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Inhaltsangabe

Anhang

Müller R, Rach C, Salloch S. Collective forward-looking responsibility of patient advocacy organizations: conceptual and ethical analysis. BMC Medical Ethics. 2021;22(1):113

Rach C, Lukas J, Muller R, Sendler M, Simon P, Salloch S. Involving Patient Groups in Drug Research: A Systematic Review of Reasons. Patient Preference and Adherence. 2020;14:587-97

Müller R, Aghdassi AA, Kruse J, Lerch MM, Rach C, Simon P, Salloch S. Lived Experience of Hereditary Chronic Pancreatitis - A Qualitative Interview Study. Chronic Illness. 2022 Dec;18(4):818-833

I Liste der dieser kumulativen Dissertationsarbeit zugrunde liegenden Publikationen

Bei den dieser kumulativen Dissertationsarbeit zugrundeliegenden Publikationen handelt es sich um:

1. Müller R, Rach C, Salloch S. Collective forward-looking responsibility of patient advocacy organizations: conceptual and ethical analysis. BMC Medical Ethics. 2021;22(1):113
2. Rach C, Lukas J, Muller R, Sendler M, Simon P, Salloch S. Involving Patient Groups in Drug Research: A Systematic Review of Reasons. Patient Prefer Adherence. 2020;14:587-97
3. Müller R, Aghdassi AA, Kruse J, Lerch MM, Rach C, Simon P, Salloch S. Lived Experience of Hereditary Chronic Pancreatitis - A Qualitative Interview Study. Chronic Illn. 2022 Dec;18(4):818-833

II Abkürzungsverzeichnis

PPI: patient und public involvement
AIDS: acquired immune deficiency syndrome
COVID-19: coronavirus disease 2019

In der vorliegenden Dissertationsarbeit wurde geschlechtergerechte Sprache mittels Nutzung des Gender:Doppelpunkts angewandt.

1. Einleitung

1.1. Entwicklung von Patientenorganisationen

Patientenorganisationen sind, angesichts des historischen Alters der Patientenrolle, ein relativ junges Phänomen. Als Vorläufer dieser Organisationen, so wie wir sie heute kennen, sind Selbsthilfegruppen anzusehen. Die „Alcoholics Anonymous“ trat als erste Selbsthilfegruppe in den 1930ger Jahren erstmals in den USA in Erscheinung. Damaliges Motiv für den Zusammenschluss der Betroffenen war das Bestreben, Anerkennung für eine Erkrankung, für die es im Gesundheitssystem aus ihrer Sicht keine angemessene Therapie gab, zu finden und fehlgeleitete Therapieansätze zu einem Ende zu bringen. Die Pionier:innen der Gruppe waren überzeugt, dass nicht ihr „schwacher Charakter“, sondern der Alkohol selbst, durch seine toxische Kombination aus starker Suchterzeugung und massiven Folgeschäden, für die Gesundheit und das Sozialleben der Betroffenen die Kernproblematik der Erkrankung darstellte. Aus dieser Erkenntnis, die aus den individuellen Erfahrungen der Betroffenen hervorging, entwickelte sich ein völlig neues Therapieziel - die Abstinenz (1).

Medizinisches Personal erkannte in der Folge den hohen Bedarf an adäquater Behandlung und den therapeutischen Nutzen von Selbsthilfegruppen, sodass „Alcoholics Anonymous“ zu einem festen Bestandteil des ersten, modernen Therapiekonzepts zur Behandlung der Alkoholabhängigkeit – einer Alkoholentzugsbehandlung – wurde (2). Der Erfolg dieser ersten Selbsthilfegruppe zog die Entwicklung zahlreicher, mannigfaltiger Patientengruppen nach sich.

Während der AIDS-Epidemie erfuhr, vorangetrieben durch starken Aktivismus vor allem in den USA, eine weiteres Ziel von Patientengruppen einen deutlichen Auftrieb: Die aktive Mitgestaltung bei Entwicklungen von Therapeutika (3). Grundlage dafür stellen die durch die Betroffenheit entstehenden Erfahrungen und dadurch resultierendes Wissen dar. In der Literatur findet dieses Phänomen unterschiedliche Namen, unter anderem „lay expertise“, „experiential expertise“ und „patient knowledge“. Häufigere Verwendung findet der Begriff „patient and public involvement“ (PPI) (4), der beabsichtigt, verschiedenen Phänomene in einem Begriff zu integrieren, dabei jedoch durch eine Generalisierung patientenspezifische Quellen für Evidenz zu verschleiern droht (5). Noch weiter als die bereits Genannten geht das Konzept „citizen science“, mit dem die Einbeziehung von unqualifizierten Personen in unterschiedlichste Forschungsbereiche gemeint ist (6). Auch in der Medizin wird dieses Konzept diskutiert, hier gibt es ähnliche ethische Überlegungen wie bei PPI zu

bedenken (7, 8). Wenngleich der Nutzen der diesen Begriffen zugrunde liegenden Ressource – nicht zuletzt durch den Erfolg der AIDS-Aktivist:innen – in der aktuellen wissenschaftlichen Debatte kaum infrage gestellt wird, ist eine genaue Definition des Phänomens weiterhin schwierig (9).

Nach der Jahrtausendwende wurden Patientenvertretungen von nationalen Institutionen, die Bewertungen der Sicherheit und des Nutzens neuer Therapiemöglichkeiten vornehmen, in die Arbeitsprozesse aufgenommen (10); eine flächendeckende, routinemäßige Zusammenarbeit zwischen Wissenschaft und Patient:innen konnte jedoch bisher nicht etabliert werden.

1.2. Funktionen von Patientenorganisationen aus heutiger Sicht

Seit der Zeit ihrer Entstehungsgeschichte haben sich nicht nur Form und Zusammensetzung, sondern auch Ziele und Verantwortungsbereiche von Patientengruppen deutlich gewandelt, auch wenn die ursprünglichen Motive bis heute fortbestehen. Vor allem in der Suchtmedizin, aber auch in anderen Bereichen wie z. B. der Onkologie (11), bestehen weiterhin Selbsthilfegruppen, deren primäres Ziel eine Förderung der Gesundheit und Krankheitsbewältigung der individuellen Gruppenmitglieder ist.

Andere Gruppen stellen die identitätsstiftende Komponente, also eine Definierung und Objektivierung der Erkrankung und des davon Betroffenseins, sowie eine gesellschaftliche Akzeptanz in den Fokus (12). Dieses Vorgehen führt nicht nur zu Identitätsfindungen einzelner Individuen, sondern auch zur Bildung eine Gruppenidentität. Diese kann sich so deutlich ausbilden, dass sie, z. B. im Falle von Körperbehinderungen, mitunter zu Ablehnung wissenschaftlicher Entwicklungen führt (13).

Die Vertretung der gemeinsamen Interessen gegenüber Dritten stellt für viele Patientenorganisationen mittlerweile die Kernaufgabe dar (14). Die Annahme dieser Aufgabe ist nicht trivial, sondern geht mit Verpflichtungen einher und macht Patientenorganisationen zu wichtigen Akteurinnen in politischen, wissenschaftlichen und gesellschaftlichen Entscheidungsfindungen. Patientenorganisationen, die einen gewissen Grad an Größe, Professionalisierung und demokratischen Strukturen aufweisen, können absichtsvoll handeln und sind daher moralisch für die Repräsentation ihrer Mitglieder sowie weiterer – gegenwärtig und zukünftig – von der

Erkrankung betroffener Individuen verantwortlich. Sie sind damit Träger einer kollektiven Verantwortung (15).

Da ihr Wirken die Lebensbedingungen von Betroffenen langfristig und maßgeblich beeinflussen kann, sollten die Absichtsbildung und die Entscheidungen von Patientengruppen idealerweise auf moralischen Grundsätze aufbauen. Als besonders geeignet erscheinen dabei die Prinzipien von Fürsorge, Autonomie und Gerechtigkeit (16).

Bei der Erhebung der persönlichen Erfahrungen von Erkrankten zur Schaffung von „experiential expertise“ empfiehlt es sich, den großen Einfluss der Krankenrolle auf das gesamte Leben der Betroffenen nicht zu unterschätzen. Insbesondere chronische Krankheiten werden je nach Leidensdruck mehr oder weniger stark in die Biographie integriert. Die Konzepte „recurrent biographical disruption“ (17) und „biographical contingency“ (18) erweisen sich als hilfreiche Instrumente, um den Einfluss auf die Identitätsbildung zu erfassen. Ersteres stellt die Erkrankung als Störfaktor dar, der vor allem bei jungen Erwachsenen die persönliche Entwicklung und Lebensqualität langfristig negativ beeinflussen kann und somit auch Einfluss auf die Identität nehmen kann (17). Letzteres dagegen beschreibt die akuten Krankheitsexazerbationen, insbesondere wegen ihrer Unvorhersehbarkeit, als abrupte Unterbrechungen des alltäglichen Lebens, welches danach weitergeführt werden kann, ohne dass es zu Auswirkungen auf die Identität der Betroffenen kommt (18).

Die Bedeutung dieser lebensformenden Erfahrungen sollte bei der Priorisierung von krankheitsspezifischen Forschungsinhalten bedacht werden und kann bei chronischen Erkrankungen beispielsweise eine Reduktion der Unvorhersehbarkeit der Kankheitsmanifestationen als Ziel in den Vordergrund rücken lassen (19).

Da medizinische Wissenschaftler:innen in der Regel nicht selbst von der Erkrankung, die sie untersuchen, betroffen sind, können sie naturgemäß nicht eigenständig „experiential expertise“ in ihre Forschung einfließen lassen. Dagegen stellt es die Grundlage des epistemologischen Anspruchs und – wie oben dargestellt – der kollektiven Verantwortung vieler heutiger Patientenorganisationen dar, in Forschung aktiv mit einbezogen zu werden (20). Es obliegt den Patientenorganisationen, „experiential expertise“ durch Zusammentragung der individuellen Erfahrungen ihrer Mitglieder zu gewinnen, z. B. durch eine strukturierte, qualitative Befragung. Dennoch werden bei PPI bisher größtenteils individuelle Patient:innen und keine Patientenorganisationen in Forschungsprojekte einbezogen (21).

1.3. Zusammenfassung der aktuellen Sachlage

Der Nutzen von PPI ist empirisch bereits gut belegt (22-25). Dennoch bestehen weiterhin Unsicherheiten über gute Herangehensweisen, um den größtmöglichen Nutzen zu erreichen. Eine Schwierigkeit für Forschende besteht vor allem in der Diversität der Gruppe, mit der sie zusammenarbeiten wollen (26). Da sich Patientengruppen, je nach Erkrankung, sehr heterogen zusammensetzen, fehlt häufig ein zentraler Anlaufpunkt. Während akademische Institutionen und kommerzielle Forschungseinrichtungen naturgemäß bereits als Handelnde in der Wissenschaftslandschaft wahrgenommen werden, ist dies bei Patientengruppen bisher nicht der Fall. Ein häufig genanntes Argument für PPI ist, oft von einem utilitaristischen Standpunkt aus formuliert, eine verbesserte Qualität der wissenschaftlichen Ergebnisse. Anders geartete Gründe, insbesondere eine normative Begründung aus Sicht der Patient:innen, sind selten vorzufinden (27). Aufgrund der häufig eingeschränkt professionalisierten Strukturen von Patientengruppen scheinen sich diese zudem den Möglichkeiten, die Ressourcen ihrer Mitglieder zu erschließen, nicht bewusst zu sein.

Die vorliegende Arbeit strebt an, Patientenorganisationen als moralisch verantwortliche Akteur:innen zu identifizieren, die von der zeitgenössischen Wissenschaftslandschaft angebrachten Argumente für und gegen eine Zusammenarbeit mit diesen zu beschreiben sowie eine auf den Erkenntnissen basierende Anwendungsempfehlung beispielhaft darzustellen.

2. Methoden und Materialien

2.1. Konzeptualisierung kollektiver und prospektiver Verantwortung von Patientenorganisationen

Die Beziehung zwischen Ärzt:innen und Patient:innen hat sich unter anderem durch den rechtlichen Rahmen, den Ausbau der Informationsmöglichkeiten sowie durch die immer weiter fortschreitenden Möglichkeiten der modernen Medizin deutlich gewandelt. Heutzutage gilt in der Behandlung von Individuen das sogenannte „shared-decision-making“ als Standard (28). Dieses Konzept kann sich naturgemäß jedoch nur auf gegenwärtige Therapieoptionen und individuelle Erkrankungen beziehen. Einen Einfluss darauf, welche Behandlungsmöglichkeiten ihnen oder anderen Erkrankten möglicherweise in Zukunft zu Verfügung stehen werden, haben Patient:innen aktuell

kaum. Dabei gibt es keine erkennbaren Gründe, weswegen hierbei die Werte, die dem „shared-decision making“ zugrunde liegen, z. B. Autonomie, nicht gelten würden.
Wenn die Idee des „shared-decision making“ über seine Grenzen (Individualität und Gegenwärtigkeit) hinaus entwickelt wird, entsteht die Idee einer kollektiven Verantwortung. Dies meint, dass eine Gruppe von Individuen moralische Handlungen durchführt, zu denen Individuen nicht imstande wären und für die sie daher auch nicht die volle Verantwortung tragen können.
Aus dem repräsentativen Auftrag, der Patientenorganisationen zugrunde liegt, ergibt sich die Notwendigkeit eines zukunftsorientierten Handelns ihrerseits.
Auf Grundlage dieser Überlegungen lassen sich Modelle entwickeln, um Verantwortlichkeiten im Gesundheitssystem zu analysieren (29, 30). Als Basis der vorliegenden Arbeit wurde unter Berücksichtigung ethisch-theoretischer Überlegungen eine Analyse der Verantwortlichkeiten von Patientenorganisationen durchgeführt. Dabei wurde ein Modell mit vier Bezugspunkten entwickelt, welches im Verlauf näher erläutert wird.

2.2. Systematische Erhebung von moral-relevanten Argumenten

Bei Betrachtung der vorhandenen Literatur wird offensichtlich, dass viele wissenschaftliche Beiträge die oben beschriebenen Grundüberlegungen bezüglich des Handlungsspielraums von Patientenorganisationen teilen und ein Ausschöpfen deren Potentials aufgrund gemeingültiger, normativer Werte fordern. Wenngleich die zugrunde liegenden, moralischen Prinzipien zumeist nur impliziert und nicht explizit ausgearbeitet werden, gibt es doch zahlreiche Argumente, die zur Begründung für eine Zusammenarbeit mit Patientenorganisationen herangezogen werden können.
In dem zweiten Artikel, der dieser Promotionsarbeit zugrunde liegt, wurden diese Argumente systematisch erhoben. Zu diese Zwecke wurde Gebrauch von einer spezifischen Methode zur Beschreibung eben solcher Argumente gemacht: dem „systematic review of reasons“ (31). Zur Eingrenzung der Forschungsfrage wurde das Spektrum der Argumente auf die Einbeziehung von Patientenorganisationen im Kontext von Arzneimittelforschung beschränkt.
Zentral für die Methode des „systematic review of reasons“ ist die Identifizierung von Gründen, wobei objektive Maßstäbe zur Suche nach Gründen allgemein (32) und spezifisch bei der Analyse wissenschaftlicher Artikel (33) angewandt wurden.

Die Zusammentragung der für die Zielsetzung relevanten Literatur (Abbildung 1) erfolgte nach den etablierten Standards für systematische Übersichtsarbeiten. Konkret wurden zwei Datenbanken mit breit gefächerten Suchstrategien durchsucht, um eine Gesamtheit der der Argumente sicherzustellen. Die so zusammengestellte Literatur wurde mittels Schlüsselbegriffen hinsichtlich ihrer Relevanz, also dem tatsächlichen Vorhandensein von Argumenten, für die Forschungsfrage gefiltert. Die danach verbliebenen Artikel wurden mittels qualitativer Inhaltsanalyse nach Mayring (34) bearbeitet und Argumente wurden extrahiert.

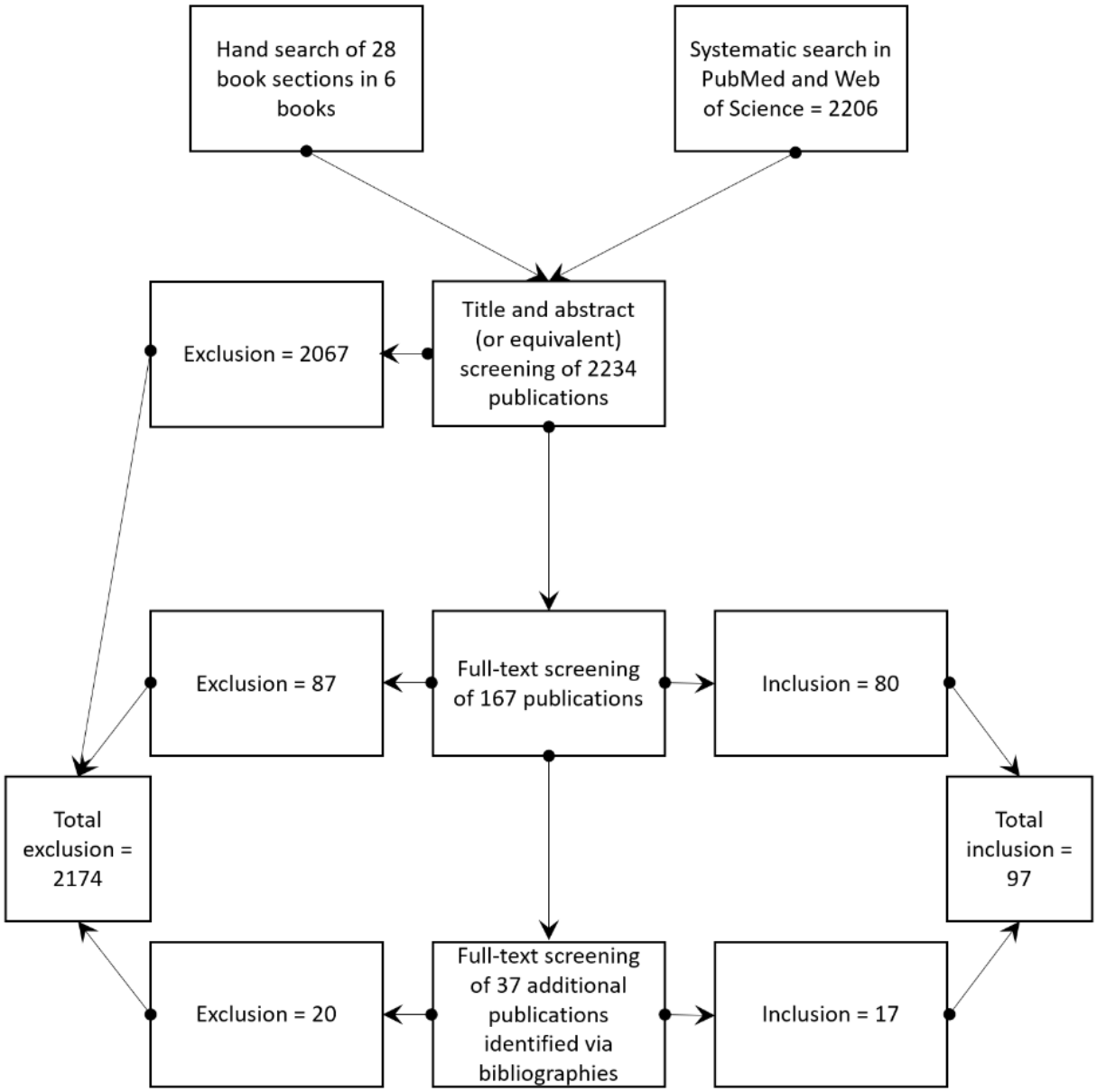

Abbildung 1 Identifikation der relevanten Literatur. Aus: Rach C, Lukas J, Muller R, Sendler M, Simon P, Salloch S. Involving Patient Groups in Drug Research: A Systematic Review of Reasons. Patient Preference and Adherence. 2020;14:587-97

2.3. Qualitative Befragung von Mitgliedern einer Patientenorganisation

Nach Analyse der moralischen Grundlage und der aktuellen Argumentationen im wissenschaftlichen Diskurs wurde geschlussfolgert, dass die Darstellung der Interessen und Bedürfnisse ihrer Mitglieder nicht nur aus normativer Begründung eine Kernaufgabe von Patientenorganisationen darstellt, sondern auch ein integraler Bestandteil für die Schaffung von Mehrwert in wissenschaftlicher Arbeit ist. Um ihre Aufgaben suffizient erfüllen zu können, ist es notwendig, dass Patientenorganisationen die Interessen und Bedürfnisse ihrer Mitglieder kennen. Dabei kommt der persönlichen Betroffenheit („experiential expertise“ oder „lived experience“) – wie die vorangegangenen Erkenntnisse bestätigt haben – eine Schlüsselrolle zu.

