Mapping Patient and Caregiver Involvement across the Orphan Drug Lifecycle and in Programs that Provide Access to Promising Therapies While Ensuring Prudent use of Scarce Health Care Resources

by

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Abstract

Patients with rare diseases face significant challenges in accessing orphan drugs in Canada because of the uncertainties that decision-makers face when deciding whether or not to provide coverage for a new drug. While all coverage decisions are made under uncertainty, this uncertainty is often greater for orphan drugs due to the poorly understood natural histories of many rare diseases and the lack of rigorous clinical trials. To address these challenges, Canada's Minister of Health announced the creation of a Canadian Orphan Drug Regulatory Framework, which aims to provide Canadians with better, timelier access to orphan drugs, and encourage and facilitate clinical research on rare diseases. Still under development, a draft of the Framework indicates that patient involvement will be incorporated into several stages of the orphan drug life cycle. Although this involvement is emphasized as a key component of the Framework, the exact ways in which patients will be involved has not yet been described.

The purpose of this thesis was to explore opportunities for patient and caregiver involvement through the orphan drug life cycle and to identify how they believe they should be involved. It is comprised of 3 papers. The first paper contains the results of a scoping review of existing and proposed opportunities for patients, caregivers and patient organizations at each stage of the orphan drug life cycle in Canada and internationally. The review demonstrated a wide variety of opportunities that fell into 12 themes: research, clinical trials, patient reported outcome measures, patient registries and biorepositories, stakeholder relationships and collaborations, education and awareness, advocacy, conferences and workshops, patient care and support, patient organization development, regulatory decision-making, and reimbursement decision-making. During a consultative webinar in which the results of the scoping review were

described, Canadian patients and caregivers demonstrated a willingness to take advantage of these opportunities and become more involved in the life cycle.

The second paper focuses on how patients and caregivers believe they should be involved, describing the results of 5 workshops with various stakeholders, including patients, caregivers, physicians, and representatives from government, pharmaceutical companies, and patient organizations, and of a deliberative session and webinar with patients and caregivers alone. The results revealed significant patient and caregiver interest in the ways in which they could be involved to help improve coverage decision-making. Participants recognized the need for prudent decision-making, but emphasized that a lack of evidence of effectiveness is not the same as evidence of a lack of effectiveness. They believed that managed access programs (MAPs) are a reasonable means of reducing uncertainty in coverage decision-making while providing patients with timely access to potentially effective orphan drugs. Participants also felt that beyond participating in MAPs, they should be involved in the design of the programs.

Building on the patient and caregiver interest in MAPs demonstrated in the results of the second paper, the third paper focuses on a patient and caregiver-designed framework for MAPs. It describes the results of two workshops with patients and caregivers from across Canada. Through the workshops it was discovered that patient and caregiver interest in MAPs is motivated by their lack of trust in decision-makers and physicians to ensure they receive access to effective orphan drugs, desperation to gain access to potentially effective drugs when no alternatives exist, and hope that access to effective orphan drugs can be improved in Canada. Participants identified 7 aspects of an ideal MAP: program goals, disease/drug priorities, program-specific governing committees, incorporation of individual patient input, learning from other countries, ongoing monitoring and registries, and appropriate outcome measures and

stopping criteria. They emphasized the need for patient involvement and transparency in all aspects of the program.

Preface

This thesis is an original work by Andrea Dunn. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Patient Preferences around Therapies for Rare Disease”, no. MS1_Pro00029603, September 3, 2014.

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Introduction

In Canada, the challenges that patients with rare diseases face in accessing orphan drugs have become highly publicized [1-4]. Orphan drugs are medicines used to treat rare diseases – life-threatening, seriously debilitating chronic conditions that, as defined in the European Union, affect less than 1 in 2,000 patients [5]. The majority of rare diseases are genetic and develop in early childhood. Often, little is known about them, and many patients struggle to receive a diagnosis [5]. Once a diagnosis is made, access to effective therapies is limited due to the uncertainties that decision-makers face when considering the coverage of orphan drugs. All drug coverage decisions are made under uncertainty, which stems from limited high-quality information on the drug when a decision needs to be made [6]. However, in the case of orphan drugs, the uncertainty is often greater because of the poorly understood natural history of many rare diseases and the lack of any rigorous clinical trials (due to small patient populations and few validated outcome measures) [7]. Consequently, decision-makers are at a greater risk of making a "wrong decision", which can lead to wasted resources and harms to patients when the treatment provided turns out to be ineffective or unsafe or when a treatment that is not provided turns out to effective. [6]. This risk has increased as new, high-cost drugs continue to be introduced into a system with finite health care resources. Manufacturers argue that these drugs are expensive to develop and the potential market for their use is small [8]. However, most rare disease patients have a high, unmet need for effective treatments [9]. Consequently, reimbursement decisions around orphan drugs are challenging.

In response to the challenges faced by rare disease patients, Canada's Minister of Health announced the creation of a Canadian Orphan Drug Regulatory Framework, which aims to 1)

provide Canadians with better, timelier access to orphan drugs, and 2) encourage and facilitate clinical research on rare diseases [5]. Although still under development, several key aspects have been announced in a draft of the Framework, including the incorporation of patient involvement at several stages of the 'orphan drug lifecycle'. This lifecycle begins with preclinical research, where newly developed drugs are tested in tissue samples and animal models [10]. This is followed by the clinical trial stage, during which the safety and efficacy of the drug in humans are assessed. The next stage comprises regulatory approval, when the drug undergoes pre-market review based on information provided by the manufacturer. Such information includes the results of the pre-clinical studies and clinical trials. Once approved for sale, 'real-world' studies are initiated to examine the drug's effectiveness when used in a typical health care setting. If manufacturers are seeking public coverage for their product, they submit a request to a drug coverage review body and the product enters into the reimbursement stage. In Canada, two centralized review processes are in place: the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) [11;12]. These review bodies provide listing recommendations to all publicly-funded drug programs in Canada, except for Quebec. Additionally, some private insurers use CDR recommendations when deciding whether or not to add "high cost" drugs to their formularies [13]. Typically, drugs that receive a positive recommendation will be approved for public coverage in the participating drug plans [11;12].

The draft Regulatory Framework states that patient involvement will be sought during clinical trials, the orphan designation process, regulatory review, and reassessment [5]. However, the exact ways in which patients will be involved have not been described. Additionally, the framework does not specifically address the latter stages of the lifecycle, including

reimbursement decision-making. Literature suggests that involvement at this stage is equally as critical [14;15] and increasingly demanded in Canada [14].

The purpose of this thesis is to explore patient, caregiver, and patient organization involvement in the orphan drug lifecycle. It consists of 3 consecutive papers, each building on the previous one. The first paper addresses the question: what roles exist or have been proposed for patients, caregivers, and patient organizations at each stage of the orphan drug lifecycle? To answer this question, a scoping review was conducted, which included a comprehensive review of relevant scholarly work and grey literature, followed by a consultative webinar with patients and caregivers to identify any opportunities that had been missed.

Building on the results of the first paper, the second paper addresses two questions 1) how do Canadian patients with rare diseases and their caregivers believe they should be involved in the orphan drug lifecycle and 2) what are their priorities for involvement? Results were obtained through a set of 5 workshops with various stakeholders, including patients, caregivers, physicians, and representatives from government, pharmaceutical companies, and patient organizations, followed by a deliberative session and webinar with patients and caregivers alone.

Results of the second paper demonstrated significant patient and caregiver interest in becoming involved in order to improve coverage decision-making. In particular, patients and caregivers were interested in participating in and helping to design managed access programs (MAPs). MAPs are arrangements that provide patients with provisional coverage of a new drug in order to facilitate the generation of the information needed to address the uncertainties that exist around the product and support a definitive coverage decision within a given period of time [6]. The third paper addresses the question: what would a patient-designed framework for managed

access programs look like? This question was answered through two workshops with patients and caregivers.

Together, these papers 1) describe the current state of the science around patient, caregiver, and patient organization involvement at each stage of the orphan drug lifecycle, 2) increase understanding of how patients and caregivers want to be involved, and 3) outline a framework for one of patient and caregiver's priorities for involvement, MAPs.

Chapter 1:
A scoping review of patient and caregiver involvement in the orphan drug lifecycle

Introduction

"Too often, Canadians dealing with rare diseases are faced with difficulties in accessing the information and medication they need…" [16]

Leona Aglukkaq, Minister of Health, Canada, 2012

In October of 2012, Canada's Minister of Health unveiled a new initiative aimed at improving the lives of Canadians suffering from rare diseases [5]. Following in the footsteps of other developed countries, the Minister announced the creation of a Canadian Orphan Drug Regulatory Framework. Still under development, the framework has two objectives: 1) providing Canadians with better, timelier access to orphan drugs (i.e., drugs that treat rare diseases) and 2) encouraging and facilitating clinical research on rare diseases.

Orphan drugs refer to medicines used to treat rare diseases, which are life threatening, seriously debilitating chronic conditions and, based on the definition used in the European Union, affect less than 1 in 2,000 people [5]. The majority of rare diseases are genetic and develop in early childhood. Given the low prevalence of these diseases, little is usually known about them and patients struggle to receive a diagnosis. When a diagnosis is made, access to effective therapies is limited due to the uncertainties that decision-makers face when considering the market approval and coverage of orphan drugs. In order to encourage the development and regulatory approval of designated orphan drugs many countries have introduced incentives, such as grants and tax credits for research market exclusivity, and fast-track assessments [17]. Such incentives have been highly effective in the United States and the European Union, significantly increasing the number of orphan drugs introduced to the market. For example, in the 8-10 years preceding the introduction of the Orphan Drug Act in the United States, 10 treatments for rare diseases were approved by the FDA. In the 24 years following the Act, 282 treatments for rare

diseases were approved. However, many patients still lack access to these drugs due to scarce healthcare resources and the unwillingness of payers to fund high-cost therapies with limited information on their effectiveness.

All regulatory and reimbursement decisions are made under uncertainty resulting from limited information on the benefits, harms, and costs of a drug [18]. This uncertainty is often greater for orphan drugs because of a lack of comprehensive information around the product at the point of decision-making, a result of the challenges faced in conducting clinical trials (e.g., small patient sample sizes; lack of validated outcome measures) [7] and the often poorly understood natural histories of rare diseases [8;9]. Additionally, orphan drugs are usually expensive, since manufacturers argue they are costly to develop and the potential market for their use is small [8]. At the same time, rare disease patients have a high, often unmet need for effective treatments [9]. For these reasons, regulatory and reimbursement decisions around orphan drugs are extremely difficult.

Health Canada's proposed Framework aims to improve patient access to orphan drugs by addressing the unique challenges faced when studying these small populations. It indicates that a technology lifecycle approach will be adopted with improved information sharing among patients and other stakeholders (e.g., healthcare professionals, researchers, payers) to help reduce uncertainties and provide greater context for decision-making [5;19]. In a lifecycle approach, an orphan drug is continually assessed along its entire lifecycle, from the initial research and development (R&D) stages to possible ultimate obsolescence. While the importance of this aspect of the framework has been made clear, the ways in which patients will be involved have not yet been explicated. In order to develop effective approaches for patient involvement, a comprehensive understanding of how they are currently involved is required.

Objective

The objective of this review is to explore existing roles for patients, caregivers, and patient organizations at each stage of the orphan drug lifecycle, as well as proposed roles.

Background

Two key features of the proposed Canadian Orphan Drug Regulatory Framework – adopting a lifecycle approach and incorporating patient involvement– are not new concepts. In fact, literature has been published on both the usefulness of the lifecycle approach for regulating drugs and the importance of seeking patient input in healthcare. These two concepts are introduced below.

Why adopt a lifecycle approach?

The lifecycle of a drug comprises 7 stages (Figure 1-1), beginning with the preclinical phase, where newly developed products are tested in tissue samples and animal models [10]. Subsequently, clinical trials begin to assess safety and efficacy of the drug when used in humans. In the regulatory stage that follows, market approval is either granted or denied based on information provided by the manufacturer, including the results of both the pre-clinical studies and clinical trials. When the drug is approved for sale, real world studies commence to assess the effectiveness of the product when prescribed in a typical healthcare setting. If the manufacturer seeks public coverage for their product, the drug enters into the reimbursement decision-making stage, where a drug coverage review body makes a decision on whether or not to list the drug based on the evidence submitted. In Canada, centralized review processes exist. The Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review provide listing recommendations to all publicly-funded drug programs in the country, except in Quebec [11;12]. Additionally, some private insurers use CDR recommendations when deciding whether or not to add "high cost" drugs to their formularies [13]. If the drug receives a positive recommendation, it is

typically approved for public coverage through the participating drug plans. As time passes and research progresses, the drug may be replaced by a new therapy, and become obsolete [10].

The early stages of the orphan drug lifecycle, R&D, are often inhibited by the difficulties of conducting clinical trials with rare disease populations [17]. Faced with small patient samples sizes and a lack of validated outcome measures to use, researchers conducting pivotal trials for orphan drugs are more likely to use less rigorous trial designs (e.g., non-randomized and un-blinded designs) and to collect surrogate measures of disease response, compared to trials for more common diseases [20]. As a result, there is often less evidence of clinical effectiveness to support applications for market or coverage approval. To facilitate decision-making on orphan drugs and improve the likelihood that an effective therapy will obtain coverage, the collection of additional evidence is often a necessity [5]. A lifecycle approach to the regulation of new drugs involves ongoing information collection, analysis, and communication throughout each stage of the cycle [21]. This allows for greater flexibility in the approval process, as new information is used to revise decisions. Within the proposed Orphan Drug Framework, this flexibility is critical for responding to the limited information that often exists around rare diseases and orphan drugs [5]. Additionally, the Framework also proposes the use of the lifecycle approach to create greater opportunities for receiving the patient perspective on their disease and available therapies.

Figure 1-1. Lifecycle of a drug.

Pre-clinical phase	Clinical trials	Regulatory approval	Real-world studies	Reimbursement decision-making	Routine clinical use	Replacement with new therapies

Why is there a need for patient involvement?

In recent years, patients have begun to take on a more active role in healthcare and research, from providing input into the evaluation and prioritization of research to participating

in decision-making through rationing exercises, priority setting, health technology assessment, and coverage decision-making [14]. In part, this has been due to the increasing recognition of the possible benefits of patient involvement in the health sector. For example, it has been suggested that active patient participation may help to improve the value of health care research by increasing the credibility and relevance of the results as well as the translation of these results into clinical practice [22]. Patient involvement in healthcare policy may lead to more responsive services and better outcomes of care [23]. It may also help to identify benefits and costs not identified in the health technology assessments of new therapies for which coverage is being considered [24]. For rare disease patients seeking access to orphan drugs in particular, patient knowledge may be used to reduce the numerous uncertainties that decision-makers face when considering these products for market or coverage approval [15].

Recognizing the potential value of increased patient involvement in addressing the many challenges around access to orphan drugs, the proposed Orphan Drug Regulatory Framework intends to incorporate it into several stages of the orphan drug lifecycle. More specifically, involvement will be sought during clinical trials, the orphan designation process, market approval application review, and reassessment [5]. Still, the ways in which patients will be involved at these stages remain unclear. Additionally, though the proposed Framework does not specifically address the latter stages of the orphan drug lifecycle (i.e., reimbursement decision-making), involvement at this point is equally as critical [14;15] and is being increasingly demanded in Canada [14].

This review will facilitate future efforts to incorporate patient input into the lifecycle, within the proposed Framework and beyond, by producing a map of the opportunities that

currently exist or that have been proposed for patients, their caregivers and the patient organizations that represent them.

Methods

A scoping review was conducted using the methodology developed by Arksey and O'Malley [25;26].

Identifying the research questions

Two research questions were developed based on the objective of this review:

1. What opportunities exist for patients, caregivers, and patient organizations to become involved at each stage of the orphan drug lifecycle?
2. What opportunities have been proposed for involving them at each stage of the lifecycle?

In this paper, 'patient' refers to an individual living with a rare disease. 'Caregiver' refers to a patient's family member who provides them with physical and emotional care. This definition of caregiver excludes professionals who are paid to provide care to patients.

Identifying relevant studies

Literature Search

The following bibliographic databases were searched for relevant peer-reviewed literature: MEDLINE, PubMed, The Cochrane Library, the Centre for Reviews and Dissemination databases (DARE, NHS EED and HTA), EMBASE, Web of Science, and EconLit. Searches were run in March 2014, with a revised PubMed search in May 2014 and monthly updates from PubMed from April 2014 until June 2015. Searches were limited to English language publications from 2000 to date. The search terms included controlled vocabulary, such as the Medical Subject Headings (MeSH): Patient Preference, Patient Participation, Consumer Participation, as well as additional keywords, such as Patient Engagement and Patient

Involvement. These were combined with terms to capture medical technologies, such as MeSH terms: Diffusion of Innovation and Biomedical Technology, as well as those for rare diseases, such as Rare Diseases and Orphan Drug Production. Searches for grey literature covered databases such as ProQuest Dissertations and Theses, NHS Evidence, and Google. The reference lists of relevant papers were also scanned to identify additional references. Full details of the search terms and sources used are provided in Appendix 1.

Review of Regulatory and Reimbursement Decision-Making Processes

The websites of regulatory and reimbursement decision-making bodies in 20 countries were reviewed to identify opportunities for involvement (e.g., patient evidence submissions; membership on advisory or decision-making committees). They represented the top 20 Organization for Economic Co-operation and Development (OECD) countries based on gross domestic product (GDP) per capita with populations of greater than 1 million people and socialized health insurance programs/universal healthcare [27]. Four countries (Qatar, Kuwait, the United Arab Emirates, and Israel) were initially included in the review, but a preliminary search revealed a paucity of information regarding decision-making processes on drugs in these countries. They were replaced with the next 4 OECD countries that fulfilled the inclusion criteria.

Twelve of these 20 countries are members of the European Union (EU). Some drugs receive regulatory approval across the EU through a centralized authorization procedure conducted by the European Medicines Agency (EMA)[28]. As it is compulsory for officially designated orphan drugs to go through this centralized procedure, EMA's regulatory approval process was reviewed but the individual regulatory approval policies for these 12 countries were not.

Searches for additional information on decision-making processes were done using the Google search engine. When opportunities for involvement were not well described, emails were sent to the decision-making organizations to request clarification.

Study selection

Literature eligibility criteria

Literature selection was completed by two reviewers who individually scanned the titles and abstracts of citations identified through the database search. Studies were included if they described the involvement of patients, caregivers, or patient organizations in any stage of the orphan drug lifecycle as defined in this review. Documents produced by patient organizations describing their work were also included. Papers describing the involvement of umbrella patient organizations were also included.

Abstracts, editorials, and perspectives were excluded, as were any studies or documents in languages other than English. Literature describing "public", "community", or "citizen" engagement was excluded, as the focus of this review was on patients, their caregivers, and patient organizations. Literature was also excluded if it described non-drug technologies or did not specifically discuss rare disease patients. Papers describing the involvement of non-rare disease patient organizations or umbrella organizations were excluded. Papers describing individual patient involvement during individual clinical decision-making were excluded as this study was a macro-level analysis focused on large-scale processes (e.g. coverage decision-making).

Decision-making process eligibility criteria

No eligibility criteria were applied to the review of decision-making processes, As such, all decision-making processes identified were included in this review.

Charting the data

One reviewer extracted data from all of the included papers using a standardized data extraction form. A second reviewer extracted data from a random sample (30%) of the included papers to assess reliability. From each selected paper, data on existing or proposed opportunities for patients, caregivers, or patient organizations to be involved in the orphan drug lifecycle were extracted. In many papers, multiple opportunities for involvement were described. For each opportunity discussed in a paper, the following information was extracted:

- Description of the activity
- Country in which it took place
- Type of disease
- Participants involved (i.e., patients, caregivers, or patient organizations)
- Participants' role
- Impact or outcome

One reviewer extracted data on each decision-making process identified. For each process, information was extracted on any aspect in which patients, caregivers, or patient organizations were involved (e.g., submitting a topic for consideration; membership on advisory or decision-making committees). Each of these aspects was defined as an opportunity for involvement.

Collating, summarising and reporting the results

Data on all identified opportunities were tabulated to facilitate analysis by the researcher. The qualitative research technique of thematic analysis was used to explore the types of activity involved in each opportunity in order to identify themes by which the opportunities could be categorized. Opportunities were also categorized as either existing (i.e., having actually taken place) or proposed (i.e., having been suggested for the future).

Consultation exercise

Members of the Patient and Caregiver Liaison Group of a Canadian research network (Promoting Rare-Disease Innovations through Sustainable Mechanisms or PRISM [29]) were invited to participate in a webinar, *Patient Involvement throughout the Lifecycle of Orphan Drugs*, to validate the findings of the literature and decision-making process review and identify any additional opportunities that were missed. These individuals were either rare disease patients or caregivers for rare disease patients in Canada. The webinar began with a brief introduction and a description of the review methodology. Subsequently, for each theme, participants were presented with existing and proposed opportunities for patients and caregivers identified in the review. They were then invited to comment on the results and asked if they knew about any other ways that patients and their caregivers are involved, or that have been suggested for involving them. Participants were then presented with existing and proposed opportunities for patient organizations. They were again given the opportunity to comment and asked if they knew about any other ways in which patient organizations are involved, or that have been suggested for involving them. Following the webinar, participants were contacted individually for any clarifications or additional information as needed.

Results

The results of the literature review are summarized in Figure 1-2 (PRISMA flow diagram) and Table 1-1. Opportunities for involvement were found to fall into 12 themes: research outside of clinical trials; clinical trials; patient reported outcome measures; patient registries and biorepositories; stakeholder relationships and collaborations; education and awareness; advocacy; conferences and workshops; patient care and support; patient organization development; regulatory decision-making; and reimbursement decision-making. The majority of the opportunities were identified as existing. In almost all cases, the impact or outcome of

patient, caregiver, or patient organization involvement was not well-described. One paper reported that:

> *"[Patient involvement] was found to be particularly effective in enhancing the design and conduct of our research."* [30]

The rest of the studies typically commented on the success of an opportunity as a whole, such as the results of a research study, but not on the impact of patient involvement specifically:

> *"The health utility values provided by this study could inform assessments of cost-effectiveness for therapies for advanced [neuroendocrine tumours]."* [31]

As such, the impact/outcome of involvement is not discussed further.

The results of the review of regulatory and reimbursement decision-making processes are summarized in Tables 1-2 and 1-3, respectively. All opportunities identified in these processes were categorized as existing and are described below under the themes of either regulatory or reimbursement decision-making.

All existing and proposed opportunities, including those identified by the participants in the consultation webinar, were mapped onto the orphan drug lifecycle (Table 1-4).

Existing opportunities for involvement in the orphan drug lifecycle

Research

Thirty-three papers reported on opportunities for patient, caregiver, and patient organization involvement in research. They described experiences in Australia, Canada, the United States, the United Kingdom, the Netherlands, Germany, France, Spain, and internationally. Patients and/or caregivers participated as subjects in studies outside of clinical trials (International [32]; Spain [30]; United Kingdom[31]; United States[33;34]), set research priorities

(Netherlands[35]; Spain[36]), initiated research studies (United States [37;38]), provided assistance to researchers conducting studies (United States [39]), led research (International [40]; United States[37]), developed or participated in research organizations/networks (Europe [41]; United States[42]), and disseminated research-related information (International [43]; United Kingdom[44]). The most frequently reported opportunity for patients and their caregivers was participation in research studies. For example, they participated in qualitative interviews investigating reasons patients participate in randomized controlled trials [33] and took part in priority-setting exercises designed to set research priorities [36].

Opportunities for patient organizations were similar to those for individual patients. Patient organizations participated as subjects in research studies (Europe[45]), set research priorities (Germany[46]; Netherlands[35]), initiated research (Netherlands [46]; United States[47]), provided assistance to researchers conducting studies (International [48]; Netherlands[35]; Spain[30]; United States[37]), led research (Europe[49]; France[50]; United Kingdom[51]; United States[37;52;53]), participated in research organizations/networks (Europe[41;54]; Netherlands[46;55]; United States[42;56-58]), and disseminated research-related information (International [43]; United Kingdom[44]). Additionally, patient organizations funded research (Germany [46]; United States [34;42;53;56;59;60]). The most frequently reported opportunity for patient organizations was leading research, which included creating and distributing quality of life surveys [49] and evaluating the effectiveness of new orphan drugs for organization members [37]. Patient organizations had also partnered with researchers to identify the gene responsible for causing a particular rare disease [37].

Clinical Trials

Opportunities for involvement in clinical trials were reported in 8 papers and described experiences in the Netherlands, the United Kingdom, the United States, and across Europe. The

only identified opportunity for patients was their participation in trials [61]. Patient organizations provided assistance to researchers conducting trials (Europe [62]; Netherlands [55]; United States [52;63;64]),funded clinical trials and clinical trial networks (Europe [65]; United States [64]), established and/or participated in clinical trial networks (Europe [65]; United States[52;56;64]), and disseminated information on the results of clinical trials (United States[52;64]). The most commonly reported opportunity for patient organizations was providing assistance to researchers conducting clinical trials. Some of the ways in which patient organizations were involved included providing input into the design of trials and treatment protocols [62], recruiting participants [62-64], and reviewing consent statements [52;64].

Patient reported outcome measures

Opportunities for involvement in the use or development of patient reported outcome measures (PROMs) were reported in 5 papers, describing experiences in Germany, the United States, and internationally. PROMs are measurement instruments that patients complete to provide information on aspects of their health status that are relevant to their quality of life, including symptoms, functionality, and physical, mental, and social health [66]. Patients and/or caregivers submitted patient reported outcomes (PROs) in studies (International [67]), participated in studies to develop and validate outcome measures (International [68]; Germany [69]; United States [70]), and assisted researchers conducting studies to develop and validate outcome measures (International [68]). Patient organizations assisted researchers in conducting studies to develop and validate outcome measures (International [71]). Patient assistance to researchers in conducting validation studies differed from that of patient organizations. While patients were consulted in developing questions to incorporate into a PROM survey [68], patient organizations helped to translate and distribute surveys [71].

Patient registries and biorepositories

Opportunities for involvement in patient registries and biorepositories were identified in 17 papers, which described experiences in Sweden, the United States, and internationally. The majority of the registries reported on were natural history registries, but contact registries, which allow researchers to get in touch with potential clinical trial participants, and registries used to track treatment outcomes were also identified. Three papers described "international" registries, such as the International Pompe Association/ Erasmus Medical Centre Pompe Survey [67]. This Survey is a joint international study and registry that has recruited patients from Australia, Canada, France, Germany, the Netherlands, the United Kingdom, and the United States.

Patients and/or caregivers enrolled in and submitted data to registries/biorepositories (International [48;67;72]; Sweden [73]; United States[34;52;59;74]), provided input on the design of patient registries/biorepositories (International [67]; Europe [54]), and were involved in the maintenance and/or management of registries/biorepositories (Europe [75]). Patients also established registries (United States [76]); however, this was usually done through a patient organization (International [67]; Europe [77]; United States [37;53;58;59;76]). Establishment of registries was the most frequently reported opportunity for patient organizations, while for patients it was enrollment in registries. Patient organizations also provided input into the design of patient registries/biorepositories (International [67]; Europe [54]; United States [78;79]), were involved in the maintenance and/or management of registries/biorepositories (Europe [75;77]), provided funding (Europe [75]; United States [78]), and recruited participants (International [67]). This work was often done in collaboration with researchers and healthcare professionals.

Stakeholder relationships and collaborations

Nine papers reported opportunities for involvement in stakeholder relationships and collaborations, describing experiences in the Netherlands, the United Kingdom, the United States, and internationally. Patients and caregivers established and maintained relationships with researchers (Netherlands [46]; United States [34]). Patient organizations facilitated relationships between different stakeholders by developing charters for collaboration [62] and hosting neutral meetings [56] (Europe [62]; United States [56]) and established their own relationships with stakeholders, such as researchers, industry members, healthcare professionals, and other patient organizations (European Union [45]; Netherlands [46]; United States [34;53;56;64]).

Education and awareness

Opportunities for involvement in education and awareness were identified in 11 papers describing experiences in Netherlands, the United States, and internationally. These opportunities were limited to patient organizations, which shared informational resources on various disease-specific topics (Europe [49]; Netherlands [55]; United States [52;53;56;63;64]), organized and sponsored formal educational activities and training programs for healthcare professionals, researchers and policymakers (United States[52;59;60;63;64]), and started awareness campaigns (United States[56;63]). The most commonly reported opportunity was sharing informational resources, which was often done through websites but also through toll-free hotlines and mentoring programs.

Advocacy

Opportunities for involvement in advocacy were reported in 8 papers, which described experiences in Germany, the United States, and Europe. Patients and their caregivers used social media to advocate for access to experimental drugs (United States [80]). Patient organizations also

advocated for drug access and coverage (United States [63]), as well as for research (Europe [77]; Germany [46]) and legislation (United States [56;60]) on rare diseases and orphan drugs.

Conferences and workshops

Eight papers described involvement in conferences and workshops in two countries, Australia and the United States. Patients and their caregivers participated in conferences and workshops, helping to identify goals and produce recommendations for a national rare diseases strategy (Australia [81]). Patient organizations also participated in conferences and workshops aimed at developing a national strategy (Australia [81]). Additionally, they hosted and funded conferences and workshops (United States [34;52;53;59;60;64]), bringing together patients, caregivers, researchers, and physicians.

Patient care and support

Opportunities for involvement in patient care and support were reported in 15 papers describing experiences in Italy, the United Kingdom, the United States, and internationally. Patients and caregivers provided social support for other patients (International [40;82]; United States [37;39]) and monitored their own clinical care through electronic health records (Italy[83]). Patient organizations provided social (Europe[49]; United Kingdom[60;63]; United States[53;63]), financial (United Kingdom[63]; United States[56;63]), and clinical care support (Europe [49;77]; United States[53;59;63]) for patients and their caregivers, and provided support for patients participating in clinical trials (Europe[62]; United States[56]). Opportunities for patient organizations were more frequently reported on than those for patients. The most frequently reported opportunities were for providing social support and clinical care support.

While patients, caregivers, and patient organizations all provided social support, the ways in which they did so differed. Patients and caregivers most often built connections and shared

information through online forums, such as Patients Like Me [40]. Patient organizations were more likely to establish online forums for patient and caregiver use, such as the Muscular Dystrophy Charity [44] and the PBCers Organization [60], as well as organize social events, and provide mentoring programs and counselling services [49;53;60;63;84].

Patient organization development

Opportunities for involvement in the development of patient organizations were reported in 5 papers describing experiences in France, the Netherlands and the United States. Patients and caregivers established patient organizations, like the French Muscular Dystrophy Organization and Chromosome 18 Registry and Research Society (France [50]; United States [37]). Patient organizations provided advice to others on how to start an organization (United States [38]), established international patient organization alliances (Netherlands [55]; United States [53]), like the International Pompe Alliance, and further developed their organization by hosting fundraising events (United States [53]).

Regulatory decision-making

Opportunities for involvement in regulatory decision-making were reported in 5 papers, describing experiences in Canada, the United Kingdom, the United States, and the European Union. Additional opportunities for involvement in these jurisdictions and in New Zealand and Switzerland were identified through the review of regulatory decision-making body websites. Patients submitted PROs for consideration by a regulatory body (Canada [85]; European Union [86]; New Zealand [87]; United States [88]). In the United States, this information was collected through public meetings where patients and caregivers commented on the disease and its impact on patients' daily lives, the types of treatment benefits that matter to patients most, and the patients' perspectives on the adequacy of currently available treatments [88]. Patients and caregivers also

provided input on proposed regulatory decisions/guidelines (Canada [85;89]; New Zealand [90]; United States [91;92]), served as members on advisory/decision-making committees (Canada [85;89]; United States [91;92]), provided input into assessments of benefits and harms (United States [93]), and reported adverse events to regulators (Australia [94]; Canada[95]; European Union [96]; New Zealand [97]; Switzerland[98]; United States[99]).

Opportunities for patient organizations in regulatory decision-making were primarily found in the European Union. Representatives from organizations sat on advisory/decision-making committees [100;101] and provided input into: pre-submission advice given to researchers regarding clinical trial protocols [100], assessments of benefits and harms [96], plans for ongoing pharmacovigilance [96], and on consumer information, such as labelling [100].

Reimbursement decision-making

Five papers discussed opportunities for involvement in reimbursement decision-making in the Netherlands, the United Kingdom, the United States, and in the Canadian province of Ontario. Additional opportunities for involvement in these jurisdictions and in Australia, Canada, Denmark, Germany, New Zealand, Sweden, Switzerland, Scotland, and Wales were identified through the review of reimbursement decision-making body websites. The majority of the identified opportunities were found in centralized drug review processes, which are single processes followed by a set of participating organizations in order to standardize decision-making [102;103]. However, opportunities were also identified in the review processes of 'safety-net' programs. These programs typically provide patients with access on a case-by-case basis for a fixed time period to high-cost therapies that either do not have market approval or are not approved for reimbursement [104-114].

Patients submitted drugs for evaluation (Australia [115]; New Zealand [116]), submitted information for use in evaluations, such as the degree of perceived benefit, subjective risk assessment, or burden of associated side effects (Netherlands [106]; New Zealand [117]; United States [118]), participated in consultations during the review process (Ontario [119]; New Zealand [117]; United States [118]), served as members on advisory/decision-making committees (Canada [120]; Netherlands [106]), provided feedback on completed evaluation reports or recommendations (New Zealand [117]; United States [121]), prepared patient submissions for consideration alongside clinical and economic evidence (Australia [115]; United Kingdom [122]; Wales [123]), presented views during review committee meetings (United Kingdom [112]; United States [118]), and consulted on the design of the evaluation process (United Kingdom [51]).

Patient organizations reviewed horizon scanning reports (United Kingdom [124]), which identify new and emerging health technologies [125], providing more up to date information on topics such as the presentation of a rare disease [124]. They also submitted drugs for evaluation (Australia [126]; New Zealand [116]), participated in consultations during the review process (Australia [127]; Germany [128]; United Kingdom [112]; Scotland [129]), served as members on advisory/decision-making committees (Sweden [130]; Switzerland [131]; United Kingdom [132]; United States [133]), prepared patient submissions (Australia [115]; Canada [134]; Ontario [119]; United Kingdom [135]; Scotland [136]; Wales [123]), provided feedback on completed evaluation reports or recommendations (Ontario [119]), launched appeals of negative funding decisions (United Kingdom [51]), and created recommendations for the design of the evaluation process (United Kingdom [51]).

