patient on my own as well. That I feel it on my own, and that I rather know what's good for me. But that does not mean that he only speaks according to his audience, or that he tells me only what he thinks I want to hear. On the contrary, […] I can say that after this conversation I have gotten so far to say, if Professor [NAME] says that it's time for therapy, […] it's time for therapy." (Patient, female, P28)*

process, the particular roles of "expert patients" or "lay experts" in the rare disease field came forth; physicians' and patients' perspectives were triangulated to validate these findings, and all items were verified in their importance.

Findings in the context of literature

First, this study analyzed the "relationship between the patient and physician" in Charles et al.'s [6] shared decision-making concept. The analysis revealed an imbalance between trust and mistrust in the rare disease field, whereby a trusting patient-physician relationship is a prerequisite for effective communication. Georgopoulou, Prothero, and D'Cruz [35], Dowell et al. [13], and the Royal Pharmaceutical Society of Great Britain, Merck, Sharp, and Dohme [14] all link a trusting relationship with a physician to many positive healthcare outcomes. Von der Lippe, Diesen, and Feragen [36] further deepen this analysis by describing a mistrust of doctors, and linking this to patients' emotional reactions. Further, Ernstmann et al. [37] found a positive relationship between trust and patient enablement, validating our overall finding that shared decision-making is still infrequently used in practice in the rare disease field.

The interviews revealed that a trusting relationship can be nurtured by, on the one hand, medical experts' transparent communication of rare disease knowledge, and on the other hand, their own engagement in the form of transfers or time invested. Literature notes transparent communication as one potential option among other tools, such as technical and interpersonal competence, physician agency, physician control, confidentiality, open communication, and disclosure [38] by systemizing the narrated items.

Aspects that undermine a trusting relationship and should be avoided include misdiagnoses, a lack of empathy, the lack of a constant contact person, the denying of treatments, and the "guinea pig" role in patients' disease treatment when therapy options are scarce. These findings can shift the awareness to rare diseases that lack approved medications [39].

Further many patients report being placed in the "psychosomatic corner", which hinders effective disease management. The acknowledgement of symptoms feeds into the patient-physician relationship Patients often report depending on a good physician, which they are "lucky" to have found. In this context, D'Elia [40] suggests a general listening concept for physicians to appreciate the entire possible spectrum of emotions that highlight doctors' valuable roles as social figures.

Finally, interactions are also characterized by the many participants involved. Other physicians as well as family members can be added to the standard patient-physician interaction. They illustrate this linked network's extent. Blöß et al. [41] verify these findings along the "diagnostic odyssey" of people suffering with rare diseases from the health expert's perspective, and conclude that diagnostic procedures still need major improvements in the rare disease field, especially in classifying incredibly rare diseases. Alternatively, Dudding-Byth [42] describes the transfers and diagnostics processes that general practitioners face.

In a second step, we carved out the extent of "participation during the decision-making process." Interviews suggest that rare diseases necessitate a broader extent of engagement, and consequently more time and effort. This is especially the case in times of diagnosis, as patients search for applicable therapy options and the initiation of medical treatment. People affected—either those who have lived with their diseases for a long time, and/or those who have chosen to settle with their diseases and take a more passive role—hand over their responsibilities to the doctor in a preferable "supervisory relationship." Tofan et al. [43] describe this process in the agency theory context; in his eyes this is rational behavior, as one presumes physicians fully follow the Hippocratic tradition.

In contrast, reports also describe an active, engaged attitude within the healthcare system, in that patients may travel several hundred kilometers to find the right physician or specialized rare diseases center. The subsequent efforts are extensive, especially when young children are affected. Similarly, Dellve et al. [44] describe the high pressure parents face in the rare disease field.

Interviews confirm the particular relevance of "information exchange" in the rare disease field. The identified themes highlight the scarce professional healthcare knowledge on rare diseases, the ideal scope of health communications, as well as the people affected, who become "patient experts" or "lay experts" on their diseases. Literature often quotes this concept [26, 45], but this is also confirmed during this study. These interviews augment this concept and depict physicians' difficult role, which shifts from a health information monopoly [46] to a new role as the sorter and structurer of available rare disease information.. Literature presents similar concerns from critics of the SDM model, who argue that most patients do not want to participate in such decisions, and revealing the uncertainties in medicine should be harmful. Further, while presenting all the potential risks and benefits across all treatment options is not feasible, the greatest concern is that increasing patient involvement in decision-making can lead to a greater demand for unnecessary, costly, or harmful medical procedures [47]. Therefore, the ultimate goal should be

to quantify costs and benefits in a controlled health-economic setting.

Potentials exist for patients who enthusiastically collect data, either from the Internet or from many interactions with experts during their path through the healthcare system. However, this potential is still hindered at a communication level, as the people affected may be concerned with negative reactions in their interactions with professionals. Literature also often describes Internet-based health information searches. For example, McMullan [48] notes different access timeframes, and highlights the threat resulting from information sources of diverging quality [45, 49, 50].

Finally, the last item suggested by Charles et al. [6] is the decision-making agreement itself. This study's interviews presented all forms of decision-making and agreement, and predominately described informed individual decision-making followed by paternalistic approaches. Although literature [7] suggests its increasing prominence, remarkably the SDM concept was rarely described. Further, SDM is difficult to identify, as the items overlap and are often difficult to grasp, as mutual acceptance and agreement can be stated at one point in time but may not hold [6]. Eliacin et al. [9] analyze patients' definitions of SDM to discover that the understanding of the concept in practice is consistent with literature. However, study participants indicated that SDM is not limited to the models suggested in literature.

Paternalistic approaches were depicted as unavoidable—such as for example in emergency situations—. These findings have also been reported by Budych, Helms, and Schulz [51], although these authors do not provide a context in which these approaches were welcome. Baron, Reyher, and Stack [52] report positive outcomes from paternalistic approaches in a crisis situation. The patients in their study were treated paternalistically, and exhibited a higher responsiveness to suggestibility ($p > .001$), felt they could depend more on the physician, perceived him as warmer and more supportive ($p > .01$), and expressed fewer incidences of physiological distress compared with patients treated in an egalitarian manner.

Informed decision-making was also often described to highlight patients' independence, and especially as they decide when to consult a healthcare professional and the extent to which patients consult their physician. Patients then decide whether to follow physicians' decisions or change medical consultants. Thus, it is often assumed that patients prefer Internet-based health information, while concerns simultaneously exist that this would lead to extensive, costly healthcare [47].

In this context, the potential of the shared decision-making process shows that integrating both "lay expert" knowledge and efforts as well as professional knowledge can soften conflicts and strengthen the rare diseases network approach at its core. Well-conducted SDM enhanced reported satisfaction, understanding, and confidence in the decisions [53]. In this regard, strengthening the patient-physician relationship through SDM can potentially diminish within the field of rare diseases the highly relevant issue of doctor shopping. Others regard the process of decision-making in its entirety, and insinuate the importance of increased involvement of participants and the approachability of providers [560]. Finally, observational studies with patients suffering from hip and knee osteoarthritis showed they choose less expensive medical procedures when SDM was chosen as a decision-making tool resulting in a cost reduction of approximately 12 to 21% [54]. This leads to the assumption that cost-effectiveness can be further improved through the implementation of such concepts. Considering the potential, we suggest further health economic evaluations in the field of rare diseases to generate knowledge on the benefits of such approaches.

The study's significance

To our knowledge, the current study is unique in its approach: it complements Charles et al.'s [6] SDM model, and integrates perspectives from physicians and patients' family members concerning this matter across a range of rare diseases. It also verifies findings from Budych, Helms, and Schultz [51], who also advocated for a conscious exchange of information in the rare disease field, although not within the context of a set framework. Moreover, they only focused on some rare diseases and the patient's perspective. The underlying study covers all disease areas and integrates different perspectives to illustrate a broader picture and contribute to an advocated network approach at a micro-level in the healthcare system.

Patients' perspectives at the macro-level are often systematically included by involving patient representatives. At the meso-level, it has been demonstrated that group decision-making tools can systematically integrate patient perspectives [21]. Thus, the question arises regarding which tool should be chosen to further implement SDM in practice. Literature suggests coaching programs or workshops [55], as well as decision boxes or tools led by nurses [11]. Scholl et al. [56] report the limited validity of SDM tools, and indicate why such concepts may not have been established in practice. Further, Elwyn et al. [5] describe criteria for a practical implementation to overcome these hurdles.

The patient participation concept has been integrated within Germany's national plan for cancer care

thus far, but has not yet become an integral part of the German rare disease national plan [20]. Following the model established by the national plan for cancerous diseases, patient perspectives can also become systematically integrated at the micro-health and economic levels. This can be accomplished by integrating SDM within various concepts for further development in the field, therefore ensuring and controlling its long-term application.

Assumptions and limitations

This study was conducted using qualitative interviews, and participants were encouraged to report their experiences with the healthcare system during their disease diagnosis and management, assuming that this reflects the actual subjective relevance in the decision-making process. The statements' validity have been verified by triangulation. Therefore, only a limited number of patients, family members, and physicians could be interviewed, but the number of participants was sufficient as a base knowledge generation was achieved. The qualitative design contributes to theory generation by gathering relevant items and avoiding absolute numerical statements; results must be verified through a quantitative study to make further projections and/or obtain evidence.

Shared-decision making was not addressed as such within the interview guide. Participants were not directly asked about SDM, but rather indirectly about their experiences within healthcare systems and health management during the information-gathering process. This approach bears some risk, in that some interviews may involve situations in which SDM did not occur. One advantage of this approach is its identification of the actual perceptions of SDM, decreasing potential biases. By avoiding the SDM concept but focusing on informed health behavior, participants cannot be cued regarding how to answer the question to appease the researchers [57]. However, this also bears the risk that the concept may not impose itself in its full extensity, as it was avoided to pinpoint participants towards the concept, by directly asking for it.

The interview study was conducted in 2014, but several new rare disease centers have been subsequently established, and a national rare disease plan has been pushed toward implementation. However, the general structure of this matter has not changed to impact the German healthcare system.

Besides, we did not interview the treating physicians of the included patients and or their family members due to organizational restraints. The patients interviewed in the current study were predominantly female; in this context, Wyatt et al. [58] reveal that no gender specifications exist in decisional conflicts, patients' satisfaction with the clinical encounter, or patients' engagement at the point of encounter. Only an increased concordance between decisions and actions were described in encounters with female clinicians, while male patients demonstrated an increased concordance in the decision aid arm compared to the control arm ($p = 0.05$). Further, women more actively manage their healthcare status; for example, woman search more often for Internet-based health information [59].

Conclusions

To the best of our knowledge, this study is the first to provide unique insights on the decision-making practice and SDM's current relevance within the rare disease field. While SDM is increasingly present, the reported processes still lack many aspects of the decision-making process in this area. Further, a shared decision-making agreement was more rarely reported; the patient-physician relationship was characterized by a distorted trust--building process; and such characteristics of rare diseases as genetic origins, severity, and chronic course may lead to patients' high dependencies on their physicians. Patients may also often suffer from stigmatization as stimulants. Although the physicians in our study noted that they would need further time to analyze rare disease cases, participation was comparably pronounced regarding their patient-side engagement. Political health efforts should strive toward these efforts and promote diminishment as strengths vanish during the odyssey through healthcare systems. The particular role of "expert patients" or "lay experts" in the rare disease field has again unfolded, and potential especially surfaces regarding the integration of the information gathered during the decision-making process.

The aforementioned efficiency potentials can be triggered through a further integration of shared decision-making, facilitating diagnostics and disease management. It is also noteworthy that the integration of shared decision-making in the rare disease field not only requires strengthening patients' positioning, but also the positioning of physicians. These potentials can be triggered by implementing further SDM processes within the rare disease field, for example, through integrating participating decision-making concepts within rare disease national plans, as has already been accomplished in the cancerous disease field. This can provide an opportunity to reinforce a crucially relevant networking approach, strengthened by rare disease centers and guides at its core, on a micro-level, and within patient-physician interactions. Further research can quantify this potential and examine the health-economic impacts of shared decision-making on overall healthcare spending.

Appendix 1

Table 5 Characteristics of patients, family members, and physicians ($N = 107$)

Parameters	Patients ($n = 55$)	Family members ($n = 13$)	Physicians ($n = 33$)
Sex			
Male	18	5	23
Female	37	8	10
Age			
Average	52	44	48
Maximum	85	60	68
Minimum	18	28	31
Civil status			
No specification	–	1	–
Married/cohabiting	34	9	–
Single	11	1	–
Divorced/Separated	7	1	–
Widowed	3	1	–
Educational qualification			
Technical collage/ university degree	14	5	–
Abitur	8	5	–
Advanced technical college degree	5	0	–
Secondary education	18	1	–
Secondary modern school qualification	10	2	–
Members of the household			–
Average	2,09	3,58	–
Maximum	5	5	–
Minimum	1	1	–
Age at diagnosis			
Average	37	8	–
Maximum	74	39	–
Minimum	0	0	–
Disease severity			
No specification	–	0	–
Low	5	3	–
Medium	26	2	–
Severe	21	7	–
Profession			
Employed	22	9	–
Unemployable	12	1	–
Pensioner	18	–	–
Student/Scholar	2	–	–
Homemaker	–	2	–
Special circumstances	1	–	–
Medical rare disease experience / RD guide	–	–	6
Regional aspects			
Rural	–	–	3
Urban	–	–	7
Metropolitan	–	–	8
Practice form			
Single practice	–	–	7
Group practice	–	–	11
Clinic level			
Basic	–	–	4
Regular	–	–	0
Specialist	–	–	1
Maximum medical care	–	–	4

Appendix 2

Interview guide

Section I: Disease.

This is for patients and their relatives when a diagnosis can be consciously discerned.

Question 1:

- I would like you to remember the onset of your / your relative's disease. What kind of changes did you perceive?

- Optional subquestion(s):

o Can you remember specific events?

o What kind of changes became noticeable within your body?

o To what extent did you perceive changes within your social environment?

o If the disease was diagnosed at birth, continue with Section II.

Question 2:

- How did the diagnosis occur?

Question 3:

- What happened after the diagnosis?

- Optional subquestion:

o How did the illness progress from there?

Question 4:

When you place yourself back in the situation, what did you feel?

Section II: Disease.

This is for patients only, when a diagnosis was not consciously discerned.

Question 1:

- I would like you to tell me about your disease and how your life changed. You may take all the time necessary for your answer.

- Optional subquestion:

o Describe the course of the disease. (For example: Were there any acute phases?)

Question 2:

- How did the illness manifest in your everyday life?

- Optional subquestion:

o Have you experienced any limitations, and if so, what kind?

Question 3:

- Some people have the desire to become informed themselves about disease. How is it with you?

- Optional subquestion:

o Can you describe a situation in which you desired to acquire more information about your disease and its management?

Section III: The search and need for information.

Question 1:

- Describe searching for information about the handling of your disease.

- Optional subquestion(s):

o Please try to remember what kind of information you searched for.

o Where did you find the information?

o How satisfied were you with your search results?

Question 2:

- Were there any events before or after which you more intensely searched for information?

- Optional subquestion(s):

o How did you proceed with your search?

Question 3:

- To what extent were there situations in which you could easily access information?

- Optional subquestion(s):

o What types of information were these?

Question 4:

- To what extent were there situations in which you strove to find information, but could not find it?

- Optional subquestion(s):

o What types of information were these?

o What kind of information would you wish for?

o What kind of information do you think you will need in the future?

Question 5:

- What moments were significant during your search?

- Optional subquestion(s):

o Was there a point in time at which you felt you had achieved a breakthrough?

Section IV: Media or respective information access points.

Question 1:

- Please consider the many possibilities through which one can presently communicate with the help of modern or classic media. When you consider your own situation, what possibilities did you use during your own search?

- Optional subquestion(s):

- What do you comprehend as the communication possibilities for modern and classic media, respectively?

Question 2:

- In what ways would you like to access information?

- Optional subquestion(s):

o Would you also like to access information using your mobile device or smartphone?

o What is your opinion of accessing information through social media, such as Twitter or Facebook?

o For example, we have considered integrating a helpline as part of a national information website. What is your opinion regarding the possibility of a helpline? How do you envision such a helpline?

Section V: Windup.

Question:

- Are there any other topics that you would like to address?

- Optional subquestion(s):

o Are there any other important aspects that we have not yet addressed?

Abbreviations

SDM: Shared decision-making; ZIPSE: Zentrale Informationsportal über seltene Erkrankungen

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Authors' contributions

AB and SL conducted the interviews with patients and relatives. VF recruited and interviewed the physicians. AB and VF analyzed and interpreted the data set. AB drafted the manuscript. JMS, JZ, and KD revised the document for important intellectual content. All authors have read and approved the final manuscript.

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Availability of data and materials

The data that support this study's findings are available from the Center for Health Economics Research Hannover (CHERH), but restrictions apply to the data availability, which were used under license for the current study, and thus are not publicly available. However, data are available from the authors upon reasonable request and with the study participants' permission.

Ethics approval and consent to participate

The ethics committee at Albert-Ludwigs-University Freiburg (number 53/14) issued a positive committee vote for the interview study conducted as part of the establishment of a central information platform on rare diseases in Germany (Zentrales Informationsportal über seltene Erkrankungen). Informed consent was obtained in writing from all participants.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

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Original Paper

Shaping an Effective Health Information Website on Rare Diseases Using a Group Decision-Making Tool: Inclusion of the Perspectives of Patients, Their Family Members, and Physicians

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Abstract

Background: Despite diverging definitions on rare conditions, people suffering from rare diseases share similar difficulties. A lack of experience by health professionals, a long wait from first symptoms to diagnosis, scarce medical and scientific knowledge, and unsatisfactory treatment options all trigger the search for health information by patients, family members, and physicians. Examining and systematically integrating stakeholder needs can help design information platforms that effectively support this search.

Objective: The aim of this study was to innovate on the group decision-making process involving patients, family members, and physicians for the establishment of a national rare disease Internet platform. We determined differences in the relevance of health information—especially examining quantifiable preference weights—between these subgroups and elucidated the structure and distribution of these differences in people suffering from rare diseases, their family members, and physicians, thus providing information crucial to their collaboration.

Methods: The included items were identified using a systematic Internet research and verified through a qualitative interview study. The identified major information needs included *medical issues*, *research*, *social help offers*, and *current events*. These categories further comprised sublevels of *diagnosis*, *therapy*, *general disease pattern*, *current studies*, *study results*, *registers*, *psychosocial counseling*, *self-help*, and *sociolegal advice*. The analytic hierarchy process was selected as the group decision-making tool. A sensitivity analysis was used to determine the stability and distribution of results. *t* tests were utilized to examine the results' significance.

Results: A total of 176 questionnaires were collected; we excluded some questionnaires in line with our chosen consistency level of 0.2. Ultimately, 120 patients, 24 family members, and 32 physicians participated in the study (48 men and 128 women, mean age=48 years, age range=17-87 years). Rankings and preference weights were highly heterogeneous. Global ranking positions of patients, family members, and physicians are shown in parentheses, as follows: *medical issues* (3/4, 4, 4), *research* (3/4, 2/3, 3), *social help offers* (1, 2/3, 2), and *current events* (2, 1, 1); *diagnosis* (6, 8, 9), *therapy* (5, 9, 7), *general disease pattern* (9, 4/5/6, 6), *current studies* (7, 4/5/6, 3), *study results* (8, 7, 8), *registers* (4, 1, 5), *psychosocial counseling* (1, 2, 4), *self-help* (3, 3, 2), and *sociolegal advice* (2, 4/5/6, 1). Differences were verified for patients for 5 information categories *(P*=.03), physicians for 6 information categories (*P*=.03), and family members for 4 information categories (*P*=.04).

Conclusions: Our results offer a clear-cut information structure that can transparently translate group decisions into practice. Furthermore, we found different preference structures for rare disease information among patients, family members, and physicians. Some websites already address differences in comprehension between those subgroups. Similar to pharmaceutical companies,

health information providers on rare diseases should also acknowledge different information needs to improve the accessibility of information.

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KEYWORDS

rare diseases; decision making; health information needs; preferences; patients; relatives; physicians

Introduction

Worldwide, approximately 350 million people are affected by rare disease [1]. Despite diverging definitions, people suffering from rare diseases share common difficulties. Particularly, health care professionals have little experience with this patient group, and patients typically wait a long time from the first symptoms to diagnosis. Moreover, medical and scientific knowledge concerning rare diseases is scarce, and low research efforts often result in, if available, unsatisfactory treatment options. When there is a treatment option available, patients still often need to consider financial aspects. Patients also frequently experience difficulties with the cost absorption of expensive treatments. Furthermore, rare diseases are very serious and chronic. Severe symptoms result in high disease burden and can have a significant negative impact on one's quality of life. Above all, patients often face a shortened life expectancy [2]. Consequently, there is an urgent need for proper health information for this population.

The Internet offers a large pool of somewhat obscure information. In this context, this study examines how information on rare diseases can be presented in a more structured way. As a second step, we also examined whether stakeholder-specific websites presenting information in accordance with the information priorities of the targeted subgroups would be necessary. We hypothesized that the information structures of patients, family members, and physicians would be identical, as family members and physicians would generally search for information to fulfill patients' needs. This would consequently lead to a single platform incorporating the overall group consensus on information priorities and therefore information presentation.

The literature, however, has not yet addressed the differing information needs between patients, family members, and physicians. Health information helps to empower patients, enabling them to understand, treat, cope, and effectively manage their disease [3-5]. Rare diseases' patients are often called *experts* of their own illnesses because they gather health information consciously through Web searches or unconsciously through numerous consultations with different health care professionals [6]. Besides, doctors' assessments of patients' preferences appear to be critical for the outcome of health services [7]. In this regard, the dialogue between patients and physicians is critical. Therefore, health care professionals must be trained and prepared to listen to patients and discuss their experiences [8,9]. Furthermore, health information searches should be facilitated and encouraged, as they enable patients to be more effective in communicating with their physicians [5]. This study contributes and adds value to this existing literature and the underlying dialogue by eliciting the different perspectives of patients, family members, and physicians on the relevance of rare disease information.

Aside from the above points, little or no scientific knowledge exists for the 5000 to 6000 different indications summarized under the term rare diseases. Adding all diseases and all different information providers together creates a huge and obscure information pool. Indeed, information providers often fail to meet the information needs of patients and families searching social media and utilizing chat rooms to obtain information; however, they might be unaware of the low quality of this information [10]. On the other hand, obtaining knowledge of the many thousands of different rare diseases is well beyond the ability of physicians. Primary physicians are only familiar with approximately 400 different indications. Primary physicians can extend their knowledge through asking questions of colleagues and reviewing paper-based data sources [11]; however, even with the advent of electronic records, it remains highly time-consuming and difficult to search for the right terms and obtain appropriate evidence. Taken together, these facts suggest that effective health information presentation is exceedingly important. Collins et al suggest that information needs can be incorporated by capturing and embedding the relevance of information [12]. This study shows how this demand can be put into practice.

Literature shows that group decision-making tools are rarely applied when it comes to the establishment of health information portals. Health information needs are often met by retrieving information from historic user statistics or triggering retrospection. Stakeholders cannot actively participate [13,14]. However, by choosing the analytic hierarchy process as a group decision-making tool, we can actively involve patients, family members, and physicians to address their unmet informational needs. Furthermore, information categories that are underrated by stakeholders (ie, patients, relatives, or physicians) can be illuminated. A number of different models have already been applied during the establishment of effective cocreative business modeling [15,16]. However, until now, there have been no attempts to devise a similar model in a transparent manner for different stakeholders in relation to rare diseases.

The following study has been conducted against the backdrop of the conceptualization of a central website for rare disease information in Germany (ZIPSE, Zentrales Informationsportal über seltene Erkrankungen or central information portal about rare diseases) [17] connecting disease unspecific and specific information, as well as quality orientation for patients, their families, and health care professionals at a central platform [18]. As part of the German National Action Plan for Rare Diseases from 2013 (NAMSE, Nationales Aktionsbündnis für Seltene Erkrankungen) following the European council recommendations [19,20], knowledge transfer is improved

through the development of Internet information systems. Already existing Internet information is collected and organized to increase the visibility of rare disease knowledge [18]. Physicians, family members, and patients are critical to this process; they are the major beneficiaries and should profit by effective health information provision.

In this paper, we describe how patients, family members, and physicians can contribute directly to this process of effectively gathering and presenting health information. More specifically, we describe an innovative group decision-making process involving these individuals aimed at establishing a national rare diseases Internet platform. This study also examined the information preferences of these stakeholders to enable health care systems, decision makers, and other national and international rare diseases portals to appropriately structure information that patients, families, and physicians strive for. The relevance of information is crucial for stakeholders' ability to relate to each other within a strong network approach. In this regard, the study provides unique insights into the quantitative structure and distribution of information preferences for these stakeholders, answering the question on how information provision in the context of rare diseases should be structured.

Methods

Ethical Considerations

The questionnaire was distributed both Web-based and as a paper-based version. Accordingly, consent was obtained in written form. The paper-based version was distributed after qualitative interviews with patients and their relatives. A positive ethics committee vote was obtained for the interview study from the ethics committee at Albert Ludwigs University of Freiburg (number 53/14). The Web-based version allowed for collecting opinions anonymously without having participants disclose personal details at any time. An information sheet was presented to all participants describing the aim and scope of the study. All participants were informed that they could withdraw from the study at any time.

Analytic Hierarchy Process (AHP)

An analytic hierarchy process (AHP) was implemented for the collection of individual preferences, as this study was devised to contribute the decision-making processes implemented in the ZIPSE project. Saaty gives detailed information on the AHP methodology [21]. Two authors also give a detailed overview of its application in health care [22,23]. Lately, the Institute for Quality and Efficiency in Health Care in Germany discussed the AHP as a method for the inclusion of preference structures into early benefit assessment. Similar to conjoint analysis, AHP raises quantifiable weights that can then be used to combine multiple endpoints into an efficiency boundary [24,25]. AHP offers a direct approach, whereas conjoint analysis compares different attributes in combination, thereby leading to an indirect calculation of weights. Furthermore, it is more intuitive and easier to understand for inexperienced participants compared with other techniques (eg, the analytic network process [26] but more informative than other techniques, eg, best-worst scaling, ranking) [27]). Quantitative preference distances make extensive evaluation of preference structures possible [20,28]. Therefore, the major benefit to AHP methodology is that it raises not only ranks but also measurable distances between criteria weights, leading to a visible preference structure. AHP does not only give a clear-cut ranking, it also indicates what categories are weighted similarly. Therefore, attributes that are weighted similarly, but ranked differently, do not need to be excluded. The AHP is able to appreciate individual judgments adequately to thereby derive an overall group consensus [29] and offers a clear-cut preference structure that can be easily applied to the presentation of health information.