Mittels semistrukturierter qualitativer Interviews (35) mit Mitgliedern der Patientenorganisation „Deutsche Pankreashilfe e.V.“ wurde diese patienteneigene Ressource bezogen auf die Krankheit der hereditären Pankreatitis erhoben. Um dem Charakter dieser chronischen Erkrankungen besser erfassen zu können, wurden bei der Erstellung der Interviewfragen die Konzepte „biographical disruption“ (17) und „biographical contingency“ (18) berücksichtigt. Die etablierte Methode der qualitativen Inhaltsanalyse nach Mayring (34) wurde auch hier zur Analyse der Interviews angewandt.

3. Ergebnisse

3.1. Kollektive Verantwortung als Bezugspunkt in Situationsanalysen

Die kollektive Verantwortung von Patientenorganisationen kann anhand von vier Bezugspunkten verdeutlicht werden: Das Subjekt, das Objekt, die Adressat:innen und die zugrunde liegenden, normativen Standards. Als Subjekt werden die Patientenorganisationen beschrieben, die aufgrund ihrer Intentionalität und Handlungsfähigkeit als eigenständige, moralisch handelnde Akteur:innen betrachtet werden können. In beiden Aspekten überwinden Patientenorganisationen dabei Limitationen von Individuen: Ihre Intentionalität formt sich aus den kollektiven Bedürfnissen ihrer Mitglieder und ihre Handlungen sind aufgrund der Kollektivität wirkmächtiger. Bei dem Objekt handelt es sich übergeordnet hauptsächlich um die Vertretung der Interessen ihrer Mitglieder, welche die Daseinsberechtigung der Organisationen darstellt. Daneben gibt es noch einige andere Rollen bzw. Aufgaben, die von Patientenorganisationen übernommen werden können; darunter fallen z. B. die Edukation und der Beistand ihrer Mitglieder. Insoweit sich eine Organisation diesen

Aufgaben verschreibt, sollte sie sich auch dafür verantwortbar zeigen. Die Mitglieder der Patientenorganisationen sind die primären Adressat:innen ihres Wirkens. In manchen Kontexten können jedoch auch Patient:innen anderer Erkrankungen profitieren, zum Beispiel wenn bei genetischen Krankheiten Grundlagenforschung grundsätzlich gefördert wird. Durch die Repräsentation von Minderheiten profitiert zudem die Gesellschaft insgesamt durch die Diversifizierung und Pluralisierung. Das Handeln von Patientenorganisationen orientiert sich an den zum jeweiligen Zeitpunkt aktuellen, allgemeingültigen Normen und wird durch rechtliche und politische Rahmenbedingungen im Wirkbereich beeinflusst.

Die Nutzung dieses Modells eignet sich für Patientenorganisationen nicht lediglich zur retrospektiven Analyse, sondern insbesondere zur prospektiven Ausrichtung von Verantwortung und zur Entscheidungsfindung bei individuellen Fragestellungen.

3.2. Systematische Übersicht der in der Literatur vorhandenen Argumente zur Beteiligung von Patientenorganisationen an Arzneimittelforschung

Die Verantwortung von Patientenorganisationen wird zunehmend von anderen Akteuer:innen im Gesundheitswesen und der Wissenschaft erkannt und bei der Durchführung eigener Aktivitäten beachtet. Besonders für die Einbeziehung in der Entwicklung neuer Arzneimittel gibt es in der wissenschaftlichen Literatur bereits zahlreiche Argumente. Passend zu der kollektiven und zukunftsorientierten Verantwortung von Patientenorganisationen handelt es sich bei der Arzneimittelforschung um langfristig angelegte und auf gesellschaftlichen Nutzen ausgerichtete Projekte, sodass die Involvierung von Patientenorganisationen naheliegt. In unserer systematischen Übersichtsarbeit fanden wir in 97 Publikationen insgesamt 124 Argumente bezüglich einer Einbeziehung von Patientenorganisationen in Arzneimittelforschung. Ein Großteil der Publikationen bezog sich auf seltene Erkrankungen. Zudem hatten die Artikel überwiegend einen naturwissenschaftlichen Hintergrund und deutlich seltener eine geisteswissenschaftliche Perspektive. Von den Argumenten wurde eine Mehrheit von fast drei Vierteln als befürwortende Argumente genutzt, während weniger als ein Viertel ablehnend verwendet wurden. Ein geringer Anteil (2,4%) wurde ambivalent genutzt. Eine thematische Gliederung der Argumente gelang in sechs Oberkategorien („Ressourcen“, „Vernetzung“, „Wissenschaft“, „Patient:innen-Community“, „Ethik“ und „gesellschaftliche Wirksamkeit“) und zahlreichen Unterkategorien. Korrelierend zur oben beschriebenen Verteilung der

Perspektiven der Autor:innen fanden sich die meisten Argumente in der Kategorie „Wissenschaft“.

Diskussionen mit Argumenten auf beiden Seiten ergaben sich vor allem bei Fragen bezüglich moralischer Verpflichtungen, Patient:innen in Arzneimittelforschung zu integrieren. Befürwortende Argumente stellten epistemische Gerechtigkeitsaspekte in den Vordergrund, während kritische Argumente einen Missbrauch bzw. eine Instrumentalisierung der Patientenorganisationen seitens der Pharmaindustrie fürchteten. Zudem wurde die Fähigkeit von Patientenorganisationen, wissenschaftlichen Mehrwert zu erzeugen, unterschiedlich eingeschätzt. Teilweise wurde die Position vertreten, dass Patient:innen als Laien im wissenschaftlichen Umfeld einen Störfaktor darstellen und Ergebnisse verzerren könnten; weit häufiger jedoch ließ sich das Argument, dass „experiential expertise“ eine patienteneigene und gewinnbringende Informationsquelle ist, finden.

3.3. „Experiential expertise“ nutzbar machen

Zur Erhebung der „experiential expertise“ können Patientenorganisationen ihre Mitglieder mittels qualitativer Interviews befragen. Damit können sie, sofern sie sich dafür entscheiden, konkrete, wissenschaftliche Daten in patientenzentrierter Forschung beitragen. Insbesondere bei den subjektiv am stärksten erlebten Belastungsbereichen bei Betroffenen einer seltenen Erkrankung gibt es wissenschaftlich nutzbare Daten, für deren Erhebung Patientenorganisationen prädestiniert sind. In Zusammenarbeit mit der Patientenorganisation „Deutsche Pankreashilfe e.V.“ erprobten wir die Erhebung solcher Daten. Zu diesem Zwecke wurden insgesamt 24 qualitative Interviews mit an hereditärer, chronischer Pankreatitis Erkrankten (17) und deren Angehörigen (7) geführt, bis eine theoretische Sättigung erreicht wurde.

Dabei wurden vier Kernthemen identifiziert, die für Patient:innen und ihre Angehörigen andauernde, krankheitsbezogene Belastungsbereiche darstellten. Dabei handelte eines von der Krankheitsschwere in akuten Krankheitsphasen („vernichtende Erfahrungen“), während sich die anderen drei („unvorhersehbarer Krankheitsverlauf“, „Integration der Krankheit ins normale Leben“ und „Reduzierung auf die Krankenrolle“) um Unsicherheiten bezüglich des Krankheitsverlaufs, der autobiographischen Integration und sozialer Konsequenzen in Phasen der Remission drehten. Aus allen vier Themen lassen sich mögliche Forschungsfragen ableiten, deren Beantwortung

den Betroffenen einen Zuwachs an Lebensqualität geben könnte. Bezüglich des unvorhersehbaren Verlaufs wäre beispielsweise die Kenntnis über mögliche Triggerfaktoren von akuten Phasen hilfreich; die Entwicklung von symptomatischen Therapien in akuten Phasen dagegen wäre hilfreich, um die belastenden Erlebnisse, die durch die hohe Symptomlast bedingt werden, zu reduzieren. Forschungen zur Gestaltung geeigneter Informations- und Aufklärungsmaterialien sowohl für Betroffene als auch für medizinisches Personal und die breite Öffentlichkeit könnten eine günstige Sicht der Betroffenen auf die eigene Krankenrolle fördern bzw. die Stigmatisierung durch Außenstehende verringern.

Diese Beispiele illustrieren anschaulich, wie insbesondere bei Krankheiten ohne kurativen Ansatz „experiential expertise“ bei der Entwicklung von Forschungsprojekten genutzt werden kann, um bestmögliche Ergebnisse zu erzielen und die Situation der Erkrankten positiv zu beeinflussen.

4. Diskussion

Betrachtet man das Verhalten von Patientenorganisationen gemäß dem oben beschriebenen Konzept unter besonderer Berücksichtigung der Norm Gerechtigkeit, lässt sich feststellen, dass sich durchaus Widersprüche ergeben. Viele Betroffene von seltenen oder stigmatisierten Erkrankungen sehen sich von der Forschung benachteiligt (36). In Bezug auf diese Adressat:innen ergibt sich also der Auftrag, die wissenschaftliche Evidenz hinsichtlich dieser Erkrankungen zu erweitern. So wird einer Vernachlässigung dieser Patient:innen im Vergleich zu Betroffenen von häufigen Erkrankungen entgegengewirkt. Jedoch gibt es viele verschiedene, seltene Erkrankungen mit unterschiedlich stark entwickelten und teils inexistenten Patientenorganisationen. Betroffene von seltenen Erkrankungen ohne starke, organisierte Repräsentation sind also im Nachteil gegenüber denen, die auf eine Patientenorganisation zurückgreifen können. Im globalen Kontext betrifft dies vor allem Patient:innen in Entwicklungs- und Schwellenländern, in denen Patientenorganisationen weniger stark vertreten bzw. weniger einflussreich sind. Eine ungerechte Verteilung von Forschungsaktivitäten und -ressourcen findet sich aus diesem Grunde auch als Argument gegen eine Zusammenarbeit zwischen Wissenschaftler:innen und Patientenorganisationen (37, 38). Ein weiteres Problem stellen Krankheiten dar, die so heterogen sind, dass sich keine entsprechenden Patientenorganisationen bilden. Hinsichtlich bakterieller Infektionskrankheiten ist

beispielsweise ein dringlicher Forschungsbedarf seit Jahren bekannt, da die Resistenzen der Keime rasch zunehmen (39, 40). Aus wirtschaftlicher Perspektive ist die Antibiotikaforschung für die pharmazeutische Industrie weitgehend unattraktiv. Aus diesem Grunde handelt es sich umso mehr um eine gesundheits- und wissenschaftspolitische (und in Deutschland bisher vernachlässigte) Aufgabe, diesen hoch relevanten Forschungsbereich effizient voranzutreiben. Eine starke Forderung nach entsprechenden Projekten seitens Patientenorganisationen wäre daher dringend notwendig, insbesondere in Hinblick auf die Gesundheit zukünftiger Patient:innen.

In der COVID-19-Pandemie sind die beiden genannten Probleme allzu deutlich geworden. Bürger:innen des globalen Südens haben signifikant seltener Zugang zu Impfstoffen, erkranken häufiger schwer an COVID-19, leiden überdurchschnittlich stark an den Symptomen und Folgen der Erkrankung und werden öfter zu „Long Covid“-Patient:innen (41). Wenngleich es nicht zu den Kernaufgaben von Patientenorganisationen gehören kann, Konflikte der Verteilungs- und Generationengerechtigkeit zu lösen, zeigen diese Beispiele doch die Limitationen der kollektiven und zukunftsgewandten Orientierung von Patientenorganisationen, die mit dem von uns entwickelten Modell analysiert werden kann. Zugleich wird die persönliche Betroffenheit als Dreh- und Angelpunkt der Patientenorganisationen illustriert. Durch den Zusammenschluss in überregionalen bzw. internationalen Dachverbänden können Gerechtigkeitsfragen bereits bearbeitet werden, die Bildung einer globalen Perspektive steht jedoch noch aus.

Bei Anwendung des Modells lässt sich zudem feststellen, dass es gegenüber Betroffenen gerecht ist, wenn sie bzw. ihre Repräsentant:innen in Entscheidungsprozesse, deren Ergebnisse ihre Leben auf absehbare Zeit beeinflussen werden, eingebunden werden. Dieses Argument lässt sich als epistemische Gerechtigkeit zusammenfassen und fand sich in unserer systematischen Übersichtsarbeit in der Literatur als Argument für eine Zusammenarbeit zwischen Forscher:innen und Patient:innen (14).

Neben diesen normativ begründeten Anreizen für eine Zusammenarbeit zwischen Patientenorganisationen und Wissenschaftler:innen gibt es zahlreiche weitere Argumente für eine Einbeziehung von Patientenorganisationen in Forschung (42).

Besonders bei Erkrankungen, für die auf absehbare Zeit keine kurativen Behandlungsmöglichkeiten zur Verfügung stehen werden, ist die die Erhebung der relevanten Belastungsbereiche mittels Nutzung der „experiential expertise“ sinnvoll.

So können, wie eingangs an den Beispielen Alkoholabhängigkeit und AIDS illustriert, Forschungsfelder mit hohem Potenzial, die Lebensqualität der Betroffenen zu verbessern, erschlossen werden. Dieser Ansatz wirkt zugleich dem Risiko, das von wirkungslosen oder gar gesundheitsschädlichen Therapien ausgeht, entgegen.

Bei schwerwiegenden Erkrankungen ist der Wunsch der Betroffenen nach Therapeutika oft groß und ein frühzeitiger Zugang zu Neuentwicklungen wird von ihnen bisweilen eingefordert (43). Die Sicherheit der Medikation, insbesondere in Bezug auf mögliche Langzeitschäden, kann zu diesem Zeitpunkt nicht abschließend gewährleistet werden. Eine Freigabe der Medikation steht damit dem Prinzip der Schadensvermeidung, welches im Ethos von medizinischem Personal verankert ist, entgegen. Das Prinzip der Schadensvermeidung gerät dabei in einen Konflikt mit dem Prinzip der Patientenautonomie und zum Teil auch dem Prinzip der Fürsorge (44). Das Dilemma wird bei neuartigen Erkrankungen mit Auswirkungen auf die breite Gesellschaft wie AIDS oder COVID-19 besonders evident (45, 46).

Bei phasenweise verlaufenden Erkrankungen kann zudem zur Nutzung der „experiential expertise“ ergänzend das „shifting perspective“-Modell (47) herangezogen werden, um die Lebenswirklichkeit und die relevanten Belastungsbereiche von Betroffenen besser zu verstehen. Dabei zeigt sich, dass das Leben von Betroffenen chronischer, phasenweise verlaufender Erkrankung nicht linear in einen gesunden Lebensabschnitt vor Ausbruch der Erkrankung und einen kranken Lebensabschnitt nach Ausbruch der Krankheit eingeteilt werden kann. Vielmehr handelt es sich um bei der Haltung zur eigenen Krankheit um einen sich immer im Wandel befindlichen Prozess. In Phasen der Remission fühlen sich Erkrankte durchaus gesund, werden mitunter jedoch als krank stigmatisiert. Insbesondere die Stigmatisierung durch medizinisches Personal, welches sich nach Erfahrung der Betroffenen häufig auf die chronischen Erkrankungen fokussieren und dabei andere Anliegen der Patient:innen vernachlässigen, wird als unangenehm erlebt. Hier könnte langfristig eine grundlegende Umstrukturierung des Gesundheitssystems bzw. ein Dogmenwechsel in der Ausbildung medizinischer Fachkräfte weg von der Orientierung an Krankheiten und Defiziten und hin zu personenzentrierter, individualisierter Medizin Abhilfe schaffen. Patientenorganisationen würden hierbei bei der Mediation zwischen Fachpersonal und Betroffenen eine Schlüsselrolle einnehmen; nicht nur in Bezug auf Forschungsaktivitäten, sondern insbesondere auch bei Hilfsangeboten. Nebst dem Beitrag der Evidenz der „experiential expertise“ ergeben sich für

Patientenorganisationen weitere Möglichkeiten, Forschungsumfelder attraktiver zu gestalten und somit Forschung deutlich zu erleichtern bzw. zu verbessern.
Neben Förderungen von wissenschaftlichen Kooperationen durch Vernetzungsarbeit helfen sie konkret bei der Planung und Durchführung von Studien, der Auswertung der erhobenen Daten, der Mobilisierung von Studienteilnehmer:innen und der Erschließung von Finanzierungsmitteln. Die genannten Beispiele sprechen zweifelsohne für eine Stärkung der Zusammenarbeit von Patient:innen und Wissenschaftler:innen, die bereits vorangetrieben wird (4, 48). Bei einer gesamtheitlichen Betrachtung des Phänomens sollten jedoch auch möglicherweise entstehende Nachteile bzw. Gegenargumente, die sich konkret auf kollaborative Prozesse in Forschungsprojekten beziehen, nicht außer Acht gelassen werden und nach Möglichkeit beim Vorbereiten einer Zusammenarbeit berücksichtigt werden (42). Wenngleich also die Einbeziehung von Patientenorganisationen in Forschungsvorhaben prinzipiell zu befürworten ist, ist eine behutsame Planung zur Erzielung des maximalen Nutzens dringend anzuraten. Welche Aspekte für ein Forschungsprojekt besonders relevant sind und näherer Betrachtung bedürfen, sollte individuell und situativ entschieden werden (42).