Opportunities for patients and patient organizations to prepare submissions for consideration by reimbursement decision-makers in the centralized drug review processes of

three countries were similar. In Australia and Canada, patient submission templates focus on 5 areas: 1) how the information in the submission was obtained, 2) the impact of the disease on patients, 3) experiences patients have with their current therapy, 4) expectations patients/caregivers have for the new drug and 5) experiences patients have had with the new drug [137;138]. In Canada, the submissions also request information on caregiver impact [137]. In the United Kingdom, the submission template is focused primarily on the new drug and requested information includes 1) expectations patients/caregivers have for the new drug, 2) expectations of the new drug compared to existing therapies, and 3) experiences patients have had with the new drug [139].

Fewer opportunities were identified for patient or patient organization involvement in safety-net processes. In Finland, patients submitted drugs for consideration in their Special License Procedure [140]. In the United Kingdom, patients receiving a drug through a Patient Access Scheme were directly consulted in the review process [112], provided feedback on evaluations or recommendations [112], and presented their views during a committee meeting [112]. In Australia, patient data was submitted into annual evaluations for reapplications made into the Life Saving Drugs Program [141].

Proposed opportunities for involvement

Nineteen proposed opportunities for involvement were identified. In all cases the descriptions of proposed opportunities were limited and the exact ways in which patients, caregivers, or patient organizations should be involved could not be identified.

> *"According to symposium participants, collaborations and networks should be premised on open communication and equal and inclusive engagement of all stakeholders, with the voices of patients, carers and families at the core of all decision-making processes."* [81]

As such, while this section outlines the ways in which it has been suggested patients, caregivers, and patient organizations *should* be involved, it was not possible to describe the exact mechanisms by which this involvement was suggested to take place.

Research

One paper described a proposed opportunity for involvement in research. At the Australian Rare Disease Symposium, it was suggested that patients and their caregivers should be directly involved in all decisions about research on rare diseases, including involvement in the decision-making processes of research collaborations and networks [81].

Clinical Trials

Proposed opportunities for involvement in clinical trials were specified in three papers. In Europe, participants in a symposium hosted by the European Haemophilia Consortium (EHC) Congress proposed that patients should be involved in ensuring the collection of real-world outcomes that they find meaningful [45]. In the United States, the National Organization for Rare Disorders (NORD) proposed that it should develop systems for improving patient access to and participation in trials [56]. Finally, the Genetic Alliance UK proposed that patient input on acceptable risk should be imbedded into R&D of new treatments, from drug design to clinical trials.

Stakeholder relationships and collaborations

One paper identified a proposed opportunity for patients in the establishment/ maintenance of relationships with stakeholders. It was suggested by the Genetic Alliance UK that dialogue between patients, manufacturers, regulatory bodies, and clinical researchers should be maintained to ensure alignment between the data required for decision-making and the data collected in clinical trials [51].

Patient care and support

One paper reported a proposed role for patients in patient care and support. The Genetic Alliance UK proposed that patients, in partnership with their physicians, should be responsible for deciding if the benefits of using a new drug outweigh the associated risks [51].

Regulatory decision-making

Three papers described proposed opportunities for involvement in regulatory decision-making. In the United Kingdom, it was proposed by the Genetic Alliance UK that patient input on acceptable risk should be incorporated into decision-making [51]. In Europe, participants in the EHC Congress symposium proposed that patient representatives should be added to advisory committees that do not currently have representation [45]. In the United States, NORD proposed that it should be involved in identifying laws, regulations and policies that need to be changed to encourage product approval [56]. It also proposed that it should consult with regulators to establish greater certainty in the orphan product approval process, especially in regards to trial design and endpoint selection [56].

Reimbursement decision-making

Three papers described proposed opportunities for involvement in reimbursement decision-making in Europe, the United Kingdom, and the United States. At the EHC Congress's Symposium, it was suggested that patient input should be sought earlier on in the health technology assessment (HTA) process [45]. It was also suggested that patient advocates and clinicians work together to create a shared consensus on evaluating the efficacy of therapies and the experiential data that are of the greatest value [45]. In the United Kingdom, the Genetic Alliance UK proposed 4 potential roles for patient involvement in reimbursement decision-making: presenting to the evaluation committee, consulting on the development of post-

evaluation research, providing input on any re-assessment of risks and benefits, and providing input into topic selection during horizon scanning [51]. The Genetic Alliance UK also proposed that patient organizations should be formally involved in drug identification and selection for reimbursement decision-making [51]. In the United States NORD proposed that patient organizations should work to assure reimbursement of off-label drug use for rare disease patients [56].

Feedback from patients and caregivers

Eight members of the PRISM Patient and Caregiver Liaison Group participated in the webinar *Patient Engagement throughout the Lifecycle of Orphan Drugs.* They represented a wide variety of rare diseases and a range of experience within their respective rare disease communities. The session lasted 2.5 hours. In general, participants agreed with the opportunities identified in the review. They also identified several opportunities that the review did not capture, particularly for patients and caregivers. These opportunities are described below. Additionally, any disagreements with the opportunities identified in the review are reported. Participants did not report any additional opportunities or disagree with any opportunities identified in the themes of Patient Reported Outcome Measures and Patient Organization Development. As such, these themes are not listed below.

Research

"Sometimes, there is no patient organization." – Caregiver 2

Participants identified additional opportunities for patient and caregiver involvement in research that were not captured in the review. Patients and caregivers have fundraised for research, including those who do not have an organization to represent them. Patients also

provided input on the format in which they would like to receive a new drug, should it come to market (e.g., pill vs. liquid)

Clinical Trials

> *"Not recruiting patients, but providing all the information necessary so the patients know what options are out there in terms of research." – Caregiver 2*

Participants differentiated between recruiting patients to clinical trials and providing them with enough information to make informed decisions on whether or not to participate. While those involved with patient organizations shared calls for participants with the members of their organizations, they did not feel it was their job to recruit participants. Additionally, participants were aware of proposals that patients should be involved earlier on in the research process to help better link collected data with what is required in the regulatory process.

Patient registries and biorepositories

Participants identified additional existing opportunities for patients and caregivers, who fundraised for patient registries (without the support of an organization) and used social media (e.g., Facebook) to encourage others to enroll in registries. The difficulties patient organizations face in attempting to establish registries were also discussed:

> *"…you've listed establish and maintain registries but a lot of organizations do not do that because it is too expensive, too onerous." – Caregiver 2*

Many organizations are doing research to identify different types of registries that they may have the capacity to establish. They have encouraged members to participate in registries set up by industry for post-market studies and requested data from these registries to share with the disease community (e.g., using data from a registry to write and present a research paper at a conference).

Stakeholder relationships and collaborations

"…sometimes, patients can be the link between stakeholders." – Patient 4

Participants described how individual patients brought different stakeholders together (e.g., linking fundraisers with patient organizations). Individual patients and caregivers also established and maintained relationships with the government through their local Members of Parliament (MPs) and Members of the Legislative Assembly (MLAs) in individual provinces. Participants indicated that some individuals were very proactive about building these relationships outside of a patient organization.

Education and awareness

"We've done that on a number of occasions as individual patients, not through the patient organization." – Caregiver 1

Participants discussed a variety of work individual patients and parents have done to provide education and spread awareness about their disease. Patients and caregivers started awareness campaigns online and in schools, presented at Grand Rounds, hosted fundraising events, and participated in standardized patient programs at Universities, which help to familiarize students in health-related fields with different medical conditions.

Advocacy

"…there's a time and place for both [patients and patient organizations] to come in and…individual patients have done a lot of individual advocacy work." – Patient 3

Participants described advocacy work being done by individual patients and caregivers that the literature did not capture. Patients and their caregivers advocated for access to new drugs well before social media existed (e.g., meeting with their local MPs). They took part in

campaigns hosted by research organizations to advocate for support. One participant pointed out that they also often advocated for the rare disease community in general.

Additional opportunities for patient organizations identified by participants include advocating for improved education, clinics, and patient care services. In addition to advocating on behalf of patients, patient organizations also guided patients in advocating for themselves. Patient organizations facilitated individual patients' advocacy efforts by linking them with resources in their community and provided them with letters of support.

Conferences and workshops

> *"...you have the expert patients who can share their knowledge and give their perspective to other patients or even to doctors and healthcare providers." – Patient 4*

Participants discussed how patients presented at conferences and shared their knowledge with other patients and healthcare professionals. One participant served on a planning committee and organized opportunities for patient involvement (e.g., sitting on a panel) to ensure that these opportunities were driven by actual patients. Another participant served as a volunteer during patient organization-hosted conferences, aiming to help the conference run more smoothly and increase involvement by assisting with aspects such as childcare.

Patient care and support

> *"It's not just social support…" – Caregiver 3*

Participants felt that 'social support' did not capture all of the ways in which patients provided support to one another. They have provided clinical care support, helping other patients to identify appropriate treatments and dosing.

They also described a key aspect of patient organizations' support to patients as providing them with information on what treatments and services are available locally, depending on the province/territory in which they live.

Regulatory decision-making

One participant discussed Health Canada's work on incorporating patient involvement in regulatory decision-making, which was an opportunity identified in the review. Two participants participated in a webinar where Health Canada discussed their pilot project; however, it was unclear as to how the patients were actually involved. No information on the current status of this project could be found.

> *"I know that they're working on patient involvement in regulatory decision-making. I don't think they've gotten very far on it…" – Patient 3*

Reimbursement decision-making

Participants described their experiences with submitting patient evidence submissions to CDR in Canada, an opportunity identified in the literature. Many felt it is unclear how the information from patient submissions is weighed in the final decision in comparison to information from other sources (e.g., clinical trial data). They displayed some skepticism regarding how the submissions are valued by the decision-making committee.

> *"…I know very little about the weight it's given. I don't think anybody knows the weight it's given" – Caregiver 2*

Participants also felt that submitting an evidence submission is only the first step for patient organizations in the reimbursement decision-making process. When a drug receives a negative recommendation, the organizations have done a significant amount of work to get patients access, going to the media and meeting with government officials in different provinces.

Other

> *"…the patients and families who are involved in that have to be ambassadors and get out there and show the rest of the research community how it works and how it was successful and what the impact was. Because we're trying to change a whole culture of how researchers think and work and that's very difficult and if they can get concrete examples of how it's worked in the past and how it's been successful and how it's enhanced the research, they may be more open to just having it proposed to them and saying hey this is what we do now in the 21st century." – Patient 3*

In addition to identifying a number of opportunities that were not captured in the review, participants spoke about the importance of sharing information on the ways they have been successfully involved at the different stages of the orphan drug lifecycle. They felt that this was particularly important when their involvement was in a non-traditional way, such as when they developed equal partnerships with researchers conducting trials.

Mapping opportunities onto the orphan drug lifecycle

Opportunities for patients, caregivers, and patient organizations were mapped onto the orphan drug lifecycle in Figures 1-3, 1-4, and 1-5, respectively (Table 1-4). Two maps were created for each patients, caregivers, and patient organizations: one map reflecting opportunities identified in the literature/website review and a second reflecting the additional opportunities identified in the webinar. These figures demonstrate that opportunities for patients, caregivers, and patient organizations exist throughout the lifecycle. In fact, 9 themes for involvement span the entire lifecycle for patients and patient organization. Additionally, it is evident that the literature reported on more opportunities for patient organizations than it did for patients and caregivers. The figures also illustrate some of the gaps in the literature that were identified and filled during the webinar. Participants in the webinar identified a number of opportunities for

patients and caregivers in Canada that were not found in the literature, but very few additional opportunities for patient organizations were identified.

Discussion

A wide variety of opportunities for patient, caregiver, and patient organization involvement were identified at each stage of the orphan drug lifecycle. The majority of these opportunities described ways in which patients, caregivers, and patient organizations are currently involved in the lifecycle (i.e., existing opportunities). A significant proportion of these existing opportunities described involvement in research. Few proposed opportunities for involvement were identified; however, those that were reported were primarily in the themes of regulatory and reimbursement decision-making.

Through the consultation exercise it became apparent that significant gaps exist in the published and grey literature. Firstly, much of the work that patients, caregivers and patient organizations do in Canada is not captured. The majority of the opportunities identified in this review took place in the United States and Europe; however, participants indicated that a number of these opportunities also exist in Canada (e.g., organizing conferences; participating in research organizations; hosting educational activities). Although these Canadian opportunities were not found in the literature, they all fell within the same themes of involvement and no new themes were identified in the Webinar. Additionally, based on the literature, it appeared that only patient organizations took part in a number of opportunities (e.g., fundraising for research; providing education healthcare professionals). However, participants described their own experiences as an individual in a number of these activities. For many rare disease patients, particularly for those with ultra-rare diseases, no patient organization exists. As such, participants indicated that they must take the initiative to pursue many of these opportunities on their own. Secondly, feedback

from the participants indicated that the literature did not accurately describe their role in some of the opportunities identified. For example, while Canadian patient organizations are able to complete a patient submission for use in CDR evaluations, the participants felt uncertain as to whether this input was actually valued in the process. There is a lack of transparency in how patient submissions are weighed compared to other information sources and participants expressed concern that completing them may not be worthwhile. This gap represents one of the main limitations of this review. Many opportunities were not described well enough for the researchers to distinguish between situations in which patients, caregivers, and patient organizations were meaningfully involved versus situations in which their involvement was tokenistic. Initially, efforts were made to evaluate each opportunity using Arnstein's ladder, a well-established scale of participation [142]; however, this proved to be impossible due to limited descriptions of each opportunity.

Participants in the webinar emphasized the importance of sharing information on how they have been involved in the lifecycle so that others may learn from their experiences. This review demonstrated a lack of such information-sharing on opportunities in both Canada and internationally, as the impact or outcome of most opportunities identified was poorly described, if at all. It became clear that it is necessary for people who are interested in introducing or participating in patient and caregiver involvement processes to ensure information about these processes is more easily accessible. However, no ideal model for reporting on patient and caregiver involvement was identified as assessing the transparency of involvement was beyond the scope of this study.

There are additional limitations of this study. To begin with, the published papers and grey literature reviewed were limited to the English language only. The review of websites was also

limited to English. As a result, some opportunities may have been missed. Another limitation of the review is that, aside from the assessment of regulatory and reimbursement decision-making processes, the results were limited to papers describing opportunities for rare disease patients only. Any papers not recorded as relating to rare diseases or orphan drugs would not have been captured in the bibliographic database search. However, the consultation webinar was conducted to reduce the likelihood that opportunities were missed.

Conclusion

There are a number of opportunities, both existing and proposed, for patients, their caregivers, and the organizations that represent them to become involved in the orphan drug lifecycle. Consultation with Canadian rare disease patients and caregivers indicates a willingness to take advantage of these opportunities. Gaps in the literature identified by patients and caregivers also demonstrate a need for greater information sharing around examples of involvement in Canada, which may help to encourage and facilitate increased participation in the future. Given that opportunities for involvement were found throughout the lifecycle, knowledge of these experiences would be relevant for not only patients, caregivers, and patient organizations, but also researchers, healthcare professionals, and policymakers. Organizations looking to undertake patient and caregiver involvement need to understand the current state of involvement in order to develop evidence-informed processes. The results of this paper can be used to direct stakeholders to relevant information that will guide them in the development of processes for patient involvement.

Figure 1-2. PRISMA diagram of literature search results & study selection for review of opportunities for patient, caregiver, and patient organization involvement in the orphan drug lifecycle.

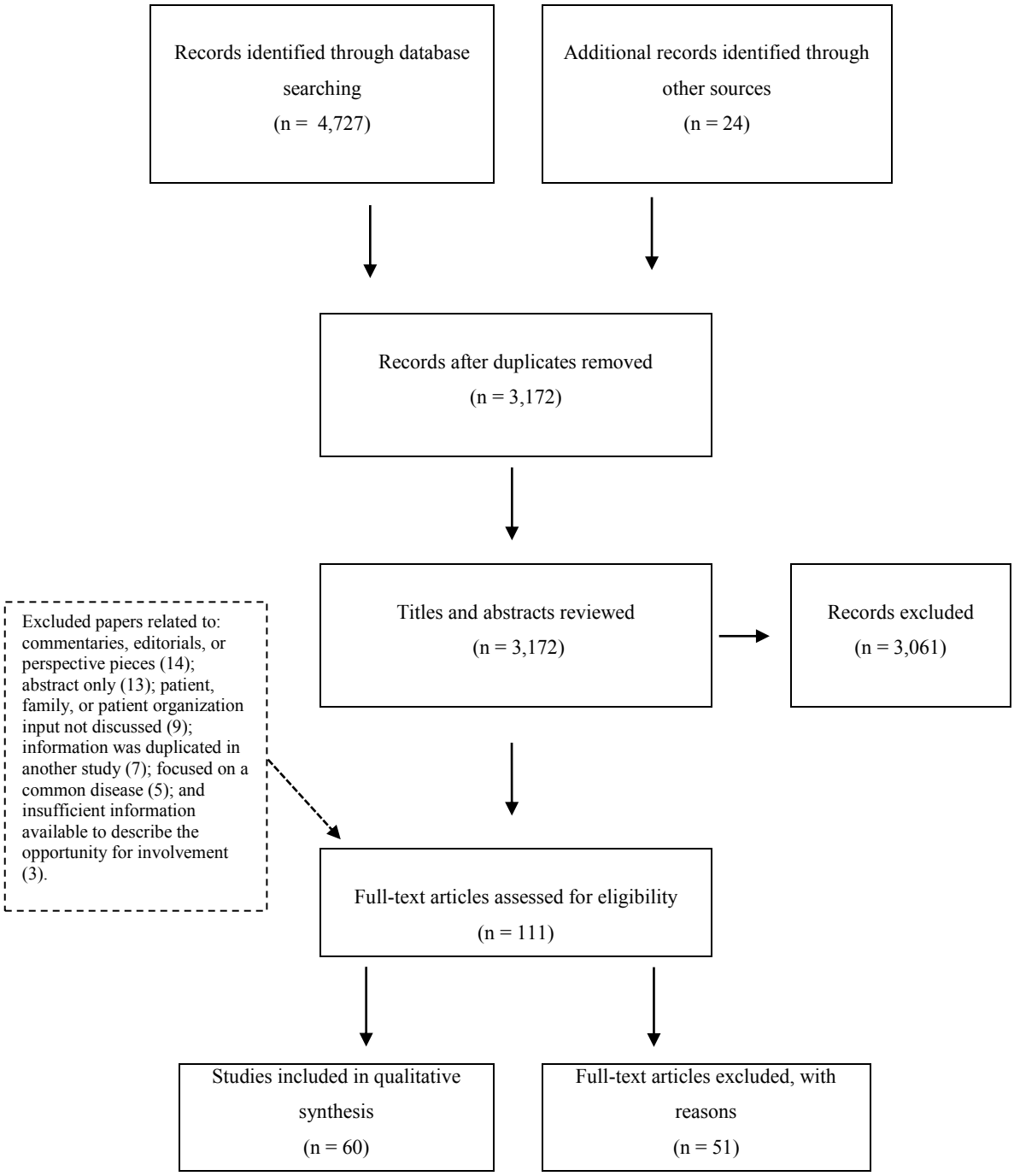


Figure 1-3. Themes from opportunities for patients identified in the literature/website review mapped onto the orphan drug lifecycle vs. additional opportunities identified in the webinar mapped onto the orphan drug lifecycle.

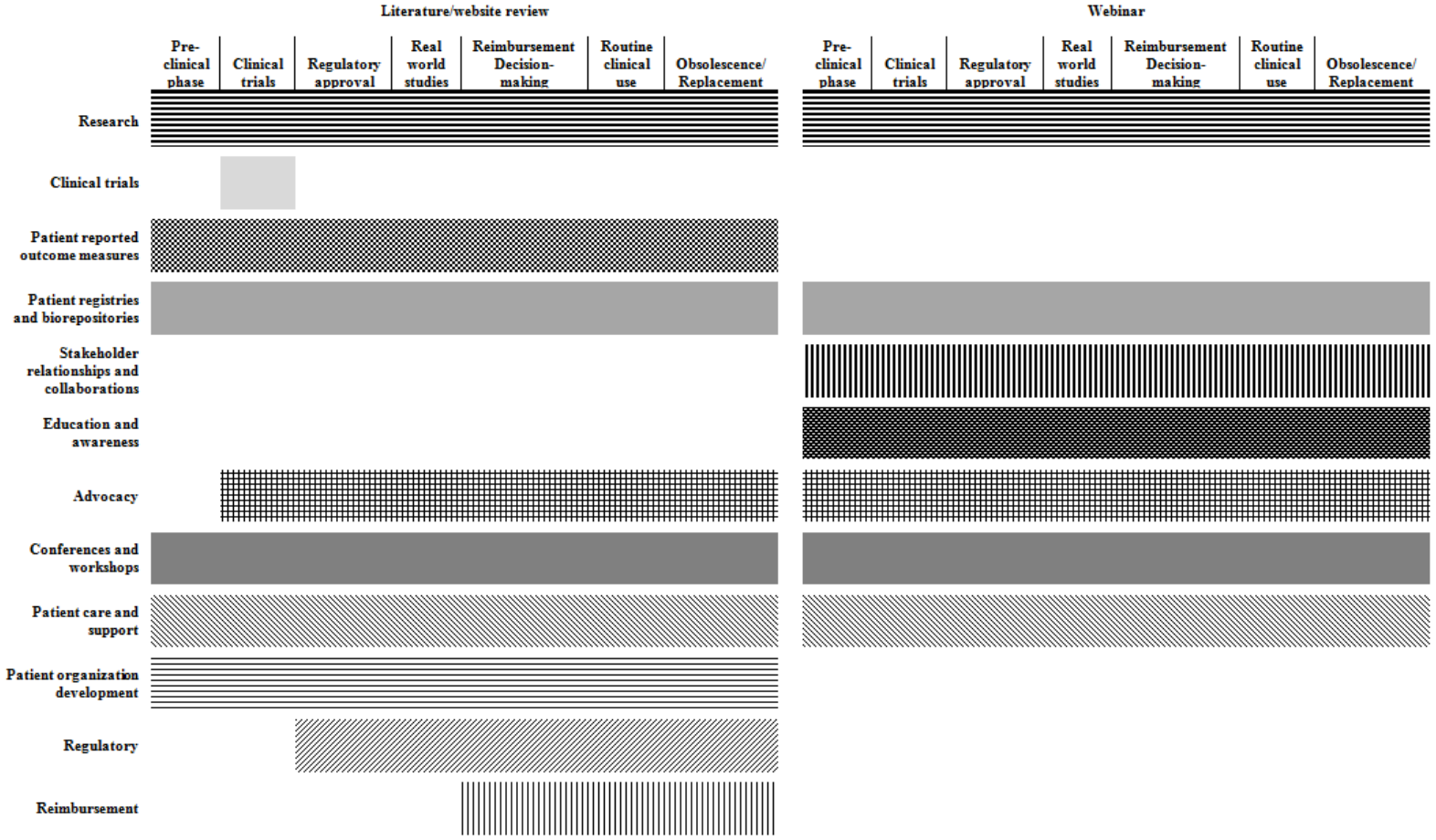


Figure 1-4. Themes from opportunities for caregivers identified in the literature/website review mapped onto the orphan drug lifecycle vs. additional opportunities identified in the webinar mapped onto the orphan drug lifecycle.

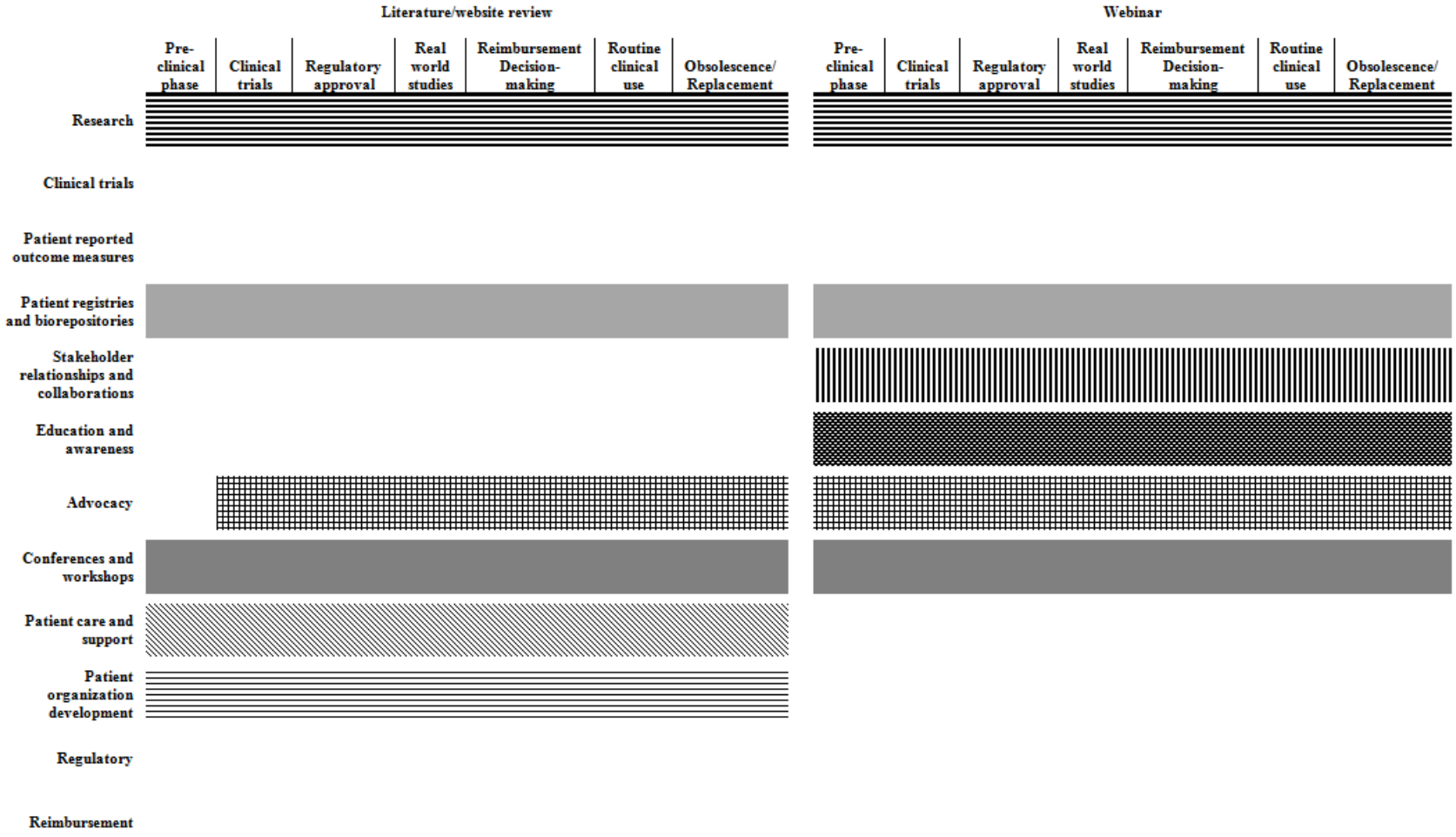


Figure 1-5. Themes from opportunities for patient organizations identified in the literature/website review mapped onto the orphan drug lifecycle vs. additional opportunities identified in the webinar mapped onto the orphan drug lifecycle.

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Research†					
Participation as a research subject					
Bedgood (2005) [32]	International (United States, Canada, United Kingdom, Australia, Colombia, Germany, Israel, New Zealand, and the Philippines)	Achalasia	Patients	• Patients completed an online survey collecting data on demographics, symptom onset, presenting symptoms, and success of current treatments	• 83 surveys were completed globally • The authors state that Internet-based surveys may be useful in the accumulation of information on uncommon diseases, which are generally difficult to study due to the limited numbers of patients at single centers
Serrano-Aguilar (2009) [30]	Spain	Degenerative ataxias (DAs)	Patients	• Patient input was incorporated into the completion of a systematic review of the literature on the effectiveness of treatment for DAs by having patients complete 3 questionnaires as part of the Delphi Method for consultation: (1) an open questionnaire on the treatments used for DA and patients' most relevant self-perceived health problems associated with their disease, (2) a prioritization of the health problems identified in questionnaire 1, and (3) an opportunity to revise earlier answers based on the overall, ranked results of questionnaire 2	• The authors indicate that patient participation was effective in enhancing the design and conduct of the systematic review •Patients were able to identify relevant research needs and highlight variations in values and access to different treatments across regions/countries • Some health problems and outcome measures identified by the patients were not found in any of the studies included in the review, indicating an evidence gap that DA researchers and policy makers should consider in the design of future projects
Swinburn (2012) [31]	United Kingdom	Advanced neuroendocrine tumors (NETs)	Patients	• Patients participated in exploratory interviews in which they described their experiences living with NETs and undergoing therapy • Patients also completed the EQ-5D assessment exercise, rating their health on 5 different dimensions • These health states were collected to be used to elicit utility values for the health states of patients undergoing treatment for NETs	• Patient interviews, along with the results of a literature review and interviews with clinical experts, were used to develop 10 vignettes describing the health states of advanced NET patients • A time trade-off methodology was then used to have members of the UK public value the health states • The authors suggest that the health utility values resulting from this study could inform cost-effectiveness assessments for advanced NET therapies
Carroll (2012)	United States	Pulmonary arterial hypertension (PAH)	Patients	• Patients participated in semi-structured interviews discussing the factors that influence their decision to	• 24 factors that influence the RCT enrollment decisions of patients with

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
[33]				enroll in randomized controlled trials (RCTs)	PAH were identified • The results indicate that by minimizing time demands of participating, providing financial remuneration, and allowing participants to continue current therapies may enhance enrollment to trials in similar disease areas •A need to ensure patients understand the distinction between research and clinical care was also found, as many patients demonstrated an increased willingness to participate based on expectations of perceived personal benefit
De Blieck (2013) [34]	United States	Juvenile neuronal ceroid lipofuscinosis (JNCL or Batten Disease)	Patients	• As part of the development and validation of a disease-specific clinical outcome measure for JNCL, patients were assessed by researchers from the University of Rochester's Batten Centre (URBC) using their Unified Batten Disease Rating Scale (UBDRS), which involves a physical examination and an evaluation of cognitive and behavioural symptoms using well-established neuropsychological measures	• 120 subjects were evaluated with the scale at least once and 95 children provided quantifiable measures of neurobehavioral function over time • Disease burden and rate of progression were evaluated and quantified using the UBDRS data in 82 subjects with genetically confirmed JNCL, representing the largest cohort of Batten-disease patients reported to date using a disease-specific rating scale • The collection of neuropsychological data permitted the objective assessment of change in neurobehavioral function over time and was also used to successfully cross-validate the UBDRS • Telemedicine for remote UBDRS assessment was also successfully piloted
De Blieck (2013) [34]	United States	JNCL	Patients	• As part of the URBC's efforts to validate a non-invasive, child-friendly method of obtaining cells for genotyping, patients participating in the URBC's UBDRS study provided buccal epithelial cell samples to the URBC for genetic diagnosis	• Patients without a prior genetic diagnosis were successfully diagnosed, with the majority of samples being collected from buccal specimens • Several novel mutations were identified through this process
O'Mahony (2014)	Europe	Hemophilia	Patient organizations	• 19 of the 43 patient organizations affiliated with the European Haemophilia Consortium (EHC) completed	• Based on the results of the survey, the EHC have produced information packs

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
[45]				an EHC survey that assessed the standard of care for people with haemophilia in all European Countries	for every National Member Organization affiliated with the countries that responded •The information provided shows exactly where the country ranks in terms of availability of care, compared with the rest of Europe and includes suggested uses for the data
Research priority-setting					
Nierse (2013) [35]	Netherlands	Neuromuscular diseases (NMDs)	Patients	• Patients participated in interviews and focus groups, and completed a questionnaire to identify their research priorities	• This study demonstrates that patients can formulate relevant research questions • Patients highly valued research on cure and prevention of the occurrence of symptoms • Patients and professionals identify a need to balance fundamental research and research on preventing and treating symptoms as well as research on slowing down disease progression • This patient-driven agenda validates the wide scope of rehabilitation described in the International Classification of Functioning, Disability, and Health (ICF) model, and also identifies the need for more interdisciplinary research
Davila-Seijo (2013) [36]	Spain	Dystrophic Epidermolysis Bullosa	Patients	• Patients participated in three phases of a priority-setting exercise (Priority Setting Partnership, or PSP, method): a consultation survey, ranking exercises, and small workshops	• 6 uncertainties were identified that patients, caregivers, and health care professionals feel are priority areas for future research • This study also demonstrated that the PSP method can be utilized in a rare diseases setting
Nierse (2013) [35]	Netherlands	NMDs	Patient organizations	• Active members of the Dutch Patient Association for NMD (VSN) participated in expert meetings to complement and validate the priority topics identified by patients during interviews and focus groups • VSN members also participated in a dialogue meeting with researchers and clinicians to develop the shared agenda	• The dialogue meeting provided a learning experience for all members involved and, as a result, the professionals acknowledged diverse areas for research that mattered to patients • Through the sharing of perspectives in