AHP is particularly interesting for the field of rare diseases as it is applicable independent of the size of the indication. Even opinions of very small rare disease subgroups can be raised and evaluated [20,28]. Moreover, AHP appreciates the heterogeneity of rare diseases, which because of its definition, summarizes quite diverging disease patterns, as subgroup specific opinions can be evaluated separately. Consequently, this study recognizes the value of AHP when examining rare diseases.

Hierarchy Definition

A total of 300 information websites addressing rare diseases were searched and scanned concerning available information on their home pages. Litzkendorf et al also collected and verified the items through a qualitative interview study [30]. Similar information categories have also been found by the Genetic and Rare Disease Information Center [31] and for other indications such as multiple sclerosis [32]. Accordingly, information categories were drafted and prestructured. Four experts in public health research and one expert in health economics research were chosen from the Center for Health Economics Research Hannover (CHERH). The major criterion for choosing these experts was a research focus on either rare diseases or patient-reported outcomes. Participants were addressed personally. An invitation for participation was forwarded via email along with an attached Microsoft Excel 2010 sheet containing the included items. Afterwards, the final definition of the items was discussed in a workshop scenario. As a result, the different information category descriptions address biases because of different interpretations of information categories. Definitions were finalized if they seemed closed to interpretation and easily understandable (see Multimedia Appendix 1). Thirteen items were chosen, which resulted in 15 pairwise comparisons. The final hierarchy is presented in Table 1.

Questionnaire Development

Other studies used computer-based programs that immediately reflected the level of consistency generated by the answer [33]. Then, corrections are initiated. However, in our study, we did not use an intelligent computer-based fill-out system, instead implemented a paper-based questionnaire. A first draft of the questionnaire was designed and pretested. The pretest revealed insufficient consistency. Therefore, the questionnaire was redrafted. A graphic showing the hierarchy structure was removed to allow space for a graphic demonstrating the exemplary filling out of one question on the questionnaire. Furthermore, a ranking task was integrated, which visualized the intrinsic priorities during the fill-out process. A research question was specified for each visual scale.

Table 1. Hierarchy for information on rare diseases.

Hierarchy level 1	Hierarchy level 2	Hierarchy level 3
Research topic	Parameters	Elements
Importance of health information on rare diseases	Medical issues	Diagnosis
		Therapy
		General disease pattern
	Research	Current studies
		Study results
		Registers
	Social help offers	Psychosocial counseling
		Self-help counseling
		Sociolegal advice
	Current events	

The end of a paragraph containing items from one hierarchy arm was highlighted to emphasize the beginning of a new category. A subsequent pretest revealed improved consistency. Before fielding the questionnaire, the usability and technical functionality of its Web-based version were tested by the authors and a collaborating institution (see Multimedia Appendix 2).

Sample

Patients, physicians, and family members were identified as the main users of health information on rare diseases [34] and a central rare diseases information portal [20]. Participants were recruited using three different recruiting strategies to ensure the adequacy of the sample. The Freiburg Center for Rare Diseases located at the Department of Dermatology of the University Medical Center, University of Freiburg contacted patients and family members using rare diseases self-help groups. Overall, 39 individuals were asked to complete the questionnaire. To participate in the study, patients had to be aged 17 years and older; if they were younger than 18 years, a close relative was invited for answering the questions instead. Interviews were predominately conducted via telephone. To ensure a broad and balanced representation of patients suffering from rare diseases, eleven groups of rare diseases were formed when this study commenced; this was believed to represent considerable variety in rare diseases. Patients were recruited in accordance with these groups. Physicians were recruited by the CHERH. First, physicians with experience in rare diseases and working for specialized rare diseases centers were recruited. Later, the target group was extended to include physicians not imperatively familiar with rare diseases. This seems legitimate, as opinions of physicians unfamiliar with rare diseases but also searching for information were included. Furthermore, a Web-based version of the questionnaire was devised. The link to the open Web-based version was stored on a website offering Web surveys and forwarded by Alliance for chronic rare diseases (Allianz chronisch seltener Erkrankungen, ACHSE) using a mailing list of ACHSE members. A short description of the study was included. All data were collected and stored anonymously. ACHSE checked the avoidance of identification of rare diseases' patients through disease characteristics. The study was initiated in August 2014, and data collection was finalized in August 2016. Overall, 112 questionnaires were answered online, and 64 paper-based questionnaires were completed.

Analysis

For each respondent, a consistency ratio (CR) was calculated. The CR was calculated in accordance with the following formula: $(\lambda_{max-}$ n)/(n−1). λ_{max}. The CR is a value which has been predefined by Saaty [21]. Following the threshold of Danner et al, we included all comparisons with a CR≤0.2; therefore, we assumed pairwise comparisons to be consistent up to this threshold [35]. Respondents with a higher CR were excluded. Individual priority vectors were calculated using the eigenvector method used in Saaty [21]. Afterwards, individual opinions were summarized using an aggregation of individual priorities method. As literature suggests that values must correspond to reciprocal values of individual participants, weights were aggregated choosing the geometric means calculation [27]. As priority values need to sum up to one, resulting local priorities were weighted accordingly. Then, local and global rankings were derived. The calculation was conducted using Microsoft Excel 2010 and R version 3.1.2 (R-project for statistical computing). Responses of patients, families, and physicians were compared. To compare differences between these three subgroups, a variance analysis should be conducted first. However, as we analyzed differences between each of the three groups, test statistics were calculated using a student *t* test. Only local weights were compared as global weights were derived from these. An analysis of sensitivity was conducted observing the stability of priority rankings. Typically, AHP studies conduct sensitivity analysis using expert choice and graphically altering the weights of decision criteria and observing how rankings of alternatives outcomes change. However, this study did not include a hierarchy level with alternative decision outcomes, only items. Therefore, we assessed the sensitivity by identifying outliers and excluding them. Thereafter, potential rank reversals were observed. The range of data was elicited by box plots.

Bootstrapping (N=1000) was conducted to assess the proximity of values in correspondence to the parameter of the population,

especially acknowledging small samples in the groups of family members and physicians.

Results

Sample Characteristics

The mean CR was 0.22 (median: 0.14, standard deviation, SD=0.24) for all 176 participants. Questionnaires with a CR above 0.2 were excluded. A mean CR was calculated for each subgroup. CR for all people suffering from a rare disease was 0.25 (SD=0.27), CR for families was 0.17 (SD=0.11), and CR for physicians was 0.14 (SD=0.10). Accordingly, the proportion of consistent answers was 56% for patients, 67% for relatives, and 83% for physicians, showing that most of the inconsistencies occurred in the patient subgroup. Solely regarding consistent answers, average CR for all participants was 0.09 (SD=0.05). Characteristics of all participants are shown in Table 2, including participants who answered inconsistently. Physicians were not asked about their civil status or the number of household members because this did not seem to serve our research question. Furthermore, disease severity and age of diagnosis were not applicable for two subgroup.

Information Priorities

Tables 3-5 show both global and local priorities of level 2 and 3 items for all participants interviewed. Standard deviations of local priority weights are presented. Resulting ranks are also listed. As bootstrapping showed that calculated geometric means systematically underestimated the weights of information category, weighted geometric means were calculated. Results are presented separately for each subgroup.

Sensitivity Analysis

The results range is displayed in Figure 1 and shows the potential sensibility of local weights to outliers. The ranking results were calculated based on the geometric means because the literature suggests that this procedure is more precise [27]. However, the following box plots show the range of results in a more intuitive manner, displaying the average mean, as well as the maximum and minimum local weights.

To test for potential rank reversal, we excluded outliers and observed whether rank reversals were of consequence. Figure 1 identifies the outliers visually. The patient subgroup displays only one outlier that results in a rank reversal for the category *research*. *Research* is consequently ranked last with a priority weight of .19. Family members show outliers for categories *medical information* (.09), *therapy* (.21), *diagnosis* (.19), and *general disease pattern* (.60). The exclusion of outliers does not cause rank reversal. For the last group, *physicians*, outliers were identified for the following items: *medical information* (.11), *diagnosis* (.22), and *research* (.17). No rank reversals were observed.

Significance of Results

To examine differences between groups, we conducted a student *t* test, assuming opinions were aggregated following the normal distribution within the population. The results are displayed in Table 6. The null hypothesis states that the importance of items is perceived equally; the alternative hypothesis states that the importance of information on rare diseases is perceived differently. Significant differences are marked.

Furthermore, bootstrapping with a 95% CI was conducted to examine whether sample results lay within specific ranges of the population regarded. The results are presented in Figure 2.

Table 2. Sociodemographic characteristics of patients, family members, and physicians (N=176).

Parameters	Patients (n=120)		Family members (n=24)		Physicians (n=32)	
	Included (n=67)	Excluded (n=53)	Included (n=16)	Excluded (n=8)	Included (n=25)	Excluded (n=7)
Sex						
Male	11	18	2	1	13	3
Female	56	35	14	7	12	4
Age						
Average	51	50	46	49	42	49
Maximum	85	87	62	62	69	56
Minimum	17	17	23	33	28	29
Civil status						
Married or cohabiting	43	37	8	7	-[a]	-
Single	11	11	3	0	-	-
Divorced	9	3	2	1	-	-
Widowed	4	2	3	0	-	-
Educational qualification						
Technical college or university degree	28	16	10	3	25	7
Abitur	9	5	3	1	0	0
Advanced technical college degree	6	5	0	1	0	0
Secondary education	17	19	3	3	0	0
Secondary modern school qualification	7	8	0	0	0	0
Members of the household						
Average	2	5	3	3	-	-
Maximum	5	2	5	5	-	-
Minimum	0	0	0	0	-	-
Age at diagnosis, years						
Average	37	37	4	15	-	-
Maximum	74	79	37	47	-	-
Minimum	0	0	0	0	-	-
Disease severity						
No specification	0	0	1	0	-	-
Low	6	3	0	0	-	-
Medium	32	21	7	5	-	-
Severe	28	29	8	3	-	-
Profession						
Employed	27	25	16	5	25	7
Unemployable	14	10	0	0	0	0
Pensioner	20	14	0	2	0	0
Student or scholar	1	2	0	0	0	0
Homemaker	1	1	0	1	0	0
Special circumstances (further education or provision of work)	4	1	0	0	0	0

Parameters	Patients (n=120)		Family members (n=24)		Physicians (n=32)	
	Included (n=67)	Excluded (n=53)	Included (n=16)	Excluded (n=8)	Included (n=25)	Excluded (n=7)
Medical rare disease experience	-	-	-	-	24	3

[a]The symbol indicates that data are not available.

Table 3. Ranking results of patients.

Parameters	Patients (n=67)				
	Local weight	SD	Global weight	Local ranking	Global ranking
Medical issues	.21	0.21		3 or 4	
Diagnosis	.34	0.24	.070	2	6
Therapy	.37	0.21	.076	1	5
General disease pattern	.30	0.19	.062	3	9
Research	.21	0.17		3 or 4	
Current studies	.32	0.22	.069	2	7
Study results	.32	0.20	.068	3	8
Registers	.36	0.26	.077	1	4
Social help offers	.30	0.19		1	
Psychosocial counseling	.35	0.22	.103	1	1
Self-help	.32	0.24	.095	3	3
Sociolegal advice	.33	0.21	.098	2	2
Current events	.28	0.22		2	

Table 4. Ranking results of family members.

Parameters	Family members (n=16)				
	Local weight	SD	Global weight	Local ranking	Global ranking
Medical issues	.13	0.18		4	
Diagnosis	.24	0.21	.031	2	8
Therapy	.20	0.18	.025	3	9
General disease pattern	.56	0.20	.071	1	3/4/5
Research	.22	0.20		2/3	
Current studies	.31	0.21	.071	2	3/4/5
Study results	.16	0.10	.037	3	7
Registers	.52	0.23	.117	1	1
Social help offers	.22	0.16		2/3	
Psychosocial counseling	.35	0.23	.075	1	2
Self-help	.33	0.27	.071	2	3/4/5
Sociolegal advice	.33	0.22	.070	3	6
Current events	.43	0.18	-	1	-

Table 5. Ranking results of physicians.

Parameters	Physicians (n=25)				
	Local weight	SD	Global weight	Local ranking	Global ranking
Medical issues	.13	0.17		4	
Diagnosis	.23	0.16	.029	3	9
Therapy	.37	0.17	.046	2	7
General disease pattern	.40	0.19	.051	1	6
Research	.18	0.14		3	
Current studies	.44	0.22	.078	1	3
Study results	.25	0.18	.045	3	8
Registers	.32	0.22	.057	2	5
Social help offers	.26	0.17		2	
Psychosocial counseling	.29	0.11	.076	3	4
Self-help	.32	0.20	.083	2	2
Sociolegal advice	.40	0.20	.104	1	1
Current events	.42	0.17		1	

Figure 1. Range of results (local weights) of consistent answers by patients, family members, and physicians. CUS: current studies; DIG: diagnosis; GDP: general disease pattern; MED: medical issues; THE: therapy; PSY: psychosocial counseling; REG: registers; RES: research; SOC: social help offers; SHE: self-help; SOL: sociolegal advice; STR: study results.

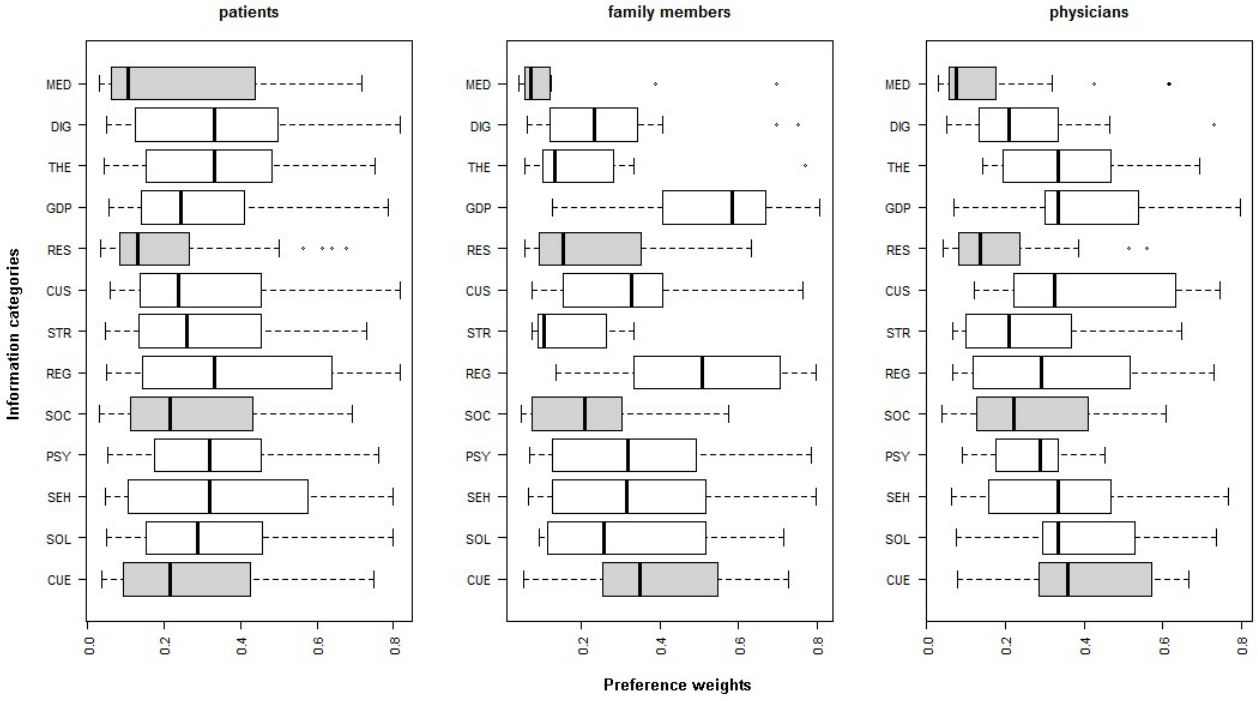
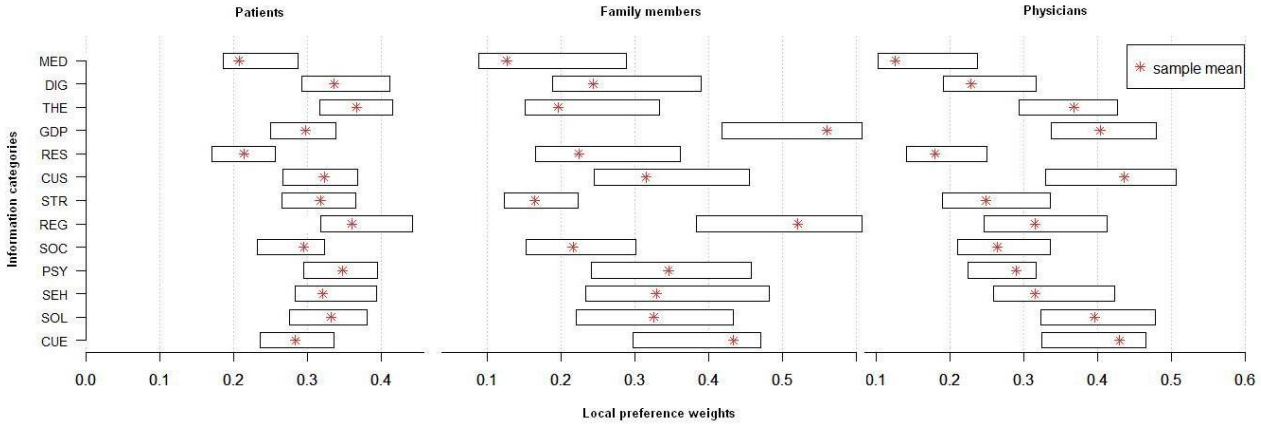


Table 6. Significance of differences between patients, family members, and physicians (n=108).

Parameters	Two-sample *t* test					
	Patients or families		Patients or physicians		Physicians or families	
	t statistic (degrees of freedom)	*P* value	*t* statistic (degrees of freedom)	*P* value	*t* statistic (degrees of freedom)	*P* value
Medical issues	1.60 (26)	.13	1.90 (55)	.06	0.04 (30)	.97
Diagnosis	1.43 (26)	.17	2.59 (62)	.01	−0.45 (26)	.66
Therapy	2.88 (26)	.01	0.07 (52)	.94	2.60 (31)	.01
General disease pattern	−4.26 (22)	<.001	−2.50 (39)	.02	−1.85 (32)	.07
Research	−0.65 (21)	.52	0.59 (54)	.56	−0.98 (24)	.34
Current studies	−0.26 (23)	.80	−1.98 (40)	.05	1.28 (34)	.21
Study results	3.99 (46)	<.001	1.20 (46)	.21	1.98 (38)	.06
Registers	−1.96 (25)	.06	0.87 (49)	.39	−2.44 (31)	.02
Social help offers	1.25 (27)	.28	0.19 (48)	.85	0.94 (34)	.35
Psychosocial counseling	0.01 (22)	.99	2.05 (78)	.04	−1.13 (20)	.27
Self-help	−0.12 (21)	.90	0.02 (48)	.98	−0.13 (26)	.90
Sociolegal advice	0.13 (22)	.90	−1.50 (44)	.14	1.17 (30)	.25
Current events	−1.98 (26)	.06	−2.52 (54)	.01	0.10 (31)	.92

Figure 2. The results of patients, family members, and physicians using bootstrapping and a 95% CI. CUS: current studies; DIG: diagnosis; GDP: general disease pattern; MED: medical issues; THE: therapy; PSY: psychosocial counseling; REG: registers; RES: research; SOC: social help offers; SHE: self-help; SOL: sociolegal advice; STR: study results.



Discussion

Principal Findings

This study shows that rare diseases information categories are weighted very differently, resulting in subgroup specific preference weight structures, distributions, and ranking results. Although *medical issues* were rated as least important by all subgroups, none of the other information categories showed an overall group consensus.

Significant differences between subgroups were confirmed by *t* tests comparing subgroup specific local weights for the following comparisons: the priority weight of patients and family members in the categories *therapy*, *general disease pattern*, and *study results* differed significantly. Moreover, patients and physicians showed significant differences within the categories of *diagnosis*, *general disease pattern*, *current studies*, *psychosocial counseling*, and *current events*. Comparing physicians' results against those of family members, *therapy* and *registers* showed statistical significance.

In quantifying these results, patients and family members showed diverging preference weights for 23% of the cases (3/13). On the other hand, patients and physicians showed different weights for 38% of the cases (5/13). Finally, physicians and family member's weights diverged only in two cases (15%, 2/13). These results indicate that patients and physicians show a comparably high percentage of diverging opinions on the importance of health information, weakening our initial hypothesis that physicians initiate their search strategy based on the patient-physician interaction. These results should be

discussed very carefully because the potential implications are hard to grasp. The statistical significance test was based on the local preference weight. However, the final result of the AHP was expressed as an absolute rank. Therefore, the results should be situated in the overall context. The local weights revealed significant differences in health information with regard to *therapy*. Specifically, patients put this category first (1) on the local level, whereas physicians put it last (3). Regarding the health information on *general disease patterns*, ranks were assigned inversely. Similar rank switches at the local level can be observed when comparing patients' and physicians' perspectives on information relating to *general disease patterns* and *psychological counseling*. Interestingly, *general disease patterns* were perceived as least important by patients (3), whereas physicians regarded it as most important (1). On the other hand, patients considered *psychosocial counseling* as the most important subcategory, whereas physicians considered it the least important.

Checking all subgroups for the sensitivity of results, a rank change could only be observed once. Therefore, we conclude that the results were relatively stable. These results are consistent with Danner et al [35], who interviewed patients while they were completing AHP questionnaires. Extreme values, which could lead to very unstable results, often go along with high inconsistencies. Per these findings, some extreme opinions could have been excluded because of the set CR threshold.

Theoretical Contributions

Interestingly, all subgroups prioritized information on *social help offers* and *current events* over hard facts such as *medical issues* and *research*. This is perhaps because certain medical topics can be discussed directly with physicians following a diagnosis. Unfortunately, we cannot directly compare these findings with the findings of other studies, as the study participants, information categories, and indications vary greatly. However, patients receiving genomic results outlined that they preferred filtering information to avoid information overload and to avoid learning what their future might look like [36]. This anxiety about the future might explain why patients rated medical information as less important, despite the fact that it was named as a main search item in studies such as that of Morgan et al [31]. On the other hand, Anderson et al [37], as well as Schwarzer [38] reported consistent findings with Australian families suffering from genetic metabolic diseases and children with anorectal malformations, emphasizing the importance of self-help groups in the long run and psychosocial counseling when self-help reaches its limits. Dellve et al [39] also highlight the importance of psychosocial counseling for family members, especially parents with a child suffering from a rare disease. These findings also quantitatively support the importance of not only research networks, as advocated for by, for instance, Aymé and Schmidtke [40], but also social networks in the field of rare diseases and inclusion of these networks within national and international rare diseases information platforms, reflecting the unique importance of self-help initiatives in the field of rare diseases. Common diseases often do not need the support of self-help groups because research and political action have already been largely implemented. On the other hand, for rare diseases, many initiatives and knowledge extensions originate from these self-help groups [6]. However, patient initiatives continue to be put at the end of the line. Given that research- and patient-oriented websites still primarily offer either websites for physicians or for patients, even though information valuable to all stakeholders are presented, this makes cocreation and the exchange of opinions even more important.

The information category *registers* was the most important category for families (at rank 1); patients regarded it highly as well, ranking it in 4th place immediately after *social help offers*. Only physicians attributed a high relevance to *current studies*. This statement emphasizes the importance of providing information on rare diseases registers and appreciates the worldwide effort put into the development of such strategies [41], mirroring the importance of longitudinal data acquisition and analysis as numerous rare diseases are connected to a genetic predisposition [19]. These results emphasize the considerable involvement of family members, as they are potentially also affected.

Relatively little interest in study results can be explained through the communication of the results itself. Long et al [42] report that participants of studies receive results only in 33% of the cases. Only half of respondents saw an opportunity to even request the results. However, in this case, almost all respondents demanded researchers to at least sometimes offer the results. The strengthening of the communication of study results can be seen as an opportunity to improve the inclusion of health innovations in health care systems.

The present health information survey among physicians and senior patients reveals some major problems when comparing these results to those of other studies. Specifically, the results vary widely, especially because the health information categories were outlined differently [43]. This indicates that further subgroup analysis can be performed while controlling for influential factors such as age and indication. However, it should also be emphasized that our study forms the basis for an Internet platform for rare diseases and therefore focused on the major relevant stakeholders for this disease category.

Besides, research has often focused on topics such as information access [44] or barriers to information access [45], which leaves the question of how information needs are specified unanswered [46]. Further research is necessary to examine this topic in more detail. Nevertheless, the results have potential for further improving the basis of physician-patient communication.

Practical Implications for Web-Based Health Information Provision

What do these results mean for rare diseases–related information providers such as ZIPSE? The differences between subgroups suggest that subgroup specific information is necessary. First, the ranking structure of rare diseases information categories can be translated, one-by-one, into website design by positioning topics in accordance with stakeholder priorities.

Besides, it seems advisable to considered Miller's Law to avoid information overflow. It appreciated that the whole load of rare diseases Internet resources cannot be processed at once [47].

Limited perception capacities of human brains make it indispensable to only display the most important information at first glance. Miller's Law states that the short-term memory of an average human brain can only absorb approximately 7 items at once, thus, limiting the effectiveness of Internet data processing. Moreover, considering Miller's Law and potential information overflow, only the most important seven items should be included. Therefore, the findings suggest that information categories such as *general disease information* (9), *study results* (8), and *current studies* (7) do not need to be presented initially. In the case of a website especially designed for family members, *current events*, *registers*, *psychosocial counseling*, *self-help*, *sociolegal advice*, *current studies*, and *general disease pattern* should be presented first. On the other hand, physicians prioritized information on *current events*, *sociolegal advice*, *self-help*, *current studies*, *psychosocial counseling*, *registers*, and *general disease pattern*.

Nevertheless, another perspective should also be thought of at this point. From an educational point of view, this study also presents information categories that currently seem undervalued. For example, patients do not perceive *current studies* (7) or *study results* (8) as important, even though these results might hold crucial information for their disease treatment or maintenance. Family members do not perceive *diagnosis* (8) and *therapy* (9) as very valuable. Group representatives often advocate for their children or partners who are suffering from a rare disease to treat these information categories as more important. Moreover, even though approximately 60% of patients see physicians as the primary source of information [14], physicians do not perceive information on *diagnosis* (9), *therapy* (7), and *study results* (8) as important. Therefore, it seems advisable to discuss whether information should be located to improve its visibility and to reflect its importance for the major stakeholder, the patient. Consequently, whether physicians' priorities should reflect patients' interests as an *information lobbyist* also requires examination. First of all, it seems advisable to not only include the underlying results into the design of information platforms on rare diseases but also to discuss information placement with experts in the field and to fully disclose information placement strategies. However, we strive for a high involvement of patients, family members, and physicians to realize efficiency potentials for health care systems. This can only be accomplished by respecting the outcome of the decision-making process translating results one-to-one.