5. Inhaltsangaben der drei Publikationen

Artikel 1: Collective forward-looking responsibility of patient advocacy organizations: conceptual and ethical analysis

In diesem Artikel wurde der Charakter von Patientenorganisationen hinsichtlich ihrer Verantwortung gegenüber ihren Mitgliedern und der Gesellschaft erörtert. Es wurde angenommen, dass die Organisationen ihre Mitglieder (und andere, an der gleichen Krankheit Erkrankte) gesammelt repräsentieren und damit eine höhere Tragweite erreichen, als es Individuen möglich wäre. Weiterhin wurde argumentiert, dass diese Wirkmacht unter Beachtung allgemeingültiger Normen, bspw. Wohltun, Autonomie und Gerechtigkeit, eingesetzt werden sollte, um die Zukunft der Repräsentierten positiv zu beeinflussen.
Auf Boden dieser Überlegungen wurde ein Werkzeug zur Situationsanalyse und Handlungsplanung für Patientenorganisationen als moralisch handelnde Akteur:innen entwickelt. Insbesondere bei möglicherweise konfliktträchtigen Interaktionen mit anderen Akteur:innen, wie z. B. Vertreter:innen aus Industrie, Politik oder Forschung, dient das angebotene Modell als Entscheidungshilfe.

Artikel 2: Involving Patient Groups in Drug Research: A Systematic Review of Reasons

Auf Grundlage der im vorangegangenen Artikel identifizierten, moralischen Verantwortung von Patientenorganisation wurde eine systematische Übersichtsarbeit zur Auflistung der bereits in der Fachliteratur vorhandenen Argumente für eine Zusammenarbeit von Forschung und Patientenorganisationen erstellt. Zur Schärfung der Forschungsfrage wurde dabei explizit Arzneimittelforschung betrachtet. Wenngleich stark überwiegend Argumente für eine Zusammenarbeit – darunter häufig die oben beschrieben Verantwortung, Vorteile für Patient:innen zur erreichen – gefunden wurden, wurden auch mögliche, negative Effekte einer solchen beschrieben – sowohl aus Sicht der Forschung als auch aus Sicht der Patientenorganisationen.

Eines der häufigsten Argumente war die Einbeziehung von „experiential expertise“ (subjektive Erfahrungen von Patient:innen) in den Forschungsprozess. Besonders häufig wurde eine Zusammenarbeit im Kontext seltener Erkrankungen gefordert.

Artikel 3: Lived Experience of Hereditary Chronic Pancreatitis – A Qualitative Interview Study

Diesem Artikel liegt eine qualitative Interviewstudie zugrunde, in der die subjektiv am stärksten erlebten Belastungsbereiche bei Betroffenen einer seltenen Erkrankung erhoben werden. Im Zuge dessen wurden mögliche Herangehensweisen für konkrete Informationserhebungen durch Patientenorganisationen, die sich gemäß den Erkenntnissen der vorherigen beiden Arbeiten ob der moralischen Verantwortung und den patientenspezifischen Ressourcen gebietet, erprobt. Zu diesem Zwecke wurden qualitative Interviews mit an hereditärer, chronischer Pankreatitis Erkrankten und deren Angehörigen geführt, bis eine theoretische Sättigung erreicht wurde.

Vier Kernthemen wurden identifiziert. Dabei handelte eines von der Krankheitsschwere in akuten Krankheitsphasen, während sich die anderen drei um Unsicherheiten bezüglich des Krankheitsverlaufs, der autobiographischen Integration und sozialer Konsequenzen in Phasen der Remission drehten. Die Ergebnisse deuten darauf hin, dass neben der Behandlung somatischer Symptome in den akuten Krankheitsphasen ein Ausbau der Psychoedukation und der gesellschaftlichen Aufklärungsarbeit einen signifikanten Beitrag zur Senkung der Krankheitslast leisten könnte und entsprechend mehr Forschung in diesem Bereich sinnvoll wäre.

6. Zusammenfassung

Die vorliegende Dissertationsarbeit analysiert die Verantwortung von Patientenorganisationen gegenüber ihren Mitgliedern und die sich daraus ergebenden Handlungsmotive.

Als zentrale Elemente erweisen sich dabei die Möglichkeiten, individuelle Krankheitserfahrungen ihrer Mitglieder zu erfassen und eine vermittelnde Rolle zwischen Patient:innen und Forschenden bzw. medizinischem Fachpersonal einzunehmen. Individuelle Krankheitserfahrungen (in der Fachliteratur überwiegend als „experiential expertise“ bekannt) stellen besonders bei chronischen und nicht heilbaren Erkrankungen eine wichtige Ressource dar. Wissenschaftliche Fortschritte, die die Krankheitslast senken und die Lebensqualität der Betroffenen erhöhen, hängen maßgeblich von dieser Ressource ab. Zugleich sind Betroffene von chronischen und nicht heilbaren Erkrankungen häufig durch starke Patientenorganisationen vertreten. Aus diesem Grunde handelt es sich bei Patientenorganisationen um die idealen Akteurinnen, um „experiential expertise“ gewinnbringend in Forschungsaktivitäten einzubringen.

Dabei werden Patientenorganisationen aufgrund der bei ihnen vorhandenen Eigenschaften Intentionalität und Handlungsfähigkeit als eigenständige, moralisch handelnde Akteurinnen identifiziert. In beiden Aspekten überwinden Patientenorganisationen Limitationen von Individuen: Ihre Intentionalität formt sich aus den kollektiven Bedürfnissen ihrer Mitglieder und ihre Handlungen sind aufgrund der Kollektivität wirkmächtiger.

Die Anwendungsrelevanz der vorgenannten Erkenntnisse wurde im Rahmen dieser Dissertation mittels einer qualitativen Interviewstudie mit an chronischer Pankreatitis erkrankten Mitgliedern der Patientenorganisation „Deutsche Pankreashilfe e.V.“ bestätigt. Die Ergebnisse zeigen, dass bei dieser nicht heilbaren und phasenweise verlaufenden Erkrankung, abseits der Behandlung der akuten Krankheitsphasen, ein Ausbau der Psychoedukation und gesellschaftlicher Aufklärungsarbeit einen signifikanten Beitrag zur Senkung der Krankheitslast leisten könnte.

Die vorliegende Dissertation liefert eine ethische Argumentation zur Nutzung des Potenzials von Patientenorganisationen zur langfristigen Verbesserung der Lebensqualität ihrer Mitglieder. Weitere Forschung ist notwendig, um eine praxisorientierte Umsetzung der Erkenntnisse bei hoher Heterogenität von Krankheiten und Patientenorganisationen zu ermöglichen.

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Collective forward-looking responsibility of patient advocacy organizations: conceptual and ethical analysis

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Abstract

Background: Patient advocacy organizations (PAOs) have an increasing influence on health policy and biomedical research, therefore, questions about the specific character of their responsibility arise: Can PAOs bear moral responsibility and, if so, to whom are they responsible, for what and on which normative basis? Although the concept of responsibility in healthcare is strongly discussed, PAOs particularly have rarely been systematically analyzed as morally responsible agents. The aim of the current paper is to analyze the character of PAOs' responsibility to provide guidance to themselves and to other stakeholders in healthcare.

Methods: Responsibility is presented as a concept with four reference points: (1) The subject, (2) the object, (3) the addressee and (4) the underlying normative standard. This four-point relationship is applied to PAOs and the dimensions of collectivity and prospectivity are analyzed in each reference point.

Results: Understood as collectives, PAOs are, in principle, capable of intentionality and able to act and, thus, fulfill one prerequisite for the attribution of moral responsibility. Given their common mission to represent those affected, PAOs can be seen as responsible for patients' representation and advocacy, primarily towards a certain group but secondarily in a broader social context. Various legal and political statements and the bioethical principles of justice, beneficence and empowerment can be used as a normative basis for attributing responsibility to PAOs.

Conclusions: The understanding of responsibility as a four-point relation incorporating collective and forward-looking dimensions helps one to understand the PAOs' roles and responsibilities better. The analysis, thus, provides a basis for the debate about PAOs' contribution and cooperation in the healthcare sector.

Keywords: Patient groups, Collectives, Patient representation, Patient involvement, Bioethics

Background

Patient advocacy organizations (PAOs) have increased in their number and social visibility over the last few decades [1–3]. There are pragmatic reasons for joining forces: Individuals together have more power and better opportunities to advocate for their specific interests than alone. However, there are also moral reasons for joining a PAO, such as helping each other and campaigning for justice. Looking at the common goals and tasks of PAOs, normative values such as justice and ethical motives such as empowerment become apparent. This shows that PAOs are not only active in advocacy, but also cover ethical issues. Moreover, their activities are subject to ethical evaluations and linked with ethical concepts, such as responsibility. The involvement of PAOs in biomedical research [1, 2, 4, 5], politics [6] and industry [7, 8], for example, is seen as controversial and raises questions about the general character of their responsibility.

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Since PAOs are confronted with normative questions of responsibility in these exemplary fields of activity, they are expected to respond. However, it is not always clear for what, to whom and on which basis PAOs are responsible given the complex healthcare systems within which they operate.

The aim of the current paper is to analyze PAOs' moral responsibility to provide guidance not only to themselves but also to political, scientific and industrial stakeholders. Responsibility is presented as a concept with four reference points: (1) The subject, (2) the object, (3) the addressee and (4) the underlying normative standard. This four-point relationship is applied to PAOs and the dimensions of collectivity and prospectivity are analyzed in each reference point.

Patient advocacy organizations

Characteristics and missions

There is a great variety of PAOs [1, 3]. They differ in size, organizational structure, level of professionalization, strategy and financial capacity. There are groups operating at the local level, while others have an international scope. Several groups are working across diseases; other groups are condition-specific [9]. Despite the diversity of the groups, many definitions describe typical attributes for PAOs, such as their nongovernmental, nonprofit and patient-driven character [1, 3, 9, 10]. The PAOs are often defined as "[…] not-for-profit organisations which are patient focused, and where patients and/or carers […] represent a majority of members in governing bodies" [11]. They usually aim at strengthening the voice of affected and sometimes overlooked individuals, and ensure that their interests are recognized [1, 3, 10]. The contribution of PAOs can, therefore, be seen as "[…] representing and voicing the situation of a specific population that would otherwise not be represented" [9]. The groups pursue this mission in various ways. Their activities cover, inter alia, interacting with patients, educational activities [9], promotion of research [2, 10] and engaging in policy and industry [7, 8]. The PAOs often bring together not only those directly affected but also related families, interested individuals, groups concerned with similar problems and professionals.

The shared mission of PAOs to advocate for those affected has its major roots in the experience of injustice, as many PAOs represent, for example, patient groups or diseases that are under-recognized, such as orphan diseases [1, 3]. Consequently, a core normative value that characterizes the work of PAOs is social justice. Moreover, the wish to help each other can be a strong motivator for affected individuals to initiate or join a PAO. Mutual support is, therefore, a further normative value strongly represented by PAOs. In addition, the normative ideal of empowerment can be found in many PAOs, for example, in statements such as 'Strengthening the patient's voice' (for instance: the 'Strengthening Patient Voices project' by the Meningitis Research Foundation). Looking at the core values of the PAOs, the principles of justice, beneficence and empowerment (as one key aspect of autonomy) crystallize. These moral dimensions of the PAOs' work, together with their non-profit and patient-focused character, distinguish PAOs from other organizations in healthcare, such as research institutions, professional bodies or insurances.

In contrast to profit-oriented or politically managed organizations, PAOs can be classified as civil society organizations (CSOs) due to the mentioned dimensions and characteristics. CSOs can generally be defined as non-governmental actors, varying from activists, small community-based groups and informal movements to highly organized institutions and international organizations or networks [12]. One common goal of CSOs is to participate in or influence (health) policy [13, 14] and research [15] on behalf of citizens or socially and economically disadvantaged groups, for example, women, persons with disabilities or migrants [16]. Due to their independence from direct governmental management, their non-economic aims and their voluntary and bottom-up way of working [11], PAOs and CSOs have much in common. However, as CSOs work on a wide-ranging scope of themes, from environment and trade to human rights, PAOs work in the context of healthcare and are motivated by the specific needs and values of patients.

Challenges

The PAOs are confronted with internal and external challenges in their various fields of action and face multifaceted ethical issues. Many activities, for example, confront them with ethical questions regarding representativeness. The criteria which qualify one or more persons to represent a group are not clearly defined and PAOs typically represent various interests simultaneously, for example, of patients and families [17–19]. Additionally, PAOs need to maintain a balance between professionalization and representativeness. More intensive contact with healthcare professionals or companies is often accompanied by less time for the PAO members and eventually can result in a loss of contact with the grassroots [9]. This is accompanied by the risk that the PAOs may decide and act independent of their members and lose sight of their interests. The question of the extent to which individual patients or members can and should participate in the collective decision-making is challenging for each PAO and needs to be addressed at the level of the PAOs' decision-making structures. The distribution of resources,

tasks and responsibilities within PAOs can lead to difficult processes.

Such ethical issues arising *within* a PAO are accompanied by ethical questions occurring *between* different PAOs and other stakeholders. The involvement in politics [6] and research [4, 5] and the cooperation between PAOs and economic stakeholders [7, 8, 20] can sometimes be problematic. Building financial relationships with industrial companies, for example, can help PAOs to pursue their goals [21] but might lead to pressure to conform to the funder's interests [20, 22]. Many organizations have committed themselves to support research. However, PAOs that want to foster biomedical research face many ethical questions, such as the extent to which they should encourage their members to participate in a study or the extent to which the specific interests of the PAO should influence the research designs [4]. Another problem for PAOs can be that external cooperation, for example, with politicians, might be characterized by tokenism [9]. Finally, given the missing access to independent and adequate resources for PAOs [9], questions regarding the fair distribution of resources arise.

These are exemplary challenges showing that PAOs are faced with various ethical questions regarding their internal structures and external activities. Focusing on these ethical issues makes the moral character of PAOs' activities more transparent. When confronted with decisions of ethical significance, justifications of their activities and their implications are required from PAOs: Their actions are then subject to ethical evaluations and linked with the concept of moral responsibility. For example, if a PAO wants to advance biomedical research and is partnering with an economic stakeholder to achieve this goal, this PAO should be able to explicate how many funds the PAO accepts from the economic stakeholder to promote that research. By being able to answer such questions, the PAO demonstrates how it acts in a responsible manner regarding these activities.

Moral responsibility

There are numerous definitions of moral responsibility [23–25], for example, backward- or forward-looking accounts [26] and collective [27–32] or individual approaches [33]. The concept of responsibility in healthcare and medicine has long been discussed [34], for example, different models of responsibility in bioethics [24], the individuals' responsibility for their own health [33, 35, 36], and collective responsibility in healthcare [37–39]. The diversity of literature on responsibility makes it almost impossible even to provide a systematic overview of the main argumentative lines of the discourse. However, responsibility can be generally understood as both a causal and a normative relation [35]. Causal responsibility merely means that somebody (or something) has caused something, whereas the attribution of the consequences remains a descriptive act [23]. In the context of PAOs, the second meaning, responsibility as a normative relation, is of interest. In this meaning, "[…] responsibility refers to the demand on a person or an institution to justify its action or actions towards another person or institution" [35]. The conditions for moral responsibility, for example, free will, are controversial. However, widespread agreement exists on the following key traits: To describe an agent as responsible for an action means that this agent fulfils some epistemic conditions and conditions of control [33]. The agent must have a certain degree of awareness of the consequences of his/her action, including an understanding of their moral significance, and sufficient control over his/her action [33].

Wrongdoings are the typical occasions for asking about responsibility and the respective debates usually refer to the attribution of harm that one individual did to another individual. However, such an individualistic, negative and backward-looking understanding of responsibility does not fully meet the circumstances of PAOs' engagement. Their activities have a collective character, do not usually focus on specific tasks but on a broad thematic issue and their orientation is prospective. Consequently, the dimensions of collectivity and prospectivity could be more appropriate for PAOs' responsibility than the often-used conditions of individuality and retrospectivity.

Collective dimension

Collective responsibility covers situations in which more than one individual can be seen as responsible for something. The responsibility is spread to (members of) a group instead of being bound to one individual [28]. Since many agents in the healthcare system, for example clinics or the medical professions, are groups to which the concept of individual responsibility does not fit, the concept of collective responsibility allows to make sense of collectives in healthcare without having to abandon the notion of individual responsibility. Moreover, modern medical technologies, such as human-machine cooperation, require a reflection on the collective dimension of responsibility in healthcare [40]. If healthcare systems should remain an area in which morality is a relevant factor, a way must be found to make the moral responsibility of these associations understandable. PAOs are only one of several groups that are operating in the healthcare system.

However, since the concept of collective agency and collective responsibility turns groups, as opposed to their individual members, into moral agents, it has been strongly scrutinized both methodologically and normatively in recent years [31]. Despite the comprehensive

research, collective responsibility remains a contentious concept, since it is still unclear whether collectives can become (moral) agents and how collective action and intention are possible at all [27–32, 41–43].