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
					the final dialogue meeting, a shared research agenda was developed • A research agenda was developed
Nierse (2013) [35]	Netherlands	NMDs	Patient organizations	• A staff member of VSN was a member of the team developing the agenda	• A research agenda was developed
Caron-Flinterman (2005) [46]	Germany	Retinitis Pigmentosa	Patient organizations	• Pro Retina, a German Retinitis Pigmentosa patient group, formulated research priorities for the scientific community	Not specified
Initiation of research					
Ferguson (2002) [37]	United States	Chromosome 18 deletion	Patients and caregivers	• A mother of a patient noticed improvement in her child's symptoms after taking human growth hormone and developed a theory to explain her observations based on available scientific literature	• Researchers tested the theory, finding it to be correct
Mai (2008) [38]	United States	Li-Fraumeni syndrome (LFS)	Patients and caregivers	• Patients participated in a workshop around clinical research on LFS at the National Institutes of Health with scientists and physicians, sharing their experiences and their goals	• Patients and caregivers identified 6 priorities for clinical research • A new advocacy group was established to facilitate effective communication between LFS families and the clinical and scientific members of the research consortium
Caron-Flinterman (2005) [46]	Netherlands	Addison's disease; Cushing's disease	Patient organizations	• The Dutch Addison and Cushing Society (NVACP) requested an independent research facility to complete a study on improved drug administration methods for the treatment of Addison's disease	• The NVACP-requested study eventually led to the establishment of a research project on delayed release tablets
Panofsky (2010) [47]	United States	Rare diseases in general	Patient organizations	• Patient organizations develop close relationships with, and between, scientists (i.e., "sociability") to influence the research process • Additional mechanisms utilized include resources; collective mobilization; timing; lay expertise; and organization controls • Note: according to the author, without sociability, these additional mechanisms are insufficient for influencing research	• "Sociability" provides benefits for patient organizations and can help scientists develop stronger research networks and improved productivity
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations promote the running of a trial by gathering researchers; demonstrating interest in new treatments; and bringing together research teams	Not specified
Landy	Not specified	Rare diseases in general	Patient	• Patient organizations have written funding proposals	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2012) [84]			organizations	to conduct their own research	
Assist in the conduct of research					
Molster (2012) [81] *Proposed*	Australia	Rare diseases in general	Patients and caregivers	• Participants in the Australian Rare Diseases Symposium suggested that patients and caregivers should be directly involved in decisions about research on rare diseases	Not applicable
Doyle (2015) [39]	United States	Cystinosis	Patients and caregivers	• Community members provided input into the development of interview guides for focus groups and interviews as part of a qualitative study exploring the experiences of patients interacting in a disease community	• Three core questions were developed • Six focus groups and 17 semi-structured interviews were conducted with adult patients and the parents of young patients
Montano (2007) [48]	International (Australia, Austria, Brazil, Canada, Chile, Colombia, Finland, France, Germany, Indonesia, Italy, Japan, Morocco, New Zealand, Poland, Puerto Rico, Saudi Arabia, Spain, Switzerland, Turkey, United Kingdom, United States) Note: study conducted out of the United States	MPS IVA	Patient organizations	• Survey questions given to individuals registered in an MPS IVA registry were first reviewed and discussed by a panel of board members from the International Morquio Organization (IMO), a patient organization for those with MPS	• The information collected will help to facilitate clinical trials on ERTs, as information on the natural history, rate of progression, and distribution of symptoms in untreated patients is necessary for developing clinical endpoints and judging therapeutic effects • The authors suggest an annual survey will allow for the collection of more data on the management of patients, efficacy of treatment, and endpoints of clinical trials
Nierse (2013) [35]	Netherlands	NMDs	Patient organizations	• The VSN helped to pilot and distribute the questionnaire, and also recruited patients for interviews and focus groups, which were used to develop the research agenda	• A research agenda was developed
Serrano-Aguilar (2009) [30]	Spain	DAs	Patient organizations	• Patient organization leaders helped to enroll research participants via email	• The authors indicate that patient participation was effective in enhancing the design and conduct of the systematic review •Patients were able to identify relevant research needs and highlight variations in values and access to different treatments across regions/countries • Some health problems and outcome measures identified by the patients were

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
					not found in any of the studies included in the review, indicating an evidence gap that DA researchers and policy makers should consider in the design of future projects
Ferguson (2002) [37]	United States	Pseudoxanthoma elasticum (PXE)	Patient organizations	• PXE International, an organization started by the parents of patients, collaborates with medical researchers, advising on symptoms of PXE and consulting on research strategies	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations provide researchers with letters of support	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations provide advice on the design of research projects	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations participate in data collection and analysis	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations help recruit research subjects	Not specified
Partner in or lead the conduct of research					
Frost (2008) [40]	International	Amyotrophic lateral sclerosis (ALS)	Patients	• Patients established a website providing a rationale for lithium treatment for ALS (based on the results of a study done in Italy) and a spreadsheet for users to report on: functional state pre- & post-initiation of lithium therapy; lithium dosage; lithium blood levels; and annotations to record side-effects, benefits, and to specify other treatments • Subsequently, Patients Like Me, in collaboration with the patients who began the study, started tracking patient experiences with lithium treatment	• The number of patients taking lithium treatment in the Patients Like Me community increased from 1 to 116 with 4 months of a post referencing a study that showed a potential benefit of its use • Since publication of the paper, patients having tried lithium increased to over 250, with 125 having completed a side-effects survey • This article does not describe the results of the patient-driven study
Ferguson (2002) [37]	United States	Chromosome 18 deletion	Patients and caregivers	• The mother of a patient, as a graduate student, developed a treatment for children with chromosome 18 deletion	• This treatment is now the first effective therapy being offered
Scarpa (2011) [49]	Europe	MPS II	Patient organizations	• Patient organizations gather information regarding the effect that treatments have on quality of life by having members complete surveys	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Rabeharisoa (2003) [50]	France	NMDs	Patient organizations	• The French Muscular Dystrophy Organization (AFM) created a scientific council, but generally establishes its own research policy through the board of governors • e.g., the establishment of Genethon, a project that produces genes maps and provides customized sequencing services to outside research teams, was done with little involvement and support from the council	• Almost half of the AFM budget is spent on research
Rabeharisoa (2003) [50]	France	NMDs	Patient organizations	• Patients and their caregivers actively partner with specialists in the production of knowledge and the care and treatment of their disease • Patients are developing the tools necessary to formalize their "experiential knowledge" so that professionals, etc. will recognize its importance • e.g., a special interest group on spinal muscular atrophy (SMA) within the AFM collected information on the experiences of patients and their parents to write a white paper on the disease	• The SMA group's white paper successfully initiated a dialogue between caregivers and specialists, resulting in the identification of different forms of the disease
Genetic Alliance UK (2014) [51]	United Kingdom	Rare diseases in general	Patient organizations	• Genetic Alliance UK has developed a project to explore the perspectives of patients and caregivers affected by genetic conditions regarding willingness to accept risk or adverse outcomes with a new treatment	Not specified
Ferguson (2002) [37]	United States	Gastrointestinal stromal tumor (GIST)	Patient organization	• The Life Raft Group, a patient group started by the husband of a patient, published a study evaluating Gleevec's effectiveness for GIST patients	• The study collected data on quality of clinical care available at clinical trial centres; attempted to evaluate the sources of information that participants relied on; developed a methodology for participants to serve as their own control group; and introduced a new scale to rate side effect severity from the patients point of view • The leader of LifeRaftGroup.org states that patient-initiated research helps reduce the lag time that professional researchers experience, helping to get important information to patients faster
Ferguson (2002) [37]	United States	PXE	Patient organizations	• PXE International was part of the research team working towards identifying the gene responsible for PXE	• The gene was identified and patented by the research team

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Seminara (2010) [52]	United States	UCDs	Patient organizations	• Within the UCDC of the RDCRN, the National Urea Cycle Disorders Foundation has developed and distributed surveys to determine attitudes and barriers to study participation	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	Von Hippel-Lindau disease (VHL)	Patient organizations	• The Von-Hippel-Lindau Alliance (VHLA) developed a VHL Research Council	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations gather data or other information • Patient organizations lead focus groups or discussion sessions for research	Not specified
Development of or involvement in research organizations					
Molster (2012) [81] *Proposed*	Australia	Rare diseases in general	Patients and caregivers	• Participants in the Australian Rare Diseases Symposium suggested that patients and caregivers should be involved in all decision-making processes within any collaborations or networks established	Not specified
McCormack (2013) [41]	Europe	NMDs	Patients, caregivers, and patient organizations	• Parents of patients and representatives of patient organizations are members of TREAT-NMD's Project Ethics Council (PEC) • Responses to questions discussed and other papers produced by the PEC are posted on the TREAT-NMD website	• The PEC has provided guidance in several TREAT-NMD projects, including the development of the network's Global Registry and has provided guidelines for relations with industry • The PEC has addressed some of the main issues around rare neuromuscular disease care, diagnosis, treatments and ethics, and demonstrates a potentially suitable model for addressing similar issues in the rare diseases field
Fleurence (2014) [42]	United States	Rare diseases in general	Patients and patient organizations	• The National Patient-Centered Clinical Research Network (PCORnet) is comprised of 18 patient powered research networks (PPRNs), led by patients in partnership with researchers, and 11 clinical data research networks • Patient roles within the networks vary, from contributing data and sharing de-identified data for research to involvement in leadership and governance • Patient organizations are also members of the PPRNs	• Through PCORnet, PPRNs can learn from each other how to increase and retain members, collect data, and prioritize research • PPRNs have the chance to work directly with larger health care systems and clinical data research networks • The first phase of PCORnet extends through to September 2015

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
				• Patients are also represented on PCORnet's Steering Committee and Executive Committee	• The author states that the network will support rapid, efficient, and cost-effective conduct of research
Duchange (2014) [54]	European Union	Leukodystrophies (LDs)	Patient organizations	• The EU LeukoTreat program, a network established to support therapy development for LDs, created its own ethics committee (The LeukoTreat Ethics Committee or LEC) comprised of clinicians, researchers, law professionals, and representatives from patient organizations • The purpose of the LEC is to provide ethical management and follow-up regarding projects in the EU LeukoTreat program	Not specified
Boon (2010) [55]	Netherlands	NMDs	Patient organizations	• The VSN cofounded a number of scientific collaborations (e.g., The European Alliance of neuromuscular disorders associations (EAMDA); The European Neuromuscular Centre (ENMC))	• An EAMDA workshop on Duchenne muscular dystrophy led to a coordinated research effort that resulted in the discovery of the gene responsible for the disease • 160 workshops run by the ENMC have brought together 2000 scientists, with the resulting reports being among the most cited NMD articles
Caron-Flinterman (2005) [46]	Netherlands	Rare diseases in general	Patient organizations	• 2 patients participate on the Steering Group on Orphan Drugs, which stimulates and facilitates research on, and development of orphan drugs • Note: The Dutch Steering Committee has been replaced by the Dutch Orphan Drug Network	Not specified
Caron-Flinterman (2005) [46]	Netherlands	NMDs	Patient organizations	• 4 representatives from the VSN are board members on the Dutch foundation for Neuromuscular Research (SONMZ), which stimulates and communicates research on the causes of, and therapies for, NMDs	Not specified
Fleurence (2014) [42]	United States	Rare diseases in general	Patient organizations	• Patients are represented on PCORnet's Steering Committee and Executive Committee	• The first phase of PCORnet extends through to September 2015 • The author states that the network will support rapid, efficient, and cost-effective conduct of research
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD and other patient organizations are involved in the NIH's Therapeutics for Rare and Neglected Diseases (TRND) initiative, which aims to help accelerate treatment development	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Cystic Fibrosis Foundation (2014) [57]	United States	CF	Patient organizations	• The Cystic Fibrosis Foundation (CFF) developed the CF Therapeutics Development Network (CF TDN) in collaboration with specialists in CF clinical research • The Network is comprised of a coordinating Centre, 77 CFF-accredited care centers (i.e. CF Therapeutics Development Centers) and laboratories and interpretation centers (i.e. National Resource Centers)	• The TDN has conducted more than 100 clinical studies since its inception in 1998
Schwartz (2013) [58]	United States	Paychyonychia Congenita (PC)	Patient organizations	• Patient organizations established the PC Project, an international collaborative network of patients, medical professionals, and scientists	Not specified
Schwartz (2013) [58]	United States	PC	Patient organizations	• Members of the PC Project established the International PC Consortium, which connects various researchers and specialists to conduct basic clinical research	Not specified
Dissemination of research-related information					
Ekins (2012) [43]	International (Note: project started in North America)	Rare diseases in general	Patients, caregivers, and patient organizations	• The Open Drug Discovery Teams app collects Tweets using particular hashtags (e.g., #sanfilipposyndrome) • Anyone may use the app and curate the content by endorsing or disapproving of each Tweet (or "factoid")	• The authors anticipate that this app will be used to disseminate information on new scientific developments, to network and discover other researchers, and to provide opportunities for collaboration by highlighting conferences, publications, or laboratory data sharing
JISC (2011) [44]	United Kingdom	NMDs	Patients	• Patients participated in the Talk Research focus group to discuss if the communication services provided by the Muscular Dystrophy Charity (MDC), now known as Muscular Dystrophy UK, meet the needs of patients and to provide feedback on language, content, and the structure of the MDC websites and publications	• Patients involved in the Talk Research focus group have become involved in other MDC activities such as reviewing grant applications
JISC (2011) [44]	United Kingdom	NMDs	Patient organizations	• The MDC communication service employs a team of people who have work in research to produce summaries of new research (e.g., lay summaries of clinical trials) • The MDC is also part of Patient Inform, which provides patients with access to research articles	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations presented research at scientific conferences, via websites and newsletters, and through the press	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations helped to prepare research reports/articles	Not specified
Provide funding for research					
Caron-Flinterman (2005) [46]	Germany	Retinitis Pigmentosa	Patient organizations	• Pro Retina funds innovative research projects	Not specified
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	Cystic Fibrosis (CF)	Patient organizations	• The CFF provides grants to fund research	Not specified
De Blieck (2013) [34]	United States	JNCL	Patient organizations	• The Batten Disease Support and Research Association (BDRSA) provides funding for the University of Rochester Batten Center's (URBC's) research activities, including clinical trials	• A controlled phase II trial has been initiated, with funding provided by the FDA and the BDSRA, to assess the use of oral mycophenolate in ambulatory children with JNCL
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD provides grant programs for medical research	Not specified
Fleurence (2014) [42]	United States	Rare diseases in general	Patient organizations	• PPRNs operating within PCORnet, a national data infrastructure that incorporates electronic health records and administrative, claims and patient-generated data for use in research	• Through PCORnet, PPRNs can learn from each other how to increase and retain members, collect data, and prioritize research • PPRNs have the chance to work directly with larger health care systems and clinical data research networks • The first phase of PCORnet extends through to September 2015 • The author states that the network will support rapid, efficient, and cost-effective conduct of research
Lasker (2005) [60]	United States	Primary Biliary Cirrhosis (PBC)	Patient organizations	• The PBCers Organization fundraises for research	Not specified
Von-Hippel-	United States	VHL	Patient	• The VHLA awards grants through a competitive	• Research supported by the VHLA has

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Lindau Alliance (VHLA) (2014) [53]			organizations	research grant application process	resulted in better understanding of the mechanism responsible for VHL tumor development, improved diagnosis and treatment of VHL, and increased average life expectancy of a person with VHL by more than 16 years
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations provide investigators with financial support	• Leaders of the organizations surveyed felt their involvement in clinical research had increased the amount of research performed on their condition of interest and had improved the overall quality of the data produced • They also felt that their involvement had increased participation rates
Clinical Trials					
Participation as a research subject					
Patient Partner [61]	Not specified	Rare diseases in general	Patients	• Patients contribute DNA, cells, or other biological material to biorepositories or databases for use in a trial	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patients	• Patients participate in trials testing the effects of a new treatment or drug	Not specified
Assist researchers in the development/conduct of clinical trials					
O'Mahony (2014) [45] *Proposed*	Europe	Hemophilia	Patients	• In a satellite symposium at the European Haemophilia Consortium (EHC) Congress, it was suggested by a panel member that to ensure the collection of real-world outcomes that are meaningful to patients, patients must work together with all stakeholders to build a credible framework based on their real-world experience • This framework will ensure that the methods used to collect evidence are robust and reliable and that the evidence collected is in-depth enough to successfully engage with health authorities	Not applicable
Dunkle (2010) [56] *Proposed*	United States	Rare diseases in general	Patient organizations	• The National Organization for Rare Disorders (NORD), an umbrella organization of rare disease patient organizations, identified one of its priorities as developing systems to improve patient access to and participation in clinical trials	Not applicable

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
EURODIS (2011) [62]	Europe	Rare diseases in general	Patient organizations	• Patient organizations help to adapt the design of clinical trials to meet patients' expectations, facilitating adherence and ensuring quality of life is taken into consideration	Not specified
EURODIS (2011) [62]	Europe	Rare diseases in general	Patient organizations	• Patient organizations discuss results with trial sponsors to contribute to the assessment of treatment benefits	Not specified
EURODIS (2011) [62]	Europe	Rare diseases in general	Patient organizations	• Patient organizations provide early information to potential participants to ensure inclusion in a trial	Not specified
Boon (2010) [55]	Netherlands	NMDs	Patient organizations	• The VSN is involved in assisting and initiating clinical trials	Not specified
Black (2011) [63]	United States	Severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome)	Patient organizations	• The IDEA League provides researchers with access to a large cohort of patients for research	Not specified
Black (2011) [63]	United States	SMEI	Patient organizations	• Centres within the IDEA League's Collaborative Clinical Research and Comprehensive Care Network collaborate to develop clinical research protocols	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• The Rare Diseases Clinical Research Network (RDCRN) obtains input from patient organizations on the development of informed consent statements, recruitment strategies, and protocols for research conducted within the Network	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations help the RDCRN to identify patient cohorts and recruit patients for studies conducted by the Network	Not specified
Seminara (2010) [52]	United States	Urea Cycle Disorders (UCDs)	Patient organizations	• The National Urea Cycle Disorders Foundation is involved in the Urea Cycle Disorders Consortium (UCDC) of the RDCRN • The foundation is directly involved in the development of protocols, consents, content evaluations, and progress reporting in RDCRN studies	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations inform patients of opportunities for taking part in clinical trials	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations assist in the development of clinical research protocols	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations review funding requests, clinical trial protocols, or patient information to be used in a trial	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations provide advice or serve as advisory members on clinical research program committees for the development of a trial	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations supply demographic and disease-specific information on members represented by the organization for use in a trial	Not specified
Provide funding for clinical trials					
Fajac (2013) [65]	Europe	CF	Patient organizations	• The European Cystic Fibrosis Society's Clinical Trial Network (ECFS-CTN) is funded by the ECFS and national patient organizations through the umbrella organization CF Europe	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations fund research conducted within the RDCRN, including travel clinics to facilitate patient access to investigators and studies within the RDCRN	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations finance or raise funds for clinical trials	Not specified
Development of or involvement in clinical trial organizations/networks					
Fajac (2013) [65]	Europe	CF	Patient organizations	• The ECFS established a clinical trial network (ECFS-CTN) comprised of 30 selected sites across 11 European countries • Current initiatives are to set up an investigator-initiated trial, to implement central laboratories for outcome measures, further develop new surrogate end points, and establish a quality-improvement program	Not specified
Fajac (2013) [65]	Europe	CF	Patient organizations	• A patient organization representative sits on the Executive Committee of the ECFS-CTN and other representatives are invited to meet with the Executive Committee once a year	Not specified
Fajac (2013) [65]	Europe	CF	Patient organizations	• Patient organizations are invited to ECFS-CTN steering committee meetings twice a year	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• Patient organizations are involved in the operations, activities, and strategy of the RDCRN • Organizations are involved in each consortium and	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
				form the RDCRN's Coalition of Patient Advocacy Groups, which participates in network-level discussions and meetings	
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• 90 patient organizations are members of the RDCRN, forming the "coalition of patient advocacy groups" (CPAG)	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• The CPAG chairperson is a member of the RDCRN Steering Committee	Not specified
Seminara (2010) [52]	United States	UCDs	Patient organizations	• The Executive Director of the National Urea Cycle Disorders Foundation (NUCDF) serves as a voting member on the UCDC of the RDCRN	Not specified
Dissemination of information on clinical trials results					
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations translate research results from the RDCRN to patient communities	Not specified
Seminara (2010) [52]	United States	UCDs	Patient organizations	• The National Urea Cycle Disorders Foundation provides information on its website about the importance of research and ongoing UCDC trials • It also publishes articles on UCDC studies in its newsletter	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations translate the results of trials into patient friendly information	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations co-write a scientific article on the results of a trial	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations review scientific papers on clinical trials	Not specified
Assessment of benefits and harms					
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Patient input on acceptable risk should be imbedded into treatment R&D, from drug design to clinical trials	Not applicable
Patient reported outcome measures					
Submission of patient reported outcome measures					
van der	International	Pompe disease	Patients	• The Pompe Survey collected patient reported	• The authors suggest that their

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Meijden (2014) [67]	(Australia, Canada, France, Germany, Netherlands, United Kingdom, United States) Note: study was based out of the Netherlands			outcomes from patients instead of gathering clinical outcome measures	assessment of quality of life and participation in daily activity allows for the measurement of patients' functioning overall and in a way that truly reflects the disease impact
Participation in a validation study					
Wicks (2009) [68]	International Note: study was based out of the United States	ALS	Patients	• 7 ALS patients answered various questions provided by the researchers • An extended scale was developed based on their results and then piloted through an online survey provided to Patients Like Me users • A 1-week retest and a 3-month follow-up survey were also performed by the Patients Like Me users	• 11 new items for the ALSFRS-R were developed based on the feedback from ALS patients •The extended scale was validated by the Patients Like Me users; however, further validation in real-world studies is necessary
Abdulla (2013) [69]	Germany	Amyotrophic Lateral Sclerosis (ALS)	Patients	• Patients completed the self-administered Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-EX) survey in German	• The ALSFRS-EX was found to have similar psychometric properties to the previously used scale, the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), with high internal consistency and reliability • Analysis of correlations with other clinical parameters and two other scales demonstrated excellent validity
Hoffman (2008) [70]	United States	Familial cold auto-inflammatory syndrome (FCAS) and Muckle-Well Syndrome (MWS)	Patients	• Patients completed daily health assessment forms (DHAFs) over 6 months, testing the relevance of symptoms identified by the researchers and the usefulness of different measurement scales • Subsequently, patients in a phase III clinical trial completed a revised DHAF (based on the results collected in the observational study) during the baseline period • A Physician's Global Assessment of Disease Activity was also completed for each patient in the clinical trial for validation purposes	• The first validated patient-reported outcome measure for patients with FCAS or MWS was developed • The measure has high internal consistency and test-retest reliability, and is highly correlated with overall assessments of disease severity and functional limitations
Assist in the conduct of a validation study					
Wicks (2009)	International	ALS	Patients	• An ALS patient and member of the Patients Like Me online community was consulted to develop questions	• 11 new items for the ALSFRS-R were developed based on the feedback from

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
[68]	Note: study was based out of the United States			around regions of function and patients' abilities to perform daily living activities	ALS patients •The extended scale was validated by the Patients Like Me users; however, further validation in real-world studies is necessary
Kodra (2007) [71]	International (Italy, France, Spain, Romania, United Kingdom, and Turkey)	Rare diseases in general	Patient organizations	• Patient organizations translated the questionnaires and distributed them amongst their members	• Completed forms were received from Italy, Romania, the UK, Turkey, France, and Spain • A tool has been developed that allows for the comparison of patient & caregiver experiences across different disease types, countries and services • The author suggests this could contribute to the implementation of an international, multidimensional and multi-disease periodic evaluation of subjective patient and caregiver experiences
Patient registries and biorepositories					
Enrollment in a registry or biorepository					
Montano (2007) [48]	International (Australia, Austria, Brazil, Canada, Chile, Colombia, Finland, France, Germany, Indonesia, Italy, Japan, Morocco, New Zealand, Poland, Puerto Rico, Saudi Arabia, Spain, Switzerland, Turkey, United Kingdom, United States) Note: study conducted out of the United States	MPS IVA	Patients	• Patients enrolled in a registry completed a questionnaire on birth and family history; age and onset of diagnosis; signs and symptoms; clinical course from infancy to adulthood; surgical interventions; current height and weight; physical activity; other complaints • Caregivers or friends helped some adult patients to complete the questionnaire	• The information collected will help to facilitate clinical trials on ERTs, as information on the natural history, rate of progression, and distribution of symptoms in untreated patients is necessary for developing clinical endpoints and judging therapeutic effects • The authors suggest an annual survey will allow for the collection of more data on the management of patients, efficacy of treatment, and endpoints of clinical trials
Pastores (2007) [72]	International (Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Japan, Korea,	Mucopolysaccharidosis Type I (MPS I)	Patients and caregivers	• Patients are enrolled in a registry voluntarily by their physician, who captures medical history data on the patient's symptoms and treatments • Patient or their primary caregiver also complete a health assessment questionnaire (MPS-HAQ) to capture data on daily activities	• Data collected in the registry is available for physicians for possible publication • Physicians also receive monthly Patient Case Reports, newsletters, and aggregate data reports on the entire registry

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
	Netherlands, Norway, Poland, Saudi Arabia, Singapore, Slovakia, Taiwan, Turkey, United Kingdom, and United States)			• Caregiver assistance questions are included to assess the support that patients require in self-care and mobility activities	population • Based on initial assessments, the Registry provides a large, broad, and representative pool of patients with MPS I • The data collected may be modified in the future to capture other specific parameters
van der Meijden (2014) [67]	International (Australia, Canada, France, Germany, Netherlands, United Kingdom, United States) Note: study was based out of the Netherlands	Pompe disease	Patients	• Patients enroll in the IPA/Erasmus MC Pompe Survey (Pompe Survey), completing a baseline survey and a follow-up questionnaire every year after • The Survey includes a Pompe-specific questionnaire as well as three generic questions regarding fatigue, participation in daily life, and health-related quality of life	• The Pompe Survey is now one of the largest databases with consistent follow-up of Pompe patients (children and adults) worldwide • The Pompe Survey has allowed researchers to quantify disease progression in untreated patients, capture disease impact on daily life, and quantify changes due to treatment (enzyme replacement therapy, ERT) over an extended period of time
Mallbris (2007) [73]	Sweden	Hereditary angioedema (HAE)	Patients	• Patients complete a questionnaire and telephone interview to capture information on demographics; social, educational, economical and health status; quality of life; family history of HAE; comorbidities; potential trigger factors; medical history; attack characterization; severity of symptoms; efficacy, safety, and outcome of different treatments; and the extent of health and social services use • Patients also provide a blood sample if they are living near a qualified lab	• The design of the registry permits analysis of subpopulations • With this registry, scientists will be able to conduct case-control and prospective cohort studies, and may also cross-link the data with other population-based registries
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	CF	Patients	• Patients provide consent to participate in the CFF registry at accredited care centres, where data is collected on state of residence, height, weight, gender, CF mutations, pulmonary function test results, medication use, and complications related to CF	• The data gathered in the registry is used by health care professionals to improve the delivery of care, study treatment effects, develop care guidelines, and design clinical trials • The registry also allows people with CF, their caregivers, and health care professionals to compare overall health of patients receiving care at one CF centre with those at other centres

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
De Blieck (2013) [34]	United States	JNCL	Patients	• Patients enroll in the URBC contact and natural history registry	• Between 2001-2012, 198 families have enrolled in the registry •120 children from 99 families have enrolled in a study to validate the Unified Batten Disease Rating Scale (UBDRS) •Other projects that families have been enrolled in include studies of socio-demographic status, visual –aid skills, attitudes and knowledge about genetic testing, and families' interests in participating in Phase II safety and tolerability clinical trials • Through the registry, patients were also recruited to participate in the URBC's phase II trial and parents were able to provide input regarding trial design (e.g., the feasibility of travel)
Richesson (2009) [74]	United States	Rare diseases in general	Patients	• Patients provide contact information, self-reported diagnosis, and demographic information to the RDCRN •Patients receive news of open or planned clinical studies on behalf of the RDCRN (e.g., title of open protocol; eligibility criteria; protocol description; open sites; contact info) • If interested in participating, patients must contact study personnel •Patients may also use a toll-free number to enroll or update their information • Standard post may be used to receive information	• Over 4,000 individuals representing 40+ different rare diseases from 61 different countries were enrolled in the Contact Registry as of 2007 • The number of enrolees varies across the consortia due in part to the promotion of the Contact Registry by certain patient organizations •The overall study participation rate in 5 RDCRN research consortia was 12% (6-27%), with the rate increasing to 16% (8-42%) and 21% (12-43%) when restricting study eligibility to within 200 miles and 100 miles of a study site, respectively
Seminara (2010) [52]	United States	UCDs	Patients	• Patients self-registered in the RDCRN Contact Registry receive information about UCDC studies via email	Not specified
Establishment of a registry or biorepository					
Workman (2013) [76]	United States	Rare diseases in general	Patients and patient organizations	• Patients, usually through organizations that receive advice from a scientific board of advisors, establish patient-powered registries (PPRs)	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
				• Patients, caregivers, or patient organizations manage or control data collection, the research agenda for the data, and the translation and dissemination of the research from the data • Many also have biorepositories • e.g., DuchenneConnect; Life Raft Group Patient Registry and Tissue Bank	
van der Meijden (2014) [67]	International (Australia, Canada, France, Germany, Netherlands, United Kingdom, United States) Note: study was based out of the Netherlands	Pompe disease	Patient organizations	• The International Pompe Association (IPA), a federation of Pompe disease patient groups, collaborated with Erasmus MC University Medical Centre to establish the Pompe Survey	• The Pompe Survey is now one of the largest databases with consistent follow-up of Pompe patients (children and adults) worldwide • The Pompe Survey has allowed researchers to quantify disease progression in untreated patients, capture disease impact on daily life, and quantify changes due to treatment (enzyme replacement therapy, ERT) over an extended period of time
TREAT-NMD [77]	Europe	NMDs	Patient organizations	• TREAT-NMD collaborated with clinicians and patient organizations internationally to create registries that aim to facilitate future clinical trials and therapy development • Registries are governed by a charter, with an oversight committee that includes patient representatives	• The global registries for Duchenne Muscular Dystrophy (DMD) and spinal muscular atrophy (SMA) are recognized as top resources for trial planning and recruitment • These registries are available to industry and academic researchers • They also provide information and feedback to patients, connecting them to the research world
TREAT-NMD [77]	Europe	NMDs	Patient organizations	• The EuroBioBank, a TREAT-NMD-integrated resource, is led by EURODIS • It is dedicated to rare diseases research	• EuroBioBank has been referenced in over 100 research papers • It has ~400,000 samples available to researchers
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	CF	Patient organizations	• The CFF established a patient registry	• The data gathered in the registry is used by health care professionals to improve the delivery of care, study treatment effects, develop care guidelines, and design clinical trials • The registry also allows people with CF, their caregivers, and health care

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
					professionals to compare overall health of patients receiving care at one CF centre with those at other centres
Ferguson (2002) [37]	United States	PXE	Patient organizations	• PXE International established a registry and tissue bank	Not specified
Schwartz (2013) [58]	United States	PC	Patient organizations	• The PC Project established the International PC Research Registry, in which patients provide personal histories and, in return, are provided with physician consultations and genetic testing	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA is planning on establishing a patient registry, which will collect data on: the incidence, prevalence, and natural history of VHL lesions; studies of clinical and environmental cofactors that may influence the natural history of VHL; and studies to predict the development of specific lesion patterns within families	Not applicable
Workman (2013) [76]	United States	Rare diseases in general	Patient organizations	• Some patient registries collaborate to form patient-powered research networks (PPRNs), developing registries with a shared infrastructure and standardized method of data collection • Data may be combined for analysis • e.g., Genetic Alliance Registry and BioBank; Patients Like Me; Registries for All	Not specified
Design of a registry or biorepository					
van der Meijden (2014) [67]	International (Australia, Canada, France, Germany, Netherlands, United Kingdom, United States) Note: study was based out of the Netherlands	Pompe disease	Patients	• The Pompe-specific questionnaire utilized in the Pompe Survey was piloted by a patient panel, which also commented on whether any topics were missing	• The questionnaire has successfully been used in the Pompe Survey to collect data on 408 Pompe patients between 2002 and 2013
Duchange (2014) [54]	Europe	Leukodystrophies (LDs)	Patients and patient organizations	• In developing a framework for the LeukoDataBase, the LEC also received input from patients and their caregivers through a survey provided to French families participating in the annual meeting of the European Leukodystrophies Association	• 55 questionnaires were returned and analyzed
Duchange	Europe	Leukodystrophies (LDs)	Patient	• One of the first tasks of the LEC was to produce	• A charter defining the binding