Study Limitations

Data interpretation was a limitation. The AHP research sample size is still a topic of discussion. It has been highlighted that AHP does not require a particularly large sample size [48]. Other authors emphasized that there is no recommendation at all for AHP sample size [23]. Both sources base their statements on the fact that AHP reflects the opinion of the specific group and is thus a group decision-making tool. However, in this study, we raise preference weights, which should be representative for groups when an adequate sample size is achieved.

The quantitative aggregation technique shapes a clear-cut implementation structure for information categories. However, it must be acknowledged that the results illustrate the average opinions of rare diseases' patients, physicians, and family members.

Another issue that should be recognized when interpreting study results is the exclusion of inconsistent answers as part of the AHP methodology. Dolan [49] found that of 20 patients, 90% were willing and capable of completing an AHP. Danner et al [34] argued that extreme values are often chosen to emphasize answers that are not willingly contributed to inconsistencies. In our study, patients delivered inconsistent answers 44% of the time, whereas family members and physicians did so in 34% and 22% of the cases, respectively. However, these results were excluded to follow theoretical AHP requirements.

During pretests of the questionnaire's paper-based version, low consistency values were generated. Ranking cards were included as first choice assistive tools to mirror ranking results immediately. During interviews with patients and family members, this tool was very helpful and led to improved CR values. However, during interviewer-led AHPs, physicians refused to use it. Nevertheless, interviewers noted the shown ranking orders verbally. Finally, a ranking task was placed before each block of comparisons in the Web- and paper-based version.

Comparing physicians with patients, low participation rates are observed. VanGeest et al [50] stated that low participation rates are very common in physicians' surveys. Postal and telephone approaches seem to be more effective than Web-based strategies. Monetary incentives were found to be an effective strategy to increase participation rates. Nonmonetary incentives reflected little changes. Unfortunately, no monetary funds were available for this study.

As already indicated, a change of medium was necessary. Initially, a paper-based version was implemented. After the first recruitment period, a Web-based questionnaire was also introduced to broaden the target group. Several studies such as those of Hirsch et al [51] and Coons et al [52] found differences between participation for paper-based and Web-based surveys. Therefore, it is beneficial to combine both approaches considering representativeness, thus capturing both infrequent and frequent Internet users.

Finally, sociodemographic data show a relatively large proportion of female participants. Literature and other rare diseases Internet providers disclaim that health information on rare diseases are more often searched for by women than by men. For instance, Morgan et al [13] determined that 95.7 % of all inquiries to the Genetic and Rare Disease Information Center came from women.

Conclusions

This study describes an innovation in the involvement of patients, family members, and physicians in effectively gathering, structuring, and presenting health information in a world struggling with an information paradox, namely, health information overflow on the one hand and a major lack of information on rare conditions on the other. This innovation comes in the form of the chosen group decision-making tool, the AHP, which has helped transform individual qualitative

perceptions into a measurable scale. Accordingly, the strength of our study is its transparent quantitative demonstration of the information needs of physicians, patients, and family members, which makes direct comparisons and simple implementation possible. More specifically, this study provides unique insights into the quantitative structure and distribution of information preferences, as well as the validity of results. We were able to verify significant differences between preference weights of patients, family members, and physicians for some items, suggesting that the importance of rare diseases information is perceived differently in these subgroups. User-oriented information providers should seek to address these differences and provide stakeholder-specific websites in accordance with the relevance of health information. Furthermore, the importance of social help offers and current events as part of the information package might be underpinned, with a particular emphasis on the importance of social networks in the field of rare diseases. The finding that communication of study results is potentially undervalued can be seen as an opportunity to improve the inclusion of information on health innovations in health care systems. As we strive for a high involvement of patients, family members, and physicians to realize efficiency potentials for health care systems, the relevance of health information should be directly translated. Results must not only be considered when creating national rare diseases information platforms such as the ZIPSE but also when updating, redesigning, and implementing national and international rare diseases information platforms.

However, as part of the cocreation process, we solely focused on the subgroups interested in information on rare diseases as an explanatory variable for different information needs. We suggest that future studies examine other potential explanatory variables such as for instance gender, educational background, and civil status.

Finally, our findings might be helpful for improving communication between patients, legal guardians or partners, and health advocates, who are closely intertwined. This seems to have high potential because social and professional networks often remain separate within discussions of rare diseases. Promoting a discussion between stakeholders can help in combining forces within the backdrop of a networking approach, which has already been communicated and pursued through the implementation of national rare diseases plans. An understanding network that engages in successful collaboration can improve the quality of life of those affected by rare diseases, as well as lessen the perceived disease burden.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Description of rare diseases information categories.

[PDF File (Adobe PDF File), 22KB - ijmr_v6i2e23_app1.pdf]

Multimedia Appendix 2

Questionnaire.

[PDF File (Adobe PDF File), 155KB - ijmr_v6i2e23_app2.pdf]

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Abbreviations

ACHSE: Allianz Chronisch Seltener Erkrankungen
AHP: analytic hierarchy process
CHERH: Center for Health Economics Research
CR: consistency ratio
NAMSE: Nationales Aktionsbündnis für Seltene Erkrankungen
SD: standard deviation
ZIPSE: Zentrales Informationsportal über seltene Erkrankungen

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Modul 6

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Measuring patients' priorities using the Analytic Hierarchy Process in comparison with Best-Worst-Scaling and rating cards: methodological aspects and ranking tasks

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Abstract

Background: Identifying patient priorities and preference measurements have gained importance as patients claim a more active role in health care decision making. Due to the variety of existing methods, it is challenging to define an appropriate method for each decision problem. This study demonstrates the impact of the non-standardized Analytic Hierarchy Process (AHP) method on priorities, and compares it with Best-Worst-Scaling (BWS) and ranking card methods.

Methods: We investigated AHP results for different Consistency Ratio (CR) thresholds, aggregation methods, and sensitivity analyses. We also compared criteria rankings of AHP with BWS and ranking cards results by Kendall's tau b.

Results: The sample for our decision analysis consisted of 39 patients with rare diseases and mean age of 53. 82 years. The mean weights of the two groups of CR ≤ 0.1 and CR ≤ 0.2 did not differ significantly. For the aggregation by individual priority (AIP) method, the CR was higher than for aggregation by individual judgment (AIJ). In contrast, the weights of AIJ were similar compared to AIP, but some criteria's rankings differed. Weights aggregated by geometric mean, median, and mean showed deviating results and rank reversals. Sensitivity analyses showed instable rankings. Moderate to high correlations between the rankings resulting from AHP and BWS.

Limitations: Limitations were the small sample size and the heterogeneity of the patients with different rare diseases.

Conclusion: In the AHP method, the number of included patients is associated with the threshold of the CR and choice of the aggregation method, whereas both directions of influence could be demonstrated. Therefore, it is important to implement standards for the AHP method. The choice of method should depend on the trade-off between the burden for participants and possibilities for analyses.

Keywords: Decision making, Analytic Hierarchy Process, Best-worst-scaling, Method comparison, Patient preferences

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Background

Measurement of patient preferences and priorities has gained more relevance in health care. One reason is the increasing importance of patient participation in health care. In Germany, the Robert Koch-Institute used to call the patients "costumers" and "evaluators" in their Information System of the Federal Health Monitoring [1]. Patients also want to decide scope of service of statutory health insurances' and which services are covered. Several studies found differences between patients' and physicians' perceptions of preferences (e.g., [2–5]). It is relevant to assess the preferences of the (potential) patients instead of proxy reports. Another reason for the increasing importance is the integration of preferences as utility in health economics evaluations and reimbursement decisions for pharmaceuticals. Knowledge of patients' preferences or priorities could be a chance for optimizing the health care system according to patients' requirements.

Decisions regarding treatment preferences must consider a variety of characteristics, so called multi-criteria decision problems. Possible options for solving decision problems are value-based methods, strategy based methods, and Conjoint Analyses (CA). The German Institute for Quality and Efficiency in Health Care (IQWiG) tested and confirmed the Analytic Hierarchy Process (AHP) method as decision making tool in health technology assessments [6]. Application of AHP for the measurement of preferences has increased during the last five years, but is still a less researched approach in health care decision making [7]. It remains unclear whether the AHP method and established decision making methods yield comparable results. Recent studies already examined the direct comparisons of AHP and CA, as seen in [8–11]. Other studies conducted comparisons between CA and Best-Worst Scaling (BWS) [12–16]. Mühlbacher and Kaczynski (2016) demonstrated the similarity of BWS results and ratings, but did not compare directly the results from AHP with BWS [17]. Although another study published by Mühlbacher et al. showed similar results for BWS and AHP methods, some of the subgroups differed in their rankings obtained by BWS and AHP method [18]. However, we found no further evidence about the similarity or differences in priorities raised by AHP, BWS, or ranking cards.

This study accompanied a research project designed to gather patient needs concerning the establishment of a central information portal about rare diseases (Zentrales Informationsportal über seltene Erkrankungen, ZIPSE). Since the available space on the website was limited, the most important information categories for patients occupy the most space followed by the less important information categories. Various information requirements on diagnosis, therapy, self-help, research, and specialized care facilities for people living with rare diseases, their relatives, and health care professionals were identified in qualitative interviews (see [19]). However, the ranking of the information criteria remained unclear. AHP was a suitable method for prioritizing these information categories in the next step (see [20]). Since AHP is a relatively new approach in health care and it is rarely been used in health care research compared to BWS and DCE, several methodological aspects remain unstandardized. Forman et al. (1998) described different aggregation methods for group decisions with the AHP method: aggregating individual judgments (AIJ) and aggregating individual priorities (AIP) by arithmetic mean or geometric mean [21]. The choice of aggregation method depends on the circumstances and the aim of the study. We wanted to examine and compare the resulting differences in decisions of the aggregation methods in our study. This paper shows outcomes for the different Consistency Ratio (CR) thresholds, aggregations methods, and sensitivity analyses. Furthermore, the study tries to identify how to validate the AHP outcomes. Outcomes were compared with the results of questionnaires using the following well established methods: BWS Case 1, and ranking cards. The first aim of this study was to demonstrate the impact of the non-standardized AHP method on priorities. Does the aggregation method influence the resulting group priority rankings? The second aim was to compare the AHP outcomes with the outcomes achieved by BWS and ranking methods to validate the resulting priorities from patient perspective (convergence validity).

Methods

AHP method and application

The AHP method originates from the marketing sector, invented by Thomas Saaty in the late 1970s. Dolan et al. applied the method of AHP the first time in the health care sector several years later in 1989 [22, 23]. Nevertheless, the AHP remains a rarely used decision making method in health care research compared to BWS, ranking cards, and DCE. The following methodological explanations are in accordance with Saaty [24]. The AHP decomposes the decision problem at different levels of hierarchy. The first level describes the aim of the decision making. This is then explained in further detail at a lower level using sub-criteria. The last level contains possible alternatives with their characteristics. In the interview, the participant compares all criteria pairwise at each level (15 comparisons in total) using a scale ranging from 9 to 1 to 9. Thereafter, the judgments of the pairwise comparisons set up a matrix. This method presumes that the reciprocal request results in reciprocal weights of judgments; therefore, only the upper half of the matrix has to be queried. The matrices are used to calculate weights by the

Eigenvector Method. Additionally, the Consistency Ratio (CR) can be computed from the matrices to examine whether the participants' answers are random. Following Saaty, the CR has to be ≤ 0.1. Other authors suggested a CR ≤ 0.2, but the threshold value is not defined consistently [8, 25]. Higher CR values indicate exclusion of answers and questionnaires due to inconsistency.

First, we briefly report the results of information requirements of patients with rare diseases. Second, we compare the results of CR ≤ 0.1 and CR ≤ 0.2 for median, quartiles, and extreme values (as box-plots). Third, different aggregation methods (geometric mean, arithmetic mean, and median) are used and the differences in results noted. Saaty suggested to calculate group priorities by aggregating judgments or final outcomes by geometric mean to satisfy the reciprocal property of the AHP [26]. Reciprocal properties present the first axiom for the AHP, meaning that the strength of one criterion's dominance over a second criterion is inversely proportional to the second criterion's dominance over the first. This implies that if criterion A is five times more important than criterion B, criterion B is one-fifth the importance of criterion A (for all axioms see [27]). This relationship must be preserved after aggregation and can be achieved by the geometric mean method. The geometric mean is always smaller than the arithmetic mean, except for one observation is zero [28]. In this sub-section, we also examine differences in the results for aggregating individual judgments (AIJ) in contrast to aggregating individual priorities (AIP). Additionally, a sensitivity analysis estimates the stability of weights. As most AHPs combine specific criteria combinations into overall alternatives (e.g., criteria combinations to describe three different cars), the sensitivity analyses focus on the stability of these alternatives. Because no standard method for the AHP without combining the attributes to alternatives was implemented, we looked at the confidence intervals (CIs) for each global weight of the criteria, and identified the stability of the ranking positions for each criterion. Therefore, we determined the BC_a bootstrap 95%-CI because our sample was small and in this case bootstrap CI were more accurate and correct than the standard CI [29]. All our analyses were conducted with the R statistic software program and the package "pmr" [30].

Methodological background of the BWS and ranking cards

As a second method in this paper, we applied BWS Case 1 in the same study population population [31]. Here, different combinations of the criteria built up the sets. The interviewee selected the best and the worst criteria in each set, resulting in two decisions per set. Each person answered seven sets. The BWS method is based on random utility theory, and uses the choice models or the count analysis. Methods used in choice approaches are multinomial logit model, conditional logit model, maximum-likelihood, or weighted least square method population [31]. Since we were not interested in predictors for the decision, but rather in rankings, we emphasized the count analysis method and rankings.

Using ranking cards resulted in an ordinal ranking of criteria, implying that distances between criteria could not be measured. Besides, it was a well-established warm-up task [32], and could support the interviewee to remain consistent with their prior ranking throughout all tasks. This survey included the ranking cards method before the AHP tasks.

Comparison of results from AHP, BWS, and ranking cards

Furthermore, the results from AHP, BWS, and ranking cards were compared. We placed the results in a table and examined differences in the rank. The AHP's weights could not be compared with the weights from the BWS, because they are based on deviating mathematical calculation methods and scales. In addition, we conducted tests for correlation between the ranks with the help of Kendall's tau b coefficient. This coefficient was used for rank ordered data, and identifies concordant and discordant rankings between two or more variables [33]. The Kendall's tau b makes adjustments for ties in the data, in contrast to Kendall's tau a.

Survey design

The study sample consisted of randomly selected participants from the qualitative main study of the ZIPSE project [19]. A positive vote was obtained from the ethics committee of Albert-Ludwigs-University Freiburg (number 53/14). As it was an accompanying research project, inclusion and exclusion criteria for participants were equal to those of the main study sample. Therefore, participants were at least 18 years old and were either suffering from a rare disease, or were the near relative of a sick individual. In this study participants were interviewed either face-to-face, or via phone with a paper-pencil questionnaire that contained AHP, BWS, and ranking tasks. Criteria development is described in detail by Babac et al. [20]. Additionally, socio-demographic and disease specific data were collected. A ranking task of cards with the criteria's descriptions should support consistent answering. Therefore, participants arranged the cards according to their preferred order, and left them next to the questionnaire during the rest of the interview. The interviewer indicated inconsistencies between ranking cards. Hence, participants could adjust either the order of the cards, or the judgment in the questionnaire.

Financial support for this study was provided in part by a grant from the Federal Ministry of Health. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

Results

Initially, we report the AHP results including the criteria description and their hierarchical arrangement. Then, we show the information criteria priorities evaluated by patients with rare diseases or their relatives. The following subsections investigate the outcomes of different methodological approaches in the AHP method. Finally, we report the comparison of AHP results with BWS and ranking tasks.

Figure 1 shows the final hierarchy for the AHP. It consists of four levels with the aim of study on the first level. The aim decomposes into information about *medical issues*, *research*, *current events,* and *social advisory and support services*. The topic of *medical issues* was again subdivided into *diagnosis*, *treatment,* and *disease patterns*. The first two were split into *provider* and *methods* at the fourth level. *Disease patterns* contained *aetiology*, *frequency*, *typical symptoms,* and *progression* at the lowest level. At the third level *research* implied *current studies*, *study results,* and *registries. Current events* at level two contained no further subcategories. The last category at level two was divided into *social law counseling*, *psychosocial counseling,* and *self-help* at level three. *Self-help* further held the subcategories of *personal contacts* and *online contacts* (fourth level). Further details and descriptions can be found in Additional file 1.

The sample for our decision analysis consisted of 31 women and 8 men with mean age of 53.82 years. The inequitable distribution of gender was due to the fact of unequal proportions in the qualitative main study.

In the first scenario, all participants who reached a CR at second level exceeding 0.1 were excluded from the analyses. Then 22 included participants (19 women, 3 men; mean age: 52.50 years) remained for further analytical steps. In this scenario, we calculated weights for each included participant and then aggregated the weights (AIP method). The first approach was aggregating the weights by median. In Fig. 2, the results are shown as boxplots including the quartiles and distribution of weights for each criterion at second level.

The boxplots show that *medical issues* were the most important criteria for the participants with a median weight of 0.4548 (SD = 0.1728), followed by *social support* (weight (w) = 0.1575, SD = 0.1777), and *research* (w = 0.1314, SD = 0.1462). The least criterion was information about *current events* with a median weight of 0.0913 (SD = 0.1550). The SDs of *social support, research,* and *current events* indicated high variations of the priorities in the sample.

Figure 3 shows the local weights of sub-criteria at the lower third level. The gray boxplots indicated the subcriteria of *medical issues* with the highest weight for *diagnosis* (median weight (mw) = 0.4517, SD = 0.2240), followed by *treatment* (mw = 0.3512, SD = 0.2223), and

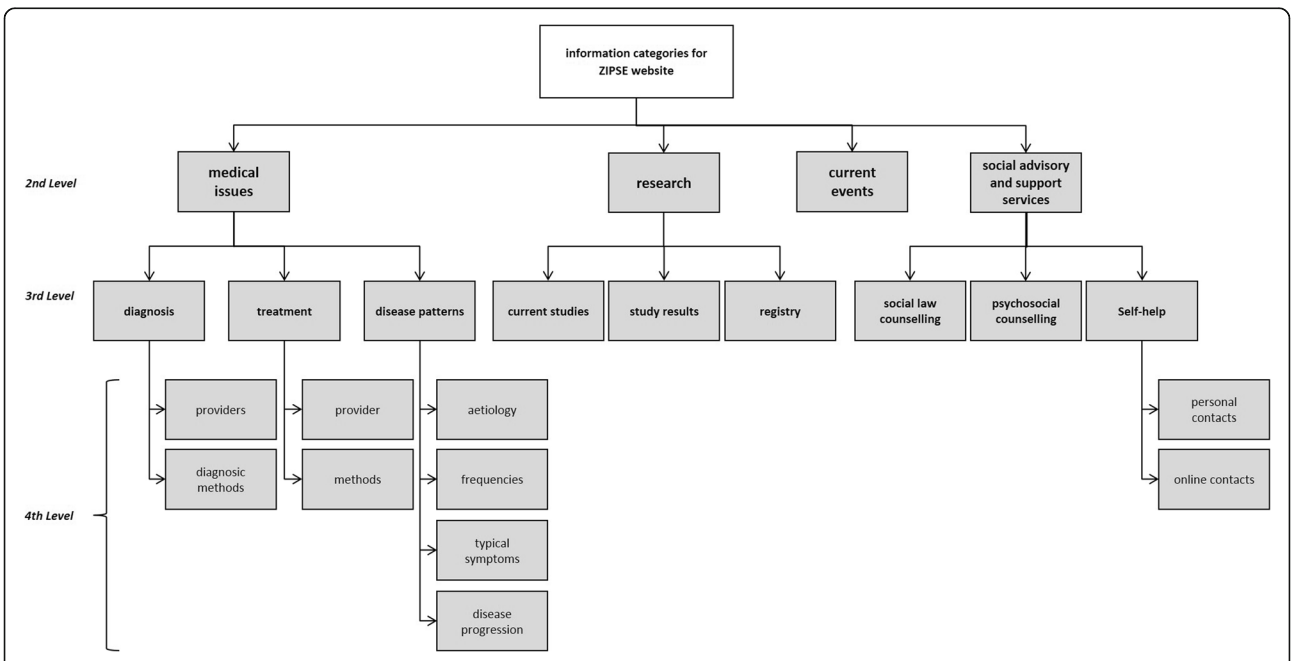

Fig. 1 Hierarchy of rare diseases information categories

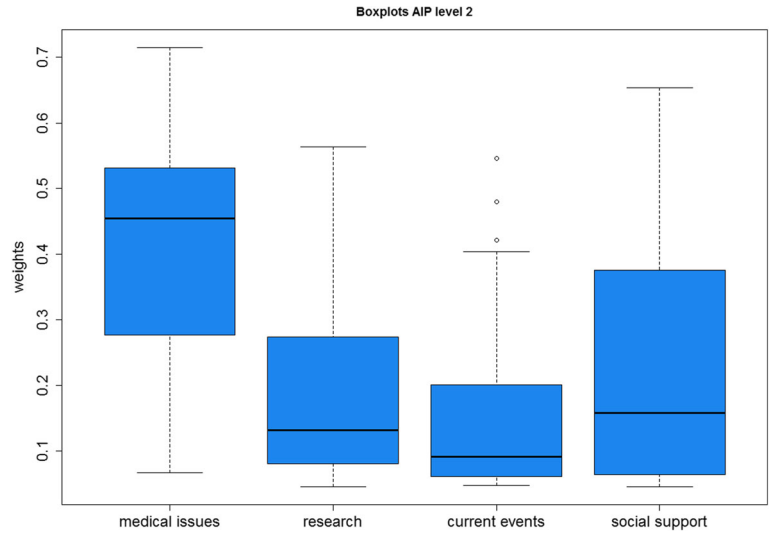

Fig. 2 Boxplots of global weights from criteria at second level

disease patterns (mw = 0.1492, SD = 0.0763). The second information criterion of *research* (blue boxplots) included *current studies*, *study results,* and *registry*. The most important sub-criterion was *study results* with a local weight of 0.4416 (SD = 0.2015), the second *current studies* (w = 0.3184, SD = 0.1955), and the third was the information about *registries* (w = 0.1429, SD = 0.2142). The green boxplots displayed the local weights for the category of *social support. Self-help* (w = 0.4663, SD = 0.2307) reached the highest weight followed by *psychosocial counseling* (w = 0.2845, SD = 0.1801), and *law counseling* with the lowest weight of 0.2167 (SD = 0.1768). We did not compare the global weights of subcriteria against each other because high weights at the second level (e.g., for *medical issues*) would highly influence the weights at the third level. Therefore, we used the sub-criteria's local weights for comparisons within each criterion because the global weights were not important for our methodological considerations.

Comparison of consistency thresholds

Figure 4 shows the boxplots for all global weights separated by level. Additionally, it compares the boxplots for a threshold of included participants with high consistency (CR ≤ 0.1) and a threshold of lesser consistency (CR ≤ 0.2). All graphs show an almost equal median for the two groups of CR and a *t*-test indicate no significant differences of median for each criterion (not shown here). However, a difference in the ranking by median occurs at level three: *law counseling* gained a higher weight for an extended threshold and received rank 9 (w = 0.0310) instead of the 13th and last rank (w = 0.0452). At the same

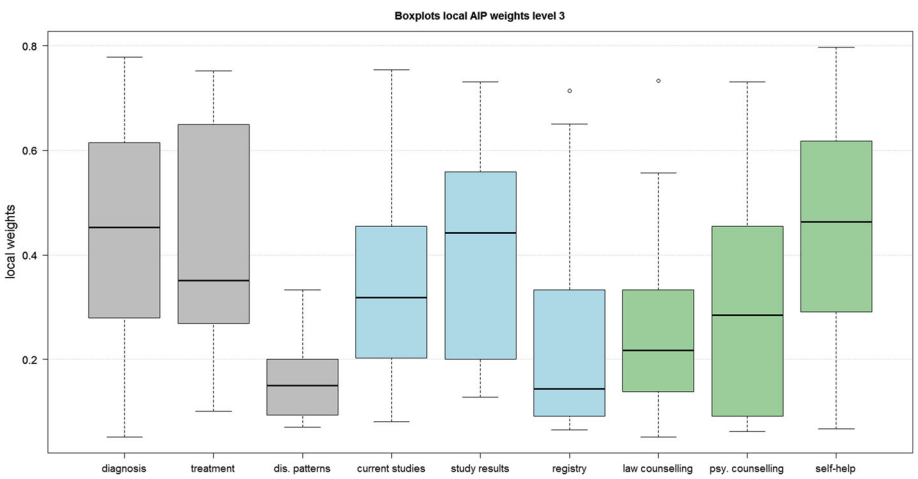

Fig. 3 Boxplots local AIP weights at third level

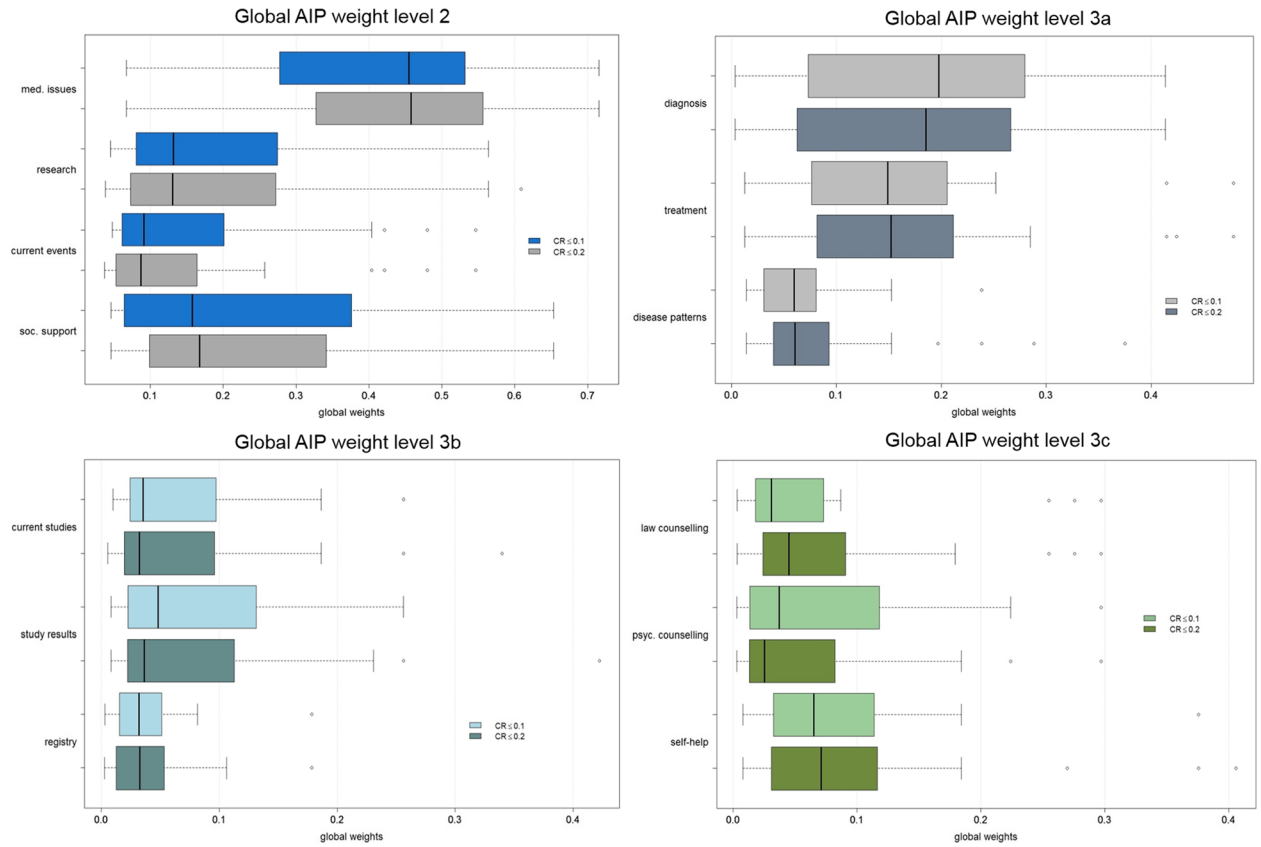

Fig. 4 Boxplots global AIP weights separated by CR

time, *psychosocial counseling* fell from rank 10 to 13 (weight 0.0372 onto 0.0254). A rank reversal occurs for *current studies* (weight 0.0353 onto 0.0324) and *registries* (weight 0.0319 onto 0.0325). In summary, the medians between a lower and a higher CR threshold did not differ significantly. Nevertheless, when small differences in weights occurred, rank reversals could be observed. In this study, rank reversals occurred only for the last four rankings.