If it is assumed that collectives can bear responsibility, the subsequent question is: how, if at all, can that responsibility be shared within the collective [28]. Some theorists argue that responsibility can only be constructed in individual terms. According to this position, the "responsibility of the group" is merely aggregated individual responsibility and the individuals in the group remain the responsible subjects [28]. The opposite opinion claims, that there is a responsibility of the group on its own and that this responsibility cannot be reduced to the individuals forming the group [28]. Peter A. French, for example, argues that collective responsibility does not entirely consist of or is exhausted by the individuals within the collective [37]. There are not only these binary counterparts, but also other models and many positions in between [39]. The current paper seizes the dispute between these two sides by examining whether a collective dimension is helpful when considering PAOs' responsibility.

Prospective dimension

The classical literature on responsibility usually refers to backward-looking concepts: Much of the literature focuses, for example, on responsibility as guilt [44, 45], accountability [46, 47] and liability [29, 48]. More recent accounts, on the contrary, often draw on forward-looking approaches [49, 50]. Retrospective (or backward-looking) responsibility covers something an agent has done (or omitted to do) and its consequences. It concerns activities in the past. Prospective (or forward-looking) responsibility refers to future activities, often to the occurrence (or prevention) of certain states, and means responsibility for something that is not yet the case [50]. The agent is not obliged to act in a concrete way but to behave in a way that is promoting a certain state. Forward-looking responsibility is often linked with backward-looking responsibility, but the relationship between these two types is controversially discussed [26].

The current paper focuses on the future-oriented dimension because this dimension seems more appropriate for the PAOs' advocacy role and their caring activities. The character of PAOs' goals are usually to change something for a better future, such as improving patient care or raising public awareness of a certain disease. The typical tasks of a PAO, such as policy, education and promoting research and development, are activities aimed at improving the conditions for the individuals affected. As PAOs usually take care of these issues voluntarily and in a patient-driven way, this article sheds light on the caring and future-oriented activities of the PAOs.

Responsibility as a relational concept

As has been mentioned above, in the context of PAOs, the meaning of responsibility as a normative relationship is of interest. Understood as a normative relationship, responsibility manifests in relations between different reference points (relata). Due to various possible relata, the relational understanding is a useful analytical tool to analyze the complex field of PAOs' activities. Although there are concepts using up to six [35] or seven [24] reference points, the following four relata seem—in the view of the authors—at least necessary for moral responsibility: Someone (the subject) is responsible to somebody (the addressee) for something (the object) regarding normative criteria. This four-point relationship will be applied to PAOs, each of the relata will be discussed, and the dimensions of collectivity and prospectivity in each reference point will be analyzed (Table 1).

Table 1 Relata of responsibility in the context of PAOs

Relata of responsibility	Context of PAOs	Dimension of collectivity	Dimension of prospectivity
Subject	PAOs	PAOs as collectivities capable of intentionality, acting and moral responsibility	Long-term structures and far-reaching goals of PAOs
Object	Patient representation and advocacy	Collective representation of a shared interest, respectively, an issue that is important for many people	Campaigning refers to future situations that are not yet the case
Addressee	From a specific (patient) group to others in the health sector and society	Direct benefits to the target group, understood as a collective, and collective, indirect benefits for others	Future patients and generations
Normative standard	Legal regulations; ethical guidelines and codices; ethical principles of justice, beneficence and empowerment	Standards that are the result of a shared deliberative process	Standards that show a certain degree of stability and long-term orientation

Responsibility of PAOs

The subject

The first reference point addresses the subject of responsibility and draws attention to PAOs as collectives and, therefore, to the underlying question whether collectives could be assigned moral responsibility. According to French "[…] something must, at least, be an intentional agent to be properly held morally responsible for its actions" [37]. The debates on responsibility exhibit a close systematic connection between responsibility and intentionality, but also a strong dispute about this relation [46–54]. Following French's argumentation, some collectives are capable of intentionality and can, consequently, bear moral responsibility [37].

French differentiates between aggregate and conglomerate collectivities. A collectivity can be understood as an aggregate "[…] if the identity of that collectivity consists in the sum of the identities of the persons who comprise the membership of the collectivity" [37]. An aggregate is, for example, the people standing on the corner [37]. By contrast, "[…] conglomerates are such that their identities do not entirely consist in or are not exhausted by the identities of the persons that are associated with them" [37]. The conglomerate's identity is insofar independent of its individual members as it is consistent with a (constantly) changing membership. An example is a clinic whose identity remains the same even if all employees change over time. The crucial factor is that conglomerates, in contrast to aggregates, have a decision procedure for determining group actions [37]. This decision structure transforms the individual intentions and acts into a corporate decision. According to French's argument, the decision structure provides the basis for the attribution of intentionality and, consequently, moral responsibility. In line with French's argumentation, the strategy of the current paper is to assign collective responsibility to those collectives, which have decision-making procedures, including (1) the capacities for forming intentions and (2) the capacities to act. Then, collectives qualify as moral agents and hence can be attributed moral responsibility.

Depending on their size and degree of professionalization, PAOs show the elements of French's approach. Due to the complexities of translational activities and the integration of different subgroups, larger and internationally organized PAOs are highly structured with different levels and positions, such as boards of directors, advisory committees and administration services. In addition, most PAOs have policies, often documented in statutes or mission statements, which make clear whether a decision has been made for corporate reasons. Since PAOs have structures for determining corporate decisions, they can be understood as conglomerates and, according to French's argument, fulfill the conditions of intentionality and moral responsibility.

In addition to the collective dimension of PAOs as subjects of moral responsibility, there is also a future-looking aspect. The prospective dimension of PAOs can be explained in terms of stability and persistence. The PAOs usually have long-term structures and pursue future-oriented goals. Moreover, when understood as conglomerates, the identity of PAOs remains even if the individual members change. Based on these long-term structures, the concept of PAOs as subjects of responsibility can be understood as extending into the future and, consequently, show the forward-looking dimension.

The object

If PAOs are the subjects of responsibility, what are they responsible for? One way to answer this question concerns roles. Roles are often linked to specific behavior and can, therefore, help to narrow down the scope of responsibility. However, the various roles of PAOs lead to different objects of responsibility. Involvement in research, for example, is accompanied by other responsibilities than engagement in politics. However, despite the diversity of PAOs, one mission seems to be common: "Many PAOs characterize their efforts as attempts to give patients a greater voice and ensure that patients' interests are acknowledged by those in positions of power" [10]. The PAOs typically understand themselves as advocates that represent the interests of those affected [1, 3]. This advocacy role of PAOs, although initially self-attributed, is increasingly confirmed by society and policy. The PAOs, for example, are often promoted by political organizations, such as the World Health Organization (WHO) because of their specific function to speak on behalf of patients [55, 56]. Due to this strong weighing, patients' representation and advocacy can be seen as the primary role and, therefore, as the main object of PAOs' responsibility. While this view does not yet provide concrete ethical obligations, it highlights the moral character of PAOs' engagement and can encourage them to emphasize their core values—representing patients and advocating their interests. Responsibilities that are more concrete, for example, regarding certain cooperation partners can build on these basic values.

However, there are several points to consider. Firstly, due to the diversity of the tasks (e.g. policy, education, promoting research) and several interests to be represented within a PAO (e.g. patients, families, carers), it is not straightforward to specify the patient representation by a PAO in a concrete task and it is often unclear who can represent the members of the PAO adequately [17–19]. The object of PAOs' responsibility remains to some degree unspecified because the concrete forms and

implementation of patient representation are manifold, ranging from interaction with individual patients, public communication and educational activities, to political and industry engagement. Secondly, even with such a broad topic as patient representation, a limit to the scope of PAOs' responsibility must be drawn. If issues are not covered or excluded from the domain of PAOs' responsibility, they must be moved to the area of someone else's responsibility in order not to be overlooked. For example, a PAO may set itself the mission of improving patient care for patients with a particular rare disease and, therefore, seek to raise awareness of that disease within medical education. However, it is not the role of the PAO to decide on the content of the medical education or to ensure the quality of the education. This remains the responsibility of the teaching institutions and the medical profession.

Finally, patient representation, for example in health politics, is the result of various activities of multiple agents and is only partially modifiable by PAOs. Consequently, PAOs should not be understood as being responsible for patient representation alone. Other stakeholders in health policy, for example, governments, political organizations such as the WHO and CSOs, whose remit can overlap with that of PAOs, should not be relieved of their responsibilities. For example, a PAO that advocates for a specific rare disease at the regional level and therefore has few members and resources might not be able to carry the overarching responsibility to represent all patients with rare diseases in international health policy. This would lie beyond the scope of that PAO and would instead be the task of international (political) bodies such as the WHO and CSOs advocating on a global level. On the national level, the PAO is also not responsible for the needs of these particular patients alone. National governments, health policy-making institutions, publicly funded healthcare systems and CSOs cannot transfer their responsibility to care for patients with rare diseases to the PAO. Regardless of these points, campaigning for a shared interest bears a collective dimension and since the relevant question "what needs to be done to help those affected?" refers to future activities and states, PAOs' responsibility for patient representation is also prospective in its direction.

The addressee

Having identified what PAOs are responsible for, the question of the addressee remains. Given their advocacy role, it seems acceptable that the addressee of PAOs' responsibility is primarily their targeted (patient) group. However, only considering distinct groups of patients can be too shortsighted in some situations. Issues regarding genetic contexts, for example, might go beyond the patients and affect other individuals or groups. A PAO that supports patients with a genetically determined condition and advocates for genetic testing in childhood or pregnancy should also consider the impact of such testing on families, patient groups with other genetic conditions and society. As this example shows, PAOs are frequently confronted with issues of ethical significance that not only affect their own members but also other groups. If PAOs only take the interests of a certain patient group into account, this can lead to questionable consequences for others. It is, therefore, within the responsibility of PAOs to consider the ethical implications of their activities. This means that PAOs should be committed to a wider range of addressees, however, the question inevitably arises regarding how far the scope of the addressees should extend.

In the context of health policy, for example, Onora O'Neill emphasizes that health issues cannot be restricted to limited groups but need to be considered in a broader context [57]. She claims that measures which are targeted at certain groups can, simultaneously, have collective benefits [57]. O'Neill's idea can be transferred to PAOs: They can be structured in such a way that they produce direct benefit for their defined target group and, in addition, indirect benefit for others. Exemplarily, although a PAO is committed to a specific disease, successfully (co-)funded basic research can help other and future patients. This does not mean that PAOs should override the interests of their target group. An expansion of the addressees, for example, to patients with similar conditions, always needs to be critically assessed. A crucial point is to find a balance between the group's own interests and the interests of other groups. Finding this balance can be especially difficult for PAOs, as PAOs are often built bottom-up. In many cases, PAOs are driven by the individuals affected who often belong to overlooked or discriminated populations. It may be difficult for them to accept that the PAO, which was established to advocate for their specific interests, is now supposed to advocate for the interests of others. However, as argued above, health issues cannot be restricted to limited groups and it is within the responsibility of PAOs to consider the ethical implications to a broader range of potentially affected individuals. Depending on the size and structure of a PAO, the leaders or board members might be in the position to undertake the difficult task of balancing.

Other addressees of PAOs' responsibility could be politicians, scientists and private stakeholders. Although they form a fruitful network for PAOs, such relationships, especially if they are financial, may lead to conflicts of interest and create, for example, biases in PAOs' educational activities [7, 8, 22]. The PAOs that establish such relationships run the risk of becoming financially

dependent and influenced in their activities and might fail to represent the patients' perspective [7, 8, 21, 22]. Due to the frequent lack of independent and adequate resources for PAOs' activities [9], PAOs are often dependent on external funding and, thus, particularly susceptible to dependencies and influences from outside. As long as patient representation is the object of a PAO's responsibility, political, scientific and private stakeholders may be helpful network and cooperation partners for PAOs, but they do not seem to be legitimate addressees of PAOs' responsibility because of the risk of ignoring the advocacy role and pretermitting the interests of the patients. Of course, PAOs have responsibilities towards politicians, scientists and industrial partners when they work together with them, for example, to keep agreements, but these responsibilities are not the subject of the current paper.

When PAOs think about collaboration with politicians etc., they should critically consider their own role and underline their core values—representing patients and advocating their interests. Emphasizing these values highlights the moral character of PAOs' work and the moral character, in turn, creates the basis for the claim that PAOs should not only consider their direct target group but also others in the domain of health. The PAOs are encouraged to go beyond their own interests and to see themselves in a broader social context. Understood in this way, the addressees of PAOs' responsibility covers collective and prospective dimensions.

The normative standard

If responsibility is assigned to PAOs, a normative judgement is rendered on their activities in relation to a normative standard [35]. Typical standards for attributing responsibility are, for example, legal frameworks or ethical principles. Which standard is chosen depends, inter alia, on the concrete situation in which the subject is located, the activities being judged and the type of responsibility (e.g. legal, political or moral) being considered. If PAOs are seen as morally responsible for patient representation and advocacy, the question remains on which standards this can be claimed.

The PAOs' demand for more patient participation in research and health policy has been increasingly recognized both legally and politically in recent decades, particularly in Europe [55, 56, 58–60]. Governments are committed, for example by the WHO, to establishing structures that enable the involvement of groups such as disease-specific advocacy organizations [56]. The way in which PAOs are supported varies greatly from country to country and the legislation is often not properly enforced [9]. However, despite this inconsistent legislative landscape, there is a tendency to see PAOs as responsible for representing the interests of the patients. Institutions, such as ethics councils, also give statements about patient and public participation in healthcare. The British Nuffield Council on Bioethics [61], the French National Consultative Ethics Committee on Health and Life Sciences [62] and the German Ethics Council [63] are examples of these and support patient and public participation as they regularly consult affected groups [64]. Insofar as laws, policies and institutional statements assign PAOs certain tasks and enable them to implement patient participation, they can serve as a normative basis for attributing responsibility for patient representation and advocacy to PAOs.

However, although social and political institutions attribute the responsibility for patient representation and advocacy to PAOs, the assignment of this responsibility comes primarily from the PAOs themselves, because the PAOs have assigned themselves this role. Looking at the PAOs' own statements and constitutions can, therefore, help to identify the normative principles for attributing this responsibility. The constitutions of the PAOs usually define their tasks, missions and core values. Consequently, it would be helpful to examine what role each PAO assigns to itself and which specific responsibilities are associated with this. A PAO that promotes patient advocacy on political committees, for example, has different responsibilities than one that supports patient involvement in clinical trials. Nevertheless, if the common goals and core values behind these specific aims are considered, normative principles can be identified.

The common mission of PAOs to campaign for those affected can often be traced back to the experience of injustice, as many PAOs represent, for example, groups that are stigmatized or diseases that are not sufficiently recognized [1, 3]. One core value that can be identified in the PAOs' statutes is, consequently, social justice. Furthermore, the wish to help each other and the benefits for their own group as well as for others might be strong motivations for PAO members to join their organization. Mutual support and empowerment are values that are strongly represented by the PAOs. By considering the common goals and core values of the PAOs, the principles of justice, beneficence and empowerment emerge. These bioethical principles can capture the PAOs' motivations, form the normative basis for their role and work and therefore for their responsibility. While these principles provide a general ethical orientation, they also leave considerable room for interpretation. Although the principles need to be concretized and weighed against each other in specific situations, PAOs can be encouraged to emphasize these ethical principles in their work and consider the implications of their activities regarding these principles.

If the PAOs are assigned responsibility, a normative standard is needed: Legal and political frameworks, but also the PAOs' own constitutions and the ethical principles of justice, beneficence and empowerment contained therein can be used. Which standards are used may vary depending on the circumstances, in which the PAOs find themselves. The collective dimension can be seen in standards that are the result of a shared deliberative process. The constitutions of PAOs might be assumed to have been elaborated and developed in such a joint process. At least, the ethical principles behind allow room for such processes. If the normative standards also show a long-term orientation, as it is often the case with PAO statements, there is additionally a prospective dimension.

Responsibility as a tool to structure situations

The PAOs can play an important role in the planning and conducting of biomedical research. Many organizations have added contribution to research on their agenda and patients participation, for example, in the design of a research project is usually considered as ethically important in the current bioethical literature [4]. However, PAOs that want to conduce to research find themselves in difficult decision-making situations and are confronted with questions of responsibility. The following example—constructed on debates in the literature and team discussions—demonstrates how the proposed framework of responsibility can serve as a practical tool to structure morally difficult situations (Fig. 1).

A PAO that is committed to rare diseases on a national level receives the invitation to join a clinical trial carried out by a public research institution together with a pharmaceutical company. The PAO could support the study

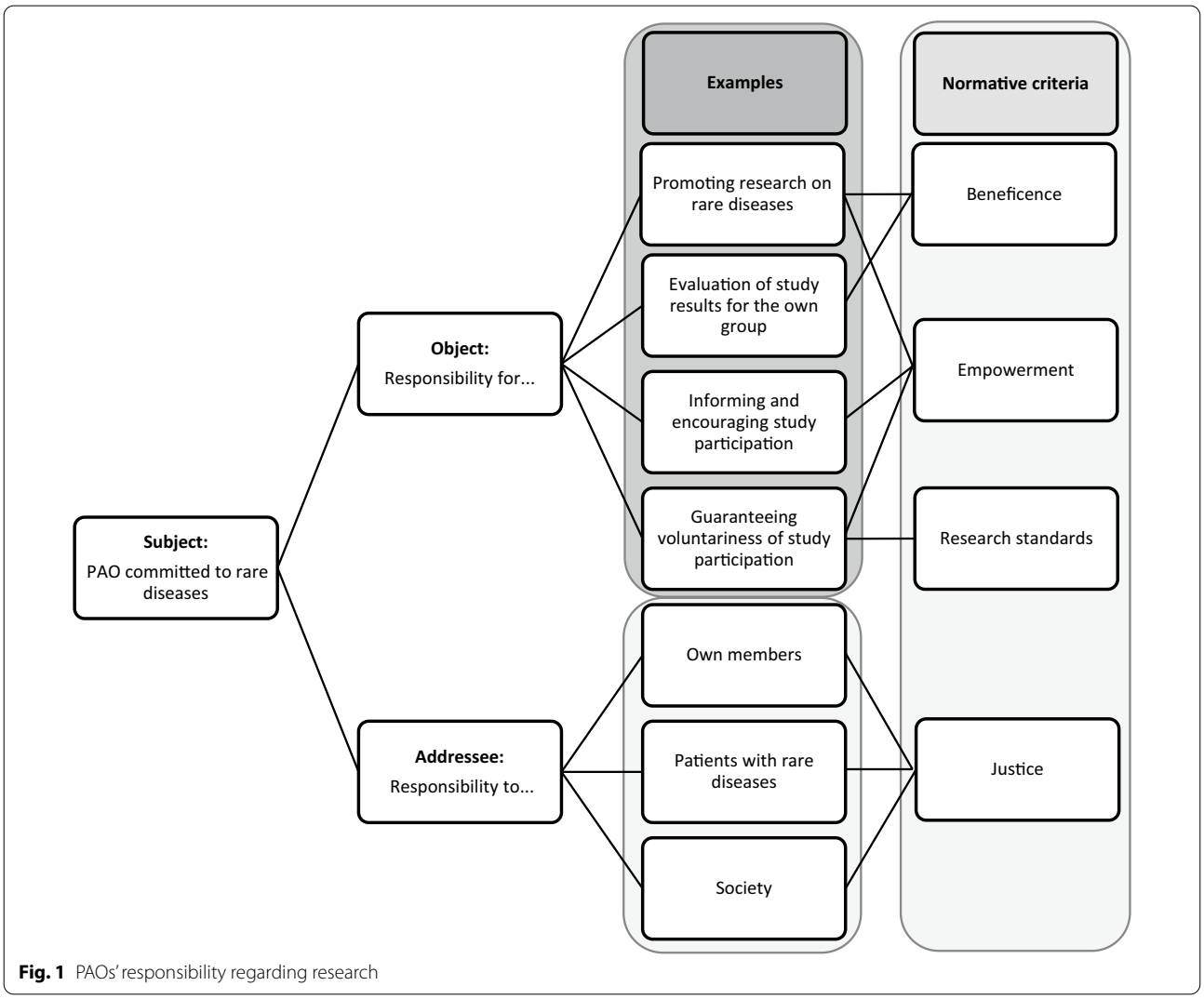

Fig. 1 PAOs' responsibility regarding research

by informing and inviting its members to participate. However, the PAO's officials are unsure whether they should recruit participants for the study. They are questioning for what and to whom the PAO is responsible in such a situation, and which normative principle can justify this responsibility. The outlined framework can help to structure the situation.