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2014) [54]			organizations	recommendations and documents to frame the LeukoDataBase, a supranational registry for patients with LDs • Patient representatives on the LEC were responsible for relaying patient expectations • Ethical issues identified and addressed by the LEC include acknowledging the line between care and research; outlining the informed consent process; providing a clear description of data collected and shared in the database; transparency of the length of data conservation; adapting information to patients' clinical situations (e.g., minors); obtaining consent from patients already included in national databases; and providing ongoing information to patients regarding the registry	commitments and responsibilities of health professionals regarding the preservation, use and sharing of participants' data within the LeukoDataBase was developed
Rubinstein (2010) [78]	United States	Rare diseases in general	Patient organizations	• Patient organizations participated in two days of presentation and breakout sessions at the "Advancing Rare Disease Research: The Intersection of Patient Registries, Bio-specimen Repositories, and Clinical Data" workshop • Discussions were had on the control of a global registry, access to data, bioethical considerations, and privacy concerns	• The workshop resulted in the production of recommendations for the next steps in producing this global registry
Rubinstein (2012) [79]	United States	Rare diseases in general	Patient organizations	• Patient organizations participated in discussions at the "Informed Consent Models/ Templates for Rare Disease Registries Linked to Biorepositories" workshop, which focused on developing guidance for contributing registries on the informed consent process • Topics discussed included: the information that should be provided to patients before they give consent, elements to be included in an informed consent form, and existing templates for short, simple, and clear informed consent forms	• The workshop resulted in the production of recommendations for information to be provided to patient before a consent form is signed in the Global Rare Disease Patient Registry and Data Repository (GRDR)
Maintenance and/or management of a registry or a biorepository					
Lochmuller (2009) [75]	Europe	Rare diseases in general	Patients and patient organizations	• Patients and patient organizations actively participate in sample collection	Not specified
Lochmuller (2009)	Europe	Rare diseases in general	Patient organizations	• Patient organizations participate at the operative level of biorepositories	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
[75]					
TREAT-NMD [77]	Europe	NMDs	Patient organizations	• TREAT-NMD collaborated with clinicians and patient organizations internationally to create registries that aim to facilitate future clinical trials and therapy development • Registries are governed by a charter, with an oversight committee that includes patient representatives	• The global registries for Duchenne Muscular Dystrophy (DMD) and spinal muscular atrophy (SMA) are recognized as top resources for trial planning and recruitment • These registries are available to industry and academic researchers • They also provide information and feedback to patients, connecting them to the research world
TREAT-NMD [77]	Europe	NMDs	Patient organizations	• The EuroBioBank, a TREAT-NMD-integrated resource, is led by EURODIS • It is dedicated to rare diseases research	• EuroBioBank has been referenced in over 100 research papers • It has ~400,000 samples available to researchers
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations are involved with research registries or biobanks	Not specified
Funding a registry or biorepository					
Lochmuller (2009) [75]	Europe	Rare diseases in general	Patient organizations	• Patient organizations fund biorepositories	Not specified
Rubinstein (2010) [78]	United States	Rare diseases in general	Patient organizations	• Patient organizations sponsored the "Advancing Rare Disease Research: The Intersection of Patient Registries, Bio-specimen Repositories, and Clinical Data" workshop, which focused on the development of a global patient registry for rare diseases	Not specified
Recruitment of registry or biorepository participants					
van der Meijden (2014) [67]	International (Australia, Canada, France, Germany, Netherlands, United Kingdom, United States) Note: study was based out of the Netherlands	Pompe disease	Patient organizations	• The IPA recruits participants to the Pompe Survey by requesting new members of the member support groups to participate	• The Pompe Survey is now one of the largest databases with consistent follow-up of Pompe patients (children and adults) worldwide • 408 Pompe patients have been tracked in the Pompe Survey between 2002 and 2013
Stakeholder relationships and collaborations					
Facilitation of relationships between stakeholders					
EURODIS	Europe	Rare diseases in general	Patient	• EURODIS, in collaboration with the Alliance	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2011) [62]			organizations	Maladies Rares, European experts, and members of the EURODIS Round Table of companies, developed a charter to outline general principles for collaborations between trial sponsors and patient organizations	
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD provides neutral meetings for communication between patients, the FDA, and industry members	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD interfaces between the FDA and manufacturers of orphan products, communicating to manufacturers information on the orphan product designation and how to apply	Not specified
Establishment and maintenance of relationships with stakeholders					
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Dialogue between patients, manufacturers, regulatory bodies, and clinical researchers should be maintained to ensure that the data required and the data collected throughout R&D, clinical trials, and regulations of new treatments are in line with each other	Not specified
Caron-Flinterman (2005) [46]	Netherlands	NMDs	Patients	• Patient develop relationships with researchers, sharing information about their disease symptoms, including their severe fatigue	• This commentary led to the initiation of a research project on the central and peripheral aspects of muscle fatigue associated with NMDs
De Blieck (2013) [34]	United States	JNCL	Patients	• Patients provide anecdotal reports on their symptoms to URBC researchers	• Based on these reports, studies have been initiated on: the perceived benefit of flupirtine treatment; sex differences in JNCL symptom onset; and rate of progression seizure characteristics, and treatments
O'Mahony (2014) [45]	European Union	Rare disease in general	Patient organizations	• Patient organizations are members of the European Union Committee of Experts on Rare Diseases (EUCERD), which aims to foster exchange of relevant experience, policies, and practices between all parties (i.e., patient organizations, Ministries of Health, research and public health experts, industry, and the European Commission) with the main goal of aiding the European Commission in the preparation and implementation of community activities in the field of rare diseases	Not specified
Dunkle	United States	Rare diseases in general	Patient	• NORD collaborates with industry, allowing	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2010) [56]			organizations	companies to participate on its Corporate Council	
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD's Medical Advisory Committee allows for the incorporation of the view of health care professionals into their advocacy process	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD and EURODIS signed a Memorandum of Understanding and are collaborating on several initiatives aiming to increase global awareness, promote R&D on new treatments, and advocating for more compassionate public policies	Not specified
Ferguson (2002) [37]	United States	GIST	Patient organizations	• The LRG established a Science Team, which reviews medical literature and communicates with leading GIST specialists	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations establish global partnerships as part of the RDCRN	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA establishes collaborations with various organizations (e.g., Genetic Alliance, National Organization for Rare Disorders) and acts as the home for the International VHL Alliance, an international network of VHL Affiliates	• The International VHL Alliance allows the VHLA to connect with 90% of all diagnosed VHL patients around the world
Education and awareness					
Informational resources					
Patient Partner [61]	International	Rare diseases in general	Patient organizations	• The Patient Partner project, a collaboration involving patient organization alliances (e.g., Genetic Alliance UK), established a set of guidelines for the involvement of patient organizations and patient representatives in clinical research • The guidelines describe clinical trials and discuss how patients and patient organizations can get involved, who they should become involved with, and ethical considerations for partnerships	Not specified
Scarpa (2011) [49]	Europe	MPS II	Patient organizations	• Patient organizations provide verbal and written information on issues like education, grants, equipment, care plans, independent living, pre-and post-bereavement support, disability benefits, respite care, and housing	Not specified
Boon	Netherlands	NMDs	Patient	• The VSN keeps track of scientific development,	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2010) [55]			organizations	annotates them, tries to clarify them, and reports on them with disclaimers to the patient community	
Black (2011) [63]	United States	SMEI	Patient organizations	• The League has a website containing information on the clinical course, etiology, epidemiology, and treatment of Dravet syndrome and provides links to other international resources and support groups, and to educational financial and health care resources for children with special needs • Information is available regarding opportunities to fund & participate in research, local events in the Dravet syndrome community, genetic testing, and regional epilepsy centers providing care to patients	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• Patient organizations created a database of medical information on rare diseases that both patients and health care professionals may access	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations are involved in educating patients, public, media, and healthcare providers within the RDCRN	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations provide disease-specific information for patients and caregivers on RDCRN website	
Seminara (2010) [52]	United States	UCDs	Patient organizations	• The National Urea Cycle Disorders Foundation helped to design content for the UCDC website and develop and distribute brochures to patients, caregivers, and health care professionals	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA publishes a VHL Handbook, providing patients with tips on diagnosis, treatment, and ways of living with VHL	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA answers questions for physicians or passes questions along to appropriate experts	Not specified
Von-Hippel-Lindau	United States	VHL	Patient organizations	• The VHLA provides a toll-free hotline and a mentoring program	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Alliance (VHLA) (2014) [53]					
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA has a website and sends out monthly wellness e-letters	Not specified
Formal educational activities and training programs					
Black (2011) [63]	United States	SMEI	Patient organizations	• The IDEA League has organized Grand Rounds on Dravet syndrome at academic institutions and sponsors educational activities for health care professionals	Not specified
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	CF	Patient organizations	• The CFF provides education and advocacy resources to patients and their families • It also provides training in quality improvement	Not specified
Groft (2013) [64]	United States	Rare diseases in general	Patient organizations	• Patient organizations fund training programs of RDCRN consortia and patient registries • They also fund training of RDCRN investigators	Not specified
Lasker (2005) [60]	United States	PBC	Patient organization	• The PBCers Organization provides educational programs	Not specified
Seminara (2010) [52]	United States	UCDs	Patient organizations	• The National Urea Cycle Disorders Foundation is directly involved in training programs within the RDCRN	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations sponsored education events, sponsored healthcare professional education events, and educate policy makers	Not specified
Awareness campaigns					
Black (2011) [63]	United States	SMEI	Patient organizations	• The IDEA League participates in national awareness campaigns	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• Patient organizations created Rare Disease Day	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Advocacy					
Advocating for research					
TREAT-NMD [77]	Europe	NMDs	Patient organizations	• Patient organizations (e.g., EURODIS) advocated for funding from the European Union to establish the TREAT-NMD network	• The network has since become a global organization bringing together leading specialists, patient organizations, and industry representatives
Caron-Flinterman (2005) [46]	Germany	Retinitis Pigmentosa	Patient organizations	• Pro Retina lobbied for public funding for research	Not specified
Patient Partner [61]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations lobby for the development of clinical trials for a specific condition	Not specified
Advocating for drug access/coverage					
Goodman (503) [80]	United States	Myelodysplastic syndrome	Patients and caregivers	• Parents of a 7 year old patient used Facebook to advocate for access to an experimental antiviral therapy produced by Chimerix after their first request made to the company was turned down	• The resulting social media response lead the FDA and Chimerix to collaborate on a small, uncontrolled pilot trial that immediately provided the drug to the 7 year old patient and 19 other patients
Black (2011) [63]	United States	SMEI	Patient organizations	• The League advocated for universal coverage of drugs shown to benefit SMEI patients • They are still advocating for full approval of stiripentol by the FDA in the United States	• The League has secured coverage of stiripentol and clobazam by 14 Medicaid Agencies and 6+ private insurance companies in the United States; the Ministry of Health in Ontario; and one of the largest HMOs in Israel
Advocating for legislation					
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD representatives testify before Congressional committees on a regular basis •Advocacy efforts of NORD have focused on: rare disease and orphan drug legislation; ensuring adequate funding for the FDA, the NIH, and the SSA; extended patent period on orphan products; the removal of lifetime caps from health insurance policies; and for legislation to improve patient access to clinical trials	• The passing of the Orphan Drug Act was due in part to the advocacy efforts of the coalition that would eventual become NORD
Lasker (2005) [60]	United States	PBC	Patient organization	• The PBCers Organization advocates for those with PBC	Not specified
Landy	Not specified	Rare diseases in general	Patient	• Patient organizations lobby policy makers	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2012) [84]			organizations		
Conferences and Workshops					
Participating in conferences and workshops					
Molster (2012) [81]	Australia	Rare diseases in general	Patients, caregivers and patient organizations	• Patients, caregivers, and patient organizations participated in workshops at the Australian Rare Diseases Symposium discussing the issues, goals, and actions relevant to the development of a national plan	• Participants identified a range of key issues for consideration, with associated goals and actions • There was agreement that the recommendations drawn out from the outcomes of the workshops should be used to inform and frame the development of a national plan
Hosting conferences and workshops					
De Blieck (2013) [34]	United States	JNCL	Patient organizations	• The BDRSA hosts an Annual Conference	• The conference provides a venue for the URBC to enroll families in the contact registry, the natural history and disease-specific rating scale study, and/or neuropsychological investigations
Lasker (2005) [60]	United States	PBC	Patient organization	• The PBCers Organization hosts conferences with medical experts	Not specified
Seminara (2010) [52]	United States	UCDs	Patient organizations	• The National Urea Cycle Disorders Foundation hosts an annual conference where educational presentations are given to patients and professionals by UCDC investigators	• The conference has helped to facilitate recruitment into UCDC studies
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	CF	Patient organizations	• The CFF hosts the annual North American CF Conference, where updates on CF care and research are shared	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	•Hosts the International VHL Medical Symposia, bringing together leaders in VHL basic, translational, and clinical researchers, as well as clinicians specializing in VHL diagnosis and treatment	• The conference helps to stimulate research and make connections among professionals
Funding conferences and workshops					
Groft	United States	Rare diseases in general	Patient	• Patient organizations fund research-based scientific	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2013) [64]			organizations	conferences and meetings for patients, families, and caregivers within the RDCRN	
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations organize and support scientific conferences	Not specified
Patient care and support					
Social support for patients					
Frost (2008) [40]	International	Rare diseases in general	Patients	• Patients participate in Patients Like Me, an online community in which data can be entered into health profiles (e.g., symptoms, treatments, functional rating etc.) and members can communicate via forums and comments on their profiles	• 3,200 members (including caregivers, providers, and researchers) have joined since 2006, with 1,750 patient users • Data is aggregated from all health profiles to create community summaries on treatments and symptoms
Hughes (2008) [82]	International	Rare diseases in general	Patients and caregivers	• Patients and their caregivers participate in discussion threads on RareConnect.org, an online patient forum • Posts tended to fall within one of the following themes: finances, difficulty in getting a diagnosis, feeling that doctors are not knowledgeable, and feelings of isolation	• The author concludes that rare disease patients provide their peers with social support and information • RareConnect.org provides the opportunity for general information sharing • However, due to the prevalence of moderators in this community, supportive and sociable relationships are difficult to develop
Doyle (2015) [39]	United States	Cystinosis	Patients and caregivers	• Through advocacy groups and the Internet, patients and caregivers interact with their disease community in 5 main ways: 1. Comfortability: they connect with others who understand their situation, allowing them to talk freely, feel understood and less guarded, and to receive comfort during difficult times 2. Comparing notes: they exchange ideas about living with the disease, sharing strategies, personal anecdotes, warnings, and information about the disease or treatment 3. Modeling and mentoring: those with more experience are seen as having greater knowledge in living with the illness, becoming models and mentors to those with less experience 4. Witnessing and scaling: they observe each other's	• The authors conclude that patients and their caregivers benefit from peer support and mentorship, and that participating in a disease community helps them to live with their illness

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
				health, progression of illness, etc., and compare it with their own health status; older patients' experience may provide hope or fear, and can also be used to encourage adherence to treatment 5. Going/being public: they share their story and opinions through Facebook groups, patient organization forums, and other message boards, giving and getting social support	
Ferguson (2002) [37]	United States	GIST	Patients	• The Life Raft Group (LRG) is an online community started by the husband of a patient with a gastrointestinal stromal tumor (GIST) • A medical librarian collects medical updates from the members and shares them with the group	Not specified
Scarpa (2011) [49]	Europe	MPS II	Patient organizations	• Patient organizations provide counselling and connect families to other affected individuals	Not specified
Scarpa (2011) [49]	Europe	MPS II	Patient organizations	• Patient organizations help patients understand their diseases	Not specified
Black (2011) [63]	United Kingdom	SMEI	Patient organizations	• The IDEA League UK established a fund to help families attend their annual "Dravet Weekend Away"	Not specified
JISC (2011) [44]	United Kingdom	NMDs	Patient organizations	• The MDC as a patient forum as well as a Facebook page and Twitter account	Not specified
Black (2011) [63]	United States	SMEI	Patient organizations	• The IDEA league established an online network allowing for social networking between families in online forums	• The online family forum has helped to identify challenges in the care of Dravet syndrome patients, including access to care, difficulties in diagnosis, treatment disparities among providers, and the need to define associated comorbidities • Information gathered in the online forums has stimulated research into associated conditions (e.g., facial anomalies)
Black (2011) [63]	United States	SMEI	Patient organizations	• The IDEA League has organized social gathering for patients and their families	Not specified
Lasker	United States	PBC	Patient	• The PBCers Organization provides electronic	• Patients were found to use the online

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2005) [60]			organization	mailing lists (listservs), chatrooms and message boards for use by patients and other informational resources	resources provided by the PBCers Organization, particularly the Daily Digest, to discuss biomedical issues (e.g., medications), but framed within the context of offering support to their peers
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA hosts an Annual Family Meeting	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations organize support groups and maintained toll-free support lines	Not specified
Financial support for patients					
Black (2011) [63]	United Kingdom	SMEI	Patient organizations	• The IDEA League UK has helped families obtain medical equipment by funding the purchases or helping families to obtain discounts	Not specified
Black (2011) [63]	United States	SMEI	Patient organizations	• The League created a medication assistance fund to help financially disadvantaged families obtain stiripentol when funding is not available	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD administers Patient Assistance Programs for uninsured and underinsured patients	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD provides drugs at no charge to eligible patients through its Medication Assistance Programs	Not specified
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD provides premium and copayment funds for patients with certain disorders, who cannot afford out-of-pocket costs associated with their plans	Not specified
Landy (2012) [84]	Not specified	Rare diseases in general	Patient organizations	• Patient organizations provide financial assistance to patients	Not specified
Support for patients participating in clinical trials					
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• Patient organizations provide travel and temporary housing assistance to patients and caregivers who must travel to participate in clinical trials	Not specified
EURODIS (2011)	Europe	Rare diseases in general	Patient organizations	• Patient organizations support patients during a study to reduce the rate of drop-outs and incomplete files	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
[62]					
Clinical care support for patients					
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Patients, in partnership with their physicians, should decide whether the benefits of a new drug outweigh its risks.	Not specified
Pattacini (2009) [83]	Italy	Hemophilia	Patients	• Patients access part of their clinical records through 'xl'Emofilia, a web-based electronic outpatients' record, in order to consult their data and record bleeding events and home infusions • Patient-entered data is validated by doctors at a treating Hemophilia Centre • Patients receive training to use these records	• Data is extracted in an anonymous format and published on a website • Some data is also processed and sent to the Italian Registry of Hemophilia and Allied Disorders • The authors state that this system has improved the management of data, facilitated work, and improved the quality of care for patients
Scarpa (2011) [49]	Europe	MPS II	Patient organizations	• A patient organization representative provided input into the development of recommendations through a project led by the Hunter Syndrome European Expert Council	Not specified
Scarpa (2011) [49]	Europe	MPS II	Patient organizations	• Patient organizations collaborate with physicians, specialist nurses, and homecare companies to make new treatment options available to patients	Not specified
TREAT-NMD [77]	Europe	NMDs	Patient organizations	• TREAT-NMD collaborated with specialist groups and patient organizations to develop international consensus documents outlining best practice in diagnosis and patient care • Patient organizations worked with TREAT-NMD and healthcare professionals to produce patient-friendly summaries of the consensus documents regarding DMD	Not specified
Black (2011) [63]	United States	SMEI	Patient organizations	• The League established the Collaborative Clinical Research and Comprehensive Care Network (CCR-CCN), a network of referral centers providing multidisciplinary care to Dravet syndrome patient • Centres within the CCR-CCN collaborate to establish more consistent standards of care	Not specified
Cystic Fibrosis	United States	CF	Patient organizations	• The CFF provides grants to fund care	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Foundation (CFF) (2013) [59]					
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	CF	Patient organizations	• The CFF established the CF Care Guidelines	Not specified
Cystic Fibrosis Foundation (CFF) (2013) [59]	United States	CF	Patient organizations	• The CFF provides accreditation to a network of over 110 CF care centres across the United States	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• Patient organizations established VHL Clinical Care Centres in the United States and around the world	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA created guidelines for screening and treatment • It also developed a VHL Clinical Advisory Council and created a position of Director of Wellness to respond to questions and concerns; provide connections to medical professionals, etc.; and direct medical questions to the Clinical Advisory Council	Not specified
Patient organization development					
Establishing patient organizations					
Rabeharisoa (2003) [50]	France	NMDs	Patient and caregivers	• The AFM was established by a mother of 4 patients	• The AFM now has 4,500 members, over 500 salaried workers, and is financially independent • It is comprised of 3 main departments: "research"; "medical and social action"; and "daily life support", ensuring that no domain is neglected
Rabeharisoa	France	NMDs	Patient and	• The AFM raises funds to support its work through a	• 80% of the AFM's annual budget of

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2003) [50]			caregivers	television-based initiative (Telethon)	~€80 million is raised through Telethon
Ferguson (2002) [37]	United States	Chromosome 18 deletion	Patients and caregivers	• The mother of a patient developed the Chromosome 18 Registry and Research Society, uniting three independent organizations	Not specified
Providing guidance on establishing patient organizations					
Mai (2008) [38]	United States	LFS	Patient organizations	• At a workshop at the National Institutes of Health, patient organizations shared their perspectives and advice on forming disease-focused support and advocacy groups	Not specified
Establishing international patient organization alliances					
Boon (2010) [55]	Netherlands	NMDs	Patient organizations	• The VSN helped to establish the International Pompe Association, an alliance of patient organizations	Not specified
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The VHLA establishes similar alliances around the world	Not specified
Fundraising to support further patient organization growth					
Von-Hippel-Lindau Alliance (VHLA) (2014) [53]	United States	VHL	Patient organizations	• The majority of funds supporting the VHLA are acquired through fundraising initiatives	Not specified
Regulatory decision-making					
Input into the regulatory decision-making process					
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Patient input on acceptable risk should be imbedded into regulatory decision-making	Not applicable
Pharma Letter (2014) [143] *Pilot project*	Canada	Rare diseases in general	Patients and caregivers	• As part of the new Orphan Drug Framework in Canada, patients provide input on how the disease affects their ability to manage their day-to-day lives, what treatments are currently available, what therapeutic benefits are most important to them, and	• This is a pilot project that will be used by Health Canada to assess and refine its approach to collecting patient input, facilitating this process in future orphan drug authorizations

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
				their risk tolerance for new treatments	
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Patient organizations are consulted on disease-specific requests by the European Medicines Agency' scientific committees and working parties • They take part in discussions on the development and authorization of medicines	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Patient organizations review written information on medicines prepared by the EMA	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Patient organizations are involved in the preparation of EMA guidelines	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Patient organizations take part in EMA conferences and workshops	Not specified
Komlos (2013) [88]	United States	Rare diseases in general	Patients and caregivers	• Patients and caregivers attend public meetings hosted by the FDA where they have the chance to discuss their disease and its impact on their daily lives, the types of treatment benefits that matter to them most, and their perspectives on the adequacy of current therapies	Not specified
Komlos (2013) [88]	United States	Rare diseases in general	Patients and caregivers	• As part of the FDA's Patient Representative Program, patients and caregivers provide input on disease-specific issues relating to medical products in various stages of development, review and approval	Not specified
Black (2011) [63]	United States	SMEI	Patient organizations	• The IDEA League contributed data used in the orphan drug designation application for stiripentol in the United States	• Stiripentol received orphan drug designation in the United States
Dunkle (2010) [56]	United States	Rare diseases in general	Patient organizations	• NORD provides input into FDA processes, such as reviewing applications and setting standards for drug and device testing	Not specified
Membership on a regulatory decision-making or advisory committee					
O'Mahony (2014) [45] *Proposed*	European Union	Haemophilia	Patients and patient organizations	• While patients currently play a role on a number of the EMA's scientific committees, a panel member at the EHC Congress satellite symposium suggested that there are still further opportunities for patient	Not applicable

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
				representation on committees • e.g., there is not yet patient representation on the Committee for Medicinal Products for Human Use (CHMP)	
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Two representatives from eligible patient organizations are members of the management board of the EMA, which governs the entire organization	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Three representatives from eligible patient organizations are members of the EMA's Committee for Orphan Medicinal Products (COMP)	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• One representative from an eligible patient organization is a member of the Pharmacovigilance Risk Assessment Committee (PRAC)	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• Two representatives from eligible patient organizations are members of the Committee for Advanced Therapies	Not specified
EMA (2012) [100] [Website]	European Union	Rare diseases in general	Patient organizations	• The representatives from eligible patient organizations are members of the Paediatric Committee (PDCO)	Not specified
Input into the design of the regulatory decision-making process					
Dunkle (2010) [56] *Proposed*	United States	Rare diseases in general	Patient organizations	• In a summit meeting NORD established that in the future, one priority of the organization should be to identify FDA laws, regulations, and policies that need to be changed to encourage product approval	Not specified
Dunkle (2010) [56] *Proposed*	United States	Rare diseases in general	Patient organizations	• In a summit meeting, NORD established that in the future, one priority of the organization should be to work with the FDA to establish greater certainty in the orphan product approval process, especially in regards to clinical trial design and endpoints	Not specified
Reimbursement decision-making					
Input into the reimbursement decision-making process					
O'Mahony (2014) [45]	European Union	Haemophilia	Patients	• It was stated at the EHC Congress satellite symposium that it is necessary to begin engaging HTA agencies, possibly through EU Network for HTA	Not applicable

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Proposed				(EUnetHTA), to allow for patient input at the earliest stage of the HTA process •It was also suggested by a panel member that there is an opportunity for patient engagement in EUnetHTA's current efforts to develop common practices across the EU that ensure consistency of data collection • e.g., it is essential that the system is capable of understanding the impact of an intervention in the context of the experience of hemophilia patients	
O'Mahony (2014) [45] *Proposed*	European Union	Haemophilia	Patients, caregivers, and patient organizations	• To ensure that health technology assessments (HTAs) consider factors beyond cost (i.e., factors that matter to patients), a panel member at the EHC Congress satellite symposium suggested that patient advocates and clinicians must work together to create a shared consensus on how to effectively evaluate the efficacy of therapies and what experiential data are of the greatest value	Not applicable
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Nominated patient experts should be permitted to present a summary of the patient evidence submission to the Evaluation Committee	Not applicable
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Patient should be formally consulted during the National Institute of Health and Care Excellence (NICE) Highly Specialized Technology (HST) evaluation process, prior to the final decision-making Committee meeting, to outline the nature and timeline of any post-evaluation research recommended by NICE	Not applicable
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• If the benefit/risk of a product is to be re-examined by NICE, patient input should be included and all information from patient representatives provided to the EMA for their benefit/risk assessment should be made available to NICE	Not applicable
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patients	• Patient input on benefit/risk should be incorporated during topic selection by the NIHR Horizon Scanning Centre	Not applicable

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Genetic Alliance UK (2014) [51] *Proposed*	United Kingdom	Rare diseases in general	Patient organizations	• Patient organizations should be involved in the process of topic identification and selection • Patient organizations play a role in informing NICE of new medicines being considered for market authorization, but a more formalized route may be necessary	Not applicable
Dunkle (2010) [56] *Proposed*	United States	Rare diseases in general	Patient organizations	• At a summit meeting, NORD concluded that a future priority for the organization should be to assure reimbursement of off-label drug use for rare disease patients	Not specified
Sussex (2013) [144] *Pilot study*	Europe	Rare diseases in general	Patient organization	• Patient representatives were involved in the pilot stage of multi-criteria decision analysis (MCDA) to establish and apply a framework of weighed attributes to value orphan medicinal products for potential use in the reimbursement decision-making process • Patient representatives were first interviewed to help identify value attributes for use in the MCDA process • Patient representatives also participated in a workshop to validate a finalized list of 8 attributes, weight these attributes, and then rate 2 case study OMPs using the weighed attributes (note: two other workshops were hosted by the researchers in this study – one with manufacturers to pilot the process, and a second with clinical and health economics experts)	• The authors suggest that, based on the success of this study, the methods described could be used in real-world settings, by decision-making groups within HTA and reimbursement bodies
Winquist (2014) [119]	Canada	Rare diseases in general	Patients	• Patients were formally consulted in Ontario's Drugs for Rare Diseases Working Group's evaluation of idursulfurase	• Idursulfurase was approved for funding by the Executive Officer of the Ontario Public Drug Programs after risk-sharing agreements were made with the manufacturer
Winquist (2014) [119]	Canada	Rare diseases in general	Patient organizations	• Upon completion of each drug evaluation between 2008-2013, outcomes of the reviews were shared with patient stakeholder groups to identify any areas of disagreement or error • Reimbursement guidelines for 3 of the drugs that underwent full evaluation were circulated to patient stakeholder groups and physicians for feedback	• Recommendations were revisited based on the feedback obtained • The 5 drugs that underwent full evaluation between 2008 -2013 were approved for funding (for certain conditions and with eligibility and exclusion criteria) by the Executive Officer of the Ontario Public Drug Programs after risk-sharing agreements were made with the manufacturer

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
Genetic Alliance UK (2014) [51]	United Kingdom	Rare diseases in general	Patients	• "Nominated experts", including patients and carers, have the opportunity to speak directly to NICE's Evaluation Committee	Not specified
Boon (2010) [55]	Netherlands	NMDs	Patient organizations	• The VSN is involved in discussions on reimbursement of therapies for NMDs	Not specified
Genetic Alliance UK (2014) [51]	United Kingdom	Rare diseases in general	Patient organizations	• Patient representatives provide a patient evidence submission during HST evaluations	Not specified
Genetic Alliance UK (2014) [51]	United Kingdom	Rare diseases in general	Patient organizations	• Patient groups identified during the evaluation are able to launch an appeal after a guidance has been issued	Not specified
NIHR Horizon Scanning Centre (2015) [124]	United Kingdom	All diseases, including rare	Patient organizations	• The NIHR Horizon Scanning Centre (HSC) received ad hoc commentary from the Gaucher Association on a briefing report regarding Miglustat for type 3 Guacher disease	Not specified
NIHR Horizon Scanning Centre (2015) [124]	United Kingdom	All diseases, including rare	Patient organizations	• In 2014, the Genetic Alliance UK agreed to serve as a conduit between the HSC and an appropriate patient group on any genetic topics on which NICE requested briefings • Subsequently, the Genetic Alliance UK facilitated comments from the MPS Society on an HSC briefing draft regarding Lamazym for alpha-mannosidosis • The MPS Society made contact with most of the 14 patients with alpha-mannosidosis in the UK, providing some replacement paragraphs with more up-to-date information	• Most of the comments made by the patient group were incorporated into the briefing
Input into the design of the reimbursement decision-making process					
Genetic Alliance UK (2014) [51]	United Kingdom	Rare diseases in general	Patients	• NICE met with patients when developing the initial interim HST framework	Not specified
Genetic Alliance UK	United Kingdom	Rare diseases in general	Patient organizations	• Genetic Alliance UK collaborated with other patient organizations to develop a set of recommendations for	Not specified

Table 1-1. Opportunities for patient, caregiver, and patient organization involvement identified in the literature review

Primary author (year)	Country	Disease area	Participants‡	Role	Impact or outcome
(2014) [51]				consideration in the 2014 review of the HST process • The Alliance also intends on holding consultations and developing another Patient Charter to identify gaps or inconsistencies between the HST evaluation and alternative routes for high cost medicines	

‡ "Participants" refers to patients, caregivers, and/or patient organizations

† Within each theme, opportunities are listed in the following order: proposed opportunities for patients and caregivers; opportunities for patients and caregivers; proposed opportunities for patient organizations; and opportunities for patient organizations

Table 1-2. Opportunities for patient, caregiver, and patient organization involvement in regulatory decision-making identified through website review

Country	Regulatory body	Role							
		Provide input in pre-submission advice on protocol	**Submit patient-reported outcomes (PROs)**	**Membership on advisory or decision-making committees**	**Provide input on proposed regulation decision or guidelines**	**Participate in benefit/harm assessment**	**Provide input on a pharmacovigilance plan**	**Report adverse events**	**Provide input on consumer information (e.g., labelling)**
Australia [94]	Therapeutic Goods Administration (TGA)	No information found (NIF)	NIF	NIF	NIF	NIF	NIF	Yes (Patients)	NIF
Canada [85;89;95;143]	Health Canada	NIF	Yes (Patients) [85]	Yes (Patients) [89 85]	Yes (Patients) [89 85]	NIF	NIF	Yes (Patients) [95]	NIF
European Union (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherland, Norway, Sweden, United Kingdom) [86;96;100;101]	European Medicines Agency (EMA)	Patient organizations: Yes [100]	Yes (Patients) [86]	Yes (Patient organizations) [100 101]	Yes (Patient organizations) [100]	Yes (Patient organizations) [96]	Yes (Patient organizations) [96]	Yes (Patients) [96]	Yes (Patient organizations) [100]
Japan [145]	Pharmaceuticals and Medical Devices Agency	NIF	NIF	NIF	NIF	NIF	NIF	NIF	NIF
New Zealand [87;90;97;146]	New Zealand Medicines and Medical Devices Safety Authority (Medsafe)	NIF	Yes (Patients) [87]	No [146]	Yes (Patients) [90]	NIF	NIF	Yes (Patients) [97]	NIF
Singapore [147] [148] [149]	The Health Sciences Authority (HSA)	NIF	NIF	No	NIF	NIF	NIF	No [149]	NIF
Switzerland [98;150]	Swiss Agency for Therapeutic Products (Swissmedic)	NIF	NIF	No [150]	NIF	NIF	NIF	Yes (Patients) [98]	No
United States [88;91;92;151]	Food and Drug Administration (FDA)	NIF	Yes (Patients) [88]	Yes (Patients) [91 92]	Yes (Patients) [91 92]	Yes (Patients) [93]	NIF	Yes (Patients) [99]	NIF

Table 1-3. Opportunities for patient, caregiver, and patient organization involvement in reimbursement decision-making identified through website review

Country	Reimbursement Process (CDR or safety-net)	Role						
		Submit topic for consideration	Submit information during preparation of evaluation report	Directly consulted during the review process	Membership on advisory or decision-making committee	Provide feedback on evaluation report and/or proposed recommendations	Prepare a "patient submission"	Present views during committee
Australia [104;105;115;127;138;152;153]	Pharmaceutical Benefits Scheme (CDR)	Yes (Patients or patient organizations) [115]	No information found (NIF)	Yes (Patient organizations) [127]	No [115]	NIF	Yes (Patients or patient organizations) [115;138]	NIF
	Life Saving Drugs Program (safety-net)	No (Physicians must submit) [104]	Yes (Patient data is submitted for yearly reapplication) [104]	NIF	No [115]	NIF	N/A	NIF
	Highly Specialised Drugs Program (safety-net)†	No [105]	NIF	NIF	No [115]	NIF	N/A	NIF
Austria [106;154;155]	CDR	No [155]	NIF	NIF	No [154]	NIF	NIF	NIF
	Individual reimbursement (safety-net)†§	No [106]	NIF	NIF	No [154]	NIF	N/A	NIF
Belgium [156]	CDR	NIF	No [156]	No [156]	No [156]	No [156]	No [156]	No [156]
	Special Solidarity Fund (safety-net)†	NIF	NIF	NIF	NIF	NIF	NIF	NIF
Canada [120;134;137;157]	Common Drug Review (CDR)	NIF	NIF	NIF	No [134]	NIF	Yes (Patient organizations) [137]	NIF
	pan-Canadian Oncology Drug Review (pCODR)	NIF	NIF	NIF	Yes (Patients) [120]	NIF	Yes (Patient organizations) [120]	NIF
Denmark [107;158;159]	CDR	No [107]	NIF	NIF	NIF	NIF	NIF	NIF
	Individual reimbursement (safety-net)†	No (Physicians must submit) [107]	NIF	NIF	NIF	NIF	N/A	NIF
Finland [140;160;160;161]	CDR	NIF	NIF	NIF	No [160]	NIF	NIF	NIF
	Special License Procedure (safety-net)‡	Yes (Patients) [140]	NIF	NIF	NIF	NIF	N/A	NIF
France [108;162;163]	CDR	No [163]	NIF	NIF	No [162]	NIF	NIF	NIF
	Temporary use	No [108]	NIF	NIF	NIF	NIF	N/A	NIF

Table 1-3. Opportunities for patient, caregiver, and patient organization involvement in reimbursement decision-making identified through website review