Comparison of aggregation methods

In the next step, we analyzed differences in global weights by different aggregation methods. All mean calculations were based on geometric mean calculation as it serves the Pareto Principle and therefore seems to be the correct approach in theory [10, 34]. In the first scenario, the AIJ was applied. This method aggregated the comparison matrices first. In a second step, priority weights were calculated for each criterion. An overall CR was calculated for level two after the aggregation of all individual opinions. In the second scenario the AIP method was applied. This methodology calculated eigenvectors and priorities for each participant first. Only participants with a CR smaller than or equal to 0.1 were included in the aggregation. Afterwards, resulting priority weights were aggregated through geometric mean calculation.

Figure 5 displays the results of the two scenarios that comprised all 31 participants for scenario 1 and 22 for scenario 2. The aggregated judgments (scenario 1) show similar global weights for most of the criteria compared to the aggregated weights (scenario 2). Rank reversal occurrs between *diagnosis, treatment,* and *research,* because for scenario 1, *research* (w1 = 0.2038) and *treatment* (w1 = 0.1862) were more important than *diagnosis* (w1 = 0.1691), whereas in scenario 2, *research* (w2 = 0.1916) and *treatment* (w2 = 0.1892) were less important than *diagnosis* (w2 = 0.1955). Likewise, the ranking differs for *self-help, study results,* and *disease patterns*: in scenario 1, *disease patterns* (w1 = 0.0940) were more important than *self-help* (w1 = 0.0871) and *study results* (w1 = 0.0860), and in scenario 2, it was the other way round (*self-help* w2 = 0.0906, *study results* w2 = 0.0786, *disease patterns* w2 = 0.0785). A third rank reversal can be seen for the two scenarios between *current studies* (w1 = 0.0721, w2 = 0.0704, rank 11 vs. 10), *psychosocial counseling* (w1 = 0.0568, w2 = 0.0547, rank 12 vs. 11), and *law counseling* (w1 = 0.0729, w2 = 0.0531, rank 10

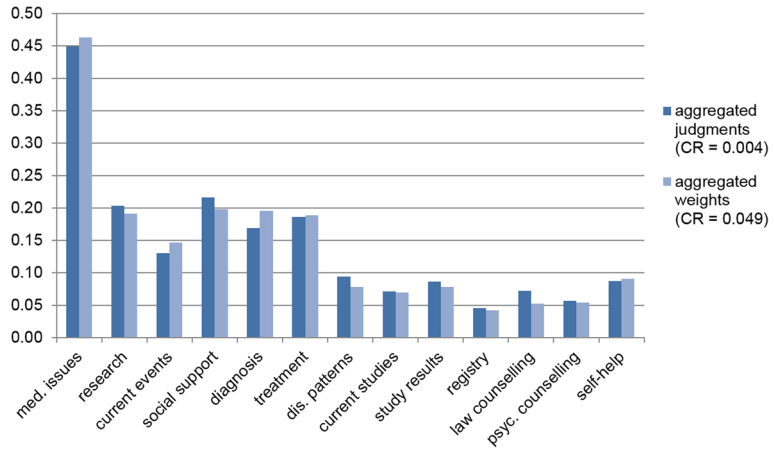

Fig. 5 Comparison of global weights for different aggregation levels

vs. 12). The CR for the second level was 0.004 in the first scenario, whereas the CR was 0.05 in the second scenario.

In the next step, the AIJ and AIP were compared by median. The table for these comparisons can be found in Additional file 2. The results are nearly identical to Fig. 5. The differences are small deviations in the weights and a few higher weights for the AIP than the AIJ (*current events*, *registries,* and *self-help*). The last comparison of AIP and AIJ was conducted by their means. Here, the AIP were markedly higher than most of the AIJ, also in comparison with the AIPs of the previously mentioned aggregation methods. Additionally, the weights summed up to 1 at first level, and they yielded the appropriate weights at lower levels. However, the most important question in this context was whether the ranking position changed through the different aggregation methods. Table 1 answers this question.

The noticeable difference occurs for the criterion *self-help*, which took the ranking positions from 7 to 13 over the different methods. Another striking criterion is *current studies*, which obtains ranking positions between 5 and 11. Two less intensive varying criteria were *social support* and *disease pattern* that differed between 5 positions. The further 9 criteria varied between 3 ranking positions, so a relatively stable valuation could be assumed.

Finally, the influence of aggregation method on CR had to be examined. The CR in the scenario of aggregation by geometric mean was markedly lower for AIJ than for AIP (CR AIJ: 0.0045; CR AIP: 0.0490), although only participants with a CR ≤ 0.1 were included for the AIP. By using the median (CR AIJ: 0.0683; CR AIP: 0.0674)

Table 1 Comparison of aggregation methods and weights

	Geometric mean ranking		Median ranking		Mean ranking	
	AIJ	AIP	AIJ	AIP	AIJ	AIP
Med. issues	1	1	1	1	1	1
Research	3	3	5	5	3	3
Current events	6	6	9	6	6	5
Social support	**2**	**2**	4	3	**7**	**2**
Diagnosis	5	4	2	2	2	4
Treatment	4	5	3	4	4	6
Disease patterns	7	8	**6**	8	9	**11**
Current studies	**11**	10	7	**11**	**5**	10
Study results	9	9	8	9	8	8
Registry	13	13	13	12	11	13
Law counseling	10	12	10	13	10	12
Psychosocial counseling	12	11	11	10	12	9
Self-help	8	**7**	12	**7**	**13**	7

The bold data highlights the results in the following text passage

or mean scenario (CR AIJ: 0.0745; CR AIP: 0.0587), the CRs were similar, but still much higher than the CR from AIJ by geometric mean, as expected.

Sensitivity analysis of AHP results

Usually AHP examine a combination of (sub-)criteria weights resulting in decision alternatives. Thereafter, the sensitivity of alternatives can be analyzed. However, the underlying study does not integrate a hierarchy level with decision outcomes, but only criteria and sub-criteria. Therefore, we looked at the stability of the criteria's ranking positions. Consequently, we calculated the CIs for each global weight (see Fig. 6). In addition, we show the mean weight of the underlying sample. The CIs distributed over three ranges for global weights. The seven lowest criteria in the figure from *self-help* to *results* showed CIs from approximately 0.03 to 0.14, and the CIs were rather small, particularly *social support*. Then, the criteria of *current studies*, *research*, *disease patterns*, *therapy,* and *diagnosis* covered a CI from approximately 0.11 to 0.30. A markedly higher CI arose for *medical issues* (CI: 0.34–0.49). It could be concluded that within the first two groups, the criteria were likely vulnerable to rank reversal. In contrast, the first rank for *medical issues* was assumed to be robust.

Comparison of methods

In the next section, we wanted to contrast the results of the AHP and the BWS. Table 2 compares the results of the methods. The most important criterion at level two was information about *medical issues* in all three methods, followed by *social support* and *research*. The least important criterion, *current events*, was also equal for AHP and BWS, but for the ranking cards it was also ranked position 3. At level three for *medical issues*, the most important criterion was *treatment* in the BWS, and diagnosis in the AHP. *Disease patterns* took the third position in both cases. The sub-criteria for *research* were ranked as followed for BWS and also AHP: 1) *study results*, 2) *current studies*, 3) *registry*. In the category of *social support,* the most important sub-criterion was *self-help*. The positions 2 and 3 differed between BWS and AHP. In the BWS, the second important sub-criterion was *law counseling,* whereas it was *psychosocial counseling* in the AHP. The ranking cards results showed doubled ranking positions at all levels, particularly when BWS and AHP were indifferent.

Because the ranking cards gave orientation for the AHP in the interviews, we assumed that there was a correlation between their results. Therefore, we did not evaluate the correlations for AHP and ranking. We examined the correlation between AHP and BWS rankings by Kendall's tau coefficient, for each hierarchical level. We found significant moderate to strong correlation between the two methods in the rankings (see Table 3).

Discussion

In this paper, we focused on methodological aspects of AHP and comparison of methods. The first step was to compare the results for different CR thresholds. Thereby, we considered the weights for including all interviewees with CR ≤ 0.1 or CR ≤ 0.2. We found that the mean weights between these two groups did not differ significantly. However, rank reversal could occur if the criteria's weights are close. For clarification, another phenomenon in AHP is also called "rank reversal": it occurs when adding or deleting an alternative leads to a shift in the previous alternatives' ranking order [35, 36]. The latter phenomenon was not investigated in our study.

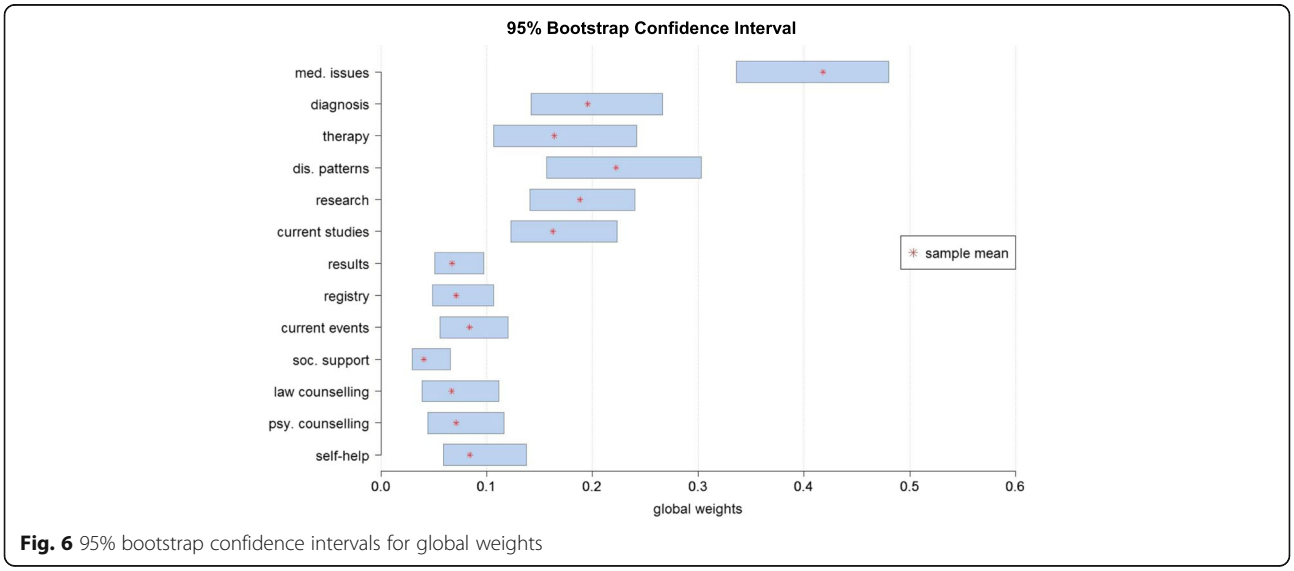

Fig. 6 95% bootstrap confidence intervals for global weights

Table 2 Comparison of BWS, AHP, and ranking cards

Criteria	BWS values	AHP local weights	BWS ranking	AHP ranking	Ranking cards[a]
Med. issues	1.000	0.368	1	1	1
Research	0.322	0.152	3	3	3
Current events	0.000	0.117	4	4	3
Social support	0.372	0.158	2	2	2
Diagnosis	0.855	0.354	2	1	1
Treatment	1.000	0.342	1	2	1
Dis. patterns	0.000	0.142	3	3	2
Current studies	0.279	0.304	2	2	2
Study results	1.000	0.339	1	1	1
Registry	0.000	0.184	3	3	2
Law counseling	0.421	0.213	2	3	2
Psyc. counseling	0.000	0.220	3	2	2
Self-help	1.000	0.363	1	1	1

[a]Equal ranking for multiple criteria permitted

The second step was to compare different aggregation methods. Therefore, we calculated the geometric means of the AIJ method (scenario 1) as well as the AIP method (scenario 2). The first difference was the number of participants that were included with a CR ≤ 0.1. In the first scenario, we included 31 participants, and in the second scenario, we had to exclude 9 participants because they showed CRs > 0.1. In the first scenario, we had a CR of 0.004 for the second level calculated after aggregating the judgments. In the second scenario, the CR at the second level was 0.05, and thus higher than in scenario 1, although the participants with CRs > 0.1 were excluded from the final CR calculation. The results received from scenario 1 showed almost the same weights compared to the results from scenario 2. Besides, the criteria's rankings differed between the scenarios, due to short distances between the weights. The AIJ method implies that the group decides as a new individual whereas the AIP method is based on the assumption that each individual decides on her or his own and the resulting decisions are aggregated [21]. Therefore, the aggregating method should depend on whether the sample is seen as one unit or a group of individuals. Forman et al. (1998) argued that for AIJ the geometric mean must be used because otherwise two social choice theory axioms (Pareto optimality and homogeneity) are not satisfied [21, 37]. The Pareto optimality axiom describes that the most frequently preferred alternative in the individual decisions must be the preferred one in the group decision. The homogeneity axiom states that the ratio between the criteria weights is the same for individual and aggregated group judgments. Our study supported Forman's demand as we saw violations of the Pareto axiom in Table 1, but not for the most preferred criterion. The homogeneity axiom was not investigated in our study. In future AHP studies, following Forman et al. (1998) and Saaty (2008) the geometric mean should be used in AIJ method.

Table 3 Correlation between AHP ranking and BWS ranking for each level

	Kendalls tau	*p*-value
Level two	0.585	<0.001
Level three a	0.543	<0.001
Level three b	0.613	<0.001
Level three c	0.668	<0.001

In the third step, we opposed the criteria's rankings received from aggregated weights and judgments by geometric mean, median, and mean. Here, the ranking positions showed deviating results and rank reversals. These aspects should be considered when results derived by different aggregation methods in studies are compared.

As no sensitivity analysis is suggested for AHPs that do not include alternatives, we tried to find an appropriate one. The aim of sensitivity analysis in AHP is to find instable criteria that could cause rank reversal. Therefore, we illustrated the 95%-CIs for all criteria. Where CIs overlap because of similar weights, the risk for rank reversal increased.

Finally, we evaluated the criteria's rankings for the different methods (AHP, BWS, ranking cards). However, we could not compare the weights from AHP with the weights from the BWS, because they use different scales. Therefore, only the rankings could be compared between the methods. Here, we found moderate to strong correlations between the AHP and BWS.

Correlated results between the methods were similarly reported by prior studies. Pignone et al. (2012) investigated differences in value elicitations with CA, rating,

and ranking tasks [38]. They concluded that the CA produced different values compared with ranking and rating, but the latter two led to similar results. Van Til et al. analyzed the differences between pairwise comparisons, BWS, five point rating scales, point allocation and ranking [39]. There were no differences between the methods at group level; however, differences occurred at the individual level and the largest differences were between pairwise comparisons and the five point rating scale. The correlation between the methods for individual weights was moderate. Furthermore, the order of the methods shown in the questionnaire influenced the weights. We did not examine this aspect in our study, because we had a small sample, and could not expect significant results regarding this question. Therefore, the order of tasks could also influence the results.

A major problem was the inconsistent response behavior of the participants in the AHP. Our sample consisted of patients with different rare diseases. The diverse clinical pictures and disease stages could have led to different priorities in the evaluation of the information criteria. Although in our study the participants used ranking cards for assistance during the AHP, the CRs were not all below the defined threshold. This phenomenon raised the question, whether the AHP method was not applicable in certain participant groups or in a heterogeneous sample. Therefore, future research projects should investigate the requirements for their participants, because this could bias the results. Further studies should also examine whether the aggregation of judgments always leads to higher values than the aggregation of weights, as detected in our study.

Another aspect was the small number of participants. Although we neglected this aspect in our study, the number of participants could also be an influencing factor of the results. Recent literature suggests that AHP is particularly useful for small groups, because priorities can be calculated for each participant [40]. As we used the sample from the main study, a larger proportion of women was included. Nevertheless, by aggregating the individual judgments or weights the researcher gave a statement for a (heterogeneous) group. Thus, we should present the results from the AHP under the restriction of their study population. The results were representative for this study population only.

Conclusion

In the AHP method, the number of patients is influenced by the CR aggregation method and the threshold of the CR, which could bias the results. Therefore, it is important to establish guidelines and investigate the differences for each study as also mentioned by Schmidt (2015) [7]. The comparison between the different methods (AHP, BWS, ranking tasks) resulted in similar outcomes.

The AHP seemed to be a challenge for some participants. Reasons could be the unusual scale and the need for consistency over several questions. However, we could not identify special groups because our sample was too small and homogenous. The BWS also forced the participants to make decisions. However, here only the best and worst decision had to be made. Therefore, the cognitive burden is reduced compared to other methods, for example, the DCE [41]. The researcher should consider the trade-off between methods that are easy to understand, and the method's gain of information as well as the method's theoretical basis. In addition, the sensitivity of each method should be calculated for each research question. In sum, the choice of method depends on the trade-off between the burden for participants and possibilities for analyses. Consequently, the method should be chosen according to the characteristics of the study sample and the aim of the study.

Additional files

Additional file 1: Description of the AHP criteria. (DOCX 15 kb)

Additional file 2: Aggregation level and different means. (DOCX 13 kb)

Abbreviations

AHP: Analytic Hierarchy Process; AIJ: Aggregation by individual judgment; AIP: Aggregation by individual priority; BWS: Best-worst-scaling; CA: Conjoint analyses; CI: Confidence interval; CR: Consistency ratio; DCE: Discrete choice experiment; IQWiG: Institute for Quality and Efficiency in Health Care; MW: Median weight; SD: Standard deviation; W: Weight; ZIPSE: Zentrales Informationsportal über seltene Erkrankungen (English: central information portal about rare diseases)

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Authors' contributions

KS carried out the analyses and drafted the manuscript. AB recruited and interviewed the participants and participated in finalizing the manuscript. FP, KD, and JMS supported the study conduct and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Modul 7

Comparison of different approaches applied in Analytic Hierarchy Process – an example of information needs of patients with rare diseases

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Comparison of different approaches applied in Analytic Hierarchy Process – an example of information needs of patients with rare diseases

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Abstract

Background: The Analytic Hierarchy Process (AHP) is increasingly used to measure patient priorities. Studies have shown that there are several different approaches to data acquisition and data aggregation. The aim of this study was to measure the information needs of patients having a rare disease and to analyze the effects of these different AHP approaches. The ranking of information needs is then used to display information categories on a web-based information portal about rare diseases according to the patient's priorities.

Methods: The information needs of patients suffering from rare diseases were identified by an Internet research study and a preliminary qualitative study. Hence, we designed a three-level hierarchy containing 13 criteria. For data acquisition, the differences in outcomes were investigated using individual versus group judgements separately. Furthermore, we analyzed the different effects when using the median and arithmetic and geometric means for data aggregation. A consistency ratio ≤0.2 was determined to represent an acceptable consistency level.

Results: Forty individual and three group judgements were collected from patients suffering from a rare disease and their close relatives. The consistency ratio of 31 individual and three group judgements was acceptable and thus these judgements were included in the study. To a large extent, the local ranks for individual and group judgements were similar. Interestingly, group judgements were in a significantly smaller range than individual judgements. According to our data, the ranks of the criteria differed slightly according to the data aggregation method used.

Conclusions: It is important to explain and justify the choice of an appropriate method for data acquisition because response behaviors differ according to the method. We conclude that researchers should select a suitable method based on the thematic perspective or investigated topics in the study. Because the arithmetic mean is very vulnerable to outliers, the geometric mean and the median seem to be acceptable alternatives for data aggregation. Overall, using the AHP to identify patient priorities and enhance the user-friendliness of information websites offers an important contribution to medical informatics.

Keywords: Decision-making, Analytic Hierarchy Process, Rare disease, Patient priorities, Internet homepage

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Background

The number of studies measuring patient priorities by using the Analytic Hierarchy Process (AHP) has increased significantly in the last few years [1]. The AHP was developed by Thomas L. Saaty in the 1970s to solve complex problems of multiple criteria decision-making [2], based on the idea that it is more reliable to judge the relative importance of several criteria with the help of respective pairwise comparison in a hierarchical structure than to judge their absolute importance [3]. The method was originally applied in the marketing sector and later in healthcare research. In addition, the AHP can be used to relate subjective criteria, which can be both quantitative and qualitative. As implied, it has been demonstrated that the AHP is a useful method for healthcare delivery as well as medical informatics decision-making [1, 4–7]. In this study, we ranked the information needs of people having a rare disease and their relatives using different AHP methods. This ranking of information needs is then transferred accordingly to display information categories on a web-based information portal about rare diseases in Germany. Because the available space on a user-friendly website homepage is restricted, the most important categories should be more accessible than less important categories. To present information categories on this website according to the user's priorities, this paper consulted both experts in medical informatics and patient-reported outcomes.

Today, approximately 4 million people in Germany suffer from rare diseases. The level in the United States is similar to that in Europe, with approximately 30 million people living with rare diseases. It is estimated that 400 million people worldwide suffer from a rare disease. Currently, international definitions of rare diseases vary greatly. For example in the EU, a disease is considered rare if it affects fewer than one in 2000 citizens, whereas in the United States a disease is considered rare if it affects fewer than 200,000 people, or about one in 1500 people [8, 9]. To improve patients' well-being, a national action plan for people with rare diseases was adopted by the Federal Government in Germany in 2013 that is supposed to coordinate national efforts invested in rare diseases. The establishment of a rare diseases information portal is one component of a broader set of planned measures, which includes 52 policy proposals [10]. Although conditions may differ significantly, patients having rare diseases and their relatives frequently face similar challenges [10, 11], which include protracted diagnosis processes as well as a deficient information base. To address these deficiencies, both medical experts and experts on medical informatics consider it relevant to assess the priorities of the (potential) patients and relatives.

As part of the development of an information portal for rare diseases, we used the AHP to identify the importance of several information types, e.g., information about therapy and social-legal advice. However, there are no best practices or a common gold standard available for applying the methods [1]. More precisely, it is noticeable that there are several methodological differences in the published studies concerning data acquisition and aggregation [1]. In some studies, single participants were interviewed (e.g. [12–14]), whereas in others, group discussions were used to analyze the priorities (e.g. [15, 16]). It therefore remains unknown which data acquisition method is more suitable for the AHP. To determine whether two methods (individual and group decisions) yield the same outcomes, we implemented them separately. The goals of this study were on the one hand to analyze the different influences of individual and group judgements on data acquisition, and on the other hand, to examine the different effects on the AHP results of using the arithmetic and geometric mean as well as the median for the data aggregation. We also discuss the degree to which the results of this study can be transferred to other disciplines. Finally, we fulfill our objective of providing a recommendation on choosing appropriate methods for further studies using the AHP.

Methods

Participants

Patients suffering from a rare disease were eligible to participate in the study. In addition, the relatives of these patients, for example, the parents of a child suffering from such a disease, were eligible to participate. The inclusion of both patient and relatives is necessary because many patients suffering from a rare disease are diagnosed as children, and the information priorities of the parents appear as a proxy for the children's priorities. Moreover, both patients and relatives will use the information portal. Patients were excluded if they were unable to concentrate continuously on the questionnaire or did not adequately understand the German language. Participants were recruited by the Freiburg Centre for Rare Diseases (Medical Center of the University Freiburg, Germany) and through rare disease self-help groups.

Analytic Hierarchy

The AHP is a stepwise problem-solving procedure. First, the decision-makers have to construct a hierarchical structure of the criteria. To achieve this, the multiple criteria decision problem must be broken down into its component parts [17]. The information needs of people suffering from a rare disease were identified by an Internet research study, including a review of already existing websites providing information on rare diseases. Furthermore, a preliminary qualitative study, the subjects of which were patients suffering from a rare disease, yielded important findings about the wording of the identified items that were regarded as

the defined targets. We designed a three-level hierarchy by grouping these items into information fields and information types.

The next step was to analyze the priorities. Patients and relatives were asked to compare every two information fields in the second level at each time with respect to the target. The information types in the third level were also compared pairwise with respect to the corresponding information field. Participants were asked to judge the importance of one endpoint as compared with another on a 9-point scale [18]. The participants also received printed ranking cards with the information fields and information types, which helped them provide consistent answers to the pairwise comparison questions. One example of a pairwise comparison is displayed in Fig. 1. It can be seen that "1" indicates that the two endpoints are of equal importance and "9" that the importance of one endpoint is extremely different from that of the other. Based on matrices of the pairwise comparisons, the standard AHP eigenvector method was used to calculate the patient's priorities using Microsoft Windows Excel [18]. The questionnaire used in the studies is avaliable as Additional file 1.

The final operation was consistency verification, which is listed as one of the key benefits of the AHP [19]. Saaty demonstrated that the consistency ratio (CR) can be calculated using the consistency index and the random index [18]. The CR value of a perfectly cardinal consistency matrix is 0. The CR value reflects the internal consistency of an observed set of judgements, and CR ≤ 0.2 has been determined to be an acceptable level of consistency [20, 21]. The results of participants who answered consistently were included in the analyses. Finally, the priorities of individual participants were aggregated to analyze the priorities of all the participants. The different data acquisition and aggregation methods are described in the following section.