Regarding the object, the PAO can emphasize its role: representing persons affected by rare diseases and advocating their interests. These interests consist, at least in the context of research, in promoting studies on rare diseases that result in findings, which helps people regarding diagnosis, therapy or coping with their diseases. It would therefore be the responsibility of the PAO to assess whether the support of this study meets these shared interests. The underlying norm of this responsibility is *beneficence*: the research to be supported is meant to help those affected. If the PAO does not observe the ethical principle of beneficence when selecting the research it wants to endorse and, for example, promotes a study that is not for the benefit of rare disease patients, the PAO may lose the trust of its members and its decision-making power. The principle of *empowerment* complements this obligation, since it is also the responsibility of the PAO to support and empower those affected; which can mean to encourage them to take a (more) active role in research processes. In advertising the study, the PAO would meet this responsibility by informing its members about current research, bringing those affected and scientists closer together and embolden its members to take a position on this research.

When assessing the study, the PAO can also consider *the question of the addressee*: Will the study only serve the group represented by the PAO or will the study have additional collective benefits, for example, for future patients, other social groups or the society? It would be the responsibility of the PAO to include not only its own group but also other addressees in the assessment. The ethical principle behind this responsibility is *justice*. According to this norm, the PAO should consider how access to and benefits of the research are distributed. In line with the PAO's mission, projects that facilitate the development and improve equitable access and distribution of rare disease treatments should be promoted. However, the PAO may consider whether it is worth investing in this individual research project or whether it would be more effective to support the development of research infrastructures in the field of rare diseases in general.

If the PAO decides to forward the invitation to participate in the study to its members, it would be a further responsibility of the PAO to ensure that the members do not feel any pressure to answer this invitation. The underlying ethical principle is *empowerment* or in a broader perspective respect for autonomy. The offer to participate in the study would probably be better accepted by the members if it was offered by the PAO and not by the pharmaceutical company. However, the PAO is responsible for ensuring that the voluntariness of the invitation is guaranteed and that the participants are sufficiently informed about the context of the invitation, for example, about the relationship between the PAO and the research project partners. In addition, the PAO's responsibility to its members can be justified by the Declaration of Helsinki [65], which emphasizes, among other research standards, the voluntariness of research participation.

The aim of this case is to illustrate the application of the four-sided model of responsibility. As the application has shown, the interpretation of responsibility regarding the PAOs' involvement in research is multifaceted and the relata of the model are often interwoven. These ambiguities can be minimised by a precise specification about who is responsible, for what, to whom and on the basis of which ethical standard. An accurate application of the model can help structuring the situation, clarifying the underlying ethical principles and thus contributing to the solution of the conflict. The four-sided model of responsibility, including collective and prospective dimensions, does not claim to be sufficient for all applications, but it can help in structuring and giving orientation.

Conclusions

This contribution provides an analysis of PAOs' moral responsibility. Focusing on the *moral* responsibility directs the attention to the moral character of PAOs' work. PAOs are more than just lobby groups: They are structured in such a way that they are moral agents—hence they are accountable for their actions and have to consider the implications of their activities. The PAOs' task is relatively clear: To represent those affected and stand up for their rights. This can hardly be taken over by an individual but requires collective efforts. PAOs are voluntary groups in society that have accepted the delegation of responsibility for the presentation of patients, therefore, they are answerable to their target groups but also toward others and the society for the successful execution of this and any deficiencies.

By encouraging PAOs to emphasize their core values, the current analysis can help PAOs to find their own position in difficult decision-making situations. The relational responsibility model is a practical analytical tool that can help PAOs to structure situations characterized by question of responsibility and identify the underlying values. Therefore, it can give PAOs general ethical orientation, help them to find their own attitude and establish

clear relationships, for example, with industrial or political agents. Correspondingly, the application of the model can help policy makers, biomedical researchers, and economic stakeholder to understand the roles and responsibilities of PAOs more clearly, which in turn, can help to develop fruitful working relationships with PAOs.

Abbreviations
CSO: Civil society organization; PAO: Patient advocacy organization; WHO: World Health Organization.

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RM, CR and SS conceived the analysis. RM researched literature and wrote the first draft of the manuscript. All authors were significantly involved in the further development of the manuscript. All authors edited the manuscript and approved the final version of the manuscript.

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Publisher's Note

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ORIGINAL RESEARCH

Involving Patient Groups in Drug Research: A Systematic Review of Reasons

This article was published in the following Dove Press journal:
Patient Preference and Adherence

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Background: Patients have evolved from mere objects of study to active contributors to drug research in recent decades. Since individual patient's influence to change research processes effectively is limited, patient groups play an important role in the planning and conducting of pharmaceutical studies. Patient group engagement in drug research is usually seen as being beneficial from an ethical viewpoint as well as from the perspective of research practice, while potential disadvantages and risks have been discussed considerably less.

Purpose: A systematic review of reasons was conducted to allow for an overview of the reasons for and against involving patient groups in drug research.

Methods: The literature search was conducted in PubMed and Web of Science. Reasons concerning the influence of patient groups on drug research were extracted and synthesized using qualitative content analysis. The review's main limitation arises from a lack of critical appraisal regarding the quality of the reasons.

Results: A total of 2271 references were retrieved, of which 97 were included in the analysis. Data extraction revealed 91 (73.4%) reasons for and 30 (24.2%) reasons against involving patient organizations in drug research, and 3 (2.4%) ambivalent reasons; amounting to 124 reasons. The main groups of reasons were clustered around the categories: quality of research, acquisition and allocation of resources, and the patient role in research.

Conclusion: This is the first systematic review of reasons concerning the influence of patient groups on drug research. It provides a basis for a continuing debate about the value as well as the limits of involving patient groups. Due to the diversity of research projects there can be no general recommendation for or against patient group involvement. More research is necessary to assess potential advantages and disadvantages of patient groups' influence on other types of research (eg genetics).

Keywords: patient organization, drug research, patient and public involvement, systematic review of reasons, bioethics

Plain Language Summary

Patient groups play an important role in the planning and conducting of pharmaceutical studies. Therefore, their engagement in drug research is usually regarded as being beneficial from both an ethical and a scientific viewpoint. Meanwhile, potential disadvantages and risks of their involvement have received little attention.

For the first time, a systematic overview of the reasons for and against involving patient groups in drug research was created. After identifying relevant literature, reasons concerning the influence of patient groups on drug research were extracted. In total, 2271 references were retrieved, of which 97 contained reasons and were included in the analysis. Data extraction revealed 91 (73.4%) reasons for and 30 (24.2%) reasons against involving patient organizations in drug research, and 3 (2.4%) ambivalent reasons; amounting to 124 reasons.

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By presenting all reasons concerning the involvement of patient groups in drug research, this review provides its readers with a basis to form an educated opinion for the continuing debate about the value and the limits of such an involvement.

Introduction

The involvement of patients and the public in science has become a major factor in the international research landscape.[1–3] Provisions for adequate involvement of patient and public representatives, for example, have become increasingly important for researchers and scientific institutions as a precondition for research funding. In addition, regulatory institutions such as the US Food and Drug Administration increasingly emphasize the importance of patients' input in drug research.[4] The variety of ways in which patients[5] and the public[6] can contribute to research has already been discussed in detail. It ranges from educating patients and the public and building a public opinion, to setting research agendas and supporting the conduct of studies.

The involvement of non-researchers in the research process has been given numerous names, for example, Patient and Public Involvement, patient engagement, public participation and Citizen Science. The way in which and the degree to which patient and public representatives influence the research process vary depending on the conceptual backgrounds. One of the most far-reaching approaches refers to the slogan: "Every participant is a PI".[7] The key idea of this concept is to encourage patients to submit personal health data to an open data repository (like Open Humans[8]) and afterwards to consistently involve them in every step of scientific knowledge production.

In the current literature, there is often no distinction between the involvement of patients and the involvement of the public. However, these differences between patients and the public are important, since each group seems to be driven by different interests.[9] The differing motives may even result in a paradox.[10] Patients can most notably contribute the experience of living with a certain disease – often called "experiential expertise" or "experiential knowledge"[11] – to the development of drugs, distinguishing them from healthy individuals. In addition, they usually have a personal incentive to get involved in drug research for a specific disease, whereas members of the public would rather work towards general improvements in health care.[12] Thus, both a conceptual as well as a practical distinction between the involvement of patients and the involvement of the public seems necessary regarding the epistemic backgrounds and interests of the groups involved.

Another point of controversy relates to the moral value of letting patients participate, for example, in the planning and design of a research project. Patient involvement is usually considered as ethically important in the current literature.[13,14] Some authors see a "compelling ethical rationale [that] supports patient engagement in healthcare research".[5] This "rationale" can, for example, be related to the idea of "epistemic justice". Besides arguing for the inclusion of experiential expertise in knowledge production, "epistemic justice" sees a moral duty in involving patients' perspectives in decisions that will affect primarily patients.[15]

In contrast, discussions about critical aspects have been widely missing, although they deserve just as much attention, as in some cases, patient involvement can be unfavorable.[16,17] A patient organization, for example, can fail to represent the patients' perspective properly and, consequently, promote researchers' rather than patients' interests.[18,19] Another example of a doubtful patient activity is demanding access to unproven and possibly harmful treatments. This creates the risks of resources being spent ineffectively and patient safety being at stake. This has been, for instance, the case with a breast cancer treatment in the 1990s.[20]

Finally, many publications on Patient and Public Involvement are restricted to certain aspects of the phenomenon. Broader assessments of the status quo of functions performed by patients and the public[5,6] and several guidelines on how to implement their involvement[21–23] exist. Seemingly, some researchers are still unsure how patient involvement can be included in their research.[24] A full picture of all reasons for and against patient group (PG) involvement in research has not yet been provided. This can only be achieved through systematic reviews (SRs). This article aims at giving researchers and healthcare decision-makers a comprehensive overview to form their opinions on involving patients in drug research. Due to the different epistemic and normative characters of the involvement of patients or the public respectively, this SR is restricted to patients, and more concretely to PGs. Since individual patient's influence to change research processes effectively is limited, PGs usually function as the major stakeholders in pharmaceutical studies.

Materials and Methods

A SR of reasons[25] with the objective of collecting all reasons regarding the involvement of PGs in drug research was conducted and is reported according to the PRISMA Statement to the extent to which it is applicable to SRs of reasons (see Additional file 1). SRs generally aim to systematically present

all evidence-based knowledge (and lack of such) concerning a specific research question.[26] In recent years, the SR methodology has been adopted and further developed for the field of bioethics, which is characterized by a close connection between normative and empirical research questions.[27] When analyzing argumentative literature, adjustments need to be made to the "classic" SR methodology.[25] There are different types of SRs of argumentative literature, for example, SRs of (ethical) issues, conclusions, concepts, recommendations and reasons.[28] Even if SRs are a rather new methodological approach within the field of bioethics, there have been comprehensive publications on the value of such reviews,[29,30] and several SRs of argumentative literature in general[31] and specifically of SRs of reasons have been already conducted and published.[32–34]

Inclusion Criteria

Two key terms were defined for the search strategy to arrive at a systematic overview of reasons regarding our research objective: "patient groups" and "drug research". We deliberately decided to use broad definitions of our key terms in order to avoid missing any relevant literature. Publications were only considered if they fitted both definitions.

"Patient group", within this review, means any group consisting of patients and/or patient advocates which consistently promotes patients' interests.[35] The activities of individual patients regarding their needs and interests were not included in the review.

Concerning the term "drug research", the review considers all phases of research and development of a medicine product from target identification to clinical Phase III studies as described in the final report of the pharmaceutical sector inquiry of the European Commission.[36]

Groups of patients may have various impacts on medical research. They may, for instance, highly influence the public acceptance and economic feasibility of research. They can also play an important political role or contribute scientifically to research.[37] All these types of impacts were considered in the review if they affected the research and development phases of a drug mentioned above. Only publications in English or German language were included, due to the authors' language capabilities. The search was not limited to a certain time period.

Database Search

After gaining an overview of the existing literature by hand and exploratory database searches, two databases were selected for the systematic search: PubMed and Web of Science. A search strategy was built based on the two key terms – PGs and drug research – and their synonyms. The search term used in PubMed is presented in Box 1. The search was conducted in March 2019.

Box 1 Search Term for PubMed

(((pharmaceutical[Title/Abstract] OR drug[Title/Abstract] OR drugs [Title/Abstract] OR medication[Title/Abstract] OR medicament [Title/Abstract] OR "medicinal product"[Title/Abstract] OR medicines[Title/Abstract]) AND ("research"[MeSH Terms] OR research[Title/Abstract] OR Development[Title/Abstract] OR design [Title/Abstract] OR discovery[Title/Abstract] OR evaluation[Title/ Abstract] OR approval[Title/Abstract])) OR "drug discovery"[MeSH Terms] OR "drug evaluation"[MeSH Terms] OR "drug approval"[MeSH Terms]) AND (("self-help groups"[MeSH Terms] OR self help group[Title/Abstract] OR self help groups[Title/Abstract]) OR (patient organisation[Title/Abstract] OR patient organisations [Title/Abstract]) OR (patient organization[Title/Abstract] OR patient organizations[Title/Abstract]) OR (patient association[Title/Abstract] OR patient associations[Title/Abstract]) OR patient advocacy[Title/ Abstract] OR "patient advocacy"[MeSH Terms] OR patient involvement[Title/Abstract] OR patient engagement[Title/Abstract] OR patient Participation[Title/Abstract] OR "patient participation"[MeSH Terms])

Some of the relevant publications identified via hand search did not appear in the results of our database search, presumably due to their being parts of books. We decided to include them in our study sample to complement the database search results.

Study Selection

Publications which address both of our key terms were included. Two authors, CR and RM, screened the title and abstract of the publications identified via hand and database search and discarded publications not meeting the inclusion criteria. Any disagreement between the two authors was resolved through discourse.

The full texts of the remaining publications were then analyzed regarding their relevance by CR and RM and the results were discussed in regular team meetings. Again, publications not meeting the inclusion criteria were discarded. The remaining publications were included in the review and their bibliographies were screened for additional relevant literature. This resulted in adding further 17 relevant publications to the finally included publications. A flow chart illustrating the study selection is shown in Figure 1.

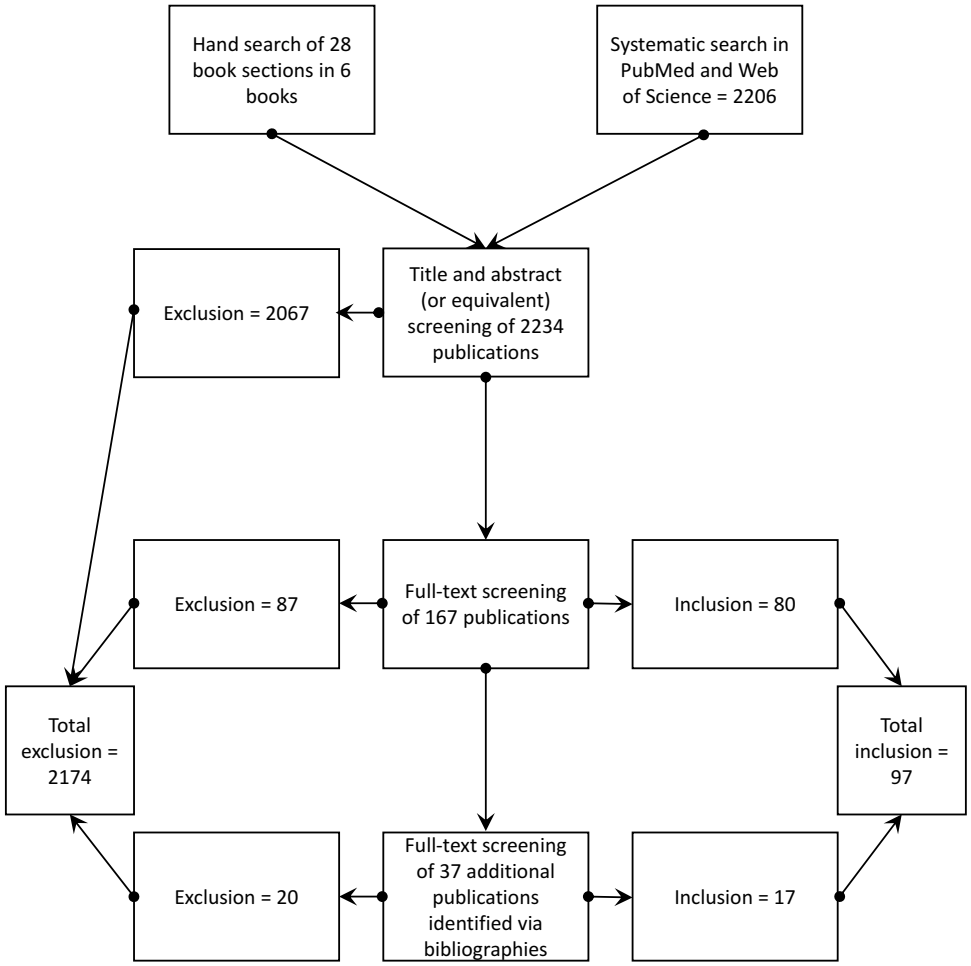

Figure 1 Flow chart of the study selection.