Country	Reimbursement Process (CDR or safety-net)	Role						
		Submit topic for consideration	Submit information during preparation of evaluation report	Directly consulted during the review process	Membership on advisory or decision-making committee	Provide feedback on evaluation report and/or proposed recommendations	Prepare a "patient submission"	Present views during committee
	authorization – individual (safety-net)‡							
	Temporary use authorization – cohort (safety-net) ‡	No [108]	NIF	NIF	NIF	NIF	NIF	NIF
Germany [109;128;164-166]	CDR	NIF	NIF	Yes (Patient organizations) [128;164]	No [165]	NIF	NIF	NIF
	Compassionate Use (safety-net)§	No [109]	NIF	NIF	NIF	NIF	N/A	NIF
Ireland [110]	Community Drugs Scheme (CDR)	NIF	NIF	NIF	NIF	NIF	NIF	NIF
	Named Patient Regime (safety-net)‡	No [110]	NIF	NIF	NIF	NIF	N/A	NIF
Italy [167]	CDR	NIF	NIF	NIF	NIF	NIF	NIF	NIF
	Individual or cohort reimbursement (safety-net)§‡			NIF	NIF	NIF		NIF
	Temporary individual reimbursement (safety-net)‡	NIF	NIF	NIF	NIF	NIF	N/A	NIF
	Individual reimbursement (safety-net)§‡	NIF	NIF	NIF	NIF	NIF	N/A	NIF
Japan	CDR	NIF	NIF	NIF	No	NIF	NIF	NIF
The Netherlands [106]	Medicines Reimbursement System (CDR)	No [106]	Yes [106]	NIF	Yes (Patients) [106]	NIF	NIF	NIF
	Safety-net‡	NIF	NIF	NIF	NIF	NIF	N/A	NIF
New Zealand [111;116;117;168]	Pharmaceutical Schedule (CDR)	Yes (Patients or patient organizations) [116]	Yes (Patients) [117]	Yes (Patients) [117]	No [168]	Yes (Patients) [117]	NIF	NIF

Table 1-3. Opportunities for patient, caregiver, and patient organization involvement in reimbursement decision-making identified through website review

Country	Reimbursement Process (CDR or safety-net)	Role						
		Submit topic for consideration	Submit information during preparation of evaluation report	Directly consulted during the review process	Membership on advisory or decision-making committee	Provide feedback on evaluation report and/or proposed recommendations	Prepare a "patient submission"	Present views during committee
	Named Patient Pharmaceutical Assessment (Exceptional Circumstances) Policy (safety-net)†	No [111]	NIF	NIF	No [168]	NIF	N/A	NIF
Norway [169;170]	CDR	No [170]	NIF	NIF	NIF	NIF	NIF	NIF
	Compassionate use program (safety-net)†	NIF	NIF	NIF	NIF	NIF	N/A	NIF
Singapore [147]	CDR	NIF	NIF	NIF	No [147]	NIF	NIF	NIF
Spain	CDR	NIF	NIF	NIF	NIF	NIF	NIF	NIF
Sweden [130]	CDR	No [155]	NIF	NIF	Yes (Patient organizations) [130]	NIF	NIF	NIF
Switzerland [131]	List of Specialties (CDR)	NIF	NIF	NIF	Yes (Individuals nominated by patient organizations) [131]	NIF	NIF	NIF
United Kingdom [112;122;132;135]	Highly Specialised Drugs Programme (CDR)	NIF	NIF	Yes (Patient organizations) [132]	Yes (Patient organizations) [132]	NIF	Yes (Patients and patient organizations) [135]	Yes (Patients) [122]
	Patient Access Scheme (safety-net)†	NIF	NIF	Yes (Patients) [112]	NIF	Yes (Patients) [112]	NIF	Yes (Patients) [112]
Scotland [66;113;129;136;171]	CDR	NIF	NIF	Yes (Patient organizations) [129]	No [66]	NIF	Yes (Patient organizations) [136]	NIF
	Patient Access Scheme (safety-net)†	No [113]	NIF	NIF	NIF	NIF	NIF	NIF
Wales [114;123]	CDR	NIF	NIF	NIF	No [123]	NIF	Yes (Patients and patient organizations) [123]	NIF
	Patient Access Scheme (safety-net)†	No [114]	NIF	NIF	No [114]	NIF	NIF	NIF
United States	CDR	NIF	Yes (Patients) [118]	Yes (Patients) [118]	Yes ("Experts in	Yes (Patients) [121]	NIF	Yes (Patients) [118;133]

Table 1-3. Opportunities for patient, caregiver, and patient organization involvement in reimbursement decision-making identified through website review

Country	Reimbursement Process (CDR or safety-net)	Role						
		Submit topic for consideration	Submit information during preparation of evaluation report	Directly consulted during the review process	Membership on advisory or decision-making committee	Provide feedback on evaluation report and/or proposed recommendations	Prepare a "patient submission"	Present views during committee
[118;133]					patient advocacy") [133]			

† Non-reimbursed therapies
§ Off-label therapies
‡ Unlicensed therapies

Table 1-4. Existing and proposed opportunities for patient, caregiver, and patient organization involvement mapped across the orphan drug lifecycle

Stage of the lifecycle	Participants		
	Patients	**Caregivers**	**Patient organizations**
Pre-clinical phase	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research • Providing input on desired format for a new drug **Patient reported outcome measures (PROMs)** Literature (existing): • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing):	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Patient registries and biorepositories** Literature (existing): • Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants **Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns

	• Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences • Sitting on organizing committees **Patient care and support** Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations	**Advocacy** Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing): • Establishing patient organizations	**Advocacy** Literature (existing): • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services • Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences **Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support **Patient organization development** Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization
Clinical trials	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed):	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information

	• Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Clinical trials** Literature (existing): • Participating as subjects in trials Literature (proposed): • Ensure the collection of real-world outcomes that are meaningful to patients **Patient reported outcome measures (PROMs)** Literature (existing): • Submitting PROs in a study • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs	research collaborations/networks Webinar (existing): • Funding research **Patient registries and biorepositories** Literature (existing): • Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing):	**Clinical trials** Literature (existing): • Providing assistance to researchers conducting a trial • Funding clinical trials and clinical trial networks • Establishing and/or participating in clinical trial networks • Disseminating information on the results of clinical trials **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants **Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns **Advocacy** Literature (existing): • Advocating for drug access/coverage • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services

	Advocacy Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences • Sitting on organizing committees **Patient care and support** Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations	• Establishing patient organizations	• Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences **Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support • Providing support to patients participating in clinical trials **Patient organization development** Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization **Regulatory decision-making** Literature (existing): • Provide input in pre-submission advice given on trial protocol
Regulatory approval	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Patient registries and biorepositories** Literature (existing):	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories**

	Patient reported outcome measures (PROMs) Literature (existing): • Submitting PROs in a study • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences • Sitting on organizing committees	• Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing): • Establishing patient organizations	Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants **Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns **Advocacy** Literature (existing): • Advocating for drug access/coverage • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services • Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences **Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support **Patient organization development**

	Patient care and support Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations **Regulatory decision-making** Literature (existing): • Consideration of PROs by decision-makers • Membership on advisory or decision-making committees • Providing input on proposed regulation decision or guidelines • Participate in benefit/harm assessment • Reporting adverse events Literature (proposed): • Provide input on acceptable risk		Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization **Regulatory decision-making** Literature (existing): • Providing data for orphan drug designation applications • Provide input in pre-submission advice given on trial protocol • Membership on advisory or decision-making committees • Providing input on proposed regulation decision or guidelines • Participate in the assessment of benefits and harms • Providing input on plans for post-market approval pharmacovigilance • Providing input on consumer information (e.g., labelling) Literature (proposed): • Participate on regulatory committees that do not currently have patient representation • Identify laws, regulations, and policies that need to be changed in order to encourage product approval • Consult with regulatory bodies to establish greater certainty in the approval process, especially in regards to trial design and endpoint selection
Real world studies	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs

	Webinar (existing): • Funding research **Patient reported outcome measures (PROMs)** Literature (existing): • Submitting PROs in a study • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences	**Patient registries and biorepositories** Literature (existing): • Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing): • Establishing patient organizations	**Patient registries and biorepositories** Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants Webinar (existing): • Encouraging enrollment in industry-led post-market studies • Requesting data from industry registries to conduct research and share with disease community **Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns **Advocacy** Literature (existing): • Advocating for drug access/coverage • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services • Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences

	• Sitting on organizing committees **Patient care and support** Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations **Regulatory decision-making** Literature (existing): • Reporting adverse events		**Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support **Patient organization development** Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization
Reimbursement decision-making	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Patient reported outcome measures (PROMs)** Literature (existing): • Submitting PROs in a study • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories**	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Patient registries and biorepositories** Literature (existing): • Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants Webinar (existing): • Encouraging enrollment in industry-led post-market studies • Requesting data from industry registries to conduct research and share with disease community

	Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences • Sitting on organizing committees **Patient care and support** Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations	• Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing): • Establishing patient organizations	**Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns **Advocacy** Literature (existing): • Advocating for drug access/coverage • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services • Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences **Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support **Patient organization development** Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization

	Regulatory decision-making Literature (existing): • Reporting adverse events **Reimbursement decision-making** Literature (existing): • Submitting topics for evaluation • Providing information for preparation of evaluation report • Directly consulted during review process • Membership on advisory/decision-making committee • Providing feedback on evaluation report and/or proposed recommendations • Preparing a patient submission • Presenting views during committee meeting Literature (proposed): • Providing input on benefits and risks during topic selection by horizon scanning producing organizations • Providing input at the earliest stages of the HTA process • Presenting a summary of patient submissions to reimbursement evaluation committees • Consulting in the outlining of post-evaluation research recommended by reimbursement decision-makers • Provide input into any re-assessments of benefits and risks		**Reimbursement decision-making** Literature (existing): • Submitting topics for evaluation • Directly consulted during review process • Membership on advisory/decision-making committee • Preparing a patient submission Literature (proposed): • Consulting in topic identification and selection • Assuring reimbursement of off-label drug use
Routine clinical use	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs

	Webinar (existing): • Funding research **Patient reported outcome measures (PROMs)** Literature (existing): • Submitting PROs in a study • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences	**Patient registries and biorepositories** Literature (existing): • Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing): • Establishing patient organizations	**Patient registries and biorepositories** Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants Webinar (existing): • Encouraging enrollment in industry-led post-market studies • Requesting data from industry registries to conduct research and share with disease community **Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns **Advocacy** Literature (existing): • Advocating for drug access/coverage • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services • Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences

	• Sitting on organizing committees **Patient care and support** Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations **Regulatory decision-making** Literature (existing): • Reporting adverse events		**Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support **Patient organization development** Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization
Obsolescence/ replacement with a new therapy	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Patient reported outcome measures (PROMs)** Literature (existing): • Submitting PROs in a study • Participating in studies to develop and validate PROMs • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories**	**Research** Literature (existing): • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Participating in research organizations/networks • Disseminating research-related information Literature (proposed): • Participate in all decisions about research on rare diseases • Participate in decision-making processes within research collaborations/networks Webinar (existing): • Funding research **Patient registries and biorepositories** Literature (existing): • Submitting data to registries and biorepositories on behalf of a patient • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders	**Research** Literature (existing): • Participating as subjects in studies outside of clinical trials • Setting research priorities • Initiating research studies • Providing assistance to researchers conducting studies • Leading research • Funding research • Participating in research organizations/networks • Disseminating research-related information **Patient reported outcome measures** Literature (existing): • Assisting researchers in conducting studies to develop and validate PROMs **Patient registries and biorepositories** Literature (existing): • Providing input on the design of registries • Serving on oversight committees • Providing funding • Recruiting participants Webinar (existing): • Encouraging enrollment in industry-led post-market studies • Requesting data from industry registries to conduct research and share with disease community

	Literature (existing): • Enrolling in and submitting data to registries and biorepositories • Providing input on the design of registries Webinar (existing): • Providing funding • Encouraging others to enroll **Stakeholder relationships and collaborations** Webinar (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Presenting at conferences • Sitting on organizing committees **Patient care and support** Literature (existing): • Providing social support • Monitoring own clinical care Webinar (existing): • Providing clinical care support **Patient organization development** Literature (existing): • Establishing patient organizations	• Establishing relationships with stakeholders **Education and awareness** Webinar (existing): • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns (e.g., fundraisers) • Participating in standardized patient programs **Advocacy** Literature (existing): • Advocating for drug access/coverage Webinar (existing): • Advocating for research **Conferences and workshops** Literature (existing): • Participating in conferences and workshops Webinar (existing): • Volunteering at conferences **Patient care and support** Literature (existing): • Providing social support **Patient organization development** Literature (existing): • Establishing patient organizations	**Stakeholder relationships and collaborations** Literature (existing): • Facilitating relationships between stakeholders • Establishing relationships with stakeholders **Education and awareness** Literature (existing): • Sharing informational resources on disease-specific topics • Organizing and sponsoring formal educational activities and training programs for health care professionals, researchers, and policymakers • Starting awareness campaigns **Advocacy** Literature (existing): • Advocating for drug access/coverage • Advocating for research • Advocating for legislation Webinar (existing): • Advocating for improved quality of life • Advocating for education • Advocating for clinics and patient care services • Facilitating patients' individual advocacy efforts **Conferences and workshops** Literature (existing): • Participating in conferences and workshops • Organizing conferences • Funding conferences **Patient care and support** Literature (existing): • Providing social support • Providing financial support • Providing clinical care support **Patient organization development** Literature (existing): • Providing advice on develop patient organizations • Fundraising to support further development of the organization

	Regulatory decision-making Literature (existing): • Reporting adverse events **Reimbursement decision-making** Literature (existing): • Providing information for preparation of evaluation report • Directly consulted during review process • Membership on advisory/decision-making committee • Providing feedback on evaluation report and/or proposed recommendations • Preparing a patient submission • Presenting views during committee meeting Literature (proposed): • Providing input at the earliest stages of the HTA process • Presenting a summary of patient submissions to reimbursement evaluation committees • Provide input into any re-assessments of benefits and risks		**Reimbursement decision-making** Literature (existing): • Directly consulted during review process • Membership on advisory/decision-making committee • Preparing a patient submission Literature (proposed): • Assuring reimbursement of off-label drug use

Appendix 1-1. Literature search strategy

Database	Vendor	Date searched	Notes	Results
MEDLINE	Ovid	5 Mar 2014		1334
PubMed	www.pubmed.gov	5 Mar 2014		1163
PubMed	www.pubmed.gov	6 Mar 2014	Additional search term	45
PubMed	www.pubmed.gov	16 May 2014	Additional search terms	137
Cochrane Library	John Wiley	6 Mar 2014	Selected results from Cochrane systematic reviews, DARE, HTA & Methods only	15
Centre for Reviews & Dissemination (DARE, NHS EED, HTA)	http://www.crd.york.ac.uk/crdweb/	6 Mar 2014		153
EMBASE	Ovid	6 Mar 2014		269
Web of Science	Thomson Reuters	7 Mar 2014		668
EconLit	EBSCOHost	7 Mar 2014		323

1. MEDLINE (Ovid; Including in-process & other non-indexed citations; searched 5 Mar 2014)

1	exp Patient Preference/	2604
2	exp Patient Participation/	17399
3	exp Consumer Participation/	31065
4	exp Consumer Satisfaction/	76415
5	exp Parents/	69675
6	exp Caregivers/	20540
7	exp Family/	229132

8	exp Patients/	64208
9	5 or 6 or 7 or 8	301461
10	(involv* or engag* or participat* or prefer* or outcome assess* or choice* or value*).ti.	334658
11	9 and 10	7108
12	exp Patient Outcome Assessment/	133
13	patient* prefer*.ti,ab.	8223
14	patient participation.ti,ab.	1254
15	patient engagement.ti,ab.	327
16	patient involvement.ti,ab.	1017
17	patient value*.ti,ab.	465
18	patient choice*.ti,ab.	1114
19	family participation.ti,ab.	273
20	family preference*.ti,ab.	130
21	caregiver participation.ti,ab.	27
22	caregiver preference*.ti,ab.	32
23	parent* participat*.ti,ab.	918
24	parent* prefer*.ti,ab.	505
25	patient reported outcome*.ti,ab.	3314
26	((pro or pros or prom or proms) and outcome*).ti.	184
27	1 or 2 or 3 or 4 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	122711
28	exp "diffusion of innovation"/	15092
29	exp biomedical technology/	7020
30	exp technology assessment, biomedical/	9064
31	exp orphan drug production/	761
32	exp rare diseases/	4641
33	exp health priorities/	8674

34	lifecycle of technolog*.ti,ab.	3
35	technolog* lifecycle.ti,ab.	4
36	orphan drug development.ti,ab.	34
37	rare disease*.ti,ab.	12115
38	rare condition*.ti,ab.	10657
39	rationing.ti,ab.	2281
40	priorit*.ti.	9871
41	health technolog*.ti,ab.	2918
42	health care technolog*.ti,ab.	474
43	healthcare technolog*.ti,ab.	276
44	medical technolog*.ti,ab.	4327
45	new treatment*.ti.	3567
46	new therap*.ti.	5239
47	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	88856
48	27 and 47	1927
49	**limit 48 to yr="2000 -Current"**	**1334**

2a. PubMed (www.pubmed.gov; searched 5 Mar 2014)

#55	Search #32 AND #53 Filters: Publication date from 2000/01/01	1163
#54	Search #32 AND #53	1702
#53	Search #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	73396
#52	Search innovation[ti]	5044
#51	Search "new therapy"[ti] OR "new therapies"[ti]	1337
#50	Search "new treatment*.ti.	1406
#49	Search "medical technolog*"	1622
#48	Search "healthcare technolog*"	12
#47	Search "health care technolog*"	28
#46	Search "health technolog*"	89
#45	Search priorit*[ti]	10136

#44	Search rationing[tiab]	2322
#43	Search "rare conditions"[tiab]	752
#42	Search "rare disease"[tiab] OR "rare diseases"[tiab]	12317
#41	Search "orphan drug development"	37
#40	Search "technology lifecycle*"	4
#39	Search technolog*[ti] AND lifecycle[ti]	2
#38	Search health priorities[mh]	8615
#37	Search rare diseases[mh]	4623
#36	Search orphan drug production[mh]	757
#35	Search technology assessment, biomedical[mh]	9036
#34	Search biomedical technology[mh]	6965
#33	Search diffusion of innovation[mh]	15035
#32	Search #1 OR #2 OR #3 OR #4 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	115767
#31	Search (pro[ti] OR pros[ti] OR prom[ti] OR proms[ti]) AND outcome*[ti]	189
#30	Search "patient reported outcomes"[tiab]	2395
#29	Search "parental preferences"[tiab]	107
#28	Search "parents preferences"[tiab]	4
#27	Search "parental participation"[tiab]	202
#26	Search "parent participation"[tiab]	137
#25	Search "parents participation"[tiab]	5
#24	Search "caregiver preferences"[tiab]	26
#23	Search "caregiver participation"[tiab]	28
#22	Search "family preferences"[tiab]	98
#21	Search "family participation"[tiab]	274
#20	Search "patient choice"[tiab]	1019
#19	Search "patients values"[tiab]	63
#18	Search "patient values"[tiab]	381
#17	Search "patient involvement"[tiab]	1018
#16	Search "patient engagement"[tiab]	352
#15	Search "patient participation"[tiab]	1280
#14	Search "patient prefer*" OR "patients prefer*"	592
#13	Search patient outcome assessment[mh]	133
#12	Search #9 AND #10	6968
#10	Search involv*[ti] OR engage*[ti] OR participat*[ti] OR prefer*[ti] OR "outcome assessment"[ti] OR choice*[ti] OR value*[ti]	340136
#9	Search #5 OR #6 OR #7 OR #8	299700
#8	Search patients[mh]	63746
#7	Search family[mh]	227887

#6	Search caregivers[mh]	20404
#5	Search parents[mh]	69239
#4	Search consumer satisfaction[mh]	76036
#3	Search consumer participation[mh]	30909
#2	Search patient participation[mh]	17294
#1	Search patient preference[mh]	2554

2b. PubMed additional search term (searched 6 Mar 2014)

#3	Search "patient oriented research"[ti] Filters: Publication date from 2000/01/01	45
#2	Search "patient oriented research"[ti] – ADDITIONAL SEARCH TERM	59

2c. PubMed additional search terms (searched 16 May 2014)

#66	Search #65 NOT #15 Filters: Publication date from 2000/01/01	137
#67	Search #65 NOT #15 – DUPLICATES FROM ORIGINAL SEARCH REMOVED	137
#65	Search #61 AND #63 Filters: Publication date from 2000/01/01	4067
#64	Search #61 AND #63	5262
#63	Search #19 OR #20 OR #21 OR #22 OR #23 OR #26 OR #28 OR #29 OR #31 OR #32	33655 7 11762
#61	Search #16 OR #18	6
#32	Search "clinical trial protocol*"[ti] – ADDITIONAL TERMS	23
#31	Search "clinical trial design"[ti]	365
#29	Search "regulatory process*"[ti]	97
#28	Search "regulatory approval*"[ti]	57
#26	Search pragmatic clinical trials as topic[mh]	36
#23	Search drug discovery[mh]	81136
#22	Search drug approval[mh]	10527
#21	Search diagnostic test approval[mh]	42
#20	Search device approval[mh]	2173
#19	Search ((diffusion of innovation[mh]) OR (biomedical technology[mh]) OR (technology assessment, biomedical[mh]) OR (orphan drug production[mh]) OR (rare diseases[mh]) OR (health priorities[mh]) OR (technolog*[ti] AND lifecycle[ti]) OR ("technology lifecycle*") OR ("orphan drug development") OR ("rare disease"[tiab] OR "rare diseases"[tiab]) OR ("rare conditions"[tiab]) OR (rationing[tiab]) OR (priorit*[ti]) OR ("health technolog*") OR ("health care technolog*") OR ("healthcare technolog*") OR ("medical technolog*") OR ("new treatment"[ti] OR "new treatments"[ti]) OR ("new therapy"[ti] OR "new therapies"[ti]) OR (innovation[ti]))	24613 6
#18	Search "patient oriented research"[ti]	59

#16	Search ((patient preference[mh]) OR (patient participation[mh]) OR (consumer participation[mh]) OR (consumer satisfaction[mh]) OR (((parents[mh]) OR (caregivers[mh]) OR (family[mh]) OR (patients[mh])) AND (involv*[ti] OR engage*[ti] OR participat*[ti] OR prefer*[ti] OR "outcome assessment"[ti] OR choice*[ti] OR value*[ti])) OR (patient outcome assessment[mh]) OR ("patient prefer*" OR "patients prefer*") OR ("patient participation"[tiab]) OR ("patient engagement"[tiab]) OR ("patient involvement"[tiab]) OR ("patient values"[tiab]) OR ("patients values"[tiab]) OR ("patient choice"[tiab]) OR ("family participation"[tiab]) OR ("family preferences"[tiab]) OR ("caregiver participation"[tiab]) OR ("caregiver preferences"[tiab]) OR ("parents participation"[tiab]) OR ("parent participation"[tiab]) OR ("parental participation"[tiab]) OR ("parents preferences"[tiab]) OR ("parental preferences"[tiab]) OR ("patient reported outcomes"[tiab]) OR ((pro[ti] OR pros[ti] OR prom[ti] OR proms[ti]) AND outcome*[ti]))	
#15	Search ((patient preference[mh]) OR (patient participation[mh]) OR (consumer participation[mh]) OR (consumer satisfaction[mh]) OR (((parents[mh]) OR (caregivers[mh]) OR (family[mh]) OR (patients[mh])) AND (involv*[ti] OR engage*[ti] OR participat*[ti] OR prefer*[ti] OR "outcome assessment"[ti] OR choice*[ti] OR value*[ti])) OR (patient outcome assessment[mh]) OR ("patient prefer*" OR "patients prefer*") OR ("patient participation"[tiab]) OR ("patient engagement"[tiab]) OR ("patient involvement"[tiab]) OR ("patient values"[tiab]) OR ("patients values"[tiab]) OR ("patient choice"[tiab]) OR ("family participation"[tiab]) OR ("family preferences"[tiab]) OR ("caregiver participation"[tiab]) OR ("caregiver preferences"[tiab]) OR ("parents participation"[tiab]) OR ("parent participation"[tiab]) OR ("parental participation"[tiab]) OR ("parents preferences"[tiab]) OR ("parental preferences"[tiab]) OR ("patient reported outcomes"[tiab]) OR ((pro[ti] OR pros[ti] OR prom[ti] OR proms[ti]) AND outcome*[ti])) AND ((diffusion of innovation[mh]) OR (biomedical technology[mh]) OR (technology assessment, biomedical[mh]) OR (orphan drug production[mh]) OR (rare diseases[mh]) OR (health priorities[mh]) OR (technolog*[ti] AND lifecycle[ti]) OR ("technology lifecycle*") OR ("orphan drug development") OR ("rare disease"[tiab] OR "rare diseases"[tiab]) OR ("rare conditions"[tiab]) OR (rationing[tiab]) OR (priorit*[ti]) OR ("health technolog*") OR ("health care technolog*") OR ("healthcare technolog*") OR ("medical technolog*") OR (ew treatment*.ti.) OR ("new therapy"[ti] OR "new therapies"[ti]) OR (innovation[ti])) – ORIGINAL SEARCH STRATEGY	5111

3. The Cochrane Library (John Wiley & Sons; issue 3 of 12, March 2014; searched 6 Mar 2014)

* scanned & selected only results from Cochrane review, Other reviews, Methods, and HTA

#1	MeSH descriptor: [Patient Preference] explode all trees	256

#2 MeSH descriptor: [Patient Participation] explode all trees 802

#3 MeSH descriptor: [Consumer Participation] explode all trees 993

#4 MeSH descriptor: [Consumer Satisfaction] explode all trees 8779

#5 MeSH descriptor: [Patient Outcome Assessment] explode all trees 3

#6 "patient participation" 1177

#7 "patient engagement" 54

#8 "patient involvement" 750

#9 "patient preference*" 2010

#10 "family participation" 21

#11 "family preference*" 10

#12 "caregiver participation" 7

#13 "caregiver preference*" 14

#14 "parental participation" 35

#15 "parental preference*" 34

#16 "patient reported outcomes" 704

#17 "patient values" 51

#18 "patients values" 57

#19 "patient choice*" 170

#20 "patient oriented research" 35

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 12999

#22 MeSH descriptor: [Diffusion of Innovation] explode all trees 145

#23 MeSH descriptor: [Treatment Outcome] explode all trees 88404

#24 MeSH descriptor: [Biomedical Technology] explode all trees 62

#25 MeSH descriptor: [Health Care Rationing] explode all trees 86

#26 MeSH descriptor: [Technology Assessment, Biomedical] explode all trees 574

#27 MeSH descriptor: [Orphan Drug Production] explode all trees 6

#28 MeSH descriptor: [Rare Diseases] explode all trees 13

#29 MeSH descriptor: [Health Priorities] explode all trees 53

#30 lifecycle and technolog* 3

#31 "orphan drug*" 25

#32 "rare diseases" 127

#33 rationing 367

#34 innovation 1252

#35 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 90534

#36 #21 and #35 3737

4. UK Centre for Reviews and Dissemination (DARE, NHS EED, HTA databases) (www.crd.york.ac.uk/crdweb; searched 6 Mar 2014)

1 (patient*):TI 8736

2 (participation):TI OR (involv*):TI OR (preference*):TI 265

3 (engagement):TI OR (engaging):TI OR (choice*):TI 101

4 ("reported outcome*"):TI OR ("patient value*"):TI OR (PROM*):TI 478

5 (parent*):TI OR (caregiver*):TI OR (family):TI 536

6 #1 OR #5 9192

7 #2 OR #3 OR #4 835

8 #6 AND #7 172

9 * FROM 2000 TO 2014 60062

10 #8 AND #9 153

5. EMBASE (Ovid; 1974 to 2014 March 05; searched 6 Mar 2014)

1	exp patient preference/	4757
2	exp patient participation/	17337
3	exp parent/	153400
4	exp caregiver/	38902
5	exp family/	336807
6	3 or 4 or 5	364464
7	(involv* or engag* or participat* or prefer* or outcome assess* or choice* or value*).ti.	410645
8	6 and 7	7834
9	patient outcome assessment.mp.	301
10	patient engagement.mp.	481
11	patient involvement.mp.	1499
12	patient reported outcome*.mp.	6483
13	PROMS.ti,ab.	298
14	patient value*.ti.	61
15	patient choice*.ti.	385
16	patient oriented research.mp.	200
17	diffusion of innovation.mp.	354
18	exp medical technology/	31486
19	health care rationing.mp.	319
20	exp biomedical technology assessment/ or technology assessment.mp.	15130
21	orphan drug production.mp.	10
22	exp rare disease/	18002
23	exp orphan drug/	1497
24	health priorities.mp.	1066
25	lifecycle of technology.mp.	2

26	technology lifecycle.mp.	4
27	orphan drug development.mp.	52
28	innovation.ti.	6578
29	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	72400
30	1 or 2 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	37793
31	29 and 30	330
32	limit 31 to yr="2000 -Current"	269

6. Web of Science (Thomson Reuters; searched 7 Mar 2014)

# 3	668	#2 AND #1 Timespan=2000-2014 Search language=English
# 2	Approximately 778,477	TOPIC: (diffusion) OR TOPIC: ("biomedical technolog*") OR TOPIC: ("technology assessment*") OR TOPIC: ("health care rationing") OR TOPIC:("orphan drug*") OR TOPIC: ("rare disease*") OR TOPIC: ("lifecycle of technolog*") OR TOPIC: ("technology lifecycle") OR TOPIC: (rationing) ORTOPIC: (innovation) Timespan=2000-2014 Search language=English
# 1	Approximately 40,682	TOPIC: ("patient preference*") OR TOPIC: ("patient participation") OR TOPIC: ("patient engagement") OR TOPIC: ("patient involvement") OR TOPIC:("family participation") OR TOPIC: ("family preferences") OR TOPIC: ("caregiver participation") OR TOPIC: ("caregiver preference*") OR TOPIC:("parental participation") OR TOPIC: ("parental preference*") OR TOPIC: ("parent* preference*") OR TOPIC: ("patient outcome assessment") OR TOPIC:("patient oriented research") OR TOPIC: ("patient* value*") OR TOPIC: ("patient* choice*") OR TOPIC: ("patient reported outcome*") Timespan=2000-2014 Search language=English

7. EconLit (EBSCOHost; searched 7 Mar 2014)

S3	(diffusion of innovation OR biomedical technolog* OR health care rationing OR orphan drug* OR rare disease* OR lifecycle of technolog* OR innovation) AND (S1 AND S2)	(323)

S2	diffusion of innovation OR biomedical technolog* OR health care rationing OR orphan drug* OR rare disease* OR lifecycle of technolog* OR innovation	(52,020)
S1	patient preference* OR patient participation OR patient outcome assessment OR patient oriented research OR patient choice* OR patient value* OR ((parent* OR caregiver OR family) AND (preference* OR participation OR value* OR choice*))	(13,544)

Grey literature searches

Source	URL	Date	Search terms	Results
ProQuest Dissertations & Theses	Subscription required	18 Mar 2014	ti(patient* OR caregiver* OR family OR parent*) AND ti((involvement OR participation OR engagement)) AND ti((technology OR technologies OR treatment* OR therapy OR therapies OR lifecycle))	59 (none relevant)
Grey Literature Collection (New York Academy of Medicine)	www.nyam.org/library/	18 Mar 2014	"(patient or family or caregiver or parent) AND (engagement OR participation OR involvement) AND (lifecycle OR technology OR treatment OR therapy)"	89 (4 possibly relevant)
KU-UC (Reseau de recherché en santé des population du Quebec)	www.santepop.qc.ca/en/recherchemotscles.html?2	18 Mar 2014	scanned all reports under keyword heading Technology Assessment searched keywords: "patient participation" "patient engagement"	214 1 4
UK NHS Evidence	www.evidence.nhs.uk/	19 Mar 2014	("patient engagement" OR "patient involvement" OR "patient participation") AND (technology OR technologies OR lifecycle)	3367 (only scanned through first 500 hits; 11 possibly relevant)

The Patient – Patient-Centered Outcomes Research	http://link.springer.com/journal/40271	18 Mar 2014	Scanned tables of contents for all issues (2008-2014)	13
US Food and Drug Administration Patient-Focused Drug Development	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm	19 Mar 2014	Scanned web page and links to meeting documents & The Voice of the Patient reports	4
European Patients Forum	www.eu-patient.eu	20 Mar 2014	Scanned web page	9
European Patients' Academy on Therapeutic Innovation	www.patientsacademy.eu	20 Mar 2014	Scanned web page	1
Patient-Centered Outcomes Research Institute	www.pcori.org	20 Mar 2014	Scanned web page	3
James Lind Alliance	www.lindalliance.org/	20 Mar 2014	Scanned web page	4
HTAi Patient & Citizen Involvement	www.htai.org	16 May 2014	Scanned web page of special interest group section	4
Google.ca	www.google.ca	19 Mar 2014	"patient focussed drug development" / "patient focused drug development" ("patient engagement" OR "patient involvement" OR "patient participation") AND (technology OR technologies OR lifecycle) "patient involvement" "technology life cycle"	4 / 301,000 (only scanned first 100 hits) 288,000 (8 possibly relevant; only scanned first 200 hits – mainly on patient engagement & information technologies) 34
Google Scholar	www.googlescholar.com	21 Mar 2014	"patient involvement in health technologies	15

			development and lifecycle” (limited 2000-2014) "patient involvement" development "orphan drugs"	 296 (33 possibly relevant)

Chapter 2:
An exploration of how patients and caregivers want to be involved in the orphan drug lifecycle

Introduction

Demand for patient involvement in health care, including patients with rare diseases, has grown exponentially in recent years. Much of this demand focuses on increasing patient involvement in treatment decisions [172;173]; however, there have also been calls for greater involvement in research [36], regulatory approval [174], health technology assessments and coverage decision-making [14]. At the national level in Canada, patient involvement has been emphasized as an integral component of the new Canadian Orphan Drug Regulatory Framework. Currently under development, this Framework aims to 1) provide Canadians with better, timelier access to orphan drugs (i.e. drugs that treat rare diseases) and 2) encourage and facilitate clinical research on rare diseases. Drafts of the Framework have outlined involvement of rare disease patients in several key stages of the orphan drug lifecycle [5;19]. Figure 2-1 depicts this lifecycle, which begins with early research and clinical trials, through to regulatory and reimbursement decision-making, followed by routine clinical use and eventually obsolescence and replacement with a new drug, if one becomes available [10]. The involvement outlined in the Framework aims to address a number of the challenges surrounding the development and regulation of orphan drugs. A wide range of existing and proposed opportunities for patient, caregiver, and patient organization involvement throughout the lifecycle of orphan drugs have been identified in published and unpublished literature [15;175]. However, ensuring meaningful patient involvement that is not tokenistic remains a challenge [22;142;176]. Currently, there is a paucity of literature on how patients with rare diseases and their caregivers would actually like to be involved in the different stages of the lifecycle.