Data acquisition

For data acquisition on individual decision-making, patients and relatives were interviewed. The interviews were conducted by telephone or in a face-to-face situation in a place familiar to the participant. In the case of telephone interviews, the AHP questionnaire was mailed to the participants a few days before the appointment. At the beginning of the interview, the structure of the AHP and the broad outline of the method, as well as all the quality criteria, were explained. Thereafter, the participants completed a guided AHP. Finally, the calculated individual weights (priorities of each criterion) were aggregated (Fig. 2) when the answers were consistent, as described above.

The same AHP questionnaire was used for the face-to-face group discussions. The group meetings were held at the Universities of Hannover, Frankfurt am Main, and Freiburg im Breisgau. After the interviewer presented a description of the structure and method of the AHP, each group member judged the relative priorities of each comparison. Then, the individual judgements (on a 9-point scale) were gathered and displayed anonymously on a screen. The group members discussed each pairwise comparison, as well as the rationales behind the individual judgements. Finally, for each pairwise comparison, a common group decision (consensus) was reached. The calculated group priorities were aggregated with all the other group priorities (Fig. 2) when the answers were consistent, as described above. The distribution of the priorities of individual and group weights was analyzed in separate box plots for each category using the statistics software R.

Data aggregation

Priorities can be aggregated using the arithmetic mean. According to a frequently used method for aggregating the priorities of individuals into a consensus rating, we also used the geometric mean [21–23]. In addition, we used the median to calculate the mean value of the priorities. The median divides the data set into two equal parts and indicates the mean value. The individual priorities were aggregated using each of these methods

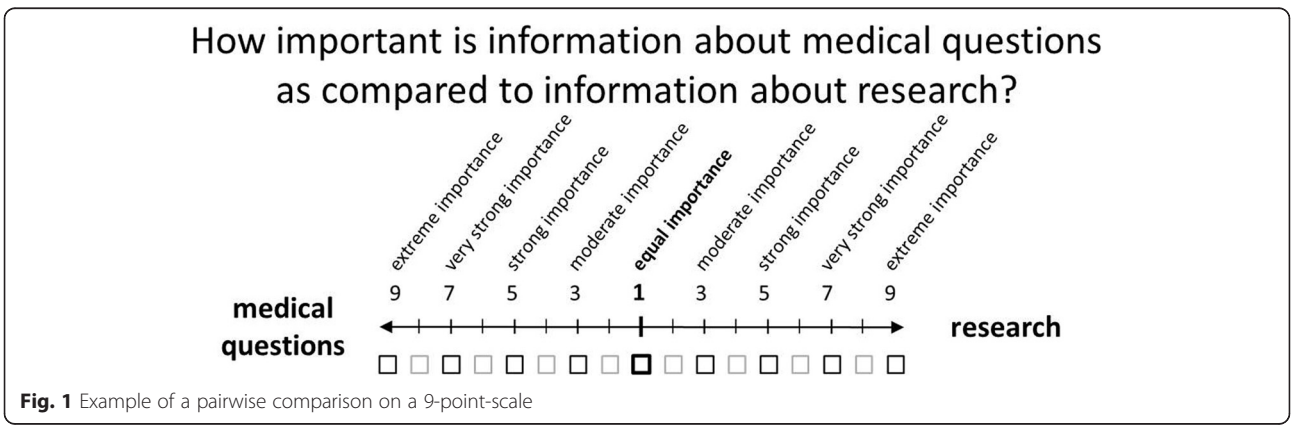

Fig. 1 Example of a pairwise comparison on a 9-point-scale

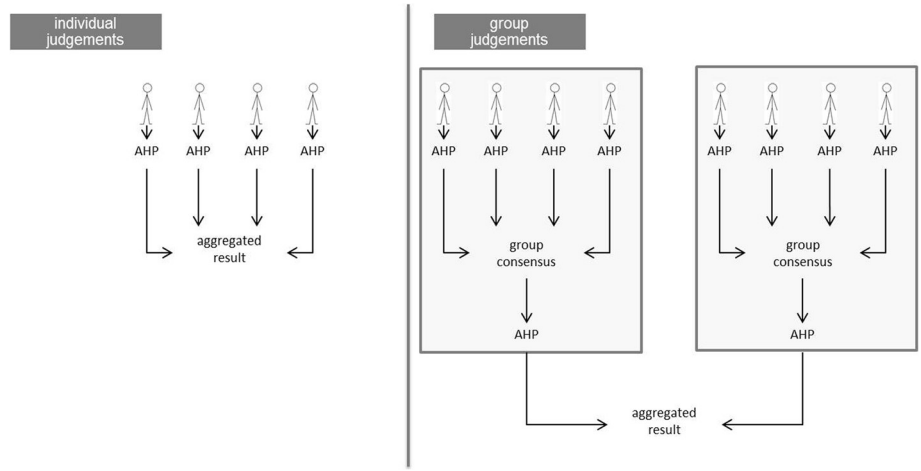

Fig. 2 Individual and group Analytic Hierarchy Process

independently to consider the different distributions resulting from the different methods. These results are presented in the "Data aggregation" subsection of the Results section.

Results

Participants

Thirty-six patients suffering a rare disease and four relatives ($n = 40$) having an average age of 50.7 years (ages ranged from 18 to 74 years) participated in the AHP in which the individual method was applied. In addition, for the group method, eight patients and three relatives were divided into three groups having a size of three or four participants. The average age of the group members was 52.2 years (ages ranged from 40 to 85 years). There were more female than male members in both populations. The average ages are relative high for both samples because adult relatives acted as a proxy for their children. Related to the issue, these relatives would search for information about rare diseases in the information portal. The following numbers of patients were suffering from the following rare diseases (note: the assignment to the orpha.net classification of rare diseases is not clearly regulated): rare skin diseases (five patients/two relatives), rare tumors (six patients), rare metabolic diseases (four patients), rare immunodeficiencies (seven patients), rare eye diseases (one patient), rare lung diseases (two patients/one relative), rare muscular diseases (two patients), rare blood count disorders (seven patients), rare genetic diseases (four patients/one relative), rare kidney diseases (two patients), rare skeletal dysplasia (one relative) and rare neurological diseases (four patients/two relatives). The demographic statistics of all the participants are displayed in Table 1. In addition to the information in the table, the average age at the time of diagnosis was 33.8 years for the individual AHP and 34.3 years for the group AHP; some patients were diagnosed at birth. The patients in the individual AHP had lived an average of 16.9 years since the diagnosis of a rare disease, and the group members had lived an average of 19 years since diagnosis. The marital status of the study population of the individual AHP was as follows: 27 of the 40 participants declared that they were married, six were divorced, and seven were living without a partner. Five of the group members were living with a partner, two were widowed, and four had no partner.

Analytic Hierarchy

The informational content of 300 websites maintained by providers of information about rare diseases was analyzed to identify the important items. These items were structured into a three-level hierarchy by grouping them into information fields and information types. We included four information fields: *medical questions, research*, *current events*, and *social counselling and assistance services*. Subsequently, we included nine information types: *diagnostics*, *therapy*, *disease pattern*, *new studies, study results*, *registers*, *social-legal advice*, *psychosocial counselling*, and *self-help*. The hierarchical structure (Fig. 3) contains the target on the first level, the information fields on the second level, and the information types on the third level. Consequently, for analyzing the priorities, 15 pairwise comparisons in each questionnaire were conducted: six comparisons of the four information fields on the second level and three times three comparisons of information types on the third level. An explanation of each information criterion was given to all participants, as shown in the Appendix.

Consistency ratio

The study sample showed a wide range of CRs. When the acceptable CR was set at a lower level, fewer participants could be included in the analyses. Moreover, the number

Table 1 Demographic statistics of the study population

Variable	Characteristics	Individual		Group	
		Frequency	Rate	Frequency	Rate
Sex	male	11	27.5 %	4	36.4 %
	female	29	72.5 %	7	63.6 %
Age	$x < 30$	2	5.0 %	0	0.0 %
	$30 \leq x < 50$	18	45.0 %	6	54.6 %
	$50 \leq x < 70$	16	40.0 %	4	36.4 %
	$x > 70$	3	7.5 %	1	9.1 %
Labor status	employed	17	42.5 %	6	54.6 %
	retired	11	27.5 %	2	18.2 %
	disabled	10	25.0 %	2	18.2 %
	student	1	2.5 %	0	0.0 %
	n/a	1	2.5 %	0	0.0 %
Estimated severity of the disorder	low	6	15.0 %	2	18.2 %
	medium	19	47.5 %	4	36.4 %
	high	15	37.5 %	5	45.5 %
Status	patient	36	90.0 %	8	72.7 %
	relative	4	10.0 %	3	27.3 %

of included participants decreased if consistency was required at all the investigated levels. Figure 4 shows an overview of the sample sizes according to the different levels of consistency. We determined an acceptable level of consistency to be a CR of 0.2 on the second level of the hierarchy. These parameters led to 31 individual judgements and all three group judgements being included in the analysis. However, the following results differed only slightly by determining a CR of 0.1.

Data acquisition

Further analyses were conducted by comparing individual and group priorities on the same level of consistency. The comparisons were conducted between individual and group priorities that were included in the CR = 0.2 category on the second level of the hierarchy. Figure 5 presents the corresponding local ranks of the information types (second level) and information fields (third level). To a large extent, the local ranks for individual and group judgements were similar. In both, *Information about medical questions* was the most relevant information type. In addition, the order of information fields (*diagnostics*, *therapy,* and *disease pattern*) in this information type was the same. Furthermore, in the second rank, information about *social counselling and assistance services* can be evaluated for individual and group priorities. Moreover, we found differences between individual and group judgements: *information about current events* was ranked higher by the group participants, and the order of the information fields *registers*, *new studies*, and *study results* differed.

In addition to the comparison above, we analyzed the weights of each category for the individual and group

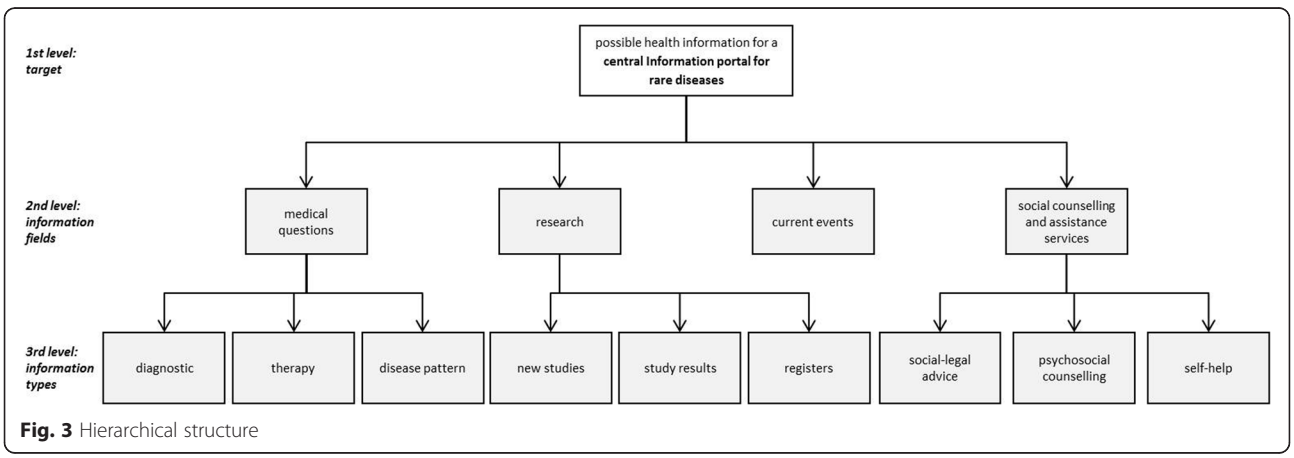

Fig. 3 Hierarchical structure

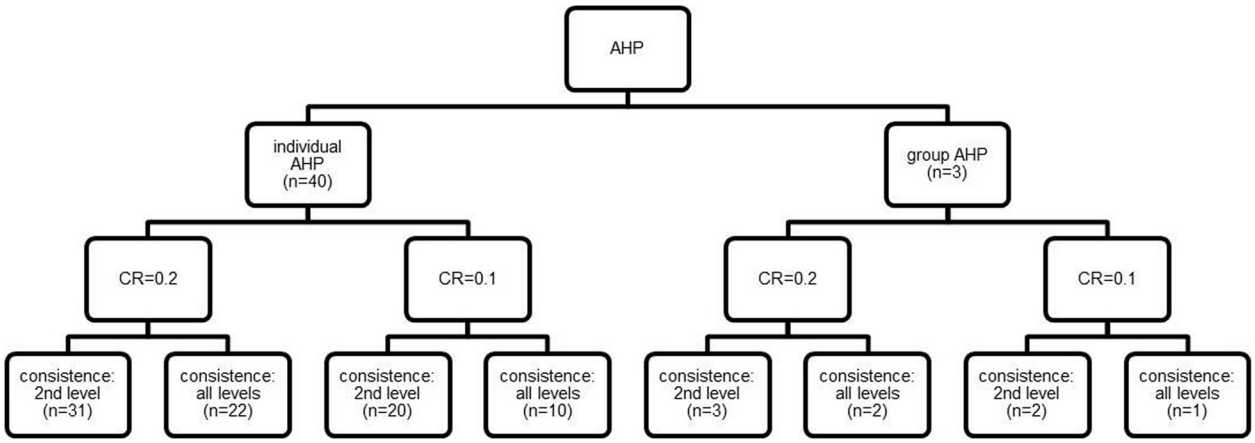

Fig. 4 Sample sizes by different levels of consistency ratio

priorities separately. The (global) weights quantify the priorities and allow all the information categories to be compared. The distribution of priorities for each category is displayed in Fig. 6. For each category, the distribution of group priorities (*group*) and individual priorities (*ind*) is shown. Based on the median, the differences between the individual and group priorities were small. For example, the weight of the category *information about medical questions* was noticeably higher for individual priorities. For the category *information about registers*, the weight was higher for group priorities. Moreover, we determined that the data span from minimum to maximum was most frequently greater for the individual priorities than for the group priorities.

Furthermore, we analyzed the answers given as individual judgements compared to those given as group judgements. The cumulative relative value distribution indicates the response behavior of individuals and groups. Figure 7 shows that group judgements frequently were in a narrower range than individual judgements; in particular, most of the judgements were located between 1 = equally important and 5 = very important. Stronger priorities (7 = very strongly important to 9 = extremely important) were not used in group judgements. The 45°-line symbolizes an equal distribution of the judgements between 1 = equally important and 9 = extremely important. Statistically significant differences between individual and group judgements ($p = 0.0027$) were found using a t-test analysis.

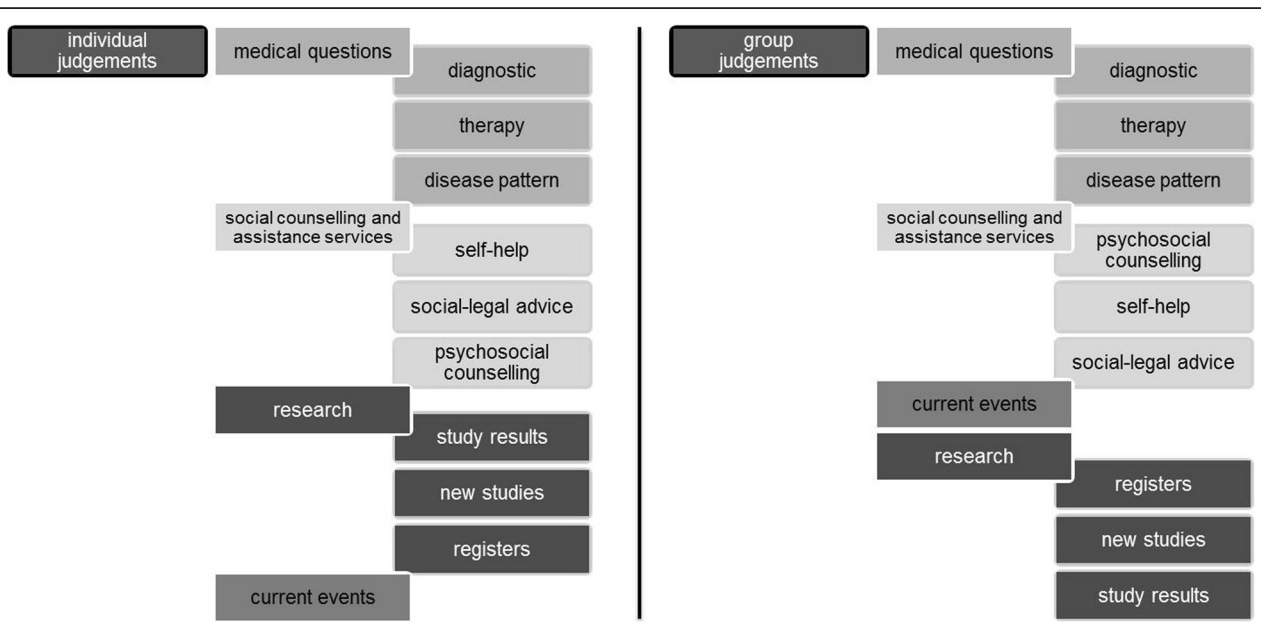

Fig. 5 Local ranks of individual and group judgements

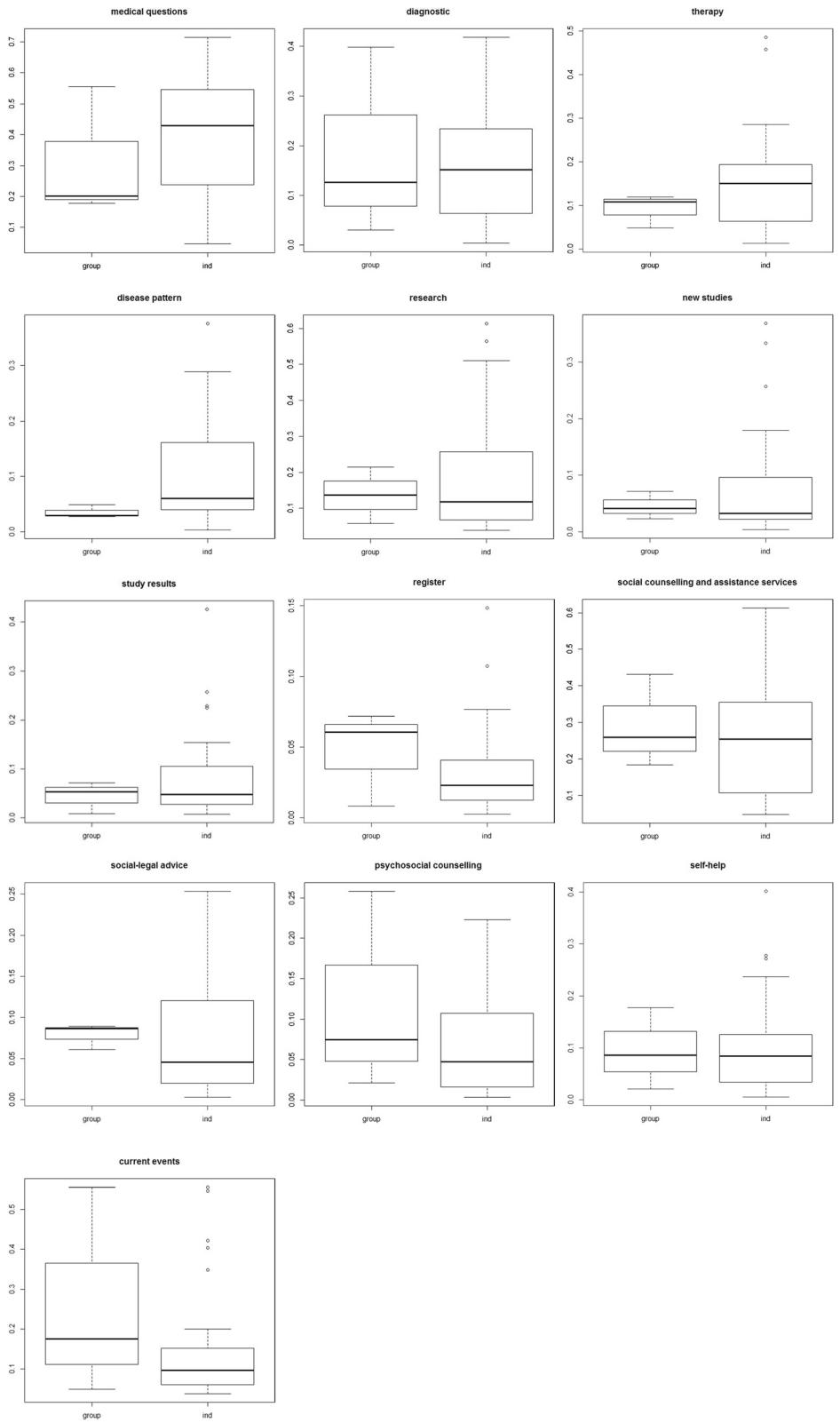

Fig. 6 Distribution of priorities of individual and group judgements

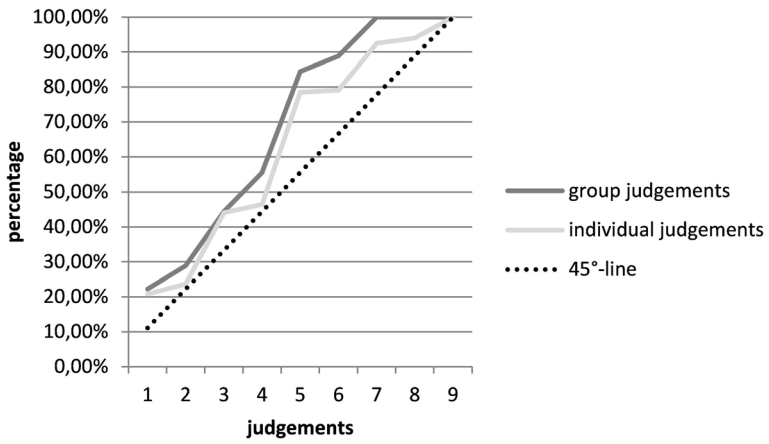

Fig. 7 Distribution of the given answers

Data aggregation

Aggregating single priorities is required to generate a summary of the study results. Depending on the data aggregation method, the ranks of the information criteria and the corresponding weights differ slightly. An advantage of using different methods separately is that the different distributions of the data sets can be considered and results can be compared between the methods.

Figure 8 shows the global ranks of the items grouped by the methods used for data aggregation (arithmetic and geometric mean, as well as the median). A comparison of the global ranks of the aggregation by the arithmetic mean with the aggregation by the geometric mean reveals that the criterion *information about diagnostics* had a lower priority if the data were aggregated by geometric mean. The same result was obtained for *information about new studies*. Other information criteria showed the same global ranking for both aggregation methods. A comparison of the global ranks of the aggregation by median with the aggregation by arithmetic mean showed that the criteria *information about self-help* and *information about disease patterns* changed ranks, as did the criteria *information about psychosocial counselling* and *information about new studies*. In summary, according to our data, there is no strong difference between the ranking of information criteria when the data are aggregated by the median or by the arithmetic or geometric mean.

Discussion

We have demonstrated that the AHP can be used to identify patient priorities with regard to the information needs of people having rare diseases. For this purpose,

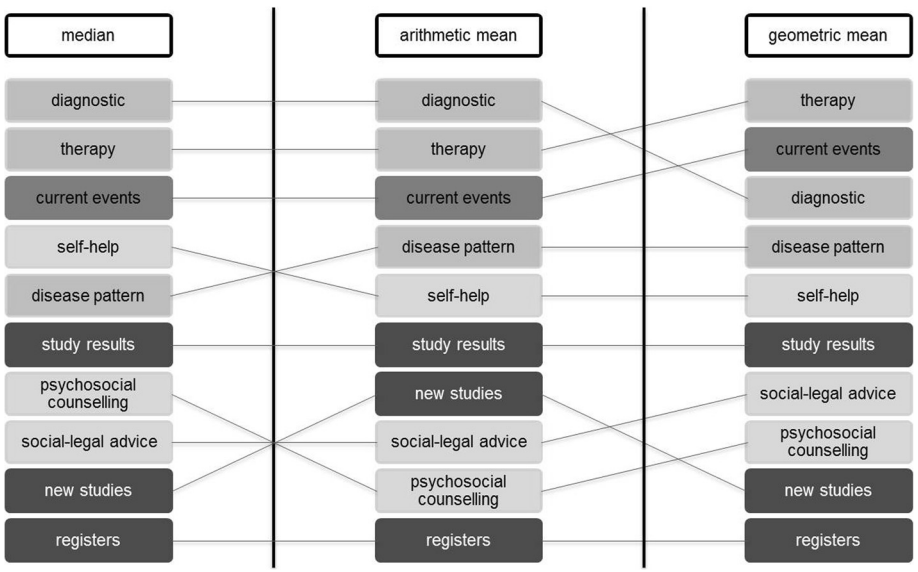

Fig. 8 Comparison of data aggregation by median and arithmetic and geometric mean

group decisions were as suitable as individual decisions. Although the local rank of the information types resulted in a similar order of individual and group decisions, their global weights varied slightly. Interestingly, we found another important aspect: group judgements were in a significantly smaller range than individual judgements. This result may be correlated with the fact that group judgements are more frequently consistent. Hence, it could conceivably be hypothesized that using smaller ranges, e.g., a 7- or 5-point scale, would lead to more consistent answers. Unfortunately, we cannot compare the response behavior with that reported in other published studies, because such an analysis was not conducted in these studies [1]. Furthermore, it can be argued that group decisions frequently represent the compromise solution of the group participants, and therefore, the group judgements are a mean of the individual judgements and consequently the group's priorities have a more limited range. We attempted to avoid a situation in which the group participants gave only the mean of their individual judgements as their answer. Frequently, the group participants discussed the rationales behind the individual judgements and decided on a common group priority that was not the mean of the individual judgements. Sometimes, the group judgement was even outside the range of the individual minimum and maximum judgements. There are, however, other possible explanations that should be investigated in further studies.

The findings of this study suggest that there is no "gold standard" method for data acquisition. According to our data, both the individual and group methods lead to very similar results. Moreover, there is no right or wrong ranking of the priorities of information needs. Researchers should select the most suitable method using other criteria, such as the thematic perspective of the study or the properties of the goods or topics that are addressed. It can be argued that, on the one hand, for free or non-rival goods, methods that involve individual decision-making are more suitable, because there is no need for the participants to be prepared to compromise; other people will not face disadvantages or advantages because of one individual's decision. On the other hand, group decisions are suitable for scarce or rival goods. Another aspect that should be considered is the peer pressure exerted in group discussions. The group situation can lead to particular disadvantages when intimate insights should be given in the interview, in which case, individual participants do not dare to answer truthfully or do not state their personal opinions. With regard to the implementation of the rare disease information portal or other websites, the order of information categories should not be influenced by other users. Therefore, an individual user's priorities shall be used to identify which information categories are more important and should be more accessible on the website than less important categories. In summary, the use of patient priorities to expand the user-friendliness of information websites using the AHP offers an important contribution for medical informatics.