Data Extraction and Qualitative Synthesis

In this review, a reason is understood as the first part of an argument (in this context, often called a "premise"), the second being a conclusion. An argument can consist of multiple reasons/premises that may all lead to one conclusion (eg "the influence of PGs is favorable").[38] This was the case in some of the publications included in the review, as they stated only an "all things considered"-conclusion, but many premises.

Publications were analyzed by two authors (CR and RM) using the method of qualitative text analysis proposed by Mayring,[39] supported by the software MAXQDA Standard 12. According to the research question, the authors screened the publications for reasons regarding the involvement of PGs in drug research. A code was assigned to each occurrence of a reason. Reasons extracted inductively from the material were labeled as narrow reason types. Deductively created categories that condense narrow reason types were labeled as broad reason types. Narrow reasons were analyzed for their alleged implications (pro, contra or ambivalent) regarding the involvement of PGs in drug research.[25] After all the publications had been analyzed once and theoretical saturation was reached, the code system was revised to eliminate doubling and overlapping reason types. All publications were analyzed a second time to ensure the assignment of the correct code from the revised code system for every reason occurrence. Publications were also analyzed for their publication type and their "all-things-considered"-conclusion, which is the final conclusion a publication comes to based on all mentioned reasons.[25]

A quality appraisal of the extracted reasons was deliberately not conducted. Firstly, assessing the quality of a reason is a complex endeavor and can only be achieved by thorough discourse.[38] Methodological standards for quality assessment in SRs of reasons are not available so far.[28] Secondly, the results of such an endeavor depend partly on the context of the particular situation at hand. Therefore, it exceeds the limits of what can be provided in a systematic review of reasons. However, we encourage the readers to assess the quality of reasons presented within the context of their research projects.

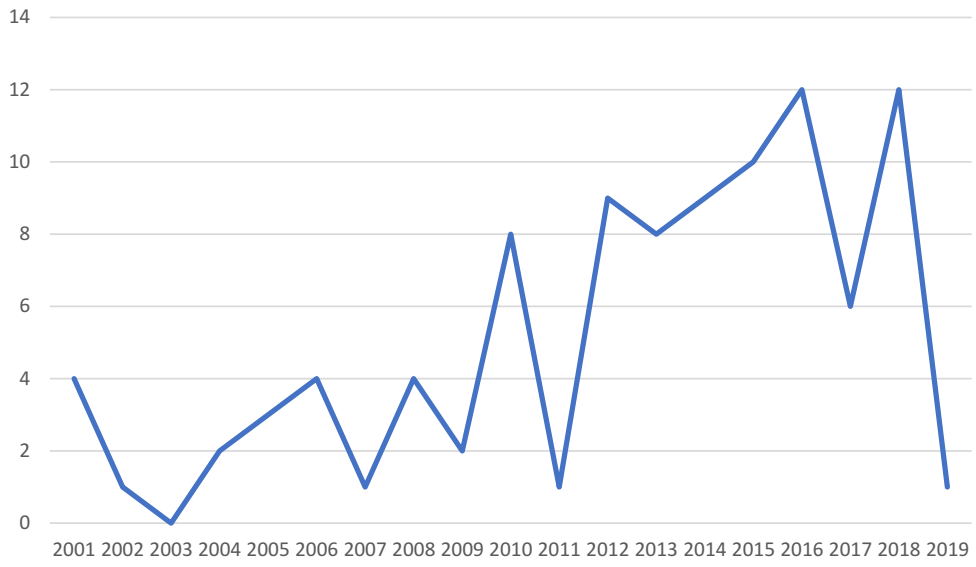

Figure 2 Quantity of publications per year.

Results

A total of 97 publications were finally included from 2271 identified publications during the systematic search. The study sample consists entirely of journal articles and book sections published between 2001 and 2019. Figure 2 shows the number of publications per year. Even though there is some fluctuation, the overall interest in the involvement of patients in drug research is gradually rising. The small number of publications from 2019 is mainly due to the database search being conducted in March 2019.

The study sample is very heterogeneous and shows a wide variety of perspectives of the authors and publication types. Most of the publications focused on rare diseases which leads to the assumption that research on rare diseases benefits greatly from patient involvement. Authors from the pharmaceutical industry were much less interested in patient involvement than patient advocates. The distribution of the authorship possibly contributed to the high number of reasons for the involvement of patients in drug research. The variety of author perspectives is shown in Figure 3 and the quantity of publication

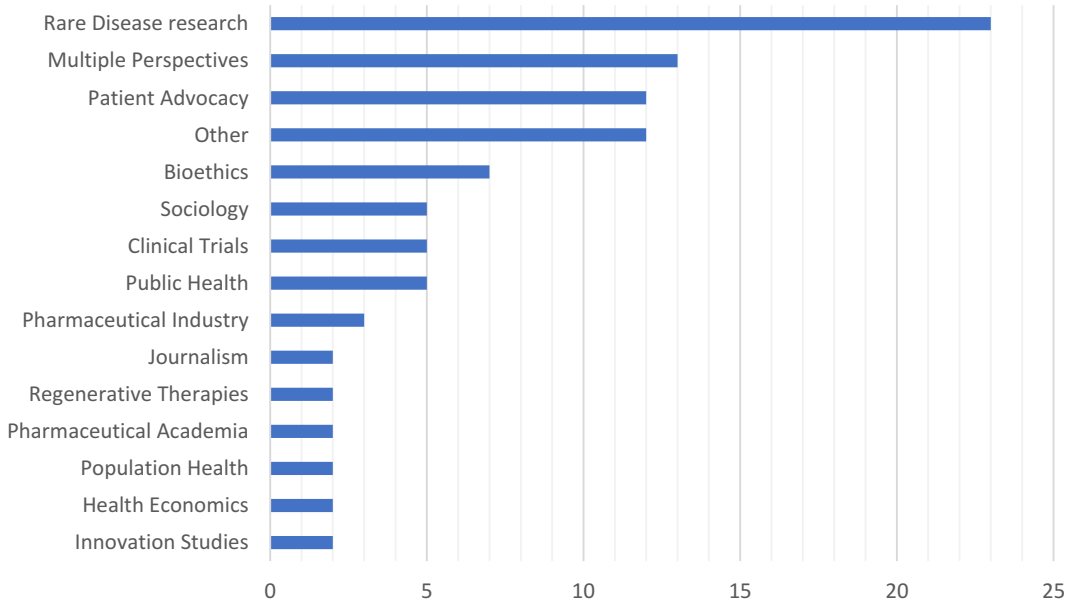

Figure 3 Quantity of authorships' perspectives.

types in Figure 4. All publications were written in English. A list of all publications included is part of the supplementary material of this article (see Additional file 2).

Despite the obvious heterogeneity of the study sample, the "all-things-considered"-conclusions were surprisingly consistent. Most publications drew the conclusion, that the involvement of PGs in drug research is or can be beneficial under certain circumstances. A minority of publications did not have a conclusion. No publication rejected the involvement of PGs entirely. However, publications with occurrences of reasons against the involvement of PGs often warned of risks and dangers, that should be avoided. A summary of the conclusions of all included publications is provided in Figure 5.

Broad Reason Types and Narrow Reason Types

Reasons were categorized during the analysis of the study sample by assigning broad reason types (BRTs) and narrow reason types (NRTs). BRTs summarize NRTs that are closely linked in content. The following six BRTs were identified:

1. Resources: Since resources are limited, many reasons relate to the question whether PGs can acquire, distribute and use resources needed for the research process effectively. Resources discussed include financial investments, research samples, scientific data and time.
2. Collaboration: The creation of new acquaintances and connections between researchers and other stakeholders was generally rated highly for the research process. PGs play a key role in establishing these collaborations.
3. Science: This BRT deals with all reasons concerning quality, conditions, aims and conduct of scientific studies. There are ways in which PGs can influence these parameters either positively or negatively. Setting research agendas is one of the topics mentioned most frequently in this BRT.
4. Patient community: Reasons regarding the quality of patient representation by PGs can be found in this BRT. Possible contributions of patients based on their unique experiences and potential benefits and risks which affect patients directly are also discussed.
5. Ethics: Justification and fairness of research with the involvement of PGs are major reasons in this BRT. PGs' handling of ethical issues is also considered.
6. Public relations: The ability of PGs to promote research-friendly political surroundings and shape the public perception of drug research is subject to reasons in this BRT.

All these six BRTs encompass reasons for and against the involvement of PGs in drug research. Ambivalent reasons can be found in the BRTs *Resources* and *Science*. Table 1

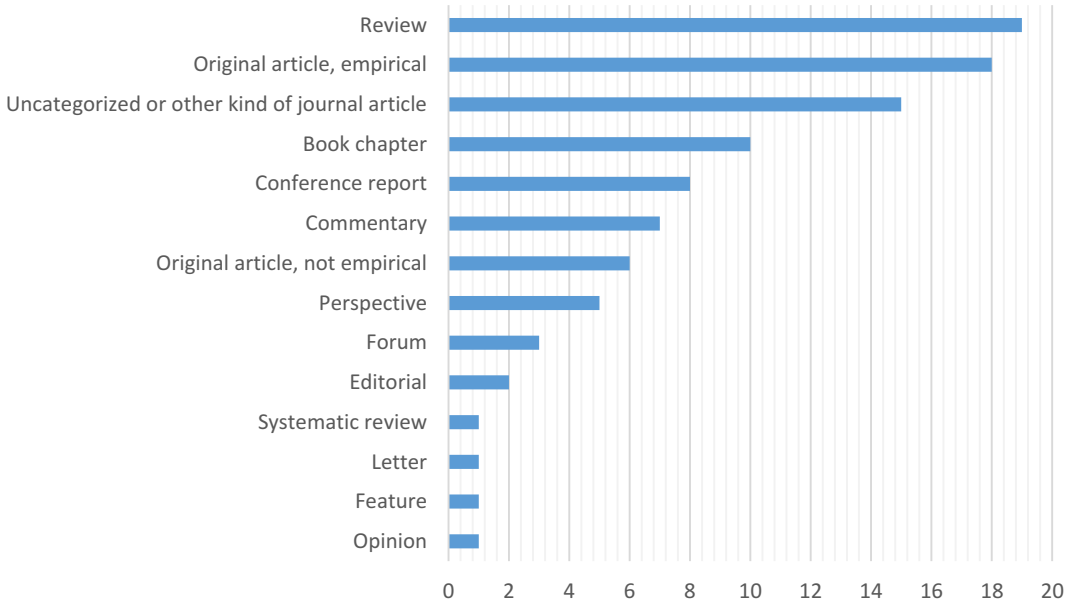

Figure 4 Quantity of publication types.

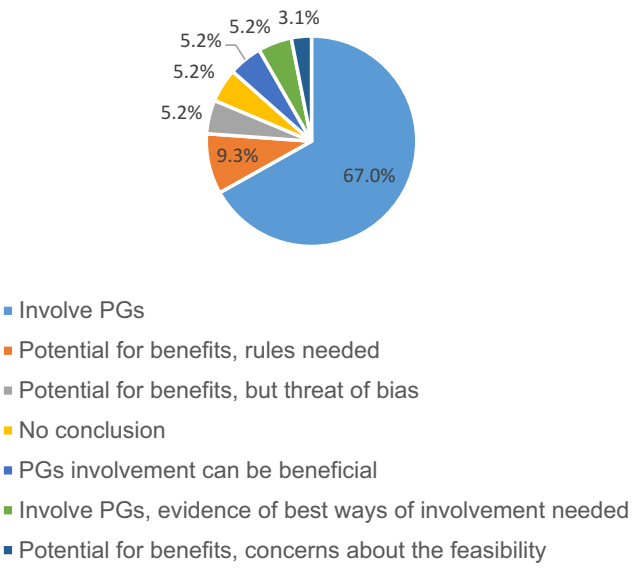

Figure 5 Quantity of "All-things-considered"-conclusions.

shows a detailed list of all reasons, the number of publications each reason occurred in and how the reasons were used. An additional table reveals, which NRTs were found in each included publication (see Additional file 3).

Discussion

As expected, a broad variety of reasons which support the involvement of PGs in drug research was found (91; 73.4%). However, the same applies to reasons against involvement on a smaller scale (30; 24.2%), while only a few reasons were used ambivalently (3; 2.4%). The reason for the discrepancy between pro and contra reasons in this SR is possibly an accurate depiction of a real difference in numbers of respective reasons. However, contra reasons have been mentioned by far fewer publications than pro reasons. Many publications included in this review do not discuss the inclusion of PGs in drug research as their central topic. These articles might tend to address the issue rather superficially and advocate the inclusion of PGs without critical reflection. Publications that cover it as a central topic tend to be more balanced.[19,40,41] They also do not draw their arguments from individual experiences or single examples of good collaboration between PGs and researchers as many of the other publications do. A generalization of these positive experiences is not possible. These findings could indicate that the real cause of the discrepancy is an underrepresentation of contra reasons.

The often-unquestioned ethical rationale whether to involve patients in research is reflected in the NRTs "Patient perspective in research" and "Poor patient representation". Indeed, there are arguments stressing that the status of being affected fundamentally distinguishes healthy people from ill people who, therefore, deserve representation.[42] While most authors agree that this is a desirable goal, some express concerns about whether and how this goal can be achieved by involving PGs. Strategies for addressing these concerns have been rarely discussed so far. One approach could be the analysis of representation and trust models applied by PGs.[43] The concept of a "collective agency"[44] examines the quality of representation in PGs more thoroughly and considers engaging other collective actors like, for example, families. In this concept, four characteristics of collective actors are identified, one of them being building "a shared practice of trust".[44]

The risk of a collaboration with PGs being misused by pharmaceutical companies for commercial purposes is reflected in the NRT "Risk of manipulation by other stakeholders". This risk is especially evident when PGs are being sponsored by companies.[45,46] On the other hand, industrial sponsoring offers opportunities for PGs. This leads to debates with good arguments on both sides.[47,48] The results of this review show that this factor has been used rather rarely as a reason against the involvement of PGs in drug research. Furthermore, it has been acknowledged in every occurrence of the reason that the risk of manipulation can be alleviated by applying preventive measures as, for example, adequate disclosure practices.[49,50]

Limitations

The review is restricted to two databases and a small selection of book chapters identified during hand search. Any other databases, including Google Books, were not considered due to a lack of relevant results in the exploratory searches.

Another limitation is the neglect of literature written in languages other than English and German. One publication (written in Dutch) had to be excluded due to this limitation. The definition of the two key terms and the inclusion of publications and reasons based on them is a crucial point of this review. The definitions developed confine the variety of reasons collected. Moreover, the decision whether a publication or a reason deals with both key terms as part of qualitative data synthesis is subjective. We made these decisions as intersubjectively valid as possible by discussing relevant decisions within the disciplinary research team and solving disagreement by discourse.

Table 1 Reasons For and Against Involving PGs in Drug Research

Reasons	Number of Occurrences	Use of Reason
Resources		
Biological resources		
Acquisition of biological specimen	13	Pro
Biobanks		
Building/Contributing to biobanks	11	Pro
Understanding biomarkers	2	Pro
Competition between PGs over resources	1	Contra
Finances		
Funding		
Funding acquisition of research equipment	3	Pro
Funding basic research	2	Pro
Funding clinical trials	5	Pro
Funding research in general	27	Pro
Funding with personal assets of patients	1	Contra
Leveraging other funding/Reducing risks for other investors	11	Pro
Targeted funding	5	Pro
Raising funds		
Raising funds for basic research	2	Pro
Raising funds for clinical trials	5	Pro
Raising funds from the government	1	Ambivalent
Raising funds in general	19	Pro
Risks of raising funds for unpromising research	1	Contra
Reducing the cost of research	9	Pro
Information		
Collecting research data	12	Pro
Creating patient registries	25	Pro
Disseminating information to patients	32	Pro
Disseminating information to scientists	7	Pro
Removing informational obstacles	3	Pro
Sharing scientific information/data	7	Pro
Providing resources (eg research tools)	11	Pro
Reduction of resources for other activities of PGs	5	Contra
Time investment	5	Contra
Collaboration		
Increasing acquaintances among stakeholders		
Building networks	13	Pro
Connecting researchers	7	Pro
Connecting researchers of different scientific fields	7	Pro
Connecting researchers and patients	7	Pro
Connecting other kinds of stakeholders	3	Pro
Increasing collaboration	28	Pro
Individual approaches of PGs hamper collaborations with them	6	Contra
Influencing attitudes of stakeholders		
Deterring stakeholders from getting involved	1	Contra
Emboldening other stakeholders to get involved	3	Pro
Emboldening scientists to get involved	8	Pro
Organizing conferences	6	Pro
Science		
Clinical Trials		
Acquisition of patients for trials	63	Pro
Organization of clinical trials		
Conduct of trials		
Collecting additional data (eg patient-reported outcome)	7	Pro
Contributing to the evaluation of trials	8	Pro
Enhancing the efficiency of trials	2	Pro
Ensuring patient safety in trials	12	Pro
Organizing/Facilitating clinical trials in general	16	Pro
Trial design		
Contributing to trial design in general	36	Pro
Developing eligibility criteria for trial participation	11	Pro
Improving outcome measures of clinical trials	18	Pro
Improving trial methodology	3	Pro
Convincing physicians to promote trials	2	Pro
Reducing risks of trials		
Paving the way for larger trials with small trials	5	Pro
Reducing risks of trials in general	4	Pro
Offering assistance to participants in trials	5	Pro
Publishing trials	5	Pro
Recommending (or not recommending) clinical trials	2	Ambivalent
Conditions for research		
Making research less attractive for scientist	2	Contra
Changing the research environment	6	Pro
Creating opportunities for innovation	3	Pro
Creating surroundings for effective research	5	Pro
Development process		
Acceleration of drug development	26	Pro
Contributing to the development of spin-off products	2	Pro
Creating new (so far unknown) risks for the development process	1	Contra
Direct scientific contributions of PGs	9	Pro
Enabling more focused research	1	Pro
Flexibility in the research process	2	Pro
Giving preference to clinical evaluation over basic research	2	Pro
Repurposing therapeutics	4	Pro
Simplifying the development process by retaining property rights	1	Pro
Supporting advance in research	17	Pro
Testing unproven therapeutics on group members	1	Ambivalent
Translating scientific knowledge into therapeutics	11	Pro
Increasing participation in research	10	Pro

(*Continued*)

Table 1 (Continued).