Figure 2-1. Lifecycle of a drug.

Objective

The objective of this study is to explore how Canadian patients with rare diseases and their caregivers believe they should be involved in the orphan drug lifecycle and to identify their priorities for involvement.

Background

A rare disease is defined in the Orphan Drug Regulatory Framework as a life threatening, seriously debilitating, or serious and chronic condition affecting less than 1 in 2,000 people [5]. Many rare diseases are genetic and develop in childhood. They are often poorly understood and patients may spend years without an accurate diagnosis for their condition. Additionally, rare disease patients struggle with limited access to effective therapies due to the uncertainties that regulatory and coverage decision-makers face when assessing orphan drugs. While all decisions around new drugs are made under uncertainty, this uncertainty is often magnified for orphan drugs [18]. This is a result of a lack of comprehensive information on a product at the point of decision-making, which is itself a result of the difficulties faced in conducting clinical trials [7] and the poorly understood natural history of rare diseases [8;9]. Decision-making on orphan drugs is further complicated by the high cost associated with these drugs [8] and the fact that, due to the life-threatening or debilitating nature of their disease [177], rare disease patients have a high and often unmet need for effective treatments [9].

Published literature suggests that the involvement of patients and their caregivers throughout the lifecycle of orphan drugs may help to reduce some of the uncertainties that

decision-makers face and improve patient access to these therapies [15]. A previously conducted scoping review identified a variety of existing and proposed opportunities for patients, caregivers, and patient organizations to be involved in the lifecycle [175]. However, this review also found significant weaknesses in literature reporting on patient involvement. The review included a consultation exercise with Canadian patients and caregivers, who identified a number of existing opportunities for involvement in Canada not found in the literature. Additionally, many of the reports in Canada and internationally did not explicitly describe how patients were involved or the impact of their involvement. Unfortunately, the way in which the information was reported did not allow for meaningful opportunities for involvement to be distinguished from tokenism.

Challenges around patient involvement, like tokenism, have been described in several published papers [22;142;176]. *A Ladder of Citizen Participation*, published in 1969, discusses differing levels of "citizen" participation based on the amount of power the citizens have [142]. This model has since been applied to patient involvement in health policy. As the author states, "participation [i.e., involvement] without the redistribution of power is an empty and frustrating process for the powerless [i.e., the patients]". Such involvement ranks low on Arnstein's ladder and serves only to "maintain the status quo" while allowing "powerholders to claim that all perspectives have been considered". For patient involvement in the orphan drug lifecycle to be beneficial, it must be meaningful to both patients and other stakeholders (e.g., payers; government; researchers; pharmaceutical companies). This study intends to identify meaningful ways to involve patients with rare diseases and their caregivers in the lifecycle of orphan drugs by exploring how patients and caregivers actually believe they should be involved and their priorities for involvement.

Methods

Rationale for research approach

As this study aims to explore the experiences and opinions of Canadian patients and their caregivers, a pragmatic qualitative research approach was used. Pragmatic qualitative research uses the most practical methods available in order to answer a given research question, which is usually to describe an experience or event as interpreted by the researcher [178].

This study was conducted within the Promoting Rare-Disease Innovations through Sustainable Mechanisms project, or PRISM, a Canadian research network that aims to improve decision making around the development, introduction, and funding of treatments for rare diseases [179]. PRISM works closely with the Canadian Organization for Rare Disorders (CORD), collaborating on the organization of events relevant to the goals of PRISM. CORD is comprised of over 80 rare disease patient organizations, providing access to patients and caregivers from a broad range of rare disease communities across Canada.

Three different data sources were used to address the research question and facilitate a deeper understanding of the ways in which patients and caregivers would like to be involved [180] (Figure 2-2). They also provided a mechanism through which triangulation of information could be achieved [181]. Data were first collected through a workshop organized at a conference hosted by CORD. Convenience sampling was used to select participants by asking all attendees at the conference to also attend the workshop. The workshop was designed to obtain a general overview of ways in which patients and their caregivers believe they should be involved in an ideal access framework for orphan drugs. While the focus of this study is on patients and their caregivers, participants in the workshop included other stakeholders. Participants were informed about several concepts prior to the workshops to facilitate their discussions, including the orphan

drug lifecycle, challenges around research and development, and the uncertainties that decision-makers face when considering orphan drugs. Deliberative methods were used to allow participants to discuss their differing perspectives, think critically about their options, and broaden their perspectives, opinions, and understandings [182].

To obtain the views of patients and caregivers alone, a deliberative session was organized at a second CORD conference. This session was designed to elicit patient and caregiver views with a greater focus on how their involvement throughout the lifecycle may help to reduce the uncertainties that exist around orphan drugs. Any patients, caregivers, and patient organization representatives attending the conference were invited to join the session. Since only those who were at the CORD conference had an opportunity to participate, the sampling approach used was convenience sampling. Again, participants were informed on the orphan drug lifecycle, challenges around research and development, and the uncertainties that decision-makers face when considering orphan drugs, prior to the session. Deliberative methods were also used to give participants the opportunity to share and learn from their differing experiences and perspectives [182].

To expand upon and further validate the previous findings, additional data were collected through a webinar with the PRISM Patient and Caregiver Liaison Group. The Liaison Group was established following the deliberative session, where participants agreed to continue working with PRISM to provide the patient/caregiver perspective to research conducted within the network. The Group is diverse, with 13 different rare diseases represented, varying in type and severity of symptoms, age of onset (pediatric vs. adult), and availability of a drug therapy. The Liaison Group was purposefully sampled to obtain feedback from well-informed patients and caregivers. Some members of the Liaison Group had also participated in the workshop. They

were further informed by the results of the scoping review of patient, caregiver, and patient organization involvement in the orphan drug lifecycle conducted prior to this study [175]. This review examined at relevant literature and the websites of regulatory and reimbursement decision-making bodies in 20 countries.

To ensure methodological rigor, the following evaluation criteria for qualitative research studies were observed: 1) appropriate method for the research question, 2) sampling adequate and information rich, 3) iterative research process, 4) thorough and clearly described interpretative process, and 5) reflexivity addressed [183]. The workshop, deliberative session, and webinar are described in detail below.

Study population

The focus of this study is on patients with rare diseases and their caregivers. More specifically, the opinions of individuals with high motivation for ensuring the availability of a treatment for their or their family member's condition and who have experienced difficulties in accessing therapies in the past were sought. In this paper, 'patient' refers to an individual living with a rare disease. 'Caregiver' refers to a patient's family member who provides them with physical and emotional care. This definition of caregiver excludes professionals who are paid to provide care to patients.

Data collection

The Stakeholder Workshop

The workshop was organized in conjunction with a two day conference hosted by CORD, which focused on the development of a Canadian Plan for Rare Diseases and a Framework for Access to Rare Disease Therapies. Participants included patients, caregivers, physicians, researchers, and representatives from patient organizations, industry, and government.

Prior to participating in the workshop, participants heard presentations on various aspects of access to orphan drugs in Canada, including on the patient experience, the proposed Canadian Orphan Drug Regulatory Framework and its use of a lifecycle approach, and health technology assessment (HTA) for orphan drugs. They also heard about the challenges of research and development, and of decision-making on orphan drugs. They were introduced to the 4 main uncertainties that decision-makers face (i.e., uncertainty in clinical benefit, value for money, affordability, and adoption and diffusion) [6]. Participants learned how these uncertainties span the entire orphan drug lifecycle and were presented with examples of existing policy tools that have been suggested for reducing uncertainty in decision-making (e.g., managed access programs). Additionally, they were introduced to the idea that patients may be able to contribute to the reduction of these uncertainties throughout the lifecycle.

Following the presentations, participants were split into 5 groups of 10 to 12 members for the facilitated workshop. They were given two questions to discuss:

1) What are the values and/or principles that underlie an "ideal" access framework or pathway for orphan drugs?
2) What are the goals of an "ideal" framework; how should patients be able to access therapies, under what conditions and with what provisions?

Participants were asked to consider patient involvement in this access framework as well as in the areas of HTA, drug access programs, special access, patient registries, and sustainable access. To provide context to the discussion, each group was presented with summary information on two orphan drugs, including the Health Canada market authorization and HTA recommendation from Canada's centralized drug review process, the Common Drug Review

(CDR), which provides reimbursement recommendations for Canada's federal, provincial, and territorial public drug plans (excluding Quebec) [102]. They were also provided with patient submissions/input and information about the rare disease treated by each drug. All members were invited to freely comment; as a result, patients and caregiver heard the perspectives of other stakeholder participants. Each group discussion was facilitated by two researchers and audio recorded.

The Patient and Caregiver Deliberative Session

The deliberative session was organized following CORD's Rare Disease Day conference, which focused on CORD's Canadian Strategy for Rare Diseases and Health Canada's proposed Orphan Drug Regulatory Framework. Patients and caregivers, some with experience working within patient organizations, were invited to attend the deliberative session.

The session began with a presentation reintroducing several of the topics that participants had heard about through their involvement in the conferences, including: the orphan drug lifecycle, the 4 main uncertainties that decision-makers face, and existing policy tools that aim to reduce these uncertainties. Participants again heard about the potential for patient involvement to help reduce uncertainty. One researcher facilitated the subsequent session, walking the participants through the orphan drug lifecycle and asking how they would like to be involved at each stage to address any uncertainties that exist. Two additional researchers took field notes, recording the responses given by participants.

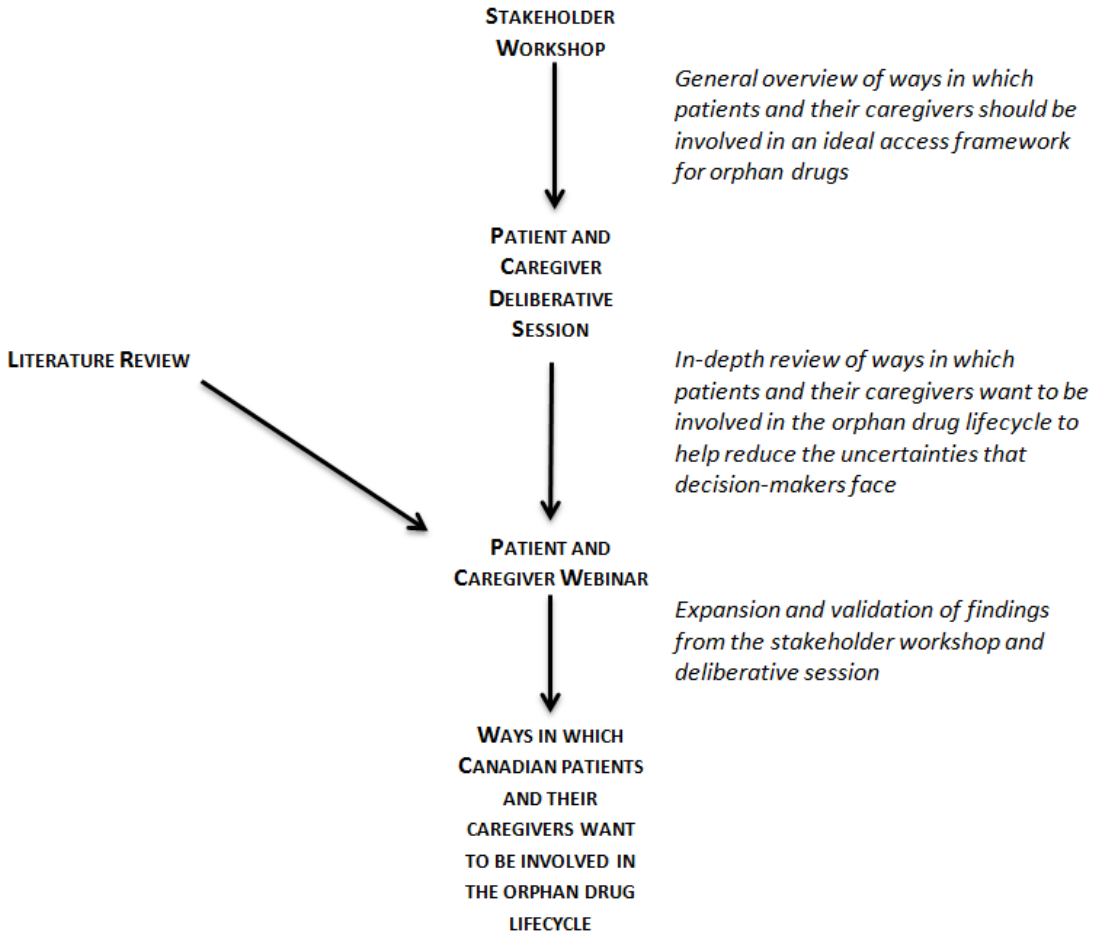
The Patient and Caregiver Webinar

The aforementioned scoping review was conducted prior to this study to explore the breadth of both existing and proposed opportunities for patient, caregiver, and patient organization involvement in the orphan drug lifecycle [175]. To validate the findings of this review,

members of PRISM's Patient and Caregiver Liaison Group were invited to participate in a webinar, *Patient Involvement throughout the Lifecycle of Orphan Drugs*. These results have been summarized in a separate study. However, the webinar also served to expand upon and validate the findings of the stakeholder workshop and deliberative session reported on in this study.

The webinar began with an overview of how and why the scoping review was conducted. Subsequently, a single facilitator described the results of the review by category and participants were asked how they feel they should be involved. The webinar was hosted using Cisco WebEx and was audio recorded.

Figure 2-2. Data Collection.



Data analysis and interpretation

The audio recordings from the workshop and the webinar were transcribed. The data collected for analysis were comprised of these transcripts and, for the deliberative session, detailed field notes. Initial reviews of the data sets indicated that multiple coding methods may be appropriate. The coding methods selected for this analysis and the rationale for their use are described below:

1) **Descriptive coding** summarizes in a word or short phrase the basic topic of a passage of qualitative data. This coding method was selected to allow the researcher to become more familiar with the data and the topics that were discussed (e.g. reimbursement decision-making).
2) **Process coding** is used to identify action in the data. This method was selected for coding how participants felt patients and caregivers should be involved in the lifecycle (e.g. participating in clinical trial design).
3) **Values coding** involves applying codes that reflect a participant's values, attitudes, and beliefs, representing his or perspectives. This method was selected for identifying participants' perspectives on the opportunities for involvement that they identified (e.g. patient organizations should complete patient submissions to coverage decision-makers because it will improve decision-making).
4) **Evaluation coding** is the application of non-quantitative codes to qualitative data that assigns judgements about the merit, worth, or significance of programs or policy. This method was used to code participants' judgements of their past experiences (e.g. participants had a positive experience with receiving guidance from other patients when they were beginning a new treatment).

5) **Emotion coding** is used to label the emotions recalled and/or experienced by participants, or inferred by the researcher about the participant. This method was used to code the emotions that participants expressed when describing their past experiences (or lack thereof) with an opportunity (e.g. feeling frustrated with having to advocate for access to an orphan drug after a negative funding decision is made).

This simultaneous application of two or more coding methods is known as Eclectic Coding [184]. In Eclectic Coding, the methods are purposefully chosen, as in this study, to serve the needs of the study and its data analysis [184]. Four examples of the analysis can be found in Appendix 2-1. Each example is an excerpt of the text along with the codes that were applied. The 5 coding methods are differentiated by a superscript number following the code (e.g. descriptive codes are followed by a [1]). This number index can be found in the Appendix. Additionally, relevant portions of the excerpts are underlined and followed by a superscript number to indicate the code that was applied to that specific section. Finally, constant comparative analysis was used to identify patterns within the workshop, session, and webinar, and across these 3 data sets.

Interpretation of the results was possibly influenced by the researcher's background. AD has past experience volunteering with youth who have life-threatening, and sometimes rare, conditions. To minimize biases and ensure the accuracy of the analysis, results were sent to patients and representatives from national rare disease organizations. There was no disagreement with the results.

Results

The Stakeholder Workshop

The workshop was split into two, hour-long sessions with one fifteen minute break. Each group was comprised of a variety of stakeholders, including: patients, caregivers, physicians,

researchers, and representatives from patient organizations, industry, and government. The composition of each group varied. As this study is focused on the perspectives of patients and their caregivers, only the responses of patients and caregivers were coded for analysis.

Participants identified 19 opportunities for patient and caregiver involvement throughout the lifecycle (Table 2-1), including involvement through patient organizations. Three themes were identified: 1) opportunities aiming to improve coverage decision-making, 2) opportunities aiming to improve care for patients, and 3) opportunities aiming to improve awareness of rare diseases in Canada. These opportunities were further categorized according to when they take place during the orphan drug lifecycle. The results are described below beginning with opportunities that span the entire lifecycle, followed by those spanning more than 1 stage, and then opportunities that take place at only 1 stage.

Goal 1 *– better coverage decision-making.*

The majority of the workshop discussions focused on the challenges associated with decisions to reimburse orphan drugs. Participants discussed limitations on the effectiveness data for these drugs due to difficulties in conducting clinical trials (e.g., small numbers of patients available for enrolment). They expressed concern that the clinical trials used to inform reimbursement decisions often use outcome measures that do not capture the meaningful benefits that patients experience. Participants emphasized the importance of ensuring that decision-makers truly understand the experiences of rare disease patients and the value that they place on the outcomes of clinical trials.

"…[patient involvement at every step] will give you course correction and also give you easier buy in at the end." – Patient 2, Group 5

To help improve decision-making, participants felt that patients should be involved in some way at every stage of the orphan drug lifecycle. More specifically, they felt that patients should enroll in registries and submit patient reported outcome measures (PROMs). Participants recognized that registries can be burdensome and that not all patients or caregivers want to participate in them. However, there was general agreement that the benefits of improved data collection outweigh the associated burden.

> *"Rare disorders need another 10-15 years to come up with the evidence that you say we have to have and that's why you deny us. Let's give it to them." – Patient 1, Group 3*

They expressed frustration that negative reimbursement decisions are often made based on a lack of long-term evidence when they are willing to enroll in registries to help generate the data required. Participants also felt that patients should allow their data to be submitted to an international registry through their electronic health records. Finally, participants felt that patients should assert themselves as experts in their disease.

> *"And I think the answer to that again is to assert ourselves as experts in this disease. We have to be at the table…the way they are in Europe." – Patient 1, Group 3*

Most agreed that participants are not currently recognized as experts in Canada and the experiences of patients in the United States and European Union, whose expertise is more readily accepted, were cited as successful examples.

Participants identified 1 way in which they felt patients should be involved that spans from real-world studies to reimbursement decision-making, which is through participation in managed access programs (MAPs).

"Could there be a time…like let's say this is a new drug, there's not enough information, could there be in the framework that…why not do a study [of] those who want to try the new drug…" – Patient 5, Group 1

MAPs are provisional coverage arrangements that aim to provide interim access while requiring the generation of the information required to support a more definitive coverage decision within a set period of time [6]. They felt MAPs are an important opportunity for patients to help improve the amount and quality of data available to decision-makers, while receiving access to new orphan drugs.

Participants identified 5 ways in which they feel patients or caregivers should be involved in clinical trials. First, patients should continue to participate in clinical trials. Several of the participants took part in past trials, even travelling to do so. While many orphan drugs have a limited evidence base, participants expressed a willingness to continue to register in trials (*"but hey, we're willing to go down a trial."*). Patients or caregivers should also be able to provide input into clinical trial design, including identifying and selecting meaningful outcome measures.

"…because we're talking about all the problems that happen after clinical trials are designed by people who know the science and the industry but don't know the disease and that's the problem. We're dealing with the problem because we're not included before the trial begins." – Patient 1, Group 3

Participants stated that they had not had this opportunity before. Their experience with clinical trials appeared to be limited to situations in which the outcomes that were collected were not meaningful to them and did not capture the benefits that they were experiencing. In their view, this was responsible for negative funding decisions. While they acknowledged that it is not feasible to bring every single patient or caregiver to the table, they felt some form of input is

essential to ensure that relevant outcomes are measured. Participants also felt that patients should be involved in interpreting the meaningfulness of the clinical data collected.

"Also quantifying those in terms of what that means in your life because to me…a grapefruit to orange…I don't know if that makes a difference…if that means you can get out of bed vs. not get out of bed…" – Patient 4, Group 5

To date, this opportunity has not existed, but participants expressed the belief that the value patients place on the outcomes they experience while using an orphan drug may be different than the value other stakeholders (e.g., payers) place on those benefits. Participants also suggested the submission of PROMs during clinical trials in order to collect important quality of life data that is not captured by the clinical outcomes. As one participant said:

"And I mean there's no measurement of cognitive function, there's no measurement of all the benefits we've seen for her, but the study was on the kidneys." – Caregiver 1, Group 2

Finally, participants emphasized that patients should adhere to treatment protocols during clinical trials to optimize data collection.

Participants identified 5 ways in which they feel patients or caregivers should be directly involved in reimbursement decision-making. First, participants felt that patients should provide input, including PROMs and views on the benefit-harm ratio and their willingness to accept risk, into the HTAs produced to support reimbursement decision-making.

"So they're aiming for clinical, scientific data whereas patient input would have tempered the data to include qualitative data." – Caregiver 1, Group 5"

Participants had not had experience with this before, but felt it would be an effective way of improving the interpretation of the clinical data analyzed in the HTA to accurately capture

patients' value of the treatment benefits. Subsequently, they felt that patients and caregivers should provide direct input into decision-making.

"And I think in terms of the quality of life definition, there should be a user statement in there that becomes acceptable evidence." – Patient 2, Group 5

Some participants had experience providing input by completing patient submissions into CDR, but there was disagreement over the effectiveness of these submissions. Some felt that describing their experiences within the submission template is too difficult:

"It's very difficult on a piece of paper trying to explain why you think you need that drug or quality of life on a piece of paper." – Patient 5, Group 1

Others felt that patients and patient organizations simply do not know how to use the submission form effectively. Regardless of these difficulties, participants felt that patients, caregivers, and patient organizations should still complete patient submissions, including using data from patients located in other countries if necessary. Some spoke of how their patient organizations had done this when there were not enough patients in Canada with experience on the drug. Additionally, patient organizations should increase their understanding of how to effectively prepare submissions.

"That was one of the issues that we talked about yesterday where we wanted feedback on the patient group submissions and CDR doesn't say you did a really good submission…" – Patient organization representative 1, Group 1

One participant sought feedback from CDR on their patient organization's past submissions. Participants also specified some of the types of input they felt patients or caregivers should provide into decision-making: on the meaningfulness of the outcomes that are considered by decision-makers (*"to better qualify what is meant by a benefit"*); on treatment burden (*"they*

thought it was just a matter of convenience"), including burden on the caregiver; on the benefit-harm ratio and their willingness to accept risk (*"what risk you're willing to take on should be taken into consideration"*); and to identify and provide information that is missing from a drug submission before a negative decision is made based on insufficient data (*"sometimes it could just be that a patient will write it out right, there's something missing"*). None of the participants described having experience with providing any of this specific input. They expressed frustration that, in their opinion, burden of the disease is not always considered. In particular, they felt caregiver burden, which may be immense, is often not considered (*"It's not just a diet; it is that [caregiver] role")*. They also felt that patient input on risk-acceptability is important to include because patients with rare diseases often have no other treatment alternatives and may be willing to accept greater risk of harm. Participants were also very frustrated that negative decisions may be made due to "insufficient data."

> *"Could you ask for more information instead of... wouldn't it be nice that you could ask? Before you say yes or no… like, rather than just saying no because you don't have enough information." – Patient 5, Group 1*

They felt that patients are capable of identifying these gaps in the submissions and should be able to help fill them before a decision is made. However, if a negative decision is made, participants felt that patients should be able to address the decision-making committee directly.

> *"...I think you should have the right, certainly at the appeal stage, to actually present their face." – Patient 2, Group 1*

None of the participants had been offered this opportunity before, but they felt that it should be an option as decision-makers are typically less familiar with rare disease patients and their experiences than with common diseases. To further familiarize decision-makers with the

challenges faced by many rare disease patients and the cost implications of remaining untreated, participants suggested that, through patient organizations, patients and caregivers should fund research that examines the *"cost [to] society of not funding rare disease"* (e.g., increased hospitalizations; decreased productivity).

***Goal 2** – better care for patients.*

Though participants primarily focused on concerns around reimbursement decision-making, they spent some time discussing ways in which the care of patients needs to be improved. They discussed the highly heterogeneous nature of rare diseases and the importance of considering individual differences when treating a patient with a new orphan drug. They also spoke about the fear and confusion that many patients and their caregivers have when starting a new treatment.

Participants identified 2 ways in which they believe patients should be involved to help improve their care and the care of other patients that span the lifecycle from real-world studies to routine clinical use. First, patients should actively engage with their physician, choosing when to start and stop a new treatment and allow for ongoing monitoring of their response to the treatment.

> *"So, instead of having specific stopping criteria that it's stated between the patient and their clinician, rather than a set rule within the drug plan criteria." – Patient organization representative 1, Group 1*

Some participants had experience with reimbursement decision-makers wanting to establish set stopping criteria based on a clinical measure (e.g., % increase in lung function). However, they felt this was inappropriate as patients have very different experiences on drugs which are not

captured by clinical outcomes (e.g., being able to walk up a set of stairs). Second, patients should develop a "buddy" system to provide support for other patients accessing new treatments.

"I mean when we're personally looking at options of treatment, one of them was really scary and I was really frightened." – Patient 2, Group 5

Several participants shared positive stories about receiving guidance from other patients who had experience with a new treatment and wanted to see more of this patient support in the future.

Participants identified 1 way in which they believe patients and caregivers should be involved in pre-clinical research, which is to encourage researchers to begin new projects on potentially beneficial treatments.

"That's how stem cell transplant therapy started…where the doctors were and the researchers were really encouraged by the parents…" – Caregiver 2, Group 5

None of the participants had been involved in this before but they were aware of patients and caregivers who had successfully piqued researchers' interest as a result of which a new drug was developed for their rare disease.

Goal 3 *– better awareness of rare diseases*

Participants frequently spoke of the lack of awareness of rare diseases in Canada and the implications that this has for patient care and access to drugs. They felt that patient organizations should work throughout the lifecycle to increase awareness and help to identify patients around the country.

"And the patient organizations can help with that. When we increase our knowledge of where the patients are and let them know that, because a lot of the patient

organizations don't know who all of the people are who have that disease, that's big" – Caregiver 2, Group 5

In the past, they have done this by travelling across Canada with a patient organization, helping to inform physicians about their disease and to identify and recruit patients and their caregivers to their organization. Participants felt that this had been an effective way to increase awareness and increase their numbers in the past and that they should continue to fulfill this role.

Other findings

While the focus of this workshop was to understand how patients and caregivers believe they should be involved throughout the orphan drug lifecycle, participants also discussed examples of past involvement. Some of these examples were opportunities that participants felt patients and caregivers should continue to be involved in and so have already been described above. However, participants also described four examples of past involvement that were not necessarily ways in which they felt they should continue to have to be involved (Table 2-2). Two themes or goals of this past involvement emerged: 1) better coverage decision-making and 2) better care for patients.

Goal 1 *– better coverage decision-making.*

Participants felt that currently there are not enough disease-specific experts involved in reimbursement decision-making. To remedy this, they have identified doctors outside of Canada, building relationships with them, and requesting submissions from them.

"…it's all from…the patient groups are getting the Canadian doctors to even have a relationship with the international doctors, and that takes years to build." – Patient 1, Group 3

However, participants seemed to feel frustrated that identifying diseases experts is, in their view, left to the patient organizations.

Goal 2 *– better care for patients*

To improve care for patients, participants described their past experience in advocating for access and applying to special access programs after negative decisions had been made. They have also advocated for access to existing therapies that treat other disease indications, which they believe may be effective for their rare disease as well (*"Like it's just like they'll do anything"*). These experiences are generally frustrating and exhausting for patients and their caregivers, particularly when negative decisions are made based on insufficient data or irrelevant outcome measures.

> *"You're already exhausted and then you got to go, oh my god I have to call the paper and the press release and go to the god blessed minister's office again. Seriously, it's exhausting." – Caregiver 1, Group 5*

Patients also have to do research to inform themselves on their disease and possible adverse drug reactions.

> *"But what we have to do is check multiple [adverse reaction] databases in different countries because there are so few people." – Patient 1, Group 5*

This is difficult for many rare disease patients because their diseases are heterogeneous and have poorly understood natural histories.

The Patient and Caregiver Deliberative Session

Fourteen individuals attended the session: 6 patients, 5 caregivers, 1 patient/caregiver, and 2 patient organization representatives. Participants represented a variety of rare diseases and range of experiences with their rare disease communities and the health care system. The session

lasted for 2 hours. Following the session, participants agreed to continue their involvement in PRISM research by forming the PRISM Patient and Caregiver Liaison Group. Nine participants had also attended the previous workshop.

Participants identified 10 opportunities for patient and caregiver involvement, including involvement through patient organizations (Table 2-3). Two themes (i.e. goals for involvement) emerged: 1) better coverage decision-making and 2) better care for patients. The results are described below beginning with opportunities that span the entire lifecycle and ending with those that take place at only 1 stage.

Goal 1 *– better coverage decision-making.*

As the focus of this session was on reducing uncertainties in decision-making, the majority of the discussions revolved around theme 1, improving coverage decision-making. Participants discussed the challenges that reimbursement decision-makers face due to a lack of information on rare diseases and the effectiveness of orphan drugs. They also discussed the use of inappropriate outcome measures during clinical trials, a major issue in the collection of accurate data on drug efficacy and effectiveness. They felt that opinions may differ on the acceptability of the benefit-harm ratios of orphan drugs and that patient opinions are likely to be influenced by the severity of their disease (i.e., patients with more severe symptoms will be willing to accept greater risk).

To improve coverage decision-making, participants identified 2 ways in which they felt patients and caregivers should be involved that span the lifecycle. First, patients should enroll in registries and submit PROMs into these registries. They discussed how some patients have privacy concerns around registries, but that many patients *"may be willing to give up some*

privacy to get the benefits" *(Patient 4)* of increased data collection. Participants thought that patient organizations should establish registries (e.g., on side-effects; disease tracking; etc.).They expressed significant frustrations around their previous experiences with the establishment and maintenance of registries, which is expensive. They described having enrolled and participated in registries, only to have them shut down due to a lack of funding. Participants agreed that patient organizations often lack the training and resources (e.g. money, time, etc.) to establish registries; however, some participants did note that in the past, with the support of other stakeholders (e.g., physicians) there are patient organizations that have been successful.

Participants identified 2 ways in which patients and caregivers should be involved that span from real-world studies to reimbursement decision-making, revolving around MAPs.

"…there should be [patient] involvement in MAPs." – Patient 5

Participants agreed that patients should participate in MAPs. Although none of the participants had previous experience with MAPs, they were very interested in them as a way of providing patients with access to potentially beneficial orphan drugs while allowing for the collection of additional data on their effectiveness with real-world use. However, they felt that it is crucial to also have patient and caregiver input into the design of the programs to ensure that their needs and perspectives are considered. The arrangements need to be *"systematic and fair on both sides" (Caregiver 4)*.

Participants identified 1 way in which they felt that patients and caregivers should be involved in clinical trials to improve decision-making, which is to provide input into clinical trial design, including identifying and selecting meaningful outcome measures. Their previous attempts to be involved in trial design were unsuccessful, including one participant who was

"invited to an investigator meeting about the design of a new trial, but not really asked for [their] input" (Caregiver 1).

Finally, participants also identified 1 way in which patients should be involved in reimbursement decision-making, which is to provide input on the acceptability of the benefit-harm ratio.

"Degrees of severity will make a big difference for preferences [on] benefit-harm ratio." – Patient 1

They did not discuss having any prior experience with providing this input but agreed that since opinions on the acceptability of the benefit-harm ratio may vary, the patients' perspective must be considered.

Goal 2 *– better care for patients.*

Participants also discussed the care that patients with rare diseases receive and described the weaknesses of clinical practice guidelines (CPGs), the difficulties faced in the development of orphan drugs, and situations in which patients have lost access to beneficial treatments after a clinical trial is completed. To deal with these issues and improve patient care, participants identified 2 ways in which they feel patients and caregivers should be involved that span the orphan drug lifecycle. First, patients and patient organizations should provide guidance to newly diagnosed patients. Participants described their own experiences in struggling to receive a diagnosis and, upon diagnosis, failing to receive proper care for a disease that is poorly understood. *"This is what a patient organization helps you with" (Patient 3)* stated one patient, who experienced negative health outcomes when they were given drugs they did not need.

"If you don't know the right questions to ask, you won't get information."—Patient 2

Having a patient organization or, when no organization exists, a single patient to help guide individuals through the process would be helpful. Participants also felt that patients and caregivers should provide input into the development of CPGs on rare diseases, as they have significant expertise on their disease. Some participants had been involved in patient organizations that made requests to pharmaceutical companies to be involved in the development of CPGs; however, their requests were denied.

"…maybe once they've drafted the guidelines they would be more comfortable." – Caregiver 2

Participants wondered if companies may be more open to their involvement once a draft of the guidelines is developed. They also suggested *"using [their] ability to provide patients to get at the table for guideline development" (Caregiver 2).*

Participants identified 2 ways in which they felt patients should be involved in pre-clinical research. Patients should provide input on their preferred format for new therapies (e.g., oral tablet vs. intravenous injection). None of the participants had experience with this, but felt it should be considered in the early stages of drug development as the patients will ultimately be the ones using the drug. Patients and caregivers should also identify new research topics to help encourage the development of new therapies. Participants were aware of examples in which patients successfully piqued researchers' interests on a new topic; though, in some cases, funding remained an issue.

Finally, participants identified 1 way in which they felt patients should be involved in clinical trials, which is to provide input on the stopping criteria used. Participants had previous experience in trials where they were taken off of a drug they felt was benefitting them, either due to the stopping criteria or because the trial was complete.

"…you can't just take the drug away when you're done your study." – Caregiver 3

This was extremely problematic, particularly because they had no other options. Participants wanted patients to have more involvement in deciding on when they are taken off a drug.

The Patient and Caregiver Webinar

Eight members of the PRISM Patient and Caregiver Liaison Group participated in the webinar, *Patient Engagement throughout the Lifecycle of Orphan Drugs.* Each of the participants had also taken part in the stakeholder workshop (1 individual), the deliberative session (3), or both (4). A variety of rare diseases were represented as were different levels of involvement within rare disease communities and the health care system. The webinar lasted for 2.5 hours.