According to our data, aggregations by median, arithmetic mean, and geometric mean lead to very similar rankings of information criteria. Because the arithmetic mean is very vulnerable to outliers, the median and the geometric mean appear to be acceptable alternatives for data aggregation, although the differences between the two methods depend on additional factors, such as the number of criteria in the hierarchy and the number of participants. Nevertheless, comparing the analyses using different methods offers the advantage of enabling consideration of the different distributions of the data sets.

The AHP method can lead to judgements that do not meet the defined CR requirement. We determined that the use of ranking cards prior to pairwise comparison of each category may help participants answer more consistently. Furthermore, we noticed that a comparison of four aspects of a category (such as the comparison of four information fields) is more challenging for participants than a comparison of three aspects of a category (such as the comparison of three information types) in terms of cardinal consistency. This fact was used to confirm the conditions for participation in this study: patients who were unable to concentrate on the questionnaire continuously were excluded, as well as children. This participation bias may lead to a non-representative ranking of the information needs of people suffering from a rare disease. Further applications of the AHP should consider restricting the number of pairwise comparisons in each category. Moreover, by setting a CR at ≤ 0.2, we could include a sufficient number of judgements in our analysis. If we had set a lower CR value, the number of included judgements would have been lower, and consequently, the informative value of this study would have been more limited.

Assumptions and limitations

The number of patients living with any one rare disease is limited. For this reason, we pooled patients with heterogeneous rare diseases, who frequently face similar challenges and have similar information needs. However, because of the relatively low number of participants interviewed in this study, the results may not be representative. Furthermore, a bias exists regarding the information criteria *current events*, because no information types were grouped in this information field. In addition, we attempted to minimize the interviewer bias, as well as the bias between telephone and face-to-face interviews.

Conclusions

To the best of our knowledge, this is the first study to investigate the differences in individual and group

judgements when conducting an AHP. Our study demonstrated the need for better strategies for choosing an appropriate method. Both methods led to similar outcomes; however, the response behavior differed. In brief, we demonstrated that the AHP can be used to identify the importance of several information types to people having a rare disease, and to order these information types on a website that presents information on rare diseases. Using the results of the AHP, we could rank the information needs of people suffering from a rare disease and their relatives according to their priorities. These priorities can be used to constitute information categories that are more important and should be more accessible on the website than less important categories. Overall, the use of an AHP to identify patient priorities and expand the user-friendliness of information websites offers an important contribution to medical informatics. According to our data, the use of different methods for data aggregation had no distinct influence on the ranking of the information criteria.

The strength of our study is in the transparent comparison of the different approaches applied in the AHP. The study indicates appropriate methods for conducting an AHP in other healthcare settings and in the field of medical informatics. Even if the results of the data acquisition methods do not differ, as was shown in our data, it is important that the researcher explain and justify the choice of method. We suggest that researchers select a suitable method based on the thematic perspective of the study or the properties of the goods or topics they are addressing. For example, it can be argued that group judgements should be used for studies addressing goods with limited availability. This investigation yielded important findings for subsequent studies that use the AHP method as a tool for medical decision-making and identifying patients' priorities.

Appendix

Definitions of the information criteria

Medical questions: Information that contains medical background information about rare diseases, e.g., information about diagnostics, therapy, or disease pattern.

Diagnostics: Information about diagnostic procedures using which a healthcare professional can identify rare diseases and make a diagnosis. In addition, contact information about specialized healthcare professionals or centers for rare diseases.

Therapy: Information about treatment procedures. In addition, contact information about healthcare professionals who can treat people suffering from a rare disease.

Disease pattern: Information about reasons for, symptoms, and progression of rare diseases.

Research: Information and results of scientists or pharmaceutical companies about new findings related to rare diseases.

New studies: Investigations of medical treatments of rare diseases that are scheduled or starting immediately for which participants are still being sought.

Study results: Results of current medical research.

Registers: Collections of disease data in the long term to improve the treatment opportunities and to monitor the distribution of the diseases.

Current events: Information and important appointments for public meetings where patients and affected persons can talk to healthcare staff.

Social counselling and assistance services: Contact data for and information about counselling centers that can help people suffering from a rare disease.

Social-legal advice: Here, answers can be found to questions concerned with the services of statutory health insurance, labor laws, or statutory pension funds.

Psychosocial counselling: Information and contact data that can provide psychosocial counselling in the case of illness-related problems of family, friends, or coworkers.

Self-help: Contact information about support groups of patients and close relatives.

Additional file

Additional file 1: Questionnaire. (PDF 556 kb)

Abbreviations

AHP, analytic hierarchy process; CHERH, center for health economics research hannover; CR, consistency ratio; Ind, individual.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FP carried out the analyses and drafted the manuscript. FP and KS prepared the data adequately. FP and AB collected the data. KS revised the manuscript. KD and MF made substantial contributions to the conception of the article. JMS revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate
Ethical approval was issued by the Ethics Committee of the Albert-Ludwigs-Universität Freiburg (53/14). Informed consent was obtained from all participants prior to the survey and interviews.

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Modul 8

Telephone health services in the field of rare diseases: A qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany

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RESEARCH ARTICLE Open Access

Telephone health services in the field of rare diseases: a qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany

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Abstract

Background: Rare diseases are, by definition, very serious and chronic diseases with a high negative impact on quality of life. Approximately 350 million people worldwide live with rare diseases. The resulting high disease burden triggers health information search, but helpful, high-quality, and up-to-date information is often hard to find. Therefore, the improvement of health information provision has been integrated in many national plans for rare diseases, discussing the telephone as one access option. In this context, this study examines the need for a telephone service offering information for people affected by rare diseases, their relatives, and physicians.

Methods: In total, 107 individuals participated in a qualitative interview study conducted in Germany. Sixty-eight individuals suffering from a rare disease or related to somebody with rare diseases and 39 health care professionals took part. Individual interviews were conducted using a standardized semi-structured questionnaire. Interviews were analysed using the qualitative content analysis, triangulating patients, relatives, and health care professionals. The fulfilment of qualitative data processing standards has been controlled for.

Results: Out of 68 patients and relatives and 39 physicians, 52 and 18, respectively, advocated for the establishment of a rare diseases telephone service. Interviewees expected a helpline to include expert staffing, personal contact, good availability, low technical barriers, medical and psychosocial topics of counselling, guidance in reducing information chaos, and referrals. Health care professionals highlighted the importance of medical topics of counselling—in particular, differential diagnostics—and referrals.

Conclusions: Therefore, the need for a national rare diseases helpline was confirmed in this study. Due to limited financial resources, existing offers should be adapted in a stepwise procedure in accordance with the identified attributes.

Keywords: Rare diseases, Telemedicine, Health-seeking behaviour, Helpline, Health information

Background

Rare diseases (RDs) are predominantly very serious and chronic diseases as approximately 80% are genetic in origin. Therefore, they often have a negative impact on the life expectancy and quality of life of those affected. In particular, people suffering from very rare RDs occurring once among 100,000 people are in danger; 5000 to 8000 different RDs have been detected thus far, accounting for 6% to 8% of the population [1]. Therefore, approximately 350 million people worldwide suffer from an RD, and half of them are children. People affected often struggle to obtain a proper diagnosis as healthcare providers have little experience of these conditions, and there is limited research evidence available. In addition, treatments, which, when available, are very expensive. These hurdles trigger an odyssey through health service systems and, in this context, the search for helpful health information. However, useful,

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high-quality, and up-to-date information is often hard to find [2].

The following article examines the potential of telephone services in satisfying this desire and elicits the revealed health-seeking behaviour. It introduces 'helplines' as services solely offering telephone-based information. Different types of information are differentiated, such as references, counselling, and/or medical information. Comparing different information access points, helplines are currently often used after the Internet and booklets [3]. Per the findings of Mevissen et al. [4]. Internet information can be delivered in addition to telephone information but should not be seen as an adequate replacement. Highlighting the importance of helplines aligned with other information access points, Ekberg et al. [5] offer an explanation for these findings as they show that emotional support needs are often intertwined with information- or advice-seeking needs.

The case of helplines in the literature

To present helpline research, a brief indicative literature review was conducted by searching the MEDLINE database. The DIMDI (Deutsches Institut für Medizinische Dokumentation und Information, German Institute of Medical Documentation and Information) platform was used as a search tool. In all, 233 results were generated, including the keywords 'helpline' and 'help line' (search date: 27 May 2016). Results concerning animal research were excluded. Exclusion and inclusion criteria were set as displayed in Table 1.

Telephone services were often mentioned as being useful as a recruitment tool for participants of other health-related studies or the evaluation of health policies. These studies were excluded as they are not relevant in this context, leaving a total of 83 results. Findings are often based on the evaluation of caller statistics illuminating the profile of callers (65%, 54/83). Besides, many studies conducted a thematic analysis of telephone conversations. Questions were raised about caller satisfaction, perceived effectiveness, and support provision. Only five studies used interviews as a research method. Another five studies conducted structured literature reviews. Health professionals were rarely included. Most of the studies evaluated helplines addressing issues such as tobacco cessation (15%) [6–19], psychological problems (13%) [20–31], cancer (14%) [32–43], and family planning and sexuality (13%) [44–54]. Trials dealing with the specific concerns of RD patients and their physicians could not be determined. Building an argument for telephone services in general proves to be very difficult as helplines contribute to very heterogeneous health-related outcomes. Two studies, for example, use a successful referral to an appointment as an endpoint for the measurement of effectiveness of a helpline on sexuality and family planning [55, 56]. Tobacco cessation helplines with proactive counselling monitor the chance of quitting, [57] and psychological helplines the number of suicide preventions [58]. Other benefits are rather intangible and therefore difficult to measure, confronting helpline research with the criticism that little robust evidence is generated [59]. For example, general practitioner (GP) helplines offer access to the health care system after closing hours [60]. Furthermore, users of helplines for family planning, addiction, and violence perceive a telephone service as beneficial due to the ability to talk anonymously about delicate health issues [54, 61]. In this regard, helplines offer the chance to identify as well as bridge gaps between patients and health care service systems and, thus, play an important role in health care systems. Therefore, existing research suggests potentials of RD helplines; however, this hypothesis still needs verification. Ferreira et al. [62] report that helplines designed after patients' needs contribute to the overall satisfaction of citizens with health care systems and their effectiveness, therefore highlighting the need for further research on what exactly is needed. The presented literature suggests that there are differences in themes, staffing and structuring of helplines, which should be thoroughly thought of. Encouraged by these findings, we further investigated potentials of RD helplines, resulting from the gap between information offering and need, to further improve health-seeking processes of people affected by RD.

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	All potential patients (not only focusing on rare diseases), family members and physicians	Studies regarding animals
Intervention	Telephone services	Email services, Internet platforms
Outcome	Examination or improvement of helpline service or design Evaluation of caller behaviour	Examination of helpline callers to examine their general health behaviour (not offering additional knowledge to helpline design)
Publication type	Caller statistics, interviews and reviews	Interventional studies
Language	English, German, and French	All other languages
Time frame	All publications up to May 27th, 2016	None

As the literature search did not reveal any RD specific publications, we added a targeted manual search aiming for literature on RD helplines. Only one paper from Houÿez et al. [63], summarizing caller statistics of the European Network of Rare Disease Help Lines (ENRDHL), was found. However, the retrospective design did not allow for any recommendations improving existing structures. Additionally, two oral presentations [64, 65] mentioning RD helplines as part of national information provision on RD were listed. Other initially identified literature reported on non-specific disease helplines. Besides, Iskrov and Houÿez [66] also analyzed ENRDHL callers. On the other hand, Mazzucato et al. [67] stressed the need for telephone services parallel to other information systems. They forward an argument for bundling RD helpline services at a national level, noting that feedback concerning the functioning of RD policies can be retrieved immediately. However, data on the operational realization has not been raised.

Political endorsement

Political processes have initiated national efforts targeted towards the improvement of the overall situation of individuals suffering from RD. In the EU, for example, policy proposals for the improvement of the overall situation were summarized in the European Commission Communication on RD in November of 2008 [68] and the European Recommendations to Member States by the Council of Ministers in June of 2009 [1]. Consequently, EU member states were encouraged to develop national plans to enact these requirements. Germany, for instance, published a National Plan for RD, the National Action League for People with RD (Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, NAMSE), in August of 2013 including 52 policy proposals [69]. Part of this action plan is the improvement of knowledge transfer through the expansion of disease-spanning, quality-orientated, and Internet-based information databases and systems. Towards this goal, the Central Information Portal for RD (ZIPSE – www.portal-se.de) was implemented. This is in line with an increasing international effort targeted towards the improvement of information structures. A growing number of national and transnational RD Internet platforms evolved [70].

Alongside an Internet-based information provider, the implementation of a telephone-based information service has been conceived as an alternative information access point. The Commission Communication also mentions the need for national RD helplines. To this end, the ENRDHL was named and created in the context of the European Rare Disease Solidarity Project (RAPSODY, September of 2006 to April of 2008). The focus of this initiative is the improvement of quality of services and providing a unified standard by sharing the experiences of European RD telephone helplines [71].

This demand is clearly highlighting the crucial point. Helplines do already exist, as an Orphanet list on international RD helplines [70], however, projects such as RAPSODY show that there are efforts necessary to set common standards. Besides, ENRDHL consists solely of members from eight countries, plus two countries in which helplines are still under construction [63]. Germany is not yet listed. However, NAMSE policy proposals 38 and 39 include the analysis of the implementation of a telephone service. NAMSE recommends to set up "[…] a pilot project to determine which target groups would make best use of such a hotline, what types of questions would most often be posed and what answers can best be delivered to these questions. This information would serve to determine the probable frequency and type of questions and how to plan to best meet these demands." [69].

The present article

The literature search shows how important telephone services are for health care service provision. Besides, there is little knowledge on RD helplines. Particularly, the perspective of potential callers has not been chosen in helpline research so far. This enables us to capture all relevant aspects for the design of a satisfying and effective RD helpline. The secondary aims of the underlying article were to add to the existing literature and to allow for substantiated decision-making in the political context aiming for the improvement of information provision for patients, family members and physicians. In this regard, the major aim of the study was to examine the needs of patients, relatives and health care professionals for a telephone based health service for RD in Germany triangulating perspectives of all potential callers, interviewing individuals suffering from RDs, their relatives, as well as health care professionals (HCPs).

Methods

Setting

The interview study was conducted as part of ZIPSE project, aiming for the implementation of an Internet platform for information on RD and considering a telephone service as an additional information access point. Patient and relative interviews were carried out between March and November of 2014 by three interviewers. HCP interviews were carried out by two interviewers between April and October of 2014. A qualitative setting was chosen as this design not only offers the opportunity to provide a first impression of a possible need structure but also drafts an RD helpline through the eyes of those interviewed. Forty Interviews

with patients and relatives were conducted face-to-face and telephone-based in 29 cases. One interview could not be evaluated as the record was not readable due to technical difficulties, leaving 68 recorded interviews from patients and family members. In the case of physicians' interviews, 39 interviews were conducted. Only seven interviews were carried out using the telephone to avoid long travel and scheduling on short notice. A change of interview medium was necessary due to the broad geographic coverage of the study within Germany.

Participants

Patients and relatives were recruited through the Freiburg Centre for RD located at the Department of Dermatology of the University Medical Centre at the University of Freiburg and through RD self-help groups. The equal coverage of the many disease groups summarized under the broad definition of RD was targeted. Therefore, six participants were equally chosen among genetic skin disorders, skeletal dysplasias, neuromuscular disorders, genetic eye disorders, disorders of the connective tissue, genetic kidney diseases, cystic fibrosis and lung diseases, inherent disturbance of haematopoiesis, immunodeficiencies, inherent metabolic disturbances, and genetic diseases of the digestive tract. However, interview results showed in nearly all cases a complex, polysystemic pattern of involvement. At least nine patients had experienced a long process of diagnosis with duration of search for a diagnosis of more than 10 years. Thus, adding 66 patient and relative interviews to 10 interviews with prolonged diagnosis, a total sample of 76 patients was planned to be recruited. Nevertheless, interim analysis showed that upon saturation of interview data, a smaller sample would suffice. Further interviewing was not performed as this would not have led to expanded knowledge on the research subject. The final sample contains 55 individuals living with an RD and 13 family members.

For HCP interviews, five different groups were incorporated: GPs, specialists, physicians working in a hospital and medical therapeutic practitioners (MTP). In this context, the term "clinicians" refers to those physicians working in a clinical surrounding. In Germany this subgroup needs to be distinguished from "specialists" who have settled in a private practice. RD guides differed in qualification (e.g. human geneticist, biologist, and physician) but were equally trained for the guidance of RD patients through the health care system. Participants were recruited by the Centre of Quality and Management in Health Care embedded in the State Medical Chamber of Lower Saxony in Hannover. All participants were recruited within the geographic region of Lower Saxony as this is regarded as representative of all areas of Germany. Only RD clinical guides were recruited all over Germany as they occur less frequently. The following selection criteria were employed: regional aspects were considered, differentiating professionals working in rural, urban, or metropolitan areas. Resident physicians were differentiated by whether their work was conducted in either single or joint practice. Regarding clinical doctors, the level of health care provision was considered, e.g. basic, regular, specialist, and maximum medical care. Finally, the hierarchy level of participants was considered, distinguishing between chief, senior, and assistant physicians.

Ethical considerations

A positive ethics committee vote was obtained for the interview study from the ethics committee of the Albert-Ludwigs-University Freiburg (number 53/14). Informed consent was obtained in writing from all participants.

Data generation and analysis

Semi-structured interviews were chosen as participants needed to be directed to the subject of interest. In some interviews, a narrative structure would have led to the extensive presentation of a single health issue, which was the focus of the person interviewed, not reflecting on other subjects, which were still important, though less so. Patient and relative interview flow was initiated by asking for experiences with diagnosis and treatment and important steps of their professional careers as well as experiences with RD patients on the side of HCPs. Then, interviewees were asked whether they saw a need for such a service. "How do you feel about the option to attain information by telephone?" If they were in favour of an RD helpline, they were encouraged to describe their mental picture of the helpline with particular reference to specific characteristics. A semi-structured interview guide was piloted during two interviews and afterwards adapted per interviewee needs. The HCP interview guide was developed in accordance with the structure of the guide for the people affected. However, some changes were necessary due to the different perspectives of HCPs on the topic. To ensure standardization, both interview guides were mutually discussed.

All interviews were recorded and later transcribed using the F4 transcription software. A standardized transcription guide was drafted for all interviews by three different interviewers. Transcripts were evaluated using MAXQDA, a programme for qualitative and mixed-methods data analysis. A structured content analysis was conducted following the guidelines provided by Mayring [72]. First, each interviewer formed categories inductively for three different interviews. Then, the chosen interviews were coded collectively to ensure inter-subjective or inter-rater reliability. Differences were addressed in the guide, clarifying a uniform coding strategy. Afterwards, attributes were extracted inductively by a single analyst to minimize

interpretation bias. Finally, results were discussed within the whole research group, and results from patients and families were triangulated with those of HCPs. All quotations were translated by an external translation service, approved by a native speaker, and then included in the paper.

To ensure the quality of evaluation, the quality criteria of Mayring [73] were complied with.

Results

Interviews were conducted until a high degree of saturation was achieved. No additional knowledge on RD information provision could be generated from further interviewing.

Following patients' reports on predominant complaints of their complex diseases, all RD-affected interview partners could be categorised within one of the predefined disease groups. Patients with diseases of the digestive tract ($n = 2$), cystic fibrosis and lung diseases ($n = 4$), genetic diseases of the eye (n = 4), and disorders of the connective tissue ($n = 5$) were difficult to represent in the sample because of limited availability and polysystemic patterns. Therefore, the following patients could be included: genetic skin diseases ($n = 10$), skeletal dysplasia ($n = 7$), neuromuscular diseases ($n = 9$), genetic eye diseases (n = 4), connective tissue diseases (n = 5), genetic kidney diseases ($n = 6$), cystic fibrosis and pulmonary diseases (n = 7), congenital blood formation disorders (n = 4), immunodeficiency (n = 7), congenital metabolic disorder (n = 7) and genetic diseases of the digestive tract (n = 2). Participants could indicate disease severity on a three-item scale. Table 2 shows a summary of socio-demographic variables for patient and relative interviews.

The table also shows socio-demographic characteristics of HCPs. One hundred and forty-one HCPs were invited to participate in the interview study. Of these, 39 candidates took part. Ensuring the diversity of participants, special regard was given to selection criteria concerning the structure of health care provision. Nine GPs, nine physicians, nine clinic doctors, six clinical guides, and six MTPs were included.

Table 2 Socio-demographic variables, patients, and relatives

Sample characteristics		
Parameters	Patients and relatives ($n = 68$)	Physicians ($n = 39$)
Sex		
Male	23	23
Female	45	16
Age		
Average	51	46
Maximum/Minimum	85/18	
Educational qualification		
Abitur/A-levels	13	
Secondary education	19	
Technical collage/University	19	39
Advanced technical college degree	12	
Secondary modern school qualification	5	
Age at diagnosis		
Average	34	
Maximum/Minimum	74/0	
Disease severity		
No specification	4	
Low	8	
Medium	28	
Severe	28	
Profession		
Employed	31	39
Housewife/Houseman	2	
Unemployable/Special circumstance	15	
Student/Scholar	2	
Pensioner	18	

Advocating for a rare diseases helpline

Of 55 RD patients, 41 advocated for the implementation of a helpline about RD. A smaller proportion ($n = 8$) objected to the service or described it as unnecessary as the telephone based information was already available online or through a physician. On the other hand, one interviewee interpreted the helpline as a tool for psychological counselling and neglected helplines in general for this reason. The remaining six participants did not offer a distinct answer. Regarding the interviews with relatives, 11 participants did endorse implementation. Two interviews could not be interpreted clearly as statements were given that were neither obviously for nor against an RD helpline. Therefore, a need for an RD helpline can be verified for some RD patients and relatives.

Of 39 HCPs, 18 endorsed the implementation of an RD helpline. Only four objected to the service or described it as unnecessary. An RD helpline was regarded as unnecessary whenever a suitable colleague was available. Physicians preferred a personal contact, they were already familiar with. A total of 17 participants offered an ambiguous or no answer. As physicians ($n = 27$) made up the largest portion of HCPs, these were evaluated separately as well. A total of 14 reported their endorsement of such a service, four claimed it to be unnecessary, and nine did not answer the question in a manner that could be definitively coded. Consequently, these findings verify for some HCPs a need for an RD helpline.

Expectations towards a rare diseases helpline

A detailed summary of the content analysis of patient and relative interviews brought forth the following necessary characteristics of a helpline. Quotations are labelled by interview code, age, and gender. The interview code consists of a letter and interview number. The following abbreviations were used: 'A' standing for relative or affiliated, 'P' for patient, 'GP' for general practitioners, 'S' for specialists, 'MTP' for medical technical practitioners, and 'G' for guides.

Staffing with professionals

Interviews demonstrated that patients and relatives perceived an RD helpline as helpful when their questions were answered by professionals. Ten of the participants explicitly highlighted this fact ($n = 10$). References to other access points, regardless of their profession, were experienced as rather unsatisfying.

> *'Currently it's like this / our people are annoyed about it – they call up the branch office of LOCATION and have to ask their questions, then they call up LOCATION in order to receive an answer, and then they have to call back the people who are involved; I can't conduct a conversation about my problems like this. I can't solve a problem with a question – that usually functions in the most…./ or somehow, we'll ask questions on Radio Eriwan, where the answers only consist of yes, no and occasionally perhaps.' (P11/53/f).*

Similar to what was observed in the patient and relative interviews, HCP participants generally asked for a professional contact at the other end of the phone ($n = 11$). In most cases, a physician was named. One participant indicated that a hotline should not be staffed with a data management employee, nurse, or secretary even though they can sometimes be of much help.

> *'If one of them is clever and can give me tips afterwards, then I thank God for it and …/ but this should always come from doctors [I1: OK], not a nurse or a secretary."* (GP02/37/m).

It was reasoned that only trained physicians could provide precise medical information. Therefore, an employee with substantive clinical experience was demanded. (S04/35/m) Expert knowledge of the person in charge was also highlighted. In the case of physicians, this meant extended training for one specialty. Nevertheless, biologists and laboratory experts were also mentioned in isolated cases. (GP05/61/m) Participants were also conscious of the difficulty of realizing this demand and therefore emphasized that an expert for each relevant medical field could not be demanded for an RD helpline. (S01/39/m).

Personal contact

Another highlighted aspect was the importance of personal contact in addition to other rather impersonal information research systems ($n = 10$). Specifically, a single point of contact was demanded. It was reasoned that this kind of contact could accelerate and ease information search. Consequently, it was seen as helpful with regard to orientation in the health care system.

> *'Then they'll surely sit down and study Internet sites and the brochures and information materials that are given out, but a human contact partner can sometimes expedite and simplify this search for information. Simply because one doesn't just enter questions onto a screen by himself, but rather because he initiates communication with someone. If this office, the information office, was really staffed with competent personnel and not just some students who are completing their internship and don't really know what it's all about, then it would be a good idea, but would then also mean that money would need to be exchanged.' (P37/46/m).*

On the other hand, psychosocial advantages were emphasised.

> *'Therefore, we have always sought out personal contact during the search and made use of it, simply because contact with a human being is much more pleasant and one can exchange information more effectively than when one simply calls up inflexible information from the Internet and then has to determine what is really applicable and what is not.' (A02/48/m).*

The importance of personal contact ($n = 7$) was also identified as a category during HCP interviews. As expected, the focus was laid on the exchange of medically relevant information. For example, psychosocial issues were not named as a reason for the demand for direct communication. Instead, personal contacts were preferred as patients could be quickly introduced, and immediate feedback could be generated.

> *'Where one can also have a telephone conversation, which, in any case, is better than sending emails back and forth, since one can then react directly, briefly introduce the patient with his symptoms and perhaps even give the patient an appointment promptly, so that he can be examined in detail.' (GP01/39/m).*

Frequently, an immediate contact and information receipt was required. (MTP02/35/f, MTP04/25/m, S04/35/m, GP01/54/f, GP03/48/f, C06/47/f) Furthermore, it was outlined that some medical issues cannot be described using predesigned web search masks given by Internet providers. Information can be searched only if previously made searchable. Fine nuances between blank facts cannot be depicted.

'So, to make a comparison once again; if I now say, as already mentioned in the example, I enter three things/ it's different to saying to a colleague: "Man, I have the feeling that he's really sick. And then it hurts somewhere on the left, sometimes more, sometimes less and so on". It doesn't make sense to enter this into a screen. [I1: Hm] And that's really important.' (GP02/37/m).

Availability

Participants ($n = 6$) expressed a wish for extended opening hours.

'And then, okay, if I have the office, let's look at the ACHSE as an example. Then that's also / and it's rather stupid, at the one, they only work a half-day and it's always … / so you always end up calling outside of business hours.' (P06/85/f).