(*Continued*)

Table 1 (Continued).

Reasons	Number of Occurrences	Use of Reason
Initiation of research		
Commissioning necessary studies	2	Pro
Starting research projects	8	Pro
Quality of research		
Improper handling of biological material	1	Contra
Increasing effectiveness and sustainability of medicines	18	Pro
Increasing the reliability of research results	2	Pro
Ineffective research due to misunderstandings regarding roles	2	Contra
Lack of evidence of the value of patient involvement	1	Contra
PG's lack of scientific knowledge reduces the quality of research	9	Contra
Poor quality of studies due to the involvement of PGs	5	Contra
Reducing bias in research	2	Pro
Supporting evaluation of research results	2	Pro
Research agenda		
Considering unconventional therapeutics, eg natural medicine	1	Pro
Coordinating research	9	Pro
Increasing the amount of research conducted	1	Pro
Identifying unmet medical needs	7	Pro
Reconciling research needs	2	Pro
Setting research priorities	27	Pro
Supporting scientists	12	Pro
Patient community		
Benefits for patients		
Access to investigational drugs	6	Pro
Creating hope for patients	2	Pro
Involvement in research strengthens patient communities	1	Pro
Involvement is a way of coping with individual hardships	1	Pro
Leading to health benefits for patients	11	Pro
Contributions of patients based on their experiences		
Experiential expertise	25	Pro
Experiential expertise is insufficient	3	Contra
Personal affliction can be a driving force in research	4	Pro
Personification of disease	4	Pro
Representation of patients		
Patient representation/perspective in research	36	Pro
Risk of poor patient representation	17	Contra
Risks		
Creating unrealistic hopes	2	Contra
Endangering patients by advocating possibly harmful drugs	5	Contra
Improper handling of patient data	1	Contra
Inappropriate motives of patients despite affliction		
Risk of manipulation by other stakeholders	8	Contra
Suspicion of conflicts of interest/bias	19	Contra
Ethics		
Alluring participants with money	2	Pro
Creating social pressure to participate	1	Contra
Dealing with research advances	1	Pro
Deliberately neglecting ethical issues in research	3	Contra
Disagreement over ownership of findings	1	Contra
Justice		
Epistemic justice	1	Pro
Ethical justification of research	1	Pro
Increasing democratic value	6	Pro
Increasing undue preference of certain research interests	11	Contra
Unjust allocation of resources	2	Pro
Pointing out ethical issues in research	4	Pro
Promoting confidentiality protections for participants	3	Pro
Restricting academic freedom of scientists	1	Contra
Public Relations		
Contributing to favorable policies/legislation for research	12	Pro
Creating unrealistic hopes	3	Contra
Exploiting sick children to raise public awareness	1	Contra
Increasing patients' trust in research	7	Pro
Increasing public debates/awareness	14	Pro
Influencing public attitude towards research negatively	1	Contra
Overly positive presentation of results	2	Contra

Notes: The six BRTs are shown as headlines in bold text. The column "Reasons" lists all reasons extracted from the data, "Number of occurrences" shows how many publications mentioned each reason and "Use of reason" indicates the alleged implication of the reason ("Pro" indicating reasons for and "Contra" indicating reasons against involvement). BRTs do not have a "Number of occurrences" and a "Use of reason" but encompass the following indented NRTs.

Conclusion

The results of this review indicate that the inclusion of PGs in research can be fruitful. Nevertheless, due to the variety of PGs, no general recommendation to involve or not involve PGs in drug research can be made from this SR of reasons. The reasons presented should, however, be considered carefully when thinking about such a collaboration. Leaders of PGs, for example, can decide whether their PG should get involved in drug research or if patients' interests can be promoted better if resources are spent on other PG activities.

Similarly, leaders of pharmaceutical companies can decide whether engaging PGs in their specific research field is likely to favor the research process. Policy-makers can use this review to create new policies that will improve the conditions for research landscapes.

The reasons presented in this review refer specifically to PGs and drug research. Although they can certainly be adapted to other contexts, there is a need for more SRs assessing reasons for patient involvement relating to other fields of research as, for example, genetics research.

Abbreviations

PG, patient group; SR, systematic review; BRT, broad reason types; NRT, narrow reason types.

Availability of Data and Material

A list of all publications included in the SR and a detailed list of all reason type occurrences in each publication are part of the additional material. Further data and material can be requested from the first author.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Original Research Article

chronic illness

Chronic Illness
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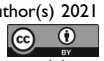
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Lived Experience of Hereditary Chronic Pancreatitis – A Qualitative Interview Study

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Abstract

Objectives: Hereditary chronic pancreatitis is a rare condition characterized by intermittent acute episodes of pancreatitis and long-term impairment of pancreatic functions. However, the subjective perspective of individuals affected by hereditary chronic pancreatitis has been little studied. This qualitative study investigates the experience of hereditary chronic pancreatitis patients and their relatives because the awareness of the needs of those affected is an essential component of a patient-centered management of chronic conditions.

Methods: Semi-structured qualitative interviews were conducted with hereditary chronic pancreatitis patients and their relatives. Data were analysed using qualitative content analysis. The concepts of 'biographical contingency,' 'biographical disruption' and the 'shifting perspectives model' served as theoretical frameworks.

Results: A total of 24 participants (17 patients, 7 relatives) were interviewed individually. Four main themes were identified: (1) The unpredictable clinical course of hereditary chronic pancreatitis; (2) hereditary chronic pancreatitis as a devastating experience; (3) hereditary chronic pancreatitis as part of a normal life; and (4) being reduced to hereditary chronic pancreatitis.

Discussion: The 'shifting perspectives model' of chronic illness covers the four dimensions adequately and can serve as a theoretical model to explain hereditary chronic pancreatitis patients' experience. A better understanding of the patients and their families' experience and the shifting

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character of hereditary chronic pancreatitis can help healthcare professionals to tailor the care to meet the needs of those affected.

Keywords
Chronic illness, hereditary chronic pancreatitis, biographical disruption, 'shifting perspectives model', bioethics

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Introduction

As a basic prerequisite for effective chronic illness care, healthcare systems have to meet the needs of those who are affected.[1] Frameworks for managing and improving chronic care processes, such as the Chronic Care Model (CCM) and its adaptation for international contexts, the Innovative Care for Chronic Conditions framework, have recommended care consistent with the patients' preferences for more than two decades.[1,2] According to the CCM, effective chronic illness care is, among others, based on the individualization of care according to patients' needs and values.[1] The implementation of the CCM can improve medical outcomes and enhance the health-related quality of life of patients with chronic illness, yet, there are some limitations of the CCM and knowledge gaps regarding the benefits and barriers during CCM implementation in different healthcare settings.[3] Although the CCM has been criticized in different aspects, for example, its lack of attention to chronic multimorbidity[4] and paediatric populations,[5] and consequently expanded, for example in the Patient-Centered Medical Home Model,[6,7] 'the model still holds.'[8]

Its core components, emphasizing the individual needs and preferences of those affected and their self-management support, are still relevant subjects of current research on chronic conditions, for example, the barriers and facilitators to self-management in chronic illness[9] or the potential improvements for patients through self-management support.[10] The subjective perceptions of patients with chronic illness have become a relevant part of this research focusing, for example, on the quality of chronic illness care,[11] the factors affecting self-management[9] and the support of self-management.[12] However, although the perspectives of patients and their needs have received increasing attention in both chronic illness care and research, many rare chronic conditions, such as hereditary chronic pancreatitis (HCP) and the specific needs associated, are still underexposed in research.

The current paper presents findings on the subjective experience of patients with HCP and their relatives as part of a larger research project on hereditary disorders of the pancreas and liver [http://www.medizin.uni-greifswald.de/peppp/index.php?id=522&L=1]. The study design has an explorative qualitative character because HCP patients and their relatives have received little systematic empirical scrutiny so far. The aim is to acquire a firsthand understanding of those living with HCP. The main research question is, therefore, how do the individuals affected (patients, partners and family members) experience HCP. The concepts of 'biographical contingency' and 'biographical disruption' and the 'shifting perspectives model' serve as theoretical frameworks.

Hereditary chronic pancreatitis

Hereditary chronic pancreatitis (HCP) is a chronically progressive, rare variant of early-onset pancreatitis. Recurrent acute episodes of pancreatitis are accompanied by a persistent impairment of the exocrine and endocrine pancreatic function[13] due to the loss of parenchymal tissue and the

formation of fibrosis.[14] The clinical symptoms can include abdominal pain, nausea and vomiting. Long-term complications are maldigestion and weight loss due to exocrine insufficiency, pancreoprive diabetes, that results from an impairment of endocrine function, and an increased risk of pancreatic cancer.[15,16] Other common complications are pseudocyst formation,[17] bile and pancreatic duct,[18] as well as duodenal obstruction.[19] Since there is no curative treatment for HCP currently, the therapy covers pain management, therapy for endocrine and exocrine insufficiency, and endoscopic or surgical treatment for bile or pancreatic duct stenosis or for the drainage of pancreatic pseudocysts.[19,20] Diagnosis, prognosis and treatment are challenging, as the course of the disease ranges from asymptomatic to very severe forms.[21]

The variations in the clinical course of chronic (and acute) pancreatitis and their adverse impact on health-related quality of life, daily activities and social life have been investigated in a few qualitative studies.[22–24] A recent phenomenological study, describing the patients' perceptions of recovering from an acute pancreatic attack, emphasized the physical and emotional burdens, such as uncertainty and anxiety, in the context of an acute attack.[23] Similar to acute attacks, the chronic form of pancreatitis is associated with psychological burdens for the patients affected.[25] A qualitative study with chronic pancreatitis (CP) patients highlighted the permanent experience of suffering and disruption at the physiological and psychological levels.[22] However, the uncertainties and worries surrounding the acute attacks affect not only the patients but also their relatives.[24] Family members additionally describe the experience of seeing relatives affected by the hereditary form of pancreatitis as a disturbing experience.[26]

Although there is a considerable amount of qualitative research on acute[23] and chronic pancreatitis,[22] there has been far less qualitative research on patients' experience with the hereditary variant of the disease. The concurrence of the dimensions *rare*, *hereditary* and *chronic* may lead to specific challenges for patients and their families, so that the existing research on acute and chronic pancreatitis and, accordingly, the therapy options and support available may not be directly transferable to HCP. Instead, the existing research needs to be expanded to give healthcare professionals a comprehensive picture of what needs to be done when they care for both patients with HCP and their relatives.

Theoretical framework

The subjective experience of living with a chronic condition has received increasing research interest both in medicine and the sociology of health and illness since the 1980s.[27–35] Ongoing debates on chronic illness focus on individual coping strategies,[35] self-management,[36,37] the consequences of a chronic illness for the identity of patients, especially of young patients,[38–40] and the correlations to employment,[41] family[42,43] and social life.[44]

The concept of biographical disruption, according to Bury,[45] often serves as a theoretical background for research on the subjective experience of chronic conditions. Bury conceptualizes chronic illness as a particular type of disruptive experience and argues that the onset of a chronic illness represents a biographical disruption, marking a life before and after illness.[45] The concept of biographical disruption has been paradigmatic in the field of chronic illness studies for a few decades. The more recent literature, however, highlights its limitations and the need for more differentiated concepts, such as biographical reinforcement,[46] biographical flow,[47] recurrent biographical disruption[48] or biographical contingency.[49] The latter approach, for example, conceptualizes chronic illness as an 'only sometimes problem'[49] and describes living with a chronic illness to a large extent as normal and, simultaneously, attributes a disruptive potential to the illness.[49]

Although the research has become increasingly differentiated, many approaches have in

common that they understand chronic conditions as predictable linear paths.[50] However, the idea that a person with a chronic illness follows a trajectory is, in Paterson's opinion, misguiding and incomplete.[50] Her 'shifting perspectives model' of chronic illness describes living with a chronic condition as an ongoing, continually changing process in which either elements of illness or wellness can be in the foreground.[50] The perspective of the patient can shift from illness (i.e. illness dominates the daily life) to wellness (i.e. illness is largely unnoticed) and *vice versa*, for example, because the subjective illness experience or the social context changes.[50] Due to the variation in the clinical course of HCP known from the literature, Paterson's account seems to be a suitable lens for the current study because of the possibility of variation and individualization of the illness experience.

Methods

Study design

The lack of research on the subjective experience of HCP in the literature influenced the development of the study aim and research question. Due to the gap, the aim of the present study is to acquire a firsthand understanding of those living with HCP. The main research question is, therefore, how do the individuals affected (patients, partners and family members) experience HCP? An exploratory qualitative design was chosen to clarify the relatively unknown experience of living with HCP.[51] Qualitative semi-structured interviews were used because they allow one to elicit data grounded in the participants' experience, while they retain some relation to the theories identified in the literature, namely, the concept of biographical disruption and the shifting perspectives model of chronic illness.

The development of the interview questions was carried out in a stepwise process. In the first step, based on the existing literature and the research team's experience, brainstorming was conducted to collect possible questions. In addition to the main research question of how those affected experience HCP, the theories identified in the literature led to further questions. The concept of biographical disruption, for example, which focuses on the onset of a chronic illness, raised questions about the diagnosis of HCP; the shifting perspectives model of chronic illness led to questions on the changes between 'normal' and 'acute' illness phases. In the second step, all questions collected were checked for their suitability, e.g. whether the questions were relevant to the objectives of the study. In the last step, the relevant questions were sorted and grouped into themes, e.g. in 'changes of illness phases.' The resulting interview guide starts with theoretically driven open-ended questions about the diagnosis of HCP, through questions about living with HCP to those about the changing illness phases, and ends with a more narrative question about the meaning of living with HCP for the person affected (Box 1).

Box 1. Interview questions (selection/version for patients).

How did you realize that you have this disease?

The diagnosis is often a long process. Would you tell me something about it?

How did you realize you were ill?

How/when did you hear that you have pancreatitis?

Has something changed since the diagnosis?

What happened after diagnosis?

What is it like to live with the disease?

Changes between 'normal' and 'acute' illness phases?

How are you doing with the disease right now?

Do you have any restrictions in your daily life?

Does the disease affect your education/job?

Does the disease affect your family life?

Would you complete the following sentence for me: Living with chronic pancreatitis means for me …

Two slightly modified versions of the interview guide, one for patients and one for relatives, were developed. One interview with a patient and one with a relative as face-to-face pilots were conducted by RM, a female PhD student. These two interviews were included in the final analysis as the pilot test resulted only in minor modifications to the interview guides.

Study participants

Both patients and their relatives were invited to participate in the current study since the family context has been proven to be a major factor in the context of chronic conditions.[24,26,42,43] A patient organization for patients with HCP and their families in Germany (Deutsche Pankreashilfe e.V.) was involved to gain access to potential study participants. This organization has had a longstanding close relationship with two of the researchers (MML and PS). The chairperson of the organization forwarded an open invitation to participate in the interview study to the members by email and verbally at events arranged by the organization. Individuals who responded to these calls received written information about the context and objectives of the study by email and post. RM contacted those interested by telephone to clarify any remaining questions. Snowballing sampling was additionally used to locate further study participants, for example, individuals who are not members of the patient organization: Those contacted through the patient organization were asked whether they could forward the open invitation to others who could be interested in becoming study participants.

The sample was restricted to patients who self-identified as HCP patients, i.e. patients who had a personal history of pancreatitis and/or had been tested for the hereditary form (PRSS1 mutations) and/or already had HCP in their family ($\geq$2 individuals with pancreatitis in $\geq$2 generations). Although HCP could not be verified in every patient by previous genetic test results, it was assumed because of the personal history of pancreatitis, the occurrence of HCP in the family and the absence of other explanatory etiologies (e.g. alcohol). Inclusion criteria regarding unaffected family members restricted the sample to the parents, children, siblings, aunts, uncles, spouses and life partners of HCP patients. The inclusion criterion, at least 18 years of age, applied to all participants. Variations in age, gender, educational level, marital status and the course of the disease were aimed for in the sampling.

Data collection and analysis

The individual face-to-face interviews were conducted by RM (trained in empirical bioethics and qualitative research) at the participant's home. If a personal visit was difficult for the interview participant to arrange, telephone interviews were offered as a backup option. The same interview guide was used in the telephone interviews as in the face-to-face interviews, but the participants were contacted by telephone prior to the actual telephone interview to build trust and rapport and enable a free-flowing conversation. In order to gain the participant's full attention during the telephone interview, instructions were given in advance to provide enough time and a quiet room without potential disturbances.

All interviews (both the face-to-face and the telephone interviews) were fully audio-recorded, transcribed verbatim and pseudonymized. In addition to the audio recording, the interviewer made field notes during and after all interviews.

The interview transcripts were analysed using content-analytical procedures. The methodology selected for the data analysis was qualitative content analysis according to Mayring.[52] Qualitative content analysis is a systematic data analysis technique. It was selected as the analytic method because it is independent of theoretical perspectives, very flexible and provides a systematic way of reducing and synthesizing a wide range of data.[53] Its

Table 1. Themes and categories with examples.