Participants identified 20 opportunities for involvement for patients and caregivers, including involvement through patient organizations. Three themes (i.e. goals for involvement) were identified: 1) better coverage decision-making, 2) better care for patients, and 3) better awareness of rare diseases. The results are described below beginning with opportunities that span the entire lifecycle and ending with those that take place at only 1 stage.

Goal 1 *– better coverage decision-making.*

Throughout the webinar, participants frequently spoke of their frustrations with the lack of outcome measures used in clinical trials that are both meaningful to patients and acceptable to reimbursement decision-makers. They also discussed the limited natural history data on many rare diseases and on the long-term effectiveness of orphan drugs. Participants described the variability in the quality of patient submissions made to CDR and their concerns about the value placed on these submissions.

To address these issues, participants identified 3 ways in which patients should be involved that span the lifecycle. Participants agreed that patients should enroll in registries (any type of registry that currently exists, including those established by pharmaceutical companies) and submit PROMs. They also expressed a desire for a registry that captures all patients, whether they are treated with a drug or not.

"…ideally I think it would be great to have all of the patients in a registry whether or not they're untreated or treated." – Caregiver 2

Participants felt that, if possible, patient organizations should establish registries (e.g., natural history; drug side-effects; etc.), but recognized that most patient organizations lack the resources to do so.

"So that's something you might want to consider as a patient organization but again you're dealing with the same questions: ethics, who is owning this, how do you guarantee the privacy and all of that?" – Patient 4

Some participants were aware of organizations that had successfully established registries and felt that it is possible, but that these organizations still face issues such as: ethics, data ownership, and privacy concerns. Given the challenges of establishing a registry, participants also felt that patient organizations should advocate for the development and maintenance of registries, including lobbying for funding from the government and pharmaceutical companies. Finally, participants felt that patient organizations should be involved in the development and validation of PROMs.

"Well you just said distributing surveys, etc. But also they should be involved, I would think, in the development of them." – Caregiver 2

It was stated that none of the participants had experience with developing/validating PROMs.

Participants identified 4 ways in which they feel patients should be involved in clinical trials. To begin with, patients should provide input into clinical trial design, including identifying and selecting meaningful outcome measures to *"[make] sure that the real-world patient-centered outcomes are there" (Caregiver 1)*. Along this line, patient organizations should survey their members to identify meaningful outcome measures and relay these measures to researchers for use in clinical trials.

> *"So I think the patient organizations have a large role to play there in terms of surveying their members and communicating with researchers who are developing products so that they can make sure that's aligned." – Caregiver 2*

Participants also emphasized the need for these outcomes to not only be meaningful to patients, but also to the reimbursement decision-makers who will be making decisions based on this data later on in the lifecycle.

> *"…but I think the idea of getting patient organizations more involved in helping to create…or not create but give suggestions on endpoints that are more valid in terms of reimbursement." – Caregiver 2*

They were frustrated that outcomes that decision-makers will find acceptable are not identified earlier on to ensure their collection in clinical trials. None of the participants had experience with providing input into trial design. Finally, participants felt patients should verify all data collected on them by researchers or their physician to ensure its accuracy and relevance.

Finally, participants identified 2 ways in which patients should be involved in reimbursement decision-making. They felt that patient organizations should continue to create patient submissions, but that they should also provide training to other organizations on how to create an effective submission.

"I think one of the ways that patient organizations can be more involved is to help each other with training on how to give really good patient submissions. Like what is it that has impact and…I know that there's guides but I don't know if people don't read the guides because we get a wide variety of submissions." – Patient 3

Participants agreed that this is an important opportunity for patient organizations to become more actively involved, particularly because there is currently significant variation in the quality of submissions made to CDR.

Goal 2 *– better care for patients.*

Participants discussed how rare diseases are often poorly understood and patients struggle with receiving proper care and access to existing treatments. To improve the care that patients receive, participants identified 2 ways in which they felt patients or caregivers should be involved that span the entire lifecycle. First, patient organizations should educate patients so they can make informed decisions.

"…you do want to educate patients so that they can make informed decisions when it comes to their treatments." – Patient 4

Second, they should teach patients about their rights and how to effectively advocate for themselves.

"…and another thing is you do want to teach patients or let them be aware of their rights so they can advocate for themselves. And organizations are doing this more so in Europe than in Canada." – Patient 4

A number of the participants were involved in patient organizations and had experience doing these things, but felt that they could be done more in the future.

Goal 3 *– better awareness.*

"Because that is really important, spreading the word. Each individual can bring ten other individuals and, you know, your numbers will multiply when you're doing a petition or letter campaign." – Patient 4

Given their low prevalence, there is little awareness of rare diseases in Canada. Participants discussed the challenges this creates for patients with rare diseases and their caregivers. To spread awareness of rare diseases across the country, participants identified 10 ways in which they feel patients or caregivers should be involved that span the lifecycle. Patient organizations should build relationships with all relevant stakeholders (e.g., funders, donors, physicians, etc.).

"You build collaboration, you find common goals, and you work on these common goals." – Patient 4

They should engage members to increase their involvement. Patient organizations should follow new research results and share them with the members of their organizations. They should actively work to convince others to join in the advocacy efforts of patient organizations.

"You need the patients and their families to convince other people to sign on." – Patient 4

Patients, caregivers, and patient organizations should promote the global Rare Disease Day on February 29th. Patient organizations should host conferences as well as attend international conferences. Finally, patients should present at these conferences and provide input into content planning for conferences.

"Yes, in some cases you have the expert patients who can share their knowledge and give their perspective to other patients or even to doctors and health care providers." – Patient 4

Participants had experiences with all these opportunities, and felt that they should continue to do so.

Discussion

Overarching themes and patterns

The results of the workshop, session, and webinar were primarily focused on improving coverage decision-making on orphan drugs (Theme 1). Participants identified opportunities for involvement spanning the orphan drug lifecycle, but the majority of opportunities were identified at the point of Clinical Trials and Reimbursement Decision-Making. Opportunities for involvement with the goal of improving decision-making that were emphasized in all 3 data sets include:

1) Enrolling in registries and submitting PROMs into these registries,
2) Providing input into clinical trial design, including identifying and selecting meaningful outcome measures, and
3) Providing input into reimbursement decision-making, including patient submissions, perspectives on meaningfulness of clinical outcomes and on the benefit-harm ratio and willingness to accept risk.

Opportunities for involvement that were emphasized in 2 of the data sets include:

1) Participating in managed access programs (MAPs).

It is clear that participants felt that, in general, patients and their caregivers could improve coverage decision-making by:

- *Contributing to increased data collection on rare diseases and the efficacy/effectiveness of orphan drugs, and*

- *Improving the meaningfulness and relevance of the data that is collected during clinical trials and real-world studies.*

There is a paucity of data on how patients and their caregivers want to be involved in the lifecycle of drugs, regardless of the disease. Studies have been published on patient involvement during individual clinical decision-making [185;186]; however, these are outside the scope of this study, which was a macro-level analysis focused on large-scale processes (e.g. coverage decision-making). Some work has been published on the goals of patient involvement in health technology assessments and reimbursement decision-making, but these do not describe goals identified by the patients themselves [14;187].

While identifying these opportunities, participants also acknowledged a number of barriers to their involvement that are beyond their control. For example, many patients and their caregivers have enrolled and are willing to continue to enroll in registries; however, the funding and maintenance of registries remain an issue. Patients and caregivers are also willing to provide their input into coverage decision-making and have already done so (e.g., patient submissions), but they remain unconvinced that this input is actually valued, or even considered, by the decision-makers. These barriers represent the need for patient and caregiver input to be valued by all stakeholders to ensure that it is collected and used in a truly meaningful way.

Several of the opportunities that participants identified were ways in which they have already been involved (e.g., registries; patient submissions). These findings are consistent with the results of the scoping review. Participants also emphasized two opportunities for involvement that were not identified in the review: an increased level of input into reimbursement decision-making (e.g., benefit-harm ratio acceptability) and participation in managed access programs.

Some of the barriers to involvement that participants identified in this study are also reflective of the scoping review findings, which showed that patient involvement is not well-reported on in Canada. The scoping review demonstrated a gap in reporting on existing opportunities in Canada as well as limited reporting on the details of involvement, preventing the assessment of potential tokenism or the impact of involvement [175]. Other research has also documented this lack of reporting [14]. Participants in this study were concerned about tokenism and ensuring their input has an impact. Addressing these barriers is important for improving existing opportunities for involvement and for introducing new ways to involve patients and caregivers.

Strengths and weakness of the study

Convenience sampling was used to obtain participants for the workshop and session by conducting them at national events hosted by CORD. It is possible that individuals who choose to participate in these events are different from those who do not and are not representative of the whole rare disease population in Canada. However, CORD is comprised of over 80 different rare disease patient organizations and encourages patients and caregivers from all communities to attend their events by covering travel costs, increasing the likelihood that the sample was not biased. Additionally, this study intended to explore the views of patients and caregivers who are highly motivated to gain access to a treatment for their disease. It is possible that these individuals are more likely to attend CORD events, particularly when the events have sessions focusing on improving access to orphan drugs in Canada. As such, the participants from these sessions (and those who later participated in the webinar) are likely to be representative of the population on whom this study is focused.

Another limitation of the study is that only one researcher coded the transcripts. However, the results of the analysis were reviewed by two additional researchers who also attended the workshops, session, and webinar.

Conclusion

Patients and their caregivers are eager to participate throughout the orphan drug lifecycle and improving coverage decision-making is a priority. They also want to ensure that their involvement is meaningful and valued by other stakeholders. Future research is needed into developing and mobilizing mechanisms that will allow for patient and caregiver involvement in the ways that they have identified, without being tokenistic.

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
Better coverage decision-making			
Patients should be involved in some way at every stage of the lifecycle.	• Patients are not currently present at every step of the lifecycle. • Having patients involved at every stage is an important aspect of an ideal framework for accessing orphan drugs. • It would improve decision-making on orphan drugs and increase stakeholder acceptance of these decisions. • Rare disease patients may have difficulties participating in different ways due to financial restraints and their current health state. • One model for involvement may be to have the pharmaceutical company pay a set of patients to work with them from developing the product to bringing it to the market.	Lifecycle	*"Because [patient involvement at every step] will give you course correction and also it will give you easier buy in at the end."* *"…right at the top you've got a focus group where maybe 10 people with the disease get together and the focus group is run by the pharmaceutical [company] to find out the patient environment, their needs, what the situation is, and everything about who they are and their environment, what works, what doesn't, income, levels of payment…"* *"Why can't you get paid for that? Why can't you get reimbursed for your travel to come represent and help the pharmaceutical company along the way to get their product out there?"* *"Treat the patient, not the disease"*
Patients should enroll in registries and submit patient-reported outcome measures (PROMs) into these registries.	• It is important to be enrolled in registries to allow for data to be collected on the natural history of rare diseases as well as the short and long-term outcomes of new orphan drugs, including PROMs. • While registries may be burdensome, the benefits of data collection outweigh the burdens of registry enrollment. • Currently, there is not enough long-term follow-up, but there is willingness for patients to enroll in registries to allow for the necessary long-term data to be collected for reimbursement decision-making. • Negative reimbursement decisions made as a result of a lack of long-term evidence are frustrating, given that patients and caregivers are willing to participate in ongoing monitoring to generate this data. • Many patients and caregivers participate in registries and should continue to do so. • Not all patients want to participate in registries as they are burdensome for patients	Lifecycle	*"Exactly. And why wouldn't you [enroll in a registry]? If it's going to help the greater good of somebody else that…"* *"So the subjective data."* *"So you might want to say patient reported outcomes or patient satisfaction. Something that captures that patient part."* *"Monitoring is an excellent extra step that benefits all of us. It is clinical data."* *"That's good, let's do it. Rare disorders need another 10-15 years to come up with the evidence that you say we have to have and that's why you deny us. Let's give it to them."* *"It's almost like saying we have to report when I infuse him. I have to report the blood product in case of recall. It's almost like me going yeah, I'm not sending that in. Why wouldn't I? You know? It's just responsibility, right?"* *"I work with a very select subset of patients who are highly motivated and probably the people who come to this meeting are also part of that elite. And I think that you have to differentiate between the subpopulation that will participate and is willing to make the effort to inform."*

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
	and caregivers.		
Patients should allow their data to be submitted to an international registry through electronic health records.	• Electronic health records are a useful way to collect data on patients and should be used to contribute patient data to an international registry.	Lifecycle	*"And also, with the global or potentially international expertise, look at the FDA and the EMA. Why can't we use their output?"* *"There should be harmonization, yeah. Why not?"* *"Why can't we just do it all together?"* *"Set up the electronic record systems so that information can automatically be input."*
Patients should assert themselves as experts in the disease.	• In Canada, patients are not at the table the way they are in Europe, where patients are paid to work and regulated.	Lifecycle	*"And I think the answer to that again is to assert ourselves as experts in this disease. We have to be at the table…the way they are in Europe. Patient experts are paid to work and regulated. They must work with the EMA and they must be on clinical trial design. We have to get that statute…to be taken seriously."*
Patients should participate in managed access programs (MAPs).	• MAPs are an appealing opportunity for involvement. • Many rare diseases are highly heterogeneous and MAPs provide a way of addressing these differences and identifying the population for whom the drug will be effective.	Real-world studies to reimbursement decision-making	*"Could there be a time…like let's say this is a new drug there's not enough information, could there be in the framework that…why not do a study that those who want to try the new drug…not everyone wants to try a new drug. Everybody's just assuming that everybody wants this. Some want it, some stay on the other. Do a comparative study and then decide whether it should be…"*
Patients or caregivers should provide input into clinical trial design, including identifying and selecting meaningful outcome measures.	• Some issues that occur later on in the lifecycle could be avoided by having patients, who are experts in their diseases, involved in the design of the trial to ensure that relevant data is collected. • It is frustrating that there appears to be no consideration of the endpoints that will be meaningful to reimbursement decision-makers earlier on. • It is not feasible to bring every patient or caregiver to the table to select meaningful outcome measures, but it is still necessary to have some input. • These endpoints need to be well-defined.	Clinical trials	*"…patients, who are experts in their own condition, with proper funding for training on how to participate in a scientific clinical trial need to be incorporated into the design of a clinical trial. Because we're talking about all the problems that happen after clinical trials are designed by people who know the science and the industry, but don't know the disease and that's the problem. We're dealing with the problems because we're not included before the trial begins."*
Patients should be involved in interpreting the meaningfulness of the data collected.	• The value that patients place on the benefits that they experience in a trial will be different than the value others (e.g., payers; society; etc.) will place on those benefits. • It's important that their input be used to capture the meaningfulness of the outcomes	Clinical trials	*"Also quantifying those in terms of what that means in your real life because to me, a grapefruit to orange, I don't know if that makes a difference…if that means you can get out of bed vs. not get out of bed, or things that are relatable to people who don't…"*

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
	collected in a trial.		
Patients should participate in clinical trials.	• Orphan drugs often do not have a strong evidence base but patients are willing to participate in trials regardless.	Clinical trials	*"Like [disease name] is a [type of condition] yet [drug name] has been shown in some trials to work on [symptoms], but hey we're willing to go down a trial."* *"Wait, I'm just going to say, to answer his question there I just think as the moms, I'm thinking quality of life. If you're saying it's toxic or whatever the effects are, obviously we would still want to try it and then see how it is and how it would affect that quality of life."*
Patients should submit patient-reported outcome measures (PROMs) during clinical trials.	• In many clinical trials, the clinical outcomes that data were collected on did not capture the positive benefits that they experienced on a new drug. • This is frustrating, as the data that is then considered by reimbursement decision-makers is incomplete. • Having the ability to report on these benefits provides important data for decision-making.	Clinical trials	*"And I mean there's no measurement of cognitive function, there's no measurement of all the benefits we've seen for her, but the study was on the kidneys."*
Patients should adhere to the treatment protocol.	• This has been an issue in the past where patients were less compliant with more burdensome treatments, negatively affecting their outcomes.	Clinical trials	*"If you don't take the drug, it's not going to work. So in our case it was compliance and adherence to the drug, which was very important."* *"…it's actually compliance that will really determine how effective the treatment is…"*
Patients should provide input, including PROMs and views on risk acceptability, into the Health Technology Assessments (HTAs) produced to support reimbursement decision-making.	• Patients have differing views on their willingness to accept risk while trying a new drug, so it is important to incorporate their input into HTAs. • Patient input will improve the interpretation of the clinical data that is analyzed in an HTA and to accurately capture how patients value the benefits of a treatment.	Reimbursement decision-making	*"I think not every…size fits all, right? So I mean, I think patient involvement [in HTA], like we had previously stated…"* *"…so how can HTA be modified to be able to analyze and understand this information as opposed to just take what you're saying and then spit it out in a really clinical fashion on the other side."* *"What about patient input in those parameters of decisions of HTA folks?"* *"Yes."* *"So we have to have flexible measures of success."* *"And again the quality of data collected. So they're aiming for clinical, scientific data whereas patient input would have tempered the data to include qualitative data."*
Patients and caregivers should provide	• Patient input is currently submitted to the	Reimbursement	*"No, we would put more emphasis on patient information and less emphasis on*

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
input into decision-making.	Common Drug Review (CDR) through patient submissions. • It is difficult to explain some experiences in a form and face-to-face input would be more appropriate. • The submission template is appropriate but patients and patient organizations do not know how to use it effectively. • Providing input on how being on a drug would affect the patients' lives is not currently an option in the patient submission.	decision-making	*scientific validity information."* *"And I think in terms of the quality of life definition, there should be a user statement in there that becomes acceptable evidence."* *"It's very difficult on a piece of paper trying to explain why you think you need that drug or quality of life on a piece of paper. Sometimes it's just much more effective when you can explain it in human being. You know, you just want to be valuable to society…"*
Patients, caregivers, and patient organizations should complete patient submissions, including, if necessary, data collected from patients in other countries.	• Clinical trials do not capture the benefits that patients are experiencing and decision-makers do not understand patients' needs or what will improve their quality of life. So patients should complete patient submissions. • Patients/patient organizations face a number of barriers to completing patient submissions. • There are not enough Canadian patients who have used a new drug to provide information to decision-makers on improvements in QOL.. • The submissions are time and resource intensive and there are significant resource inequities between patient organizations. • Communication from CDR around when patient submissions are being accepted is poor and the time-limit imposed (30 days) is prohibitive for many organizations. • CDR has a responsibility to ensure that patient input is obtained, especially when there is no patient organization. • It is also imperative that the decision-makers actually consider and value these submissions.	Reimbursement decision-making	*"So part of the rejection is that they don't have enough data from patients, and they didn't ask the patients."* *"It's very difficult on a piece of paper trying to explain why you think you need that drug or quality of life on a piece of paper."* *"The patient submission template has addressed those things quite well. What I hear you saying is there's… my experience in kind of dealing with this is there's a lack of understanding by patient groups of how to do it effectively. Patients often think that if we say it loud enough, you know if we say it enough times and loud enough, it will be heard. It's way more effective to do it other ways."* *"The one thing, we have… not as many patients in Canada that actually use the drug. But that doesn't stop you from letting other patients, because we have patient input from America and Australia and England as well and we've asked… is it okay for us to include this data, because we don't have enough patients who have experience on this to give us the information that you're asking for. How is it affecting them when they're on the drug? And they said that's fine, it's still patient input on how it's affecting patients so we included that in the submission."*
Patient organizations should increase their understanding of how to effectively prepare patient submissions.	• Patient organizations struggle to create effective patient submissions. • It is frustrating that CDR does not provide feedback on the submissions that patient organizations make.	Reimbursement decision-making	*"That was one of the issues that we talked about yesterday where we wanted feedback on the patient group submissions and CDR doesn't say you did a really good submission but we want more information on the drug, how it's different from being off it. They don't have that currently, but what they're currently pursuing is they're doing a summary."*

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
	• These frustrations have been expressed to CDR, and soon all submissions will be published online alongside the recommendations that are made. This will give patient organizations the opportunity to see how different submissions have been prepared.		*"That was one of the issues that we talked about yesterday where we wanted feedback on the patient group submissions and CDR doesn't say you did a really good submission but we want more information on the drug, how it's different from being off it. They don't have that currently, but what they're currently pursuing is they're doing a summary."*
Patients should be able to provide input on the meaningfulness of the outcomes that are used in reimbursement decision-making.	• Quality adjusted life years (QALYs) do not accurately capture the benefits that they experience while on a new drug. QALYs are fundamentally flawed in their design. • Patients should able to explain what the clinical improvements (e.g., improved kidney function) translate to in terms of quality of life (e.g., ability to engage in sports, ride a bike, etc.).	Reimbursement decision-making	*"One thing that we discussed at the other table was when we evaluate output or develop the output necessary for the basis of recommendations for approval was that there be a patient involvement, parent involvement, caregiver involvement, physician involvement… so those committees should cover, essentially to better qualify what is meant by benefit. So we focused a lot on benefit and what is benefit."* *"So when they're deciding does this drug have a good… is it worth it? Is it not? What they're thinking about are ICERs and QALYs and all these things and what the heck does that mean to a patient…"* *"Nothing."*
Patients should provide input on the burden associated with different treatments.	• It is important to consider treatment burden (of both the new treatment and the existing standard of care) when making a funding decision on a new drug. • Treatment burden influences patient compliance, ultimately impacting the outcomes of the drug.	Reimbursement decision-making	*"Well if you look at it it's actually compliance that will really determine how effective the treatment is and if you don't do your chelation your iron overload will cause heart damage, liver damage, diabetes, all of the above. And some patients have gone through liver transplants, which is very costly to the system. People sitting on that review panel didn't see that. They thought it was just a matter of convenience rather than sticking yourself with a needle you just want to take a pill which is X dollars more money to the system."*
Caregivers should provide input on caregiver burden.	• Caregiver burden can be high and it is frustrating that burden is not always considered when a reimbursement decision is being made on a new treatment that helps to reduce the burden on caregivers. • It is important that the broader impact of the drug is considered.	Reimbursement decision-making	*"I know. It's not just a diet, it is that role. But you understand, right? There's impact all the way down. He even talked about his own family and how it's going to affect…like you taking this million dollar drug or potential, how it's going to affect his family and his quality of life. So there's that caregiver, there's the patient…"*
Patients should provide input on the benefit-harm ratio and their willingness to accept risk.	• This opportunity does not exist currently. • Patients have different experiences with their disease and some may be willing to accept more risk (e.g., a patient who is close to death). • Patients' views on the risks associated with using a new drug should be considered as part of the patient submission; however, we are not	Reimbursement decision-making	*"We could look at patient submissions dealing with how much risk they're willing to assume."* *"…your own assessment and what risk you're willing to take should be taken into consideration. So it should be a part of the submission."* *"…part of the patient submission could be a part on the weighing of the risks as*

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
	always aware of all of the potential harms associated with new drugs. • Patients' views on risk acceptability should also be incorporated in their decision to start a new therapy, which is a decision that should be made in partnership with their doctor.		*seen through the lens of the patient."*
Patients should be able to identify and provide information that is missing from a drug submission before a negative decision is made based on insufficient data.	• It is frustrating that negative reimbursement decisions are made due to a lack of information. • Decision-makers should be asking for more information instead of saying no. • Patients may be able to fill in the information gaps.	Reimbursement decision-making	*"No, sometimes it could just be that a patient will write it out right there's something's missing. Could you ask for more information instead of… wouldn't it be nice that you could ask? Before you say yes or no, like rather than just saying no because you don't have enough information?"*
Patients should be able to address the decision-making committee.	• This opportunity has been denied in the past but is important in order for decision-makers to "put a face" to patients suffering from rare diseases. • It is a common worry that negative decisions may be made on orphan drugs because decision-makers are less familiar with rare disease patients and their experiences. • Having the opportunity to appeal negative decisions face-to-face would address this issue. • Brining an appeal back to the same decision-makers might be problematic as they have already "made a decision." Having an independent committee for appeals may be more appropriate.	Reimbursement decision-making	*"I mean one of the things that… the whole question of right to appeal needs to take into account that not only do you have the right to submit an application, which remains anonymous, but I think you should have the right, certainly at the appeal stage, to actually present their face."* *"…and I think patients have certain rights in this regard and that is that we should be able to address…since this is a rare drug or a rare disease situation, you're not talking about hundreds of people all seeing the committee. Individuals should in fact be able to present their case."* *"Yeah but independent of the CDR. A smaller group perhaps…similar to a court appeal in Ontario."*
Patient organizations should fund research that examines the impact of not funding orphan drugs in general (e.g., increased hospitalizations; decreased productivity).	• This type of research is very important, but it is unclear which, if any, patient organizations would fund such work.	Reimbursement decision-making	*"Is this something CORD would fund? A respected academic study of…Couldn't we get someone to do this for us? The cost of society of not funding rare diseases."*
Better care for patients			
Patients should actively engage with their physician, choosing when to start and stop a new treatment and allow for ongoing monitoring of their response to the	• Having set stopping criteria for a treatments is inappropriate due to disease heterogeneity and differing opinions on the meaningful benefits that the treatment provides.	Real-world studies to routine clinical use	*"It sort of goes to what she mentions about just having proper medical supervision or monitoring of the medication, to adjust it or even to possibly withdraw it. To get a proper treatment, I think it's important that you have a very active involvement with your medical provider."*

Table 2-1. Stakeholder Workshop Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
treatment.			*"…because when they wanted to introduce a stopping criteria, they wanted physicians to say if your lung function for us drops below a certain level, you're off the drug. And what we were arguing was the well every patient is different. You might say that, you know, this is how much you need to improve, but to a patient if it makes the difference between being able to walk a flight of stairs, that might mean more to them than it would to the government. So instead of having specific stopping criteria that it's stated between the patient and their clinician, rather than a set rule within the drug plan criteria."*
Patients should develop a buddy system to provide support and guidance for other patients, by sharing information on new treatments, processes for accessing those treatments, and teaching them how to advocate for themselves.	• There is limited information on rare diseases, existing and new treatments, and processes for accessing those treatments. • Accessing existing treatments is often confusing and scary. • When beginning a new treatment, receiving guidance from patients with more experience is very helpful. • Having a buddy system in place would provide necessary support to patients and should involve people with no conflicts of interest.	Real-world studies to routine clinical use	*"I'd like to see support for those that want to do the transition [to a new treatment]. I mean when we're personally looking at options of treatment, one of them was really scary and I was really frightened."* *"Fortunately he's now back on a clinical trial because my daughter sent it to him. This is ridiculous, unacceptable I've got a child with a rare disease and now you're getting something done and it's working and she's not going to let it slide this time. But not all of us are like that, so you know there are patients…you say you can't find patients, but they're out there. They just don't know how to get to us, to get to the right people."*
Patients and caregivers encourage researchers to start new projects.	• Launching orphan drugs in Canada is risky, but patients encourage researchers to do so any way.	Pre-clinical research	*"That's how stem cell transplant therapy started…where the doctors were and the researchers were really encouraged by the parents…"*
Better awareness of rare diseases			
Patient organizations should help to increase awareness and identify patients across the country.	• There is a lack of awareness on rare diseases and where the patients are within Canada. • Patient organizations have experience travelling across Canada spreading awareness amongst physicians and recruiting patients.	Lifecycle	*"And the patient organizations can help with that. When we increase our knowledge of where the patients are and let them know that, because a lot of the patient organization don't know who all of the people are who have that disease, that's big."* *"Yeah, like we go around and travel all across Canada and update and send out invitations to the physicians and stuff. Oh yeah, well we've more than doubled."*

Table 2-2. Stakeholder Workshop Results: past examples of patient and caregiver involvement in the orphan drug lifecycle.

Description of involvement	Participant opinions on existing involvement	Stage of lifecycle	Supporting excerpts from transcripts
Better coverage decision-making			
Patients and caregivers identify and encourage relationships with international experts.	• There are no disease experts involved in reimbursement decision-making.	Reimbursement decision-making	*"… It's all from… the patient groups are getting the Canadian doctors to even have a relationship with the international doctors, and that takes years to build."* *"And that's true because they're willing to do it. Because with our group we could just as [doctor's name] to make a submission."* *"I could get the international experts in our disorder in a flash. It's much harder for me to get the Canadian doctors involved and they don't know."*
Better care for patients			
Patients and caregivers identify and advocate for access to these therapies.	• Existing therapies may be beneficial for rare diseases but are not indicated and patients struggle to gain access.	Real-world studies onward	*"Okay, so EB is wounds and people that have chronic wounds and they continue and continue often squamous cell carcinoma, which is a killer. So hyperbaric oxygen therapy might be an effective treatment that's non-drug for this disease."* *"It's almost how desperate families are and again if you're in our group you can see these desperate families are crazy right now about trying to get that CBD oil. Like it's just like they'll do anything."*
Patients and caregivers advocate for access after receiving a negative recommendation, going to the media and the minister's office, as well as applying for special access programs.	• Patients struggle to obtain access to effective therapies after a negative reimbursement decision is made.	Reimbursement decision-making onward Reimbursement decision-making onward	*"It is. You're already exhausted and then you got to go, oh my god I have to call the paper and the press release and go to the god blessed minister's office again. Seriously, it's exhausting."* *"The CDR really only came out a month or so ago. So we're circling the wagons and making a decision about what to do next… except that we have to get it. My daughter did get temporary access for 6 months through Alberta. That was before the CDR ruling by the way."*
Patients inform self on disease and possible adverse drug reactions.	• Disease heterogeneity results in the potential for adverse reactions to a variety of different treatments, including OTC medications.	Lifecycle	*"…in our disease we have hundreds, thousands, of medications that can trigger an attack. So we have to go to safe databases of drugs but sometimes the reports are n of 1…1 person has a bad reaction but at least it's not a lot. But what we have to do is check multiple databases in different countries because there are so few people."*

Table 2-3. Session Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle
Better coverage decision-making		
Patients should enroll in registries and submit PROMs.	• When registries have been established, funding remains an issue and in some cases the registries have not been maintained even though patients have been willing to enroll.	Lifecycle
Patient organizations should establish registries (e.g., on side-effects; disease tracking; etc.).	• Establishing registries is difficult for patient organizations, which do not necessarily have the resources or training to do so. • Support from others (e.g., physicians) has allowed some patient organizations to create registries. • Patients do have some privacy concerns about registries, although some patients/ caregivers are willing to give up their privacy to get the benefits.	Lifecycle
Patients should participate in MAPs.	• If patients have the opportunity to participate in MAPs, they should do so.	Real-world studies to reimbursement decision-making
Patients and caregivers should provide input into the design of MAPs.	• Patient and caregiver involvement in MAPs is essential. • Involvement at a guideline level would but ideal, but rare diseases may be too different to have a set of general guidelines for all MAPs.	Real-world studies to reimbursement decision-making
Patients and caregivers should provide input into clinical trial design.	• Previous attempts have been unsuccessful as, although patients were invited to a meeting about the trial design, they were not actually asked for their input.	Clinical trials
Patients should provide input on the acceptability of benefit-harm ratio.	• Patients have not been able to provide this input previously, but believe it is important. • Opinions on the acceptability of benefit-harm ratio of an orphan drug will vary between patients and be influenced by the severity of a patient's disease.	Reimbursement decision-making
Better care for patients		
Patient organizations should provide guidance to newly diagnosed patients.	• Patient organizations provide important information and guidance to newly diagnosed patients. • Not all rare disease patients have a patient organization to represent them. • Without guidance from others, many patients struggle with receiving improper treatments.	Lifecycle
Patients and caregivers should provide input into the development of clinical practice guidelines on rare diseases.	• Previous requests from patient organizations to be involved have been denied.	Lifecycle
Patients should provide input on the format of a new therapy.	• Patients have not been able to provide this input previously, but believe it is important.	Pre-clinical research
Patients and caregivers should identify new research topics.	• Patients have successfully piqued the interest of researchers on certain topics; however, funding remains an issue.	Pre-clinical research
Patients should provide input on the stopping criteria used in clinical trials.	• Patients have lost access to effective therapies in the past when a clinical trial that they are a part of has stopped. • They have not provided input on stopping criteria in the past, but see it as an important way for patients or patient organizations to ensure that patients maintain access.	Clinical trials

Table 2-4. Webinar Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
Better coverage decision-making			
Patients should enroll in registries and submit PROMs.	• Participation in pharmaceutical company registries is encouraged, but these will never be fulsome. • Ideally all rare disease patients would be enrolled in a registry whether they are treated or not. • It is difficult for patient organizations to establish and maintain registries. • The Canadian government should establish and fund a registry for all Canadian rare disease patients. If they cannot afford it, it is a lot to expect patient organizations, which are often small, to be able to do so. • Taking advantage of existing technology and registry platforms may be one way to overcome some of these hurdles.	Lifecycle	*"I think [participating in pharma registries] is a great thing, it's better than nothing but I mean ideally I think that it would be great to have all of the patients in a registry whether or not they're untreated or treated. So that then falls out of the scope of the post-market registry. So I think that using some of the infrastructure that's already there is most efficient but I to be honest don't know the answer to that because I think it's pretty complex. So I know people are using some of the registries that are out there on the market but it is a little bit daunting to sort out what is the best method. I don't know the answer to what the best method is. But I know it's not possible for a small patient organization to run a robust registry."* *"So yeah, I feel pretty strongly that our government, our federal government, should have Canadian, you know, registries of Canadian rare disease patients. But I don't see that happening because they won't pay for it either, right?"*
Patient organizations should develop registries.	• It is possible for some patient organizations to establish registries; however, they will face the same challenges as other the organizations (e.g., government; pharma) who establish registries, such as funding, ethics, data ownership, privacy, etc.	Lifecycle	*"They have been sometimes; I've seen them developed by patient organizations. So that's something you might want to consider as a patient organization but again you're dealing with the same questions: ethics, who is owning this, how do you guarantee the privacy and all of that."*
Patient organizations should advocate for registries.	• Regardless of the type of registry, an important role for patient organizations to fulfill is advocating for the development of registries.	Lifecycle	*"It could be for products, it could be for patients, it could be for research purposes, but I think the role of the organizations should be to actually advocate for these registries because funding them is a huge amount and where you house it. But the advocating for them is very important because we do need to have them and should be provided…and the funding should be provided either through government or pharma."*
Patient organizations should be involved in the development and validation of PROMs.	• It is important for patient organizations to be involved beyond distributing surveys on behalf of researchers who are validating PROMs.	Lifecycle	*"Well you just said distributing the surveys, etc. But also they should be involved, I would think, in the development of them."*
Patients, caregivers, and patient organizations should provide input into clinical trial design, including identifying and selecting meaningful outcome measures.	• This opportunity does not currently exist but is an important opportunity for involvement, particularly for ensuring that the data that is meaningful to reimbursement decision-makers is collected during trials. • It is important that this input is sought earlier on in the lifecycle to ensure that the appropriate data is collected.	Clinical trials to reimbursement decision-making	*"…but I think the idea of getting patient organizations more involved in helping to create… or not create, but give suggestions on endpoints that are more valid in terms of reimbursement. That came up in the last round of comments under the last topic. I think that's really important nowadays in Canada. Having endpoints that are not only clinically relevant but also kind of strategic so that they can help lead to actual reimbursement down the line."* *"…so that patients are involved in making sure that the real world patient-centered outcomes are there but it's that link to the, like [participant name] said, to the*