Interviewees hope to avoid waiting periods and to receive contemporary answers. Waiting lines raise dissatisfaction and impatience (P17/47/f) similar to answering machines or automatic answers. (P51/62/f) It was reported that there should be at least enough human resource capacities to ensure a return call within an appropriate timeframe. (P14/57/f, P50/51/f).

HCPs referred to availability during four interviews (n = 6). HCPs did not highlight an uninterrupted 24/7 availability as important. In acute and/or life-threatening situations, an RD helpline would not be the first choice. In such a situation, an emergency call asking, for example, for a poison centre would be preferred. One GP mentioned that availability during regular office hours would be absolutely satisfying. Following the results of interviews with patients and relatives, it was also indicated that immediate availability is necessary, especially avoiding waiting lines.

'Personally, I find telephone conversations better, [I1: Hm] But I know how awful it is to be put on hold. [I1: Yes] [I2: Hm] Then one calls from here [I1: Yes] and tries to get connected. I know, I've had REALLY bad experiences there. If I want to reach anyone and I say to someone: I have five women here [I1: Hm] and then you get someone simply hangs on stubbornly. It can sometimes take HOURS. [I2: Hm, simply lay the receiver to the side] exactly! Lay the receiver to the side and wait until the call back comes through. That's useless. [I2: Hm] I can't afford to waste time like that here.' (S04/35/m).

This demand is in line with the demand for fast and immediate access to information. On the other hand, a dial-back system, collecting calls and answering them afterwards at a particular date, was also suggested by one participant (S13/50/m). Remarkably, this would contradict the demand for a fast access to information previously mentioned during interviews with patients, relatives, and HCPs.

Low technical barriers

The telephone is also mentioned as an alternative to web access ($n = 6$) that is also suitable for the elderly and information seekers with no affinity for or no available Internet access. Additionally, one interviewee noticed that some people with RDs are limited in their mobility through their disease. Consequently, these people are unable to reach personal contact partners such as physicians and other therapeutic personal.

'However, the problem is often those people who can't do it. We have a contact partner per telephone for those who are not mobile / great restrictions for the illness [AM]. Another example is the case of the DM 1 advanced stage, where the people are often no longer able to go places by themselves / they need so much strength and energy in order to cope with the few daily tasks, then they have something for it / but good, one always wants everything in any case.' (P11/53/f).

Asking HCPs for their opinion on the telephone as an alternative to the Internet as an information medium, results were heterogeneous. While younger HCPs preferred the Internet over a telephone and did not assign an important role to it, HCPs of higher age were rather indifferent or clearly preferred the telephone:

'Personally, I'm a big fan! [I1: Yes] So, the telephone— I would always give the telephone preference [LAUGHING], over some impersonal Internet site. But I think that's also really "old-fashioned"' (C07/42/f).

HCPs even align with the need for a low technical barrier for certain patient sub-groups such as the elderly.

'Yes, I believe that exactly those people who, let's say don't have Internet access or who lack the knowledge, we're talking about the older members of the public/. […]' (C03/46/m).

Topics of counselling

Further, patients and relatives described possible topics that were expected to be discussed on the phone. Psychosocial and medical aspects were predominately named. Interviewees described the following medical contents: They hoped for an explanation of their disease pattern and of symptoms at hand.

'[…] first of all, the symptoms of the clinical picture, of course, and how the people affected deal with them. And then, of course, also self-help groups.' (P52/39/f).

In particular, participants demanded answers not only of general questions but also of questions concerning specific sections of the disease as well as information on the genetic background. (P12/58/f, P51/62/f) Concerning disease development information, possible methods to stop or lessen the burden of disease were reported to be most relevant. (P53/51/m) This was found in combination with the demand for information concerning the application of medication dosages or therapy and behaviour in the case of emergency. (P50/51/f, P54/40/m) Aside from these, patients also wished to be informed about the status of research. (P07/70/m).

In addition, persons concerned also brought forward psychosocial aspects. (A12/32/f, P47/59/m) Patients and relatives reported that they do see a need for the resolution of general problems arising from disability as well as specific disease problems. (P25/58/f, A05/60/f) Furthermore, it was perceived as helpful to talk about diseases, learn how other patients handle their disease, and learn whether self-help groups already exist. (P52/39/f) The importance of practical information on everyday life was highlighted again at this point. (A05/60/f) Just one person explicitly negated such an offer, claiming to be in no need of a helpline where one can have a good cry. (P04/39/m) On the other hand, a contact person was seen as an opportunity to counterbalance the desperation of one's own situation with the prospect of being counselled and reserved when necessary. (P23/48/f) One interviewee noted that other sites did not take one seriously and hoped for an improvement. (A06/50/m) Similarly, when disorientated, a contact person was sought to aid with calming down, helping with the search, and coming up with concrete help.

'Yes, that one has a competent person on the other end of the line, so that one, for example, if he is doing badly or if he has any problems, that he receives the help he needs. In other words, that there is someone available for the moment. He doesn't have to bring everything back into tip-top shape immediately. Just perhaps someone who is there to say: "Yes", and "try to stay calm" for now, or, "I'll help you, I will sort it out, I'll do it" / "I'll check up on it" and so forth, so that one isn't simply/ yes, that one isn't turned away, but rather… / or be subjected to long waiting times.' (P21/53/f).

When discussing topics of counselling, some HCPs specifically mentioned the need for endorsement concerning medical issues ($n = 7$). In particular, medical cases were reported as needing to be discussed via telephone, describing symptoms and patient histories. Three HCPs specified this demand, highlighting the need for differential diagnostics or a demand for assistance with the differential diagnostic process of elimination. (GP03/46/f, MTP04/25/m, S04/35/m).

'I would also think that this could be useful for rare diseases, so that one could simply receive a differential diagnosis, a second opinion. So, I'll tell you what the symptoms are and you can tell me what it could be.' (MTP04/25/m).

Participants also demanded information on self-help groups. (GP05/61/m).

Guidance

Those polled also talked about the necessary functions of a helpline. Often, aiding orientation within an information overflow or during information undersupply seemed to be necessary. Additionally, the sample demanded a guide to lead the way through information chaos. (P09/47/m) Beyond that, advice for further research was seen as beneficial. (P52/39/f, P29/44/f, P38/60/f) Even a general reference suggesting that such information exists was perceived as helpful. (P13/54/f) Therefore, it is not surprising that the scope of available information was most commonly underestimated.

'Although sometimes one naturally also …/ one thinks he is well informed, and he has no idea that there is actually still much, much more information available or that a variety of other opportunities exist for him.' (P32/40/f).

This category did not occur during HCP interviews.

Referral

Another function that was additionally demanded was referral. For example, information about care facilities and physicians was cited (A06/50/m, P10/50/f), indicating that

this is of special importance at the beginning of a disease. (P47/59/m) Nevertheless, it was also highlighted that this was not the only task.

'A12: Yes, I find it good (info hotline). But, in my opinion, as I have just indicated, that would need to be a little larger. That psychosocial counselling services are referred to.

Interviewer: Yes, OK.

A12: and that one does more than to just say, "Yes, there's the doctor."' (A12/32/f).

HCPs also mentioned the need for referral in addition to medical counselling ($n = 3$). At this point, HCPs reported that they realize that it is impossible to make their wish for immediate specialist knowledge for each medical field come true. On the contrary, they realize the impracticability of this demand.

'That makes sense, yes. That makes sense. Well, I wouldn't expect to be able to call the medical association, for example, and say that I have someone on the phone who is experienced in this area. [I1: Hm] You can't expect that. But if you can call and say: 'Do you have a contact that is particularly responsible for such and such a disease pattern'? That makes sense.' (S01/39/m).

'Let me say, in order to be in a position to address his request, and I believe that this telephone opportunity is really good here, since it gives us the opportunity to shift and sort a little and [I1: okay] to say who belongs here and who doesn't.' (G07/31/f).

In this regard, HCPs emphasize that the number of referrals can and must be minimized to shorten odysseys through health care systems. (GP03/48/f).

Discussion

Patient and relative interviews showed that helplines are predominantly necessary due to the possibility of personal contact and low technical barriers. RD patients and relatives wish for a helpline run by professionals with extended availability. An RD helpline should offer information on medical and psychosocial issues. In addition, participants hope for guidance through information chaos as well as referral where needed.

In general, the need for an RD helpline from the perspective of HCPs was confirmed with some minor differences, even though no statements to the extent of the demand can be made to a comparably high percentage of unspecific answers. An RD helpline should be staffed with professionals. However, a medical professional was specifically demanded. Criteria for staffing should be broad knowledge of RD, a multidisciplinary orientation, and knowledge of differential diagnostic procedures. Personal contact was preferred as details of medical cases could be described, even if not put in words easily. HCPs also asked for additional referrals to other experts. Good availability was specified as reachability during office hours suggesting that a request surplus could be managed through a call-back system. As this proposal is not in line with patient and relative interviews, it is not considered for the final concept. Medical professionals recognized a low technical barrier as an important issue for themselves and people affected.

Many studies report the staffing of helplines with nurses [74]. In this study, patients, family members, and physicians particularly demanded the employment of professionals with a special emphasis on physicians. McKenzie, [75] for example, reported the successful commitment of GPs for the coverage of after-opening hours. In this regard, the broad knowledge of GPs seems to be a suitable qualification for the management of an RD helpline potentially incorporating the need to familiarize with various diseases across different medical disciplines. Besides, GPs are familiar with transferring patients and communicating with various medical professionals. GPs also add their expertise when it comes to long-term differential diagnostics. On the other hand, training can add to the necessary qualification spectrum especially when it comes to very rare diseases or psychosocial needs and seem to be quite suitable for the management of helplines even though a re-alignment of practice is necessary due to the interaction via telephone [75]. Advice has been obtained by the German Cancer Information Center which offers a German Cancer Helpline. In this context, psychologist or social workers are often added to the Team rendering advice to other counsellors [76–78].

The importance of personal contact was highlighted during the interviews. Even though interviews raised ease of information search as an argument for building a helpline, the psychological value of personal contact also needs to be stressed. Anderson [79] raised a high negative impact even on family members of children suffering from RD and demanded more psychological support. Helplines salvage the potential of reducing this distress [67] and therefore offer high psychological value.

Availability is a very subjective topic. As RDs mostly show a chronic pattern, emergency situations will not arise that often. Emergency calls can be addressed to emergency helplines. Nevertheless, the demand for extended opening hours remains unclear in its specification and requires further discussion.

Even though we live in a technically advanced digital age, there are still some EU households with

no Internet connection (32%). On the other hand, 98% have telephone access, either through a fixed or mobile device [80]. Adding to this, telephone services are always available in local languages while many websites on RDs are only available in English language, adding a language barrier to the technical one [67]. Nevertheless, it must be outlined that these barriers will be further reduced as technologic advancement progresses. Besides, there are already some translation programmes available online, which will most certainly be further developed.

Friedmann et al. [81] confirm the necessity of a multidisciplinary team for the coverage of inquiries of callers of a HCP helpline and therefore underpin the broadness of questions.

Originally, primary care physicians took on the role of guides when communicating and assessing health information. Therefore, it is not surprising that this category did not emerge within HCP interviews as they identify with this role. Nevertheless, Coumou and Meijman [82] state that GPs do have approximately 400 indications at hand. It is very likely that common indications are kept in mind rather than RDs, which are very unlikely to appear in their practice. These findings underpin the role of guides, which already exists as part of many RD centres and whose expertise is demanded in this case.

Tariq et al. [83] confirm the importance of referrals carried out by helplines. It quantifiably contributes to the effectiveness of health care systems. For example, an after-hours service helpline prevented 1363 people from unnecessarily attending an emergency department. Further, 228 individuals underestimating their conditions could be referred to an adequate health service provider.

Study significance

We suggest that our study has significance for the establishment of nationwide and centralized RD helplines worldwide due to shared problems such as long delays in diagnosis and dense RD health care infrastructure. In addition, the study broadens the perspective on RD telephone services rendered within the literature thus far by including potential users who have not yet called a helpline but would if services were adapted. In contrast, previous studies interviewed callers of existing helplines, focusing on affected people who were already interested in the service of the helpline [61, 64]. This new perspective offers a way to improve RD counselling, making it more attractive to the potential user pool and, therefore, extending its benefits to all those affected within society. Besides, many studies dealing with the question of health information provision do not include the possibility of different information access points. However, existing studies—for example, Mooney et al. [84]—found that patients suffering from anti-neutrophil cytoplasmic antibodies tended to reject detailed information on their disease and disease management when given the diagnosis through a physician as it was a lot to take in. At a later stage, truthful information was difficult to access, substantiating the benefit of a telephone service. Other studies analysing patients and families dealing with late stage cancer underpin the assertion that trained physicians may not communicate effectively due to missing knowledge of information needs of this patient group, [85] indicating the need for specialized and broadly available service providers.

Most heatedly discussed was the implementation of a central RD helpline considering all 5000 or 8000 very heterogeneous diseases. Implementing this kind of service necessitates an extensive financial budget. The estimation of necessary financial resources proves to be quite difficult as many assumptions and projections are necessary. A high-budget case with 60,589 estimated contacts per year necessitates an annual budget of 2.59 € million with 35 full-time employees (FTE).[1] As full case coverage requires extensive budgeting, the calculation is rather an indicator for what is already done for other diseases and could be done in the field of RD. However, a competent counselling service can be offered. In this case, the overall estimated need for RD information need cannot be covered. Costs for a base case scenario mount up to approximately 300.000 € (4 FTE) annually.[2] An evaluation of European telephone services by Houÿez et al. [53] shows similar results. According to the report, RD helplines should be staffed with a minimum of 1.5 (FTE), leading to annual costs of 150,000 to 300,000 €. Therefore, it can be suggested that, starting from this level, a stepwise implementation of the ideal scenario should be pursued.

As a solution for the shortage of monetary funds, a central telephone service offering referrals is often suggested. Such a service could bundle the heterogeneous landscape of existing RD telephone-based or disease-related information services in a similar manner to how ZIPSE is bundling web information. However, the implementation of such a service would contradict the results of the study as patients, relatives, and HCPs ask for direct contact with professionals. Therefore, a telephone service bundling all RD helplines and giving references cannot be suggested. Nevertheless, it can be suggested that existing RD-related helplines may be shaped following the results of this interview study. For example, the service of the Alliance of Chronic Rare Diseases (Allianz chronisch seltener Erkrankungen, ACHSE) can be further extended. Services of RD guides located at specialized centres for RDs can be adapted, bearing thoroughly in mind the wish of patients and relatives to not only be forwarded from one contact point to another.

Assumptions and limitations

This study was designed qualitatively to capture information needs, which could be served using a telephone service without guiding answers beforehand. Instead, participants were encouraged to give their own ideas on an RD helpline, assuming these to be of most relevance. Therefore, a limited number of patients, relatives, and HCPs could be interviewed. The qualitative design contributes to theory generation. The quantitative structure of interview results has been included to increase the transparency of result communication. To make projections and/or quantifiable statements, results need to be verified through a quantitative study.

Only 39 HCPs participated in the study from 141 invited. Studies show that physicians are more likely to respond when a small financial incentive is given. During this study, no financial resources were available for this purpose [86].

Many female individuals were interested in participating in the study. That is why the sample is biased towards women. Even though this should be kept in mind, studies show that health information providers are more often used by women as they are more likely to search for health information in general. Some providers report up to 97.5% female users [87].

The study was conducted against the backdrop of the German NAMSE process asking for the design of a national RD helpline. In order to minimized the bias towards favouring the establishment of a RD helpline interviewers first openly asked how participants feel about helplines to avoid putting neither negative nor positive words into the mouth of participants as suggested by Mayring 2002 [72]. Therefore, participants were not influenced towards a specific outcome.

Additionally, patient and relative interviews were conducted by three different interviewers. HCP interviews were held by two different interviewers partially conducting interviews together. Even though interview structure was discussed beforehand and interview guides were established and adapted after piloting, individual interview styles need to be recognized as an influential factor.

Interviews were not able to capture juridical topics during the questioning concerning the helpline. Therefore, it is obviously necessary to analyse why respondents did not include juridical or access to treatment matters even though experiences of other helplines show that people affected do not solely search for this via other media [63]. ACHSE user statistics (2011–2013; unpublished, based on private email communication) indicate that problems with cost takeover and other social legal problems are topics of counselling. Independent Patient Consultancy (Unabhängige Patientenberatung Deutschland, UPD) reports proportions of 66% and 67% [78, 79] medical-juridical questions within their annual patient monitor, pointing to the most likely reason for not mentioning juridical issues during the interviews. Obviously, they are closely linked to medical questions and not visible at first glance using structured content analysis.

Conclusions

Even though new technologies enable patients, relatives, and HCPs to access information rapidly, this study shows that there is still a point in making information accessible the 'old-fashioned way' via telephone. The telephone offers the unique chance to make professional insights directly available for all stakeholders, including exchanging medical and psychological issues. However, putting all desired aspects simultaneously into practice in an ad hoc implementation process with a central RD helpline offering information for all patients, relatives, and HCPs potentially calling the helpline would necessitate a huge financial budget. Therefore, a stepwise implementation is suggested. As a first step, it is suggested to improve major existing helplines to meet the identified needs. Afterwards, service availability can be extended. In the long run, existing services should be evaluated with regard to the fulfilment of these factors. The expertise from institutions as centres for RDs should be further included, bearing in mind the wish of patients and relatives to not be pushed from one information access point to another.

Endnotes

[1]In an ideal scenario, all identified relevant aspects should be put into practice. This first scenario demonstrates how many monetary resources could be put into a telephone-based information service when aiming for a service quality similar to that of the UPD and the KID. User statistics of the KID show that only 1.51% of the patient pool uses the information service, resulting in 23,024 contacts per year [78]. Extrapolating from this number, an RD helpline would need to expect 60,589 requests per year, making 35 employees necessary to answer all requests [76–78]. Average human resource costs of an interdisciplinary team are estimated to be 59,006.61 € per employee and year. Costs were calculated including monetary funds for rent, staffing, office equipment, publicity, and employee development. Calculating overall material costs makes an estimation of material cost per person possible, approximately 14,911.20 € in the initial year and 12,907.83 € for the following years. The calculation is based on German average wages of a mixed team consisting of physicians, social workers, and lawyers. Accordingly, an RD helpline makes funding of 2.59 € million in the first year necessary.

[2]Because of limited budgets, a low-budget case has been discussed as a second scenario. Following interview results, the most important aspect, 'quality of counselling by

experts', shall be obtained. Therefore, a multidisciplinary team shall be preserved, aiming for a minimum staffing by one physician, one social worker, one lawyer, and one temporary employee. Hence, a quality counselling service can indeed be offered, but, comparing both cases, the counselling team in the latter case is significantly shorthanded and therefore unable to cover all potential requests. In a base-case scenario, considering four full-time employees, overall material costs add up to 59,644.80 € for the initial year. For the following years, 51,631.30 € in costs are estimated. As previously mentioned, average human resource costs add up to a total of 236,026.44 €. Finally, the calculation results in overall costs of 295,671.24 € for the first year and 287,657.74 € for the following years.

Abbreviations

A: Affiliated or relative; ACHSE: Allianz chronisch seltener Erkrankungen, Alliance of Chronic Rare Diseases; C: Clinician; ENRDHL: European Network of Rare Disease Help Lines; FTE: Full-time employees; G: Guide; GMS: German Medical Science; GP: General Practitioner; HCP: Health Care Professionals; KID: Krebs Informations Dienst, German Cancer Information Service; MTP: Medical Therapeutic Practitioner; NAMSE: Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, National Action League for People with Rare Diseases; P: Patient; RAPSODY: European Rare Disease Solidarity Project; RD: Rare Diseases; S: Specialist; UPD: Unabhängige Patientenberatung Deutschland, Independent Patient Consultancy

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Availability of data and materials

The dataset generated and analysed during the current study is not publicly available as the anonymity of participants should be preserved; this anonymity is in danger due to the small prevalence of single rare diseases. However, the dataset is available from the corresponding author on reasonable request.

Authors' contributions

AB, MF, SL, and VL planned and designed the study. AB, SL, and DR conducted the interviews with patients and relatives. FS recruited patients and relatives. VL recruited and interviewed all HCPs. AB and FP conducted the cost analysis. HS and TH critically reflected on and analysed data on informatics. LB critically reflected on and analysed data on rare disease helpline management. AB coded the interview data. The acquired dataset was than discussed and verified by all researchers. AB drafted the manuscript. JMS, TOF, and MF revised the document for important intellectual content. All authors have read and approved the final manuscript.

Competing interest

The authors declare that they have no competing interest.

Ethics approval and consent to participate

A positive ethics committee vote was obtained for the interview study from the ethics committee of the Albert-Ludwigs-University Freiburg (number 53/14). Informed consent was obtained in writing from all participants.

Consent for publication

Not applicable.

Publisher's Note

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Modul 9

Conceptualization and Implementation of the Central Information Portal on Rare Diseases: Protocol for a Qualitative Study

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Protocol

Conceptualization and Implementation of the Central Information Portal on Rare Diseases: Protocol for a Qualitative Study

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Abstract

Background: Recently, public and political interest has focused on people living with rare diseases and their health concerns. Due to the large number of different types of rare diseases and the sizable number of patients, taking action to improve the life of those affected is gaining importance. In 2013, the federal government of Germany adopted a national action plan for rare diseases, including the call to establish a central information portal on rare diseases (Zentrales Informationsportal über seltene Erkrankungen, ZIPSE).

Objective: The objective of this study, therefore, was to conduct scientific research on how such a portal must be designed to meet the needs of patients, their families, and medical professionals, and to provide high-quality information for information seekers.

Methods: We chose a 3-step procedure to develop a needs-based prototype of a central information portal. In the first step, we determined the information needs of patients with rare diseases, their relatives, and health care professionals by means of qualitative interviews and their content-analytical evaluation. On the basis of this, we developed the basic structure of the portal. In the second step, we identified quality criteria for websites on rare diseases to ensure that the information linked with ZIPSE meets the quality demands. Therefore, we gathered existing criteria catalogs and discussed them in an expert workshop. In the third step, we implemented and tested the developed prototypical information portal.

Results: A portal page was configured and made accessible on the Web. The structure of ZIPSE was based on the findings from 108 qualitative interviews with patients, their relatives, and health care professionals, through which numerous information needs were identified. We placed particularly important areas of information, such as symptoms, therapy, research, and advisory services, on the start page. Moreover, we defined 13 quality criteria, referring to factors such as author information, creation date, and privacy, enabling links with high-quality information. Moreover, 19 users tested all the developed routines based on usability and comprehensibility. Subsequently, we improved the visual presentation of search results and other important search functions.

Conclusions: The implemented information portal, ZIPSE, provides high-quality information on rare diseases from a central point of access. By integrating the targeted groups as well as different experts on medical information during the construction, the website can assure an improved search for information for users. ZIPSE can also serve as a model for other Web-based information systems in the field of rare diseases.

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KEYWORDS

rare diseases; health information exchange; quality control; qualitative research

Introduction

Finding Reliable Information on Rare Diseases as a Major Challenge

In Germany, an estimated 4 million people live with rare diseases [1]. Rare diseases, as defined by the Community Action Programme on Rare Diseases 1999-2003, are those with a prevalence of ≤1 per 2000 persons in the European Union [2]. Accordingly, of all known diseases, about 7000 can be considered rare. Even though causes and symptoms can widely vary, patients with rare diseases and their families often face similar challenges [3]. Among others, the affected people often lack reliable information about their own or their relatives' disease due to unfamiliarity with information services or information retrieval systems. Additionally, for physicians who rarely encounter rare diseases in their daily practice, finding reliable information on diagnosis and treatment is a major challenge. Consequently, patients often wander from one doctor to another for years, until they receive a correct diagnosis and obtain access to specialized care. Therefore, in 2013, the federal government adopted a "National Action Plan on Rare Diseases" to improve patients' health situation. Establishing an information system suitable for patients is one component of a broader set of measures to achieve this goal [4].

Currently, patients, their families, and health professionals have some difficulties in finding high-quality information on rare diseases [3]. Although there are plenty of websites, portals, and databases on rare diseases in the World Wide Web, including those on specific conditions and rare diseases in general, people do not know about these websites or struggle to find them in the vastness of the internet. Moreover, not every information website is suitable for different types of users and their specific needs. One of the largest databases on rare diseases in Europe, for instance, is Orphanet [5], which provides comprehensive information on a large number of rare diseases. Nonetheless, the information offered on this database meets the requirements of health professionals more than those of laypersons. Furthermore, there are some national and international information services, such as the National Organization for Rare Diseases in the United States and the Alliance of Chronic Rare Diseases in Germany [6,7]. However, the former as well as other foreign language offerings are not suitable for all people in Germany affected by or interested in knowing about the disease, due to language barriers. Yet, it is essential to understand disease information accurately. The latter only contains information on a small number of rare diseases, such that its usability is limited.

Apart from the aforementioned sources, centers for rare diseases and patient organizations often provide comprehensive and reliable information. Especially for patients and their relatives, the latter are important contact partners that help them access specialized care or offer advice on all questions relating to their disease. For people affected by a rare disease, physicians can be another important source of information [8-12]. However, apart from those who deal with these conditions on a regular basis, for instance, physicians working in centers for rare diseases, general practitioners, as well as specialists in private practice often lack such information.

Developing a Central Information Portal on Rare Diseases

Therefore, this project aimed to conceptualize and implement a central information portal on rare diseases (ZIPSE) on the internet, through which people affected by a rare disease, their families, and relatives, as well as medical professionals can obtain access to high-quality information in German language. This should be done based on scientific methods and with the involvement of the different target groups. However, the portal's editorial staff will not be generating the information provided on ZIPSE. Rather, it will identify, check, and link with ZIPSE, existing information sites on rare diseases, if they provide user-relevant information.

Methods

Evaluating the Information Needs of Patients, Relatives, and Health Care Professionals

To develop an information portal that suits the needs of patients, their relatives, and health professionals equally, over the entire course of the project, we aimed to integrate all target groups who may use the portal in the future. To ensure that the information provided on ZIPSE fulfills the needs of each target group as closely as possible, we initially evaluated the information needs of patients, relatives, and people working in the health care sector. Due to insufficient data on information needs in the field of rare diseases, we decided to use qualitative methods. For patients and their families, we developed an interview guide for eliciting information about their medical history, diagnostic processes, experience of living with the disease, and information searches. As many patients and their relatives ultimately join patient organizations, which can influence their awareness and knowledge of rare diseases, we asked them about their early experience of information gathering. To test whether the interview guide is suitable to identify individuals' information needs, it was pretested with 2

patients and 1 relative. We subsequently adjusted the guide for those diagnosed before or shortly after birth, who could not remember their diagnostic paths.

To recruit a broad and balanced sample, we formed 11 groups of rare diseases at the beginning of this study, which represented a comprehensive variety of rare diseases. We planned to interview 6 patients or their family members in each group. Moreover, we conducted 10 interviews with patients who had waited for at least 10 years for diagnosis. Thus, we intended the sample to comprise 76 patients and close relatives. However, upon saturation of interview data, we found that a smaller sample was sufficient. Participants were recruited through the Freiburg Center for Rare Diseases at the University Medical Center Freiburg, University of Freiburg, Germany.