Themes	Categories	Sub-categories	Representative quotes
Unpredictable clinical course of HCP	HCP as an ongoing but unstable condition	Episodic occurrence; disappearance; comparison with a cycle	*Yes, it does restrict me, but not as much as another illness that I would have all the time. Because in my case it only occurs in episodes and then it usually goes away again.(Interview 5)*
Unpredictable clinical course of HCP	Unpredictability; not knowing; fear of attacks; helplessness	Unpredictable clinical course; Russian roulette; disease not known; always expecting an attack; reason for the attack unknown; at the mercy of the disease	*Especially in the beginning, the first few years, it was unpredictable and because I didn't know what I had, it was like a game of roulette or Russian roulette for me, where I always had to expect that I would be lying down the next day and that I wouldn't know why and was at the mercy of it. (Interview 11)*
HCP as a devastating experience	Restrictions	Restrictions in general; effects in many areas; not being able to do things as wanted	*Well, for me, it means restrictions in many areas, you can't do the things the way you want but, on the other hand, it's also a disease that you can definitely live with. (Interview 15)*

central idea is to assign categories to text passages through a qualitative-interpretative act.[52] The analysis follows a systematic procedure and strict content-analytical rules combining deductive and inductive category development.[52]

Correspondingly, the transcripts were worked through with a previously developed, deductively formulated category system derived from theory. RM and SS categorized the interview text into clusters of conceptual categories with the aid of the deductively formulated category system and the software program MAXQDA12. Additionally, new categories were formulated out of the text. A coding scheme was created using the deductive and inductive category development and deliberated in recurring team meetings (for examples of the themes and (sub-)categories, see Table 1). Finally, the coding scheme was applied to all transcripts and the results were further interpreted regarding the categories generated. The team discussions and the different professional backgrounds of the researchers (medicine, philosophy and ethics) are intended to mitigate the rater influence.

The present study is reported according to the COREQ checklist for qualitative research (Supplement 1) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants and they were informed that study participation was voluntary. Other research ethics requirements, such as data protection, were followed diligently. The institutional Ethics Committee of the University Medicine Greifswald approved the study (ref. BB 074/17).

Results

Twenty-six participants were enrolled in the interview study between July 2017 and December 2019. Two participants declined to be interviewed for personal reasons, resulting in a total of 24 individual interviews. Of these 24 interviews, 17 were with patients and 7 with relatives. Twenty-two participants were interviewed in their own homes; two interviews were conducted by telephone. The interviews lasted an average of 44 minutes (median: 43 minutes), ranging from 16 to 91 minutes.

Table 2. Sample characteristics.

Characteristics	Patients (n = 17)	Relatives (n = 7)	All (n = 24)
Age	20–70 (median: 49)	47–78 (median: 67)	20–78 (median: 52.5)
Age groups			
18–30	2		2
30–50	7	1	8
50–70	7	5	12
70–90	1	1	2
Gender			
Male	7	3	10
Female	10	4	14
Genetically tested	11		11
In acute episode	1		1
Education			
A-level	10	2	12
Secondary school	5	2	7
Other	2	3	5
Marital status			
Single	5		5
Married	11	7	18
Living together	1		1
Has children	12	7	19
Employment	13	5	18
Member of patient organization	11	3	14
Relationship to patient			
Parent		3	3
Spouse		4	4

Reprinted: Müller et al.[64].

Different stages of HCP were covered in the study. The patients had had a clinically overt condition since their birth, childhood or adulthood and one patient was in an acute phase of the condition during the interview process. In order to cope with complex familial relationships during the interview study, participants were asked to assign a role to themselves, which resulted in the three categories: Patient, partner and parent. Most participants were married, well-educated and more than 30 years old. Most of the participants had children and worked at the time of the interview study. Further characteristics of the interview participants can be seen in Table 2. Since HCP patients and their relatives are a relatively small group in Germany, characteristics such as the role of the interview participant, their gender and age are not indicated in the following quotes to guarantee anonymity. More information about the study results is available from the first author upon request.

Four topics were chosen as the focus of the current paper due to the richness of the results: (1) The unpredictable clinical course of HCP; (2) HCP as a devastating experience; (3) HCP as part of a normal life; and (4) being reduced to HCP.

The unpredictable clinical course of HCP

The study revealed that those affected by HCP experienced the illness as an ongoing but unstable and unpredictable condition. The participants described that the acute phases of the illness always return, likening it to a cycle. They emphasized, additionally, that the course of the illness could not be predicted. The participants could not say when and how long the acute phases would last. Phases of one to several days were reported. Some participants experienced several phases in short intervals, others no acute phases for many years. The participants reported uncertainty and feelings of powerlessness regarding the acute phases because they could not say what caused an impending exacerbation. In addition, from their perspective, nothing could be done in advance against becoming symptomatic

again. Since they could influence neither the occurrence nor the course of the acute phases, both patients and family members felt helpless and at the mercy of the illness.

> You just got over it, and then it started again. [Interview 15]

> We live on a powder keg. We don't know when it will come because it is so, well, unpredictable. It can go bad; it can go well for a long time. [Interview 17]

Some participants said that they were always vigilant of new episodes. They highlighted that they always had to be prepared for potential acute phases. One participant reported, for example, that the laundry was constantly done so that everything was ready should an acute phase of the illness come. Relatives particularly referred to an increased attention and alertness in their daily lives. One relative, for example, reported phases in his/her family life, in which he/she continuously paid attention to the noises at night to hear if there might be something wrong with the family member affected, even if he/she was not in an acute phase of the illness.

> Well, a certain fear is stored somewhere inside yourself that now, suddenly, a phase will come, and you would be at the mercy of it again. Yes, you're always a little bit on guard. [Interview 11]

The participants also indicated various restrictions and turning points in their lives due to the unpredictable character of the illness, for example, in terms of education, job fulfilment or family planning. Other aspects of life in which the participants felt restricted by the unstable course of the illness extended to vacation plans, going abroad, sports, leisure and social activities. The participants reported that they had had to cancel their plans or appointments due to acute phases and that it was difficult to plan anything at all.

> At the beginning, I dare not go anywhere. Now, I can't go on holiday with my grandchildren alone because if I had such a phase somewhere […] it would be a shock for them [the grandchildren]. [Interview 3]

> At university, I had been promised that I could go to the USA, but due to the illness, which occurred for the second or third time, there were problems with the health insurance […] that was also a limitation, which hurt me very much. [Interview 4]

HCP as a devastating experience

The acute phases were described very differently by the participants, ranging from mild to very severe. The severe phases were usually described as lasting a few days, but one participant also spoke of several weeks. Again, the participants could not say with certainty what had triggered an acute exacerbation. In the case of the latter, the participants reported that they were extremely weak. They described, for example, a rapid loss of physical energy and feelings of being ineffective and impassive. Furthermore, they could no longer eat and drink and, in the worst case, had had to go to the hospital. The description often focused on extreme pain, which could not be treated but was actually unbearable. The pain and weakness particularly brought them to their physical and psychical limits.

The participants who had experienced a severe phase designated it as a disruptive experience. They described it as devastating, very frightening and reported fear of death as an example. Furthermore, they emphasized that the severe phases took them out of their everyday life, for example, from work, that they had no longer been able to do anything and that the severe phases are very difficult to endure.

> This [the acute phase] is really a point where you think, well, it can't go on. […] and you can't really go back into life because you always have some pain and so on and you don't know

what's going on now. That worries you. [Interview15]

Family members expressed similar feelings regarding severe phases. When acute phases occurred, relatives were very concerned about the patient's well-being and afraid that the phases could worsen. Some reported concern about repeated visits to the hospital and physicians; others stated the fear of the patient's death. Relatives who had observed the patient's suffering reported that the severe phases would be extremely difficult to bear for them.

HCP as part of a normal life

The participants also experienced long episodes in which the illness remained unremarkable and unnoticed. Some participants reported no acute phases for several years or even decades. The participants emphasized that the illness disappeared after acute phases and explained that their lives were then comparable to those of healthy people. Several participants did not label themselves or their relatives as being ill but, on the contrary, as being healthy. Parents particularly did not want to talk about their children as being ill.

But as soon as I'm out of the hospital and go back into everyday life and realize, ah, everything is fine and everything is the same as with everyone else, then it's hard for me to say, yes, I have an illness, because it's not present at that moment. [Interview 5]

In addition, the participants regarded HCP as an inevitable part of their existence, as a part that has always been part of their lives because nothing could be done about it. Some participants saw HCP as an essential component, which had made them the person they are today. In several interviews, the participants relativized restrictions and difficulties, which they had mentioned previously. Comparisons to other conditions, such as cancer, were often used to relativize HCP and the associated burdens.

On the other hand, our neighbor has pancreatic cancer now. By comparison, I'm fine at my age. Or when I was in rehab and saw the problems of others, I told myself, I have nothing bad at all. [Interview 3]

Being reduced to HCP

Some participants criticized that others tended to reduce those affected to their illness and the associated aspects. They experienced that other people only noticed the disease and not the person or the current context of the person's state of health and illness. One participant reported, for example, that once he/she had mentioned the disease, the conversation partner only wanted to talk about HCP, although the participant him/herself would have preferred to talk about other topics. Another example was the participants' experience in healthcare, particularly during medical examinations. They reported that other health issues had been overlooked by the medical staff as they focused exclusively on the pre-diagnosed HCP.

[…] and you're often reduced to the disease […] this is often worse for me than anything else. So, this is sometimes forgotten a bit, that you can be a normal person in addition to the disease and still have other problems […]. So, if I just go to a doctor now and say I have the disease, then he just looks at me at this point and at nothing else. I always say, yes, but I also have other things. That is, I think, very, very important. [Interview 5]

In this context, the participants spoke about expectations regarding the patients' behaviour, which often came with the attribution of illness. Some participants had experienced, for example, that others expected them to eat healthily, not to drink alcohol, smoke or do risky sports. One participant, for instance,

stated that in his/her childhood he/she had been excluded from sport because of HCP, even though he/she would have been able to attend sports classes.

Discussion

The results present four categories describing the subjective experience of those living with HCP and show particularly the unpredictable dimension of living with the illness. The findings show that HCP is an illness with a very unstable character whose manifestation can range from mild to very harmful experiences. Although their interview study focuses on acute pancreatitis, the results of Boije et al.[23] confirm the wide variation of the intensity and duration of acute pancreatic phases. Furthermore, the participants described feelings of uncertainty, anxiety and fear due to the lack of knowledge regarding why and at what time the pancreatic attack had occurred.[23] In a previous survey by Shelton et al.[24] participants with hereditary pancreatitis (HP) expressed similar feelings, describing the worry and uncertainty about when an acute phase will occur. Moreover, feelings of helplessness were described by both the patients regarding their own disease and relatives observing the patients' suffering.[24] The participants in the present study confirmed these findings by reporting fear, uncertainty and helplessness due to the unplannable and sudden experiences of the acute phases.

The impact on health-related quality of life, for example, regarding daily activities and psychosocial well-being, described in the survey by Shelton et al.[24] were echoed in the current study, demonstrating restrictions regarding social activities, education and job fulfilment. Related findings have been described in the interview study by Boje et al.[23] indicating that the physical suffering of pancreatic attacks has adverse effects on every day and social life. A recent qualitative study with CP patients by Cronin and Begley[22] highlights the permanent experience of disruption at the physiological, social and psychological level. By contrast, participants in the current study depicted phases of exacerbation but, in between, the disease was predominantly invisible.

In the current study, both patients and family members have described the acute severe phases as a devastating experience. This disturbing dimension of the illness can be found in other studies. Although in the context of genetic testing of HP, both a survey by Applebaum-Shapiro et al.[26] and the one by Shelton et al.[24] refer, for example, to the 'disturbing nature of seeing relatives affected with HP.' At first glance, the description of the devastating experience by the participants in the present study is reminiscent of Bury's concept of biographical disruption.[45] According to Bury, the onset of a chronic illness separates the patient's life into a lifespan before and after illness. In the study with CP patients by Cronin and Begley, the participants described such a shift from a well person to a person with CP.[22] The unplanned and sudden transformation from being healthy to being in an acute phase were also described in the study with patients with acute pancreatitis by Boije et al.[23]

However, the participants in the current study did not report such a clear transition. They spoke instead of recurring disruptive moments as part of their ongoing biography. The disruptive dimension of HCP refers neither to the participants' entire biographies, nor to a single point in their lives, but rather to the recurring difficulty of integrating the acute illness phases into daily life. The concept of biographical disruption by Bury, thus, cannot completely mirror the viewpoints of individuals affected by HCP. These findings are in accordance with several studies which show that the concept of biographical disruption is only relevant to the experience of chronic illness to some extent.[46–49,54]

Most participants in the current study had grown up with the diagnosis of HCP and/or were already familiar with the illness because of its occurrence in the family. However, even if familiar with or expected, the acute phases could be disruptive. The

unpredictability of the phases was, besides their strength, an important reason for this. Patients with acute pancreatitis similarly described the burden of the unplanned and sudden occurrence of the acute phases, which includes shocking and unreal sensations.[23] The experience of HCP patients is, thus, in accordance with the concept of biographical contingency.[49] This concept describes life with a chronic illness as normal, which means undisturbed, to a large extent. Since the chronic illness is only experienced from time to time, the biographies and the daily routines are disrupted only momentarily.[49] By describing life with a chronic illness as normal and, at the same time, granting the disease a disruptive potential, the concept of biographical contingency covers the dimensions expressed by the study participants adequately.[49]

Altogether, the study reveals that HCP can be understood neither as a linear predictable path nor as a dichotomy of life before and after illness but as a continuous, constantly shifting process. This description is covered by Paterson's 'shifting perspectives model' of chronic illness.[50] As described in the current interview study, the perspectives of the participants can shift in the model from illness (i.e. an acute phase is in the foreground) to wellness (i.e. HCP is largely unnoticed) and *vice versa*.[50] Paterson's model helps to resolve the seemingly contradictory statements of the participants. Several participants, for example, stated that living with HCP was never normal because they always had to be vigilant about acute phases. At the same time, the participants said that the disease had disappeared after the acute phases and then they led a normal life. In addition, the illness in itself and the associated difficulties were often relativized throughout the interviews. Paterson's model can cover these variations in the participants' attention to HCP and meets the individual character of the illness experience.

The ethical problem of being reduced to HCP is linked with the shifting process. The changing character of HCP can lead to diverging perceptions. Because the illness is not always present, participants describe themselves as healthy, whereas others label them as ill. This misattribution can be seen as a form of pathologization.[55–57] The experience of being reduced to the illness and labelled as ill is described by the study participants as problematic because the attribution often leads to expectations regarding the participants' behaviour and can even pave the way for a depersonalization or objectification of the participants. A reductive view can lead to severe problems for the individual in the healthcare system, for example, when other diseases or symptoms are overlooked. In addition, conflicts can arise if the perceptions of those affected and healthcare professionals diverge and patients or their relatives do not behave as expected by the healthcare professionals.[58] The experience of being reduced to the illness could be prevented in the context of the healthcare system by focusing on the patient and his/her interests rather than the disease. The exchange with other affected patients and family members could provide further assistance, especially in dealing with feelings of helplessness, being at the mercy of the illness and reduced to it. Consequently, a next step could be to develop a program of psychological support for HCP patients and their families and to provide more support for different forms of patient self-help.

A further step to develop better care and support for those living with HCP could be to ensure long and constant but, at the same time, phase-specific support. Trustful collaborations between patients, families and healthcare professionals are essential for high-quality care, especially in the context of long-lasting chronic conditions.[58,59] A better understanding of the shifting character of HCP and the associated problems can help healthcare professionals to establish a trustful relationship and provide sustainable support. In addition to trustful and permanent support, specific assistance in the respective phases is very important. Consequently, it should be ensured that the

knowledge of the changing character of HCP is integrated into the scientific and practical education of healthcare professionals.

Strengths and limitations

The current study was designed to elicit a deeper understanding of living with HCP and, as far as the authors are aware, it is the only study of this kind. One strength of this study is the use of semi-structured interviews because they allowed more in-depth information and provided detailed insights into how those affected experience HCP. Another strength is the inclusion of both patients and their relatives. Partners and family members often added further information to the findings. Maximum variation sampling was used to ensure the inclusion of participants of differing gender, in different parts of their lifespans and with varying levels of HCP. HCP is a rare disease. The prevalence of the disease and the difficulty in diagnosing and recruiting HCP patients and their families for a research study, therefore, limits the sample size of this study. The participants were contacted via a patient organization, thus, it is possible that the participants were reluctant to make comments that might be perceived as critical about the support of the organization. The recruitment via the patient organization also resulted in a slight majority of patient organization members among the individuals interviewed. Individuals with HCP who were not members of the organization were much more difficult to contact by the research team and, therefore, represent a smaller proportion in the sample. The membership of an organization could indicate a more 'engaged' cohort.

It was not possible for two participants to conduct the interviews at home. These interviews were, therefore, conducted by telephone. There are differences in the data collection between face-to-face interviews and interviews by telephone and an important and unresolved issue about social desirability bias generated through telephone interviews.[60] The nuances of body language, for example, and other non-verbal cues associated with face-to-face interaction may be lost over the telephone, and trust is difficult to establish.[60]

Furthermore, the participants' medical conditions might have had an influence on the study results. Only one of the participants interviewed was in an acute episode at the time of data collection. Talking from a place 'outside their disease,' the participants might have reported other aspects than they would have had in an acute phase. Finally, the study does not have a longitudinal design but instead reproduces the participants' views at a particular point in their lifespan. Longitudinal qualitative research with repeated interviews throughout could provide further information on the subjective experience of HCP. The analysis of qualitative data is not a straightforward process, often accompanied by concerns, e.g. on reliability and generalizability, and there are different opinions about which criteria are the best for evaluating the trustworthiness of qualitative content analysis.[61–63] Concerns related to trustworthiness are minimized in the current study by several strategies, such as protocolling the different stages of the analysis, regular reflective discussions within the research team and full reporting of the process of data analysis. In addition, researchers with different disciplinary backgrounds were part of the study team to mitigate assumptions and bias during data analysis.

Conclusion

The current paper presents findings on the subjective experience of patients with HCP and their relatives showing implications resulting from HCP as a chronic but constantly changing condition. A better understanding of the unpredictable and shifting character can help healthcare professionals to tailor the care to meet the needs of those affected. Individual support for HCP patients should be patient-focused, cover psychological support and be carried by both the healthcare system and the social network, for example, patient self-help groups. Further

research should investigate what specific forms of support HCP patients and their families need and how the different forms of support can help in the acute phases, affect the phases between the acute attacks, and help to deal with the problem of pathologization. The focus of the current study is on the experiences of HCP, but the issues discussed are potentially relevant to other chronic conditions that are variable in their nature. Further research should address how the unpredictable and constantly changing character of chronic conditions can be better considered in the research and development of therapies and the scientific and practical training of healthcare professionals.

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Supplement 1: COREQ Checklist

Trial registration

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Guarantor

RM

Contributorship

RM, SS, SP and MML conceived the study. MML, PS and RM were involved in patient recruitment. RM conducted the interviews. RM and SS conducted the data analysis. RM, SS, CR and JK interpreted and discussed the data. RM wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Supplemental material

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