Our final sample involved a total of 68 participants, including 55 patients and 13 relatives (Table 1). Due to limited access to some patient groups, we could not ascertain the targeted number of interviews in all groups of diseases. However, as it became clear during the study that further interviews do not lead to further identification of information needs, no further recruitment was done.

To identify the information needs of health care professionals, we decided to conduct expert interviews. For this, we developed and pretested different structured interview guides for the different groups surveyed. In our sample, we considered physicians who are not related to centers of rare diseases and hence are inexperienced in information searches on rare diseases. These included general practitioners and medical specialists in private practice, as well as clinicians. Moreover, we interviewed medical technical assistants from in and out-patient care. Thus, experts in the care system, who are specialists in the field of rare diseases and guide patients or people suspected of suffering from a rare disease by the appropriate points of contact, comprised the interview sample. Apart from sociodemographic variables such as gender and age, other parameters integrated in sample selection included the nature of practice and geographical location. We did not strive for a certain sample size at the beginning of this study, but rather tried to reach theoretical saturation by conducting as many interviews as necessary with each sample group (physicians, medical technical assistants, and experts in rare diseases). The results of the interviews with the doctors were validated in a quantitative Delphi survey. Our final sample of health care professionals involved 28 physicians, 6 nurses, 4 guides, and 2 biologists.

We analyzed the interviews according to the structured content analysis method developed by Philipp Mayring [13]. Each audio recording was verbally transcribed and transferred to the MAXQDA (Verbi Software GmbH, Berlin) analysis software. Subsequently, 4 researchers examined the interviews independently, to mark all text passages providing information on people's information needs.

Afterwards, an extensive system of categories using a deductive-inductive approach was developed. Therefore, the researchers processed 5 interviews to transfer the contents from the marked text passages into main- and sub-categories that represent detailed aspects of people's information needs (inductive approach). Additionally, the researchers derived several categories (deductive approach) based on previous research on current information on rare diseases from the internet and published literature review [14-17]. These were integrated into the inductive categories stemming from the text (inductive approach). Then, we applied the system of categories to the rest of the marked text passages and modified or rather complemented it, if necessary.

Furthermore, we presented and discussed the information needs found in the interviews in 4 focus groups, to enable consensual validation. Participants of the focus groups were recruited chiefly from the initial study sample. In addition, some consultants from patient organizations were invited to participate. On the basis these results, the basic structure of the ZIPSE portal and information paths were developed.

Defining the Quality Criteria for Websites on Rare Diseases

Defining the quality criteria for websites on rare diseases was the next step, as, owing to the large number of rare diseases, we planned to provide references to other internet sites instead of providing primary information. Therefore, we examined all quality certifications, catalogs of criteria, and recommendations for information on the Web existing in Germany, and compiled them in 1 conceptual map. In a workshop, several experts on quality of online information discussed this conceptual map with the project team to decide which quality criteria should be considered while linking information websites with the ZIPSE portal. Accordingly, we created a set of specific quality criteria on rare diseases.

Additionally, we conducted extensive research on existing German information websites on rare diseases to create a basic database for the subsequent inclusion of websites in accordance with the quality criteria. Therefore, we screened the internet for information websites on rare diseases using the German Orphanet list of rare diseases and their synonyms [18]. This list included all registered rare diseases. Several research assistants searched the most common browsers for all these diseases, and subsequently screened the first 20 entries offering information on the specific disease on which they sought information.

Table 1. Patient and relative demographics.

Characteristics in participants (N=68)	Statistics
Age (years), mean	50.5
Gender, n (%)	
Female	45 (66)
Male	23 (34)
Rare disease, n (%)	
Genetic skin diseases	10 (15)
Skeletal dysplasia	7 (10)
Neuromuscular diseases	9 (13)
Genetic eye diseases	4 (6)
Connective tissue diseases	5 (8)
Genetic kidney diseases	6 (9)
Cystic fibrosis and pulmonary diseases	7 (10)
Congenital blood formation disorders	4 (6)
Immunodeficiency	7 (10)
Congenital metabolic disorder	7 (10)
Genetic diseases of the digestive tract	2 (3)
Status, n (%)	
Patients	55 (81)
Relatives	13 (19)

Technical Implementation and Usability Tests

We used the information paths and functions developed based on the derived information needs to develop a prototype information portal. Thus, we set up a Uniform Resource Locator, on which essential elements could be activated and tested it concomitantly [19]. Initially, within the framework of the focus groups described above, we introduced patients and relatives, who had already participated in the interviews, to the preliminary version of the information portal, and they provided their opinion. Thus, we derived potential for improving the design of the home page of the website and of the search function within the portal. Subsequently, to check whether the derived information paths corresponded to people's information needs, we conducted usability tests with patients, their relatives, and physicians. For this purpose, we asked the testers to browse through the portal and search for specific information on their disease while thinking aloud. Among the testers were 9 patients with rare diseases and 10 physicians, who did not participate in the interviews. As a result, authors could identify at which points of their search users may have problems in acquiring the information sought. Moreover, we measured their satisfaction with the use of the portal in personal discussions with the testers. A written survey was not conducted due to the small number of tests.

Results

Information Needs of Patients, Relatives, and Health Care Professionals

The findings of this study revealed a variety of information needs of patients with rare diseases and their families, which are published in detail elsewhere [20]. On the basis of content analysis, we derived various information areas relevant for the interviewees. First, we found that people's information needs varied depending on the type and stage of illness. Shortly after diagnosis, the affected individuals reported the need for easily comprehensible and concise information, enabling an overall understanding of the disease, its causes, symptoms, and impact on their everyday life. Moreover, the participants stated that they wished for information on personal contacts of other patients or their relatives after they had received a diagnosis. At a later stage, people often mentioned the need for more detailed information on their disease. For example, they would like to know if there were any research efforts in which they or their relatives could participate. Knowledge about research on their illness is an important factor for many patients because it helps them cope with the illness and remain confident. Especially for those suffering from a severe rare disease that has not yet been researched intensively, this can be of enormous importance.

Content analysis showed that health care professionals' needs partly overlapped with those of patients and their relatives. According to the respondents, doctors preferred to have basic information (eg, regarding prevalence or the course of the

disease) about rare diseases before diagnosing the disease and assistance in the diagnostic process (eg, by obtaining information on special laboratories or specialized centers). Once the disease is diagnosed, the information needs to be shifted to the field of therapy coordination. The respondents assigned great importance to information about the counseling and care of patients with rare diseases as well as to a list of referred physicians and experts for further assistance. In addition, they deemed information on possibilities of exchanging experiences with other health professionals as well as medical education and training in the field of rare diseases necessary. The health care professionals also placed importance on research (eg, existing studies concerning disease progression). All the health care professionals stressed the importance of patient organizations and self-help groups. We verified the results of the interviews with the doctors in a Delphi survey.

We then used these information needs to further develop the ZIPSE information portal by placing these main information areas prominently on the ZIPSE start page, as well as by integrating them in the layout of the hit list display. Information on registered websites is assigned to these topics so that users can easily search those information topics. Clearly understandable icons, which are displayed on the hit list, indicate what information each individual information website covers.

Quality Criteria for Websites on Rare Diseases

Overall, we identified 9 criteria catalogs and guidelines with recommendations for high-quality health information on the internet from a literature review. A total of 304 single items were extracted, which were reduced to 163 different criteria. Considering the large number of websites on rare diseases, quality criteria for the ZIPSE portal could not refer to the accuracy of all information offered, but to the quality of the information as well as of the preparation of information and of the website. Therefore, we selected criteria to assess how, by whom, and based on which sources the offered information had been collected; how data safety was to be addressed; and how users could contact the website operator. In a workshop with several experts from the field of medicine regarding high-quality online information, the conceptual map comprising 163 different criteria was reduced to a catalog containing 13 criteria, which was used for assessing information websites (Textbox 1). Among others, these criteria included data on the creation process, authors, sources, as well as creation and updating, data security, and declaration of evidence. Some of the criteria could be labeled as “essential criteria” (creation and updating date, data security, imprint, and contact information). Only if these essential criteria are fulfilled, a website will be displayed in the quality assured area of the portal. A criterion containing more than 1 term is deemed to be met when at least 1 term may be considered to be fulfilled. Websites that do not meet all essential criteria will be linked in a separate area. Users can actively request those, but we have to confirm that these websites do not meet the essential quality criteria. We published a detailed description relating to the adoption of quality criteria for websites providing medical information on rare diseases elsewhere [21].

We transferred all the identified quality criteria into a Web-based questionnaire that can be filled online either by the providers of information themselves or by the ZIPSE editorial team. Moreover, we conducted a comprehensive research on existing websites on rare diseases. We identified several hundred websites including those of patient organizations, research institutes, and care facilities and transferred them into a database containing information on the URL, the website provider, and the diseases. Subsequently, we contacted the website provider with a request to register or the editors of the ZIPSE portal registered their information themselves. The information websites were then visible and saved in the administration area of the portal’s home page. When website providers registered themselves, the editors of the ZIPSE portal reviewed all information for accuracy and integrity. If necessary, we corrected or completed data. Completely revised information websites that met the essential criteria were then activated, after which they were visible to people searching for related information in the hit list. Nonquality assured information websites were linked to a downstream area.

Technical Implementation and Usability Tests

We set up a webpage on which we placed the basic developed framework of the ZIPSE portal [19]. During the course of the project, we added and evaluated various services, including a disease-specific search function as well as filter options. Through these features, users could search for information on a specific disease and filter search results by topic, information provider, or website features. Moreover, an administration interface was activated. In this interface, all data stored in the system (addresses, contact persons, information on the websites, and its quality aspects) could be managed. Thus, the quality of linked websites could be checked and documented recurrently.

To check whether the information paths, which were developed earlier, suited the target group’s specific needs, we conducted focus groups as well as usability tests. Initially, we created an extensive presentation to provide patients with rare diseases and their relatives an overall picture of the portal. Within the framework of focus group discussions, the participants reported high satisfaction regarding clarity, functionality, and comprehensibility. Nevertheless, they reported some points for improving the layout, such as the structural arrangement of the start-up page as well as the display of the hit list, among others. The results directly contributed to the further development and optimization of the ZIPSE portal. Elements on the home page, which were less important to the testers such as the offer to recommend or register a website, can now be found at the bottom of the start-up page, whereas main information areas as well as a mapping of care facilities were placed at a more prominent location. Additionally, new, self-explanatory pictograms for the hit list were created. In the usability tests with patients and physicians, it followed that several aspects could be revealed, which we subsequently revised, including a larger representation of the search field, a clearer presentation of the filter options, and an unambiguous representation of icons and images.

Textbox 1. Zentrales Informationsportal über seltene Erkrankungen (ZIPSE) quality criteria.

Creation process

- Do you perform systematic (literature) research for information creation on your home page? If yes, please describe this process.
- Are experts involved in information creation? If yes, which?
- Is the process of building information on the website documented? If yes, what does this documentation look like? (Please describe)
- Do you illustrate the information building process for your users? If yes, please describe the presentation and name the respective Uniform Resource Locator (URL).

Authors

- General information (names and qualifications) about the authors has been mentioned.
- Other persons, who contributed to developing information, are mentioned.
- Contents authored by users have been labeled and equipped with a user name.

Sources

- Do you provide self-created information?
- If no, do you mention external sources?

Creation and updating (essential criterion)

- The creation date of the information has been mentioned.
- The updating date of the information has been mentioned.

Data security (essential criterion)

- By means of a privacy policy, do you inform the user about the usage, storage, and disclosure of personal data?
- Do you inform the user in a prominent position about the storage of personal data for internal usage (eg, research) with an analysis tool? Does the user have the option to disagree?
- Does the user need to agree actively to the disclosure of personal data to third parties?

Declaration of the evidence

- Is all medical information evidence-based, whereby it is discernible on which basis points are made (eg, studies and expert statements)?
- Do you show the user references to limits of the evidence respectively name more evidence needs?

Marking of conflicts of interests

- Advertisements have been marked as such clearly.
- Sponsors have been named.
- Targets and purposes of the home page have been published clearly (eg, commercial interest).
- The funding (except from self-financing) source has been published.
- Conflicts of interests have been declared.

Consideration of target group

- Information is target-group specific.
- It is discernible to whom the information is addressed (eg, patients or doctors)?

Evaluation

- An archive of former or changed contents exists.
- The accuracy of all the information has been checked consistently.

Review process

- Do you have an internal review process (content quality assessment) for the evaluation of the contents?
- If yes, please describe it.

Characteristics of the website (low-barrier)

- Did you check the website for accessibility through a Barrierefreie Informationstechnik-Verordnung-Test (better: barrier-free information technology regulation test?)? If yes, how many points has the website achieved on this test?
- Is the font size of the website adjustable?
- Do you consider persons with color deficiency in your coloration?
- Can the main menu be accessed without a mouse?
- Is the information available in a simple language (eg, according to the rules of the network simple language)?
- Is the information website available in several languages?
- It is possible to subscribe to a newsletter?
- Is the information available in a printable version?
- Are multimedia contents available (eg, videos and photos)?

Imprint (essential criterion)

Does the imprint contain the following information:

- Name and address of the publisher
- Email address of the publisher
- Declaration of the commercial register, the register of associations, etc, in which the provider is registered, and the respective registration number)

Contact (essential criterion)

- Users can provide feedback or contact the operator.
- A contact sheet is easy to access.

Figure 1. Layout of the Zentrales Informationsportal über seltene Erkrankungen (ZIPSE) start-up page.

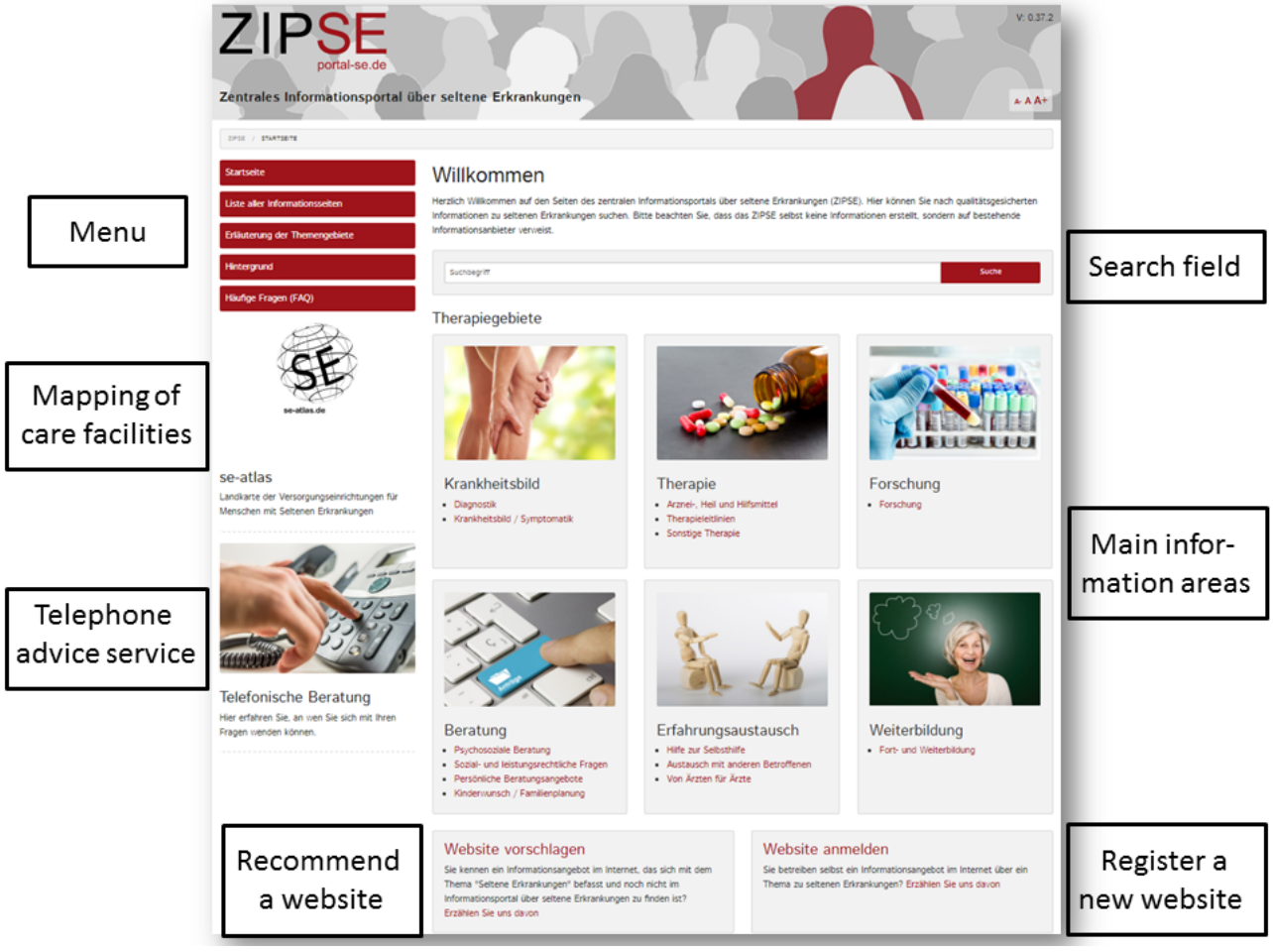
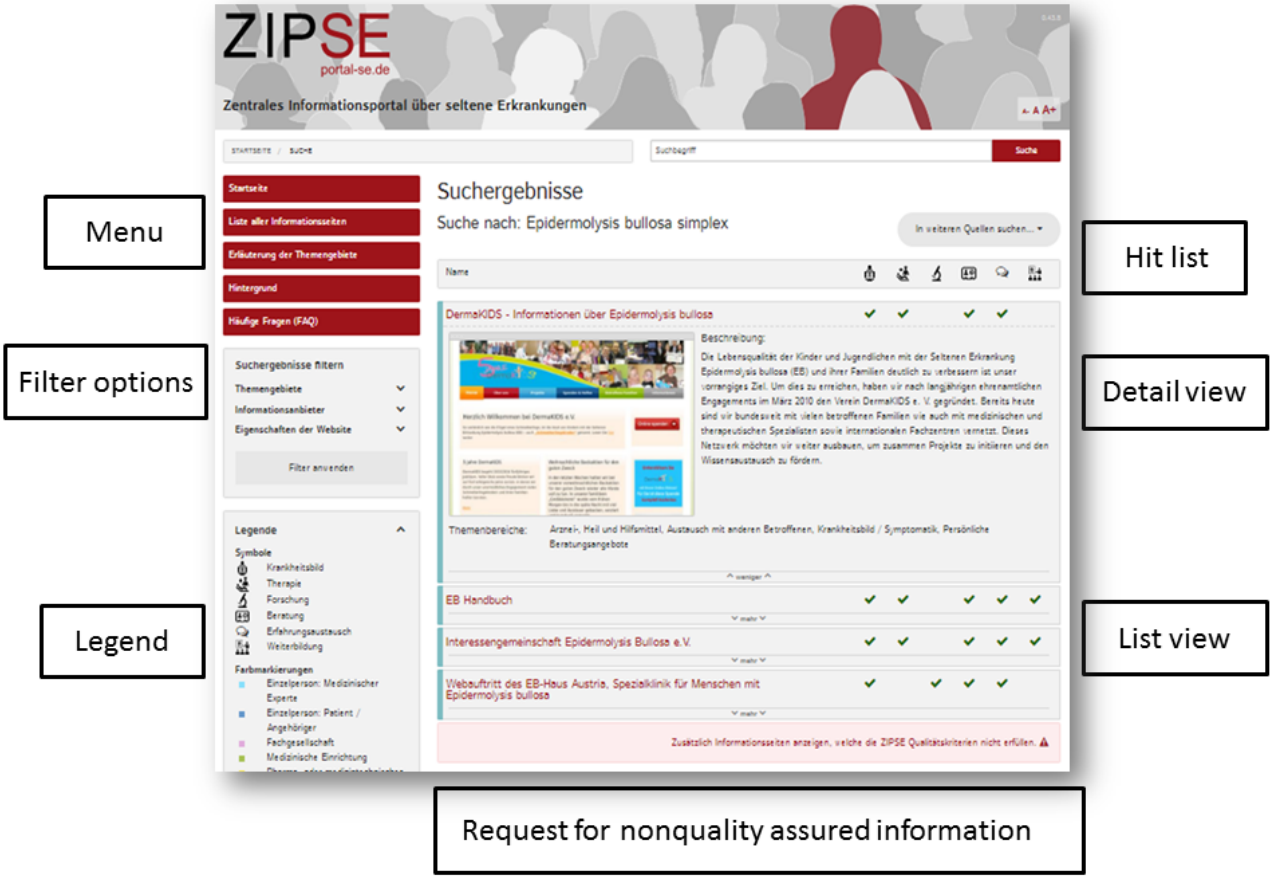


Figure 2. Layout of the Zentrales Informationsportal über seltene Erkrankungen (ZIPSE) hit list page.



Prototypical Implementation of the Central Information Portal on Rare Diseases

As a result of the procedure described above, we created a functioning information portal. Figure 1 shows the structure of the ZIPSE start-up page. Below the ZIPSE header, users can find the search field in which they can conduct a disease-related search. The menu is displayed in the upper left corner, under which a link to the se-atlas, a mapping service for care facilities on rare diseases, as well as information about telephone advice has been provided. At the bottom of the website, users can find the option to either propose the addition of an information website on rare diseases by providing its name and contact persons, or to register themselves in case they operate a website on a rare disease. Above this option, a selection of different information areas of particular importance regarding the needs identified earlier has been displayed prominently.

When searching for a disease using the search field, a list of linked information websites appears (Figure 2). In this list, all the relevant websites on that specific disease, which have been registered and reviewed positively regarding the essential quality criteria, are presented alphabetically. Next to the name of each information website, an overview of the information areas covered by each site appears (represented by green checkmarks). Moreover, on the left side, users can filter all hits regarding further information areas (which might not have been considered directly in the hit list, but still are relevant), the type of provider, as well as characteristics of the website (such as accessibility and multilingualism). Clicking on one of the matches produces a detailed view of the website. This includes a screenshot of the webpage's start-up page, as well as a short description of the contents of this site. The users then have the option to be forwarded to the website by clicking on its image. Information websites that do not meet the essential quality criteria can be requested at the bottom of the hit list. By clicking the corresponding button, these are shown in the hit list and are clearly marked.

Discussion

Principal Findings

During the course of the project, we developed and implemented a prototype of a central information portal on rare diseases that fulfills the needs of patients, their relatives, physicians, and other health care professionals. Currently, 720 information websites have registered on the portal. About half of the websites meet the essential quality criteria, whereas the other half can be found in the nonquality assured area of the portal. A total of 239 websites refer to genetically caused diseases (239/720, 33.1%). Another 92 websites focus on neurological conditions (92/720, 12.7%). This is followed by 72 websites on neoplastic diseases (72/720, 10.0%) as well as 40 websites on developmental defects during embryogenesis (40/720, 5.5%). All other disease groups are in the lower single-digit percentage range.

The information needs identified through qualitative interviews were in line with different international studies [14-17] as well as with information offerings on a random sample of existing websites on rare diseases, selected from the ZIPSE database. On the ZIPSE portal, users can search for information on rare diseases from this central point of access. There also lies the crucial benefit over other online offerings on rare diseases, which are often widely dispersed over the internet. To switch from one source to another can be challenging for information seekers. ZIPSE combines all the varying kinds of information websites at one central point. Moreover, all the available information on ZIPSE can be easily filtered by topics that have been shown to be particularly important or by the type of provider as well as by characteristics of the website. Thus, the compiled high-quality information will be more accessible to the interested or affected people.

To offer added value to people with rare diseases, continuous maintenance and optimization of the information portal and its structures and services is of utmost importance. Not only must existing links and contents be kept up to date, but other information websites, including websites from English-speaking countries, must also be identified and integrated within the portal. Especially for people with diseases for which little information is available in German, such information in English could be very useful. Therefore, we will maintain, update, and continuously develop ZIPSE. However, to sustain the availability of ZIPSE, a major challenge for the near future would be to find funding sources. To make sure that all work continues, we are constantly developing different solutions for sustainable funding after the end of this publicly funded project.

By compiling information on rare diseases at one central point of access, in the future, people can identify gaps in knowledge about specific diseases more easily. One can infer that there is insufficient information on all rare diseases, especially on very rare diseases, where only little research has been carried out owing to financial restrictions as well as small numbers of available patients. Without research, no knowledge and information can be generated. This explains why for many (very) rare diseases only little or no information is available online. Addressing these knowledge gaps could be an important task for future studies.

Our concept of a central information portal on rare diseases could be useful as a model for other information providers in the field of rare diseases, for the development of similar information systems. Even though there is a range of other information systems providing information on rare diseases to different target groups, this is the first one that was developed by using extensive scientific methods and integrating all target groups in its development. Due to this study's underlying scientific approach regarding the collection of people's information needs and definition of quality criteria, as well as the involvement of patients, their relatives, and physicians at all stages of the project, one can assume a high target group–specific alignment that could be transferred to other systems.

Limitations

Due to the limited financial and personnel resources in this publicly funded research project, some of the ideas regarding the structure and function of the information portal could not be fully developed. These include, for example, the establishment of a newsletter that informs users about newly included information sites on specific diseases or issues when requested. This could be a task for future operators of the website.

Conclusions

Dealing with the various challenges arising from rare diseases has become an important task for most health care systems. Especially, the gaps in knowledge and the uncertain quality of information pose challenges for the establishment of networks of information infrastructures. Even though there is information on many rare diseases, it is often insufficiently known and used due to low visibility. Establishing a central information portal like ZIPSE makes the existing but widely dispersed information accessible to the various groups of people dealing with rare diseases.

For patients and their families, this offers an opportunity for easy access to extensive information on topics that are important to them, such as therapy, social and legal issues, and self-help. For doctors and other medical professionals, the ZIPSE portal can help to accelerate the diagnostic process and improve patient care by providing information on rare disease diagnostics, therapy, and specialized care facilities. Therefore, bundling high-quality information at one central access point can improve people's health care sustainably. In the future, it will be easy to find trustworthy information for people living with a rare disease by using the ZIPSE portal. Furthermore, with reference to professional caregivers, reducing uncertainties in diagnostics and therapy could prevent the overuse, underuse, and misuse of information in the health care sector. Moreover, the ZIPSE portal can help raise awareness about rare diseases in general. One of the current challenges concerning rare diseases is not only missing information but also the lack of awareness about them. Along with closing gaps in people's knowledge, the ZIPSE portal can help sensitize people regarding rare diseases.

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Conflicts of Interest

None declared.

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Abbreviations

BMG: Federal Ministry of Health Germany
ZIPSE: Central Information Portal on Rare Diseases

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