Table 2-4. Webinar Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
			funding or to the regulatory framework approvals that…" *"I think what we talked about earlier, being involved… I would suggest that patients are involved earlier on in the regulatory process, earlier on in the lifecycle."* *"Yeah I would say that's great but I would say also other, you know, making sure the relevance…that the outcomes are relevant, the endpoints are relevant, etc."*
Patient organizations should survey their members to identify meaningful outcome measures and relay these measures to researchers.	• This opportunity does not exist currently, but is an important role for patient organizations to fill.	Clinical trials	*"So I think patient organizations have a large role to play there in terms of surveying their members and communicating with researchers who are developing products so that they can make sure that's all aligned. Because we've seen that so many times where research…the data is strong enough for regulatory approval but not the kind of data that they want in terms of making a funding approval."*
Patients should verify all data collected by researchers or their physician.	• It is important for patients to review the data collected by researchers or clinicians during clinical trials to ensure its accuracy	Clinical trials	*"If somebody's on a clinical trial and …through a researcher or a clinician, when the patient consults the clinician a form would be completed as to how do you feel today and what symptoms are showing. I think the patient should be signing that document along with the physician as its going then and forwarded onto the researcher so that you've then got a true validation that this data that's being collected is accurate."*
Patient organizations should continue to make patient submissions to CDR.	• Patient organizations are able to make patient submissions to CDR, but it is unclear if this input is truly valued and used to make the coverage decision.	Reimbursement decision-making	*"It would be great if they didn't pay lip service to the patient involvement, saying yep patients gave input but we'll just ignore it all."* *"Well at least more transparency on what the weighting is so that you know how much weight it's given. I never understood that. Maybe somebody does understand that. Does anyone? You know and having patients on some of those committees…that's been done, right?"*
Patient organizations should provide training to other organizations on how to create an effective submission.	• This is an opportunity for patient organizations to become more involved.	Reimbursement decision-making	*"But I think one of the ways that patient organizations can be more involved is to help each other with training on how to give really good patient submissions. Like what is it that has impact and…I know that there's guides but I don't know if people don't read the guides because we get a wide variety of submissions. Some are excellent and some are, you know, not really helpful very much. So there's a lot of work to be done in training a patient organization towards submitting a patient submission."*
Better care for patients			
Patient organizations should educate patients so they can make informed decisions.	• Patient organizations are not doing enough of this work in Canada.	Lifecycle	*"… you do want to educate patients so that they can make informed decisions when it comes to their treatment"*
Patient organizations should teach patients about their rights and	• Patient organizations are not doing enough of this work in Canada.	Lifecycle	*"…and another thing is you do want to teach patients or let them be aware of their rights so they can advocate for themselves. And organizations are doing this more*

Table 2-4. Webinar Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
how to effectively advocate for themselves.			*so in Europe than in Canada."*
Better awareness and advocacy			
Patient organizations should build relationships with all relevant stakeholders, including funders, donors, care providers, etc.	• It is important for patient organizations to build relationships and collaborate with all stakeholders and this can be done by finding common goals to work towards together. • Without donors, patient organizations do not have the funds to support their work and so these relationships are of the utmost importance.	Lifecycle	*"But yeah, I mean you need to…collaborations with all stakeholders…you know, funders, donors, care providers, doctors, everyone you can think of that's involved or would be benefitting from improving the patient outcomes."* *"You build collaboration, you find common goals and you work on these common goals."* *"The other relationships that's important in terms of a stakeholder for an organization is the relationships with their donors because without the donors' engagement and involvement, you don't have the funds to do any of your work."*
Patient organizations should engage members to increase their involvement.	• This is a challenge for most organizations but is the only way in which the organization can grow.	Lifecycle	*"I think a challenge with patient organizations in this field is engaging the members to get more involved . Because you know you can really only ever grow with the involvement of a community and sometimes that's really challenging."*
Patient organizations should follow new research results.	• This is essential for patient organizations to effectively advocate for patients and to be involved in research; however, research results are not always easily accessible to them.	Lifecycle	*"I can verify from personal experience that not having access to the research data or the results. And I think for the patient organizations it's important to because advocates for the disease group and also for research and those kinds of things, it's important for the patient organization to come from a place of experience and knowledge, right?"*
Patients and caregivers should actively work to convince others to join in the advocacy efforts of patient organizations.	• Patient organizations need patients and their caregivers to spread the word and convince others to join the cause.	Lifecycle	*"You need the patients and their families to convince other people to sign on."* *"Because that is really important, spreading the word. Each individual can bring ten other individuals and you know your numbers will multiply when you're doing a petition or letter campaign."*
Patients, caregivers, and patient organizations should promote the global Rare Disease Day on February 29th.	• Very little has been done to promote this date in Canada. In the future more work needs to be done to expose the public to the different rare diseases that exist in Canada.	Lifecycle	*"Well I'd always like to promote the one big event each year which is on February the 29th, the global rare disease day recognized throughout the whole world. We've done very little around that date here in Canada as an exposing the public or bringing the public awareness to the many different rare diseases we have in our country."*
Patient organizations should host conferences.	• Patient organizations also need to be strategic in planning their meetings/conferences in order to maximize patient involvement.	Lifecycle	*"Planning national meetings is really hard in Canada because there's such a large distance separating the members and with rare disease it's difficult to have regional meetings because often you don't have enough people to have a small regional meeting , so that's kind of the challenge. So I think patient organization need to sort of be strategic about planning the meetings and, you know, sorting out when a*

Table 2-4. Webinar Results: ways in which patients and caregivers believe they should be involved in the orphan drug lifecycle.

Description of proposed involvement	Participant opinions on proposed involvement	Stage of lifecycle	Supporting excerpts from transcripts
			regional meeting can work or provide funding for small regional meetings. Getting together in a large group though is really important because often that's the only way you can get that kind of critical mass together. So we started offering more bursaries, more and more travel bursaries, to make that happen."
Patient organizations should attend international conferences.	• Patient organizations need to attend these meetings to stay on top of research and care issues, etc. and share this information within their community.	Lifecycle	*"And then also getting involved in participating in international meetings that are around your disease itself so that you're really on top of the cutting edge research and care issues etc. that are happening in your specific disease areas. And then you can share that information of course. That's the job, to share the info so that you share it with your community."*
Patients should present at conferences.	• While this is currently being done, it should be done more to allow for patients to share the perspective and knowledge with other patients, caregivers, health care providers, etc.	Lifecycle	*"Yes, in some cases you have the expert patients who can share their knowledge and give their perspective to other patients or even to doctors and health care providers."*
Patients should provide input into content planning for conferences.	• Identifying topics that patients want to hear could help to guide the content of conferences. If patient organizations are hosting the conference, they should seek input from their members to incorporate.	Lifecycle	*"I guess just one small thing would be perhaps soliciting fellow patients to find out what they want to hear within reason. It's a little bit hard to get responses from people but it might help guide the content."*

Appendix 2-1. Examples from thematic analysis of transcripts.

Coding index

[1] Descriptive codes (i.e. general topic of excerpt)

[2] Process codes (i.e. opportunity for patient or caregiver involvement)

[3] Values codes (i.e. participant perspectives on the opportunity)

[4] Evaluation codes (i.e. participant judgement of the merit of the opportunity)

[5] Emotion codes (i.e. participant feelings on past experiences (or lack thereof) in an opportunity)

Note: letters are used to further differentiate between codes (e.g. 2 different descriptive codes may be identified as [1a] and [1b]).

Example 1

Facilitator 1: … What I'm hearing around the table is kind of like yeah there's a lot of negatives about this case that we read on page 11, but there's also a lot of potential about this drug because this is a life-threatening condition and it appears to save lives[3a]. So there's a real balance[3a] here and we're trying but we don't have enough information to figure out what that balance is ourselves[3a]. But what would be some other approaches? One is to say no, they're right. If we can't prove it, we should just forget it. But should we be looking at making it available under certain conditions and how and what would we be looking for? What conditions?

Patient/caregiver: We could look at patient submissions[1a, 1b] dealing with how much risk they're willing to assume. So you could consider the risk the patient is willing to assume when given that drug[2]. So if you think at death's door, you're willing to risk much more than you do if you're maybe using a wheelchair. But if you've got 6 months left and you can't get a transplant, maybe you'd be willing to risk it[3b]. Does that have any weight in the decision-making process?

Other stakeholder: Along those lines, what would you do? What would the nature of that submission be? So in my mind I see a 43 page contract that's drawn up by a lawyer that you sign and witness…how should that information be…

Patient/caregiver: No I think that's a decision you have to make with your doctor. But I think that it should be recorded. Your opinion of the risk should be recorded, and I think the doctor has to act with action that is representative of their knowledge and of their profession, that they're the experts. But your own assessment and what risk you're willing to take should be taken into consideration. So it should be part of the submission[1c, 2].

[1a] Patient submissions

[1b] Reimbursement decision-making

[1c] Risk-benefit ratio

[2] Providing input on risk-benefit ratio

[3a] Improving coverage decision-making

[3b] Differing opinions on benefit-harm ratio

[4] None

Example 2

Patient/caregiver: I'd also like to see support for those that want to do the transition[1]. I mean when we're personally looking at options of treatment, one of them was really scary and I was really frightened[5]. I need a portacath and all this and I was like ***gasps*** and I literally called somebody who had gone through it and they spent 2 hours on the phone to talk me through the experience[4]. You know, some handholding of the transition[1]. So if you do have something where there's… there's so close and, you know, there should be some support for that transition…handholding, buddy system[2].

Facilitator: Sure. So like we have navigators for history in terms of rules of access, maybe down here for patients you have navigators for understanding the choice.

Patient/caregiver: For tricky choices.

Facilitator: sort of like the buddy program.

Patient/caregiver: Yeah so someone can say here's the pros, the cons, what I went through…

Patient/caregiver: that personal support program that none of us have had access to that we should have[3].

Patient/caregiver: So maybe if a name was made available to me to say call this person, here are 3 people that have gone through it[2]; give them a call. And they're on a peer-to-peer group program and that information can be made available.

[1] **Using a new treatment**

[1] **Patient support**

[2] **Providing support and guidance**

[3] **Improving patient care**

[4] **Positive**

[5] **Fear**

Example 3

Patient/caregiver: I don't want to disagree… it's the end of the day…it's really in defining what the endpoints[1a, 1b] are. So we had cases…

Facilitator: So the validity of outcomes? The validity of endpoints, is that what you're getting at?

Other stakeholder: Well-defined endpoints.

Patient/caregiver: I just want them defined. And I want, you know, everyone needs, well not everyone, but there should be a panel, an informed panel, that decides on what those endpoints are to then make the recommendations[2]. But in one of these case studies it was a 6 minute walk test. Well, everyone knows that's of very little value[3a, 4].

Facilitator: Yeah.

Patient/caregiver: So well-defined endpoints leading to informed decision making[3b].

Facilitator: Sorry, when we say well-defined…maybe we should just define more well-defined?

laughter

Facilitator: Does that mean validated?

Patient/caregiver: well, informed. You're bringing together the mother, I'm not saying bring every mother around the table, but I'm saying the mother, the physician…[2]

Other stakeholder: Patient informed endpoints.

Patient/caregiver: Or caregiver or whatever it could be.

[1a] Clinical trials

[1b] Outcome measures

[2] Identifying and selecting outcome measures

[3a] Irrelevant outcome measures

[3b] Improving coverage decision-making

[4] Negative

Example 4

Facilitator: Okay so let's start at the top then in terms of the questions focusing first on HTA[1a].

Patient/caregiver: Patient input.

Facilitator: Patient input. Now do you think patient input could have avoided or managed some of the issues that happened down here in terms of access? People having to go on to advocate…I think so. That might have taken some of the need for all that external advocacy.

Patient/caregiver: Yes, it's exhausting.

Facilitator: Well yeah, I mean, you were saying there were hurdles

Patient/caregiver: It is. You're already exhausted[4a, 5] and then you got to go, oh my god I have to call the paper and the press release and go to the god blessed minister's office again[2a, 4a]. Seriously, it's exhausting[5].

Facilitator: So you know what, you don't know if all of the hurdles have been taken down but it's interesting to look back 10 years now to that situation and say okay, a few of the hurdles might have been dealt with if we were reviewing the same drug today with the process we have today. So I think that's one of the lessons learned.

Patient/caregiver: And again the quality of the data collected[3b]. So they're aiming for clinical, scientific data whereas patient input[2b] would have tempered the data[3b] to include qualitative data[1b, 2b].

Facilitator: The values would have been skewed.

Patient/caregiver: Yeah.

[1a] **HTA**

[1b] **Quality of life**

[2a] **Advocating for access**

[3] **Improving care for patients**

[4a] **Negative**

[5] **Exhaustion and frustration**

[2b] **Submitting PROMs**

[3b] **Improving coverage decision-making**

[4] **None**

Note: two opportunities were identified in this section of text, 1 example of their past involvement and 1 way in which participants felt patients should be involved.

Chapter 3:
A patient and caregiver designed framework for managed access programs

Introduction

In recent years, limited patient access to orphan drugs in Canada has become a well-publicized issue [1-4]. Orphan drugs are medicines used to treat rare diseases – life-threatening, seriously debilitating chronic conditions that, as defined in the European Union, affect less than 1 in 2,000 people [5;5]. Typically little is known about rare diseases and many patients struggle to receive a diagnosis [5]. Once they receive a diagnosis, access to effective therapies is limited due to the uncertainties that decision-makers face when considering the coverage of orphan drugs [5].

All drug coverage decisions are made in the face of uncertainty [6]. This uncertainty stems from a lack of high-quality information on the drug when a decision needs to be made. Typically, these uncertainties relate to 1) clinical benefit, 2) value for money, 3) adoption/diffusion, and 4) affordability. Coverage decision-making is often more difficult for orphan drugs than for drugs that treat common conditions due to higher levels of uncertainty. The natural histories of rare diseases are often poorly understood, and conducting rigorous clinical trials on orphan drugs is difficult due to small patient sample sizes and a lack of validated outcome measures [7]. As a result, decision-makers are at risk of making a "wrong decision", wasting resources and potentially causing harm when access to an ineffective or dangerous treatment is provided or when access to an effective treatment is denied [6]. This risk has grown as more new, high-cost drugs are introduced into a system with finite health care resources. Orphan drugs are usually expensive as manufacturers argue that they are costly to develop and the potential market for their use is small [8]. However, rare disease patients have a high, often unmet need for effective treatments [9] and for this reason, reimbursement decisions around orphan drugs are challenging.

To address these risks while ensuring patients are still able to receive access to potentially beneficial drugs, innovative approaches for the introduction of new drugs into the health care

system have been developed, including managed access programs (MAPs) [6]. MAPs are arrangements that provide patients with provisional coverage of a new drug in order to facilitate the generation of the information needed to address the uncertainties that exist around the product and support a definitive coverage decision within a given time period. Patients with rare diseases, their caregivers, and patient organizations have become increasingly vocal about the need for improved patient access to orphan drugs that is affordable and sustainable [188]. As such, they have supported the implementation of MAPs for orphan drugs [189]. However, they believe that their involvement in the design of these programs is essential to their success [189]. There are currently no existing frameworks for MAPs that have incorporated patient input into the design.

Objective

The aim of this study is to outline a patient-designed framework for managed access programs and obtain stakeholder input to assess the feasibility of this framework.

Background

In this section, background information is provided on MAPs, the context in which they operate (i.e. the orphan drug lifecycle), and the research approach used in this study, participatory action research.

Managed Access Programs

Different forms of MAPs have been used in countries throughout the world, including Australia, Canada, France, Italy, the Netherlands, the United Kingdom, and the United States [6]. While other names for these programs exist (e.g. access with evidence development, coverage with evidence development, only with research), this study uses MAPs as an umbrella term for any program that provides patients with temporary coverage of a new drug while collecting the information required to support a definitive coverage decision in a set time period. An earlier

international review has identified 2 types of MAPs, those that provide coverage as part of a clinical study and those that provide coverage linked to an outcomes guarantee (either financial or health outcomes) [6]. Coverage linked to an outcomes guarantee is more commonly used for the introduction of new drugs than coverage as part of a clinical study. In both cases, uncertainty in clinical effectiveness is the most commonly reported rationale behind the introduction of a MAP.

The Orphan Drug Lifecycle

Coverage decisions and MAPs exist within the context of the drug lifecycle (Figure 3-1). The lifecycle begins with the pre-clinical phase in which new products are tested in tissue samples and animal models [10]. Clinical trials follow, assessing the safety and efficacy of the drug when used in humans. In the regulatory stage, the drug undergoes pre-market review based on information provided by the manufacturer, including the results of the pre-clinical studies and clinical trials. Once approved for sale, studies begin to examine the effectiveness of the drug when used in the real world (i.e. a typical health care setting). The drug enters the reimbursement decision-making phase when manufacturers seek public coverage for their product and submit a request to a drug coverage review body. In Canada, two centralized review processes are in place: the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) [11;12]. These review bodies provide listing recommendations to all publicly-funded drug programs in Canada, except for Quebec [11;12]. Additionally, some private insurers use CDR recommendations when deciding whether or not to add "high cost" drugs to their formularies [13]. Typically, drugs that receive a positive recommendation will be approved for public coverage in the participating drug plans [11;12]. It is at this point where a MAP would be introduced in order to make a more informed decision when there is a significant amount of uncertainty around the product. Over time and with new research and development, the drug may be replaced by a new therapy [10].

Figure 3-1. Lifecycle of a drug

Participatory Action Research and the Research Question

Participatory action research (PAR) is a dynamic research approach in which researchers work together with the community affected by a problem to identify what exactly the issue is and develop an appropriate solution [190]. PAR projects are typically initiated by the affected community as a result of a perceived need for action and for which existing approaches to knowledge gathering and change are not adequately addressing the problem [190]. In recent years, the Canadian rare diseases community has been vocal about the challenges that patients face in receiving appropriate diagnosis and care, including access to new, potentially beneficial orphan drugs. Previously conducted research has also demonstrated the variety of ways in which patients, caregivers, and patient organizations have sought to be involved in the orphan drug lifecycle [175;189]. Much of this involvement has been with the aim of improving coverage decision making and patients were found to have great interest in MAPs as a reasonable way to obtain access to orphan drugs while allowing for the collection of essential data on their effectiveness with real-world use [189]. They have also emphasized the importance of their involvement in the design of these programs to ensure their needs and perspectives are considered [189]. As such, PAR was identified as the most appropriate approach to conducting this study.

Methods

Rationale for research approach

This study focused on the experiences and opinions of patients and caregivers within the Canadian rare disease community; therefore a qualitative research approach was deemed most

appropriate. The study was developed through PAR, in which the "problem" was brought to the attention of the general population, in part, by the rare disease community. To encourage a collaborative approach in line with the principles of PAR, data collection was done through 2 workshops using deliberative methods. Workshops are similar to focus groups in that they bring together a group of individuals selected by researchers to explore their views and experiences around the research question at hand [178;191;192]. However, facilitators take a more active role in workshops, answering questions, participating in the discussions, and encouraging participants to generate new ideas [191]. Deliberative methods involve exposing participants to multiple perspectives and giving them the opportunity to discuss these views with each other, critically think about their options, and broaden their perspectives, opinions, and understandings [182].

This study was conducted within the Promoting Rare-Disease Innovations through Sustainable Mechanisms project, or PRISM, a Canadian research network that aims to improve decision making around the development, introduction, and funding of treatments for rare diseases [179]. PRISM works in collaboration with the Canadian Organization for Rare Disorders (CORD) to organize events at which work relevant to the goals of PRISM may be conducted. CORD provides access to a broad range of stakeholders within the rare diseases field in Canada, including patients, caregivers, and patient organizations from a range of rare disease communities.

To ensure methodological rigor, the following evaluation criteria for qualitative research studies were observed: 1) appropriate method for the research question, 2) sampling adequate and information rich, 3) iterative research process, 4) thorough and clearly described interpretative process, and 5) reflexivity addressed [183].

Study population

This study was focused on rare disease patients and caregivers with a high motivation for ensuring the availability of a treatment for their or their family member's condition and who have experienced difficulties in accessing therapies in the past. In this paper, 'patient' refers to an individual living with a rare disease. 'Caregiver' refers to a patient's family member who provides them with physical and emotional care. This definition of caregiver excludes professionals who are paid to provide care to patients.

Data collection

In the spring of 2014, the Canadian Organization for Rare Disorders (CORD) hosted 6 regional fora, with 2 days of interactive sessions focused on further developing CORD's Canadian Strategy for Rare Diseases, which is an action plan aiming to address the challenges that the Canadian rare disease population faces (e.g. unnecessary delays in testing, misdiagnoses, and missed opportunities to treat) [193]. Topics discussed during the sessions included: using the lifecycle approach to collect safety and effectiveness data on orphan drugs; health technology assessment; improving the responsible use of orphan drugs; CORD's Strategy; the Orphan Drug Access Framework, a Canadian initiative that aims to improve the lives of rare disease patients by 1) providing them with better, timelier access to orphan drugs and 2) encouraging and facilitating clinical research on rare diseases [5]; and a pathway for appropriate access to orphan drugs. At 2 of the fora, patients and caregivers were invited to attend a workshop following the second day of sessions.

Each workshop was facilitated by 1 researcher and began with a brief presentation on MAPs and past examples of their use. The workshop itself was guided using a set of 9 pre-determined questions. These questions were developed by a 3-member research team after reviewing relevant literature and discussing aspects of the use and design of MAPs. The first 2

questions focused on identifying the situations in which a MAP is appropriate. The remaining 7 questions focused on outlining what a MAP should look like.

A. When should we use MAPs?
    1. Is there anything about the disease that makes MAPs a funding option?
    2. Is there anything about this drug that you think makes it a good candidate for a MAP?

B. What should a MAP look like?
    3. Who should be involved in determining the conditions of the MAP (i.e., patient eligibility criteria)?
    4. Who decides on what data should be collected?
    5. What would that process look like?
    6. What do you think the role of the patient advocacy group is for a MAP?
    7. What would you expect as part of a MAP?
    8. How do we arrive at stopping criteria for a MAP?
    9. How do we make sure that everybody will abide by the conditions of the MAP?

Both workshops' proceedings were audio recorded.

Data analysis and interpretation

Both recordings were transcribed. Thematic analysis of the data was completed following the thematic network approach outlined by Attride-Stirling [194]. Thematic networks are a tool used to organize the different levels of themes that emerge in a thematic analysis of qualitative data. The transcripts were first coded using descriptive coding methods [178]. Coding was completed inductively, with no coding-framework being established a priori. Codes were then clustered into 'basic themes', which describe the basic premises of the coded data (e.g. no

legitimate drug alternatives) [194]. Basic themes focusing on similar issues were then grouped into 'organizing themes' (e.g. drug priorities for MAPs) [194]. Finally, the organizing themes were organized into 'global themes', capturing what the transcripts are about as a whole (e.g. best practices for an ideal managed access program) [194]. Constant comparative analysis was used to compare codes and organize them into the above themes [178]. The results of the analysis were converted into questions in order to create a patient-designed, ideal MAP checklist. The checklist was designed in a similar format to commonly used critical appraisal tools [195].

Interpretation was possibly influenced by the researcher's background. AD has past experience volunteering with youth who have life-threatening, and sometimes rare, conditions. To minimize biases and ensure the accuracy of the analysis, results were sent to patients and representatives from national rare disease organizations. There was no disagreement with the results.

Results

Each workshop began with an overview of the 9 aforementioned questions. However, the discussions were ultimately led by the participants, whose comments often focused on their experiences within the orphan drug lifecycle and the challenges that they face in obtaining access to orphan drugs. Thematic analysis of the transcripts revealed 5 global themes (Table 3-3). The first 4 themes were notions that participants had around obtaining access to orphan drugs and which appeared to guide their beliefs about what an ideal MAP should look like. The 5th global theme captured the explicit MAP characteristics outlined by participants. Through the iterative process, an additional level of themes was revealed that spanned all 5 global themes. These were termed "motivating themes" and captured why patients felt MAPs were important and why they

wanted to be involved. The results are described below beginning with the 3 motivating themes, followed by the 5 global themes.

Why MAPs?

Three motivating themes were identified that captured why participants felt MAPs are a reasonable solution for addressing the uncertainties that coverage decision-makers face (Figure 3-2). To begin with, participants frequently demonstrated a lack of trust in other stakeholders. They felt uncertain that the outcome measures used in decision-making are outcomes that are meaningful to them. They also did not trust the decision-makers to be transparent about the decision-making process (*"Maybe they don't want us to know" – Patient 4, Workshop 1)*. Additionally, they did not always trust their physicians to know which therapies they require:

> *"There has been treatment options that I've done that I've now found out with the third rare condition I have I should have never, ever, ever have done" – Patient 7, Workshop 2*

Some participants felt that their physicians chose not to inform them of all their treatment options, *"making treatment decisions based on the cost of the drug" (Patient 2, Workshop 1)* not on its potential effectiveness because they assume *"[the patient] can't afford it" (Patient 3, Workshop 1)*. Participants wanted a solution in which they could be sure decision-makers would consider the outcomes that they consider meaningful and that physicians will base their recommendations on clinical effectiveness, not cost.

The second motivating theme that participants revealed was the desperation that many patients feel to find a treatment for their disease, particularly when they have no other alternatives. They described the willingness of patients to try anything and to make their own decisions about what benefit-harm ratio they feel is acceptable. According to participants,

patients *"[are] emotional, [and they] want to get better" (Patient 1, Workshop 1)* so if they are offered access to a drug in a trial or a MAP *"[they'll] sign anything" Patient 9, Workshop 1)* to participate, even if they do not agree on certain aspects of the program, such as stopping criteria.

Finally, the third motivating theme was hope, as participants made it clear that they believe patient access to orphan drugs can be improved.

"...I'm not giving up. I'm not giving up for anything. And if my son doesn't make it, I'll also be fighting for the other ones." – Caregiver 2, Workshop 1

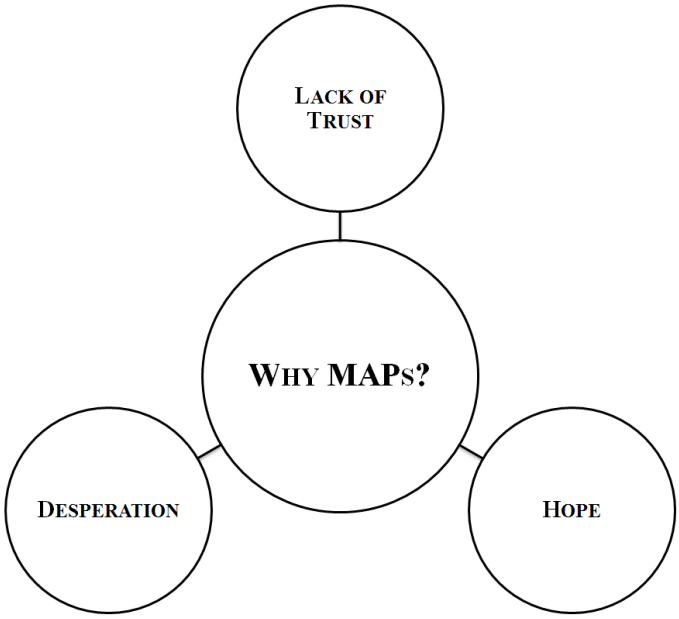
This theme was apparent in both the participants' willingness to take part in a workshop around the design of an ideal MAP and in their discussions around uncertainty and the difficulty it creates for decision-makers.

"...it's fairly easy to ask the [patients] what they would see as success." – Patient 1, Workshop 2

Participants recognized that these uncertainties are an issue, but they also believed there are ways they could be involved to help reduce them, such as identifying meaningful outcome measures and sitting on decision-making committees.

"It's just like, get [it] done. Like what can we do? Let's get [it] done with a group." – Caregiver 2, Workshop 1

Figure 3-2. Motivating themes.



Notions behind an ideal MAP

A notion is defined as an individual's conception or impression of something known, experienced, or imagined [196]. In this paper, notions are the global themes that capture patient and caregiver's perceptions around their experiences with a rare disease and accessing orphan drugs in Canada, which seemed to guide their beliefs around what aspects comprise an ideal MAP. Four notions were identified. The thematic networks around each notion are illustrated in Figure 3-3, 3-4, 3-5, and 3-6. Discussions around these notions revealed the challenges and uncertainties that exist around orphan drugs, as well as some ways in which they may be addressed. In Table 3-1 the basic themes within each notion are mapped onto the uncertainties that were revealed. This was done by reviewing the basic themes and identifying how they related to the 4 main uncertainties that decision-makers face. Basic themes that related to uncertainties other than clinical benefit, value for money, adoption/diffusion, and affordability were noted.

All stakeholders have roles and responsibilities in the orphan drug lifecycle

Participants believed that all stakeholders have roles and responsibilities within the orphan drug lifecycle.

> *"Because everybody has a role and everybody has a responsibility." – Patient 5, Workshop 1*

In their view, patients and their caregivers are disease experts. Patients decide how to approach their care and choose which treatments to take. Caregivers or other family members have a responsibility to help their patients in making treatment decisions when necessary. For example, they can help patients work through decision-making tools, which are designed to help patients understand their options. Beyond treatment decision-making, participants felt that patients have a responsibility to be involved in the system in general:

> *"All the people at home are saying ' I don't have to because somebody is going to do it for me, somebody's going to do it for me, somebody's going to do it for me… and then they've lost their right. I'm sorry, it's like if you don't go to vote, you can't complain!" – Caregiver 1, Workshop 1*

They also felt that, once involved, patients must share what they've learned with the rest of their disease community. Participants expressed the opinion that patient organizations know the disease community and patients within it the best. Given this expertise, they have a responsibility to identify and inform patients about opportunities to be involved in the lifecycle, such as informing them about opportunities to provide input into the coverage decision-making process. Additionally, they should help to manage the patient community's expectations of new therapies that have a limited evidence base. They also believed that patient organizations should educate patients, caregivers, and physicians on various topics. For example, they may produce decision-making tools to help guide patients in deciding which treatments to use. Finally, participants

indicated that physicians are responsible for ensuring their patients are aware of all treatment options, regardless of the cost. They also felt that physicians could, like patient organizations, ensure patients are aware of opportunities to become more involved in the lifecycle.

Participants also described the barriers that stakeholders face in fulfilling these roles.

"…but at the same time, at the end of the day, the patient is a patient." – Patient 3, Workshop 1

They felt that *"every disease needs support" (Caregiver 2, Workshop 1)* but that rare disease communities receive less support because they are unknown to the general population. Patients are limited by physical, mental, and emotional barriers to involvement. Family members who do not act as caregivers are less familiar with their family member's disease and treatment protocol and have difficulty helping them make decisions. They also experience push-back from physicians who do not respect patients' expertise on their condition:

"They're not open. Because… how she said her body reacted…mine is also like that and pretty badly sometimes and I make corrections to the medications and you know…kind of outrage…not outrage, but kind of you know…but they don't always listen. One told me… one doctor told me one day 'you're not a doctor'…" – Patient 8, Workshop 2

They described their own experiences with physicians who struggle to effectively treat patients due to their unfamiliarity with rare diseases:

"He didn't read the literature. Next going into hypoglycemic shock and nobody's picking up on it." – Patient 5, Workshop 2

Finally, participants felt that patient organizations have a limited capacity to take on work within their role often struggling to advocate effectively and maintain member support.

Participants' comments on their experiences within the orphan drug lifecycle and the challenges they face in becoming more involved revealed challenges in coverage decision-making that result from uncertainties around orphan drugs. The discussions often alluded to uncertainties related to clinical effectiveness, the value placed on the treatment benefits given associated opportunity costs (value for money), the eligible patient population (adoption/diffusion), and if the system could afford to fund the drug (affordability). Uncertainty in clinical effectiveness is one of the main uncertainties that decision-makers face, who are primarily concerned with ensuring resources are not wasted on ineffective drugs. However, it is also of concern to patients, who are worried that the efficacy and effectiveness of the drug will not be adequately captured in the clinical trials and real world studies, respectively. The concern stems from participants' past experiences in which outcome measures used did not capture the benefits that they were experiencing:

> *"…one clinician told me what kind of discussions they have in these committees sometimes which is if the average distance that a patient could walk in the six-minute walk was just a 100 m, you know, what would that change in that patient's life?" – Caregiver 3, Workshop 2*

They also referred to the uncertainty that patients have as to whether or not they will be able to access a therapy when their physician may not be aware of it.

In discussing roles for patients and patient organizations, participants identified ways in which they may help address some of these uncertainties. For example, patients providing input into the coverage decision-making process may help to reduce uncertainties around clinical benefit. Patient organizations who know who the patients are throughout the country may help to

answer the question of how many patients will be eligible to use the product, information which could be used to reduce uncertainties in adoption/diffusion and affordability.

All patients are unique

Participants firmly believed that all patients are unique and that it is impossible for one patient to represent the experiences and views of all patients with the same rare disease.

"…we're not just one experience. Everyone is unique." – Patient 1, Workshop 1

They described how patients have very different experiences with their condition as rare diseases are highly heterogeneous. For example, patients may differ in the symptoms or the severity of their disease. For rare diseases that are progressive, patients will have very different experiences depending on the stage they are at. Additionally, patients with the same disease sometimes respond very differently to the same treatment. Some patients may find a drug beneficial while others are unable to tolerate it, *"barfing their brains out" (Patient 3, Workshop 1).*

They also discussed the different values that patients may have in terms of treatment benefits and so *"you can't do a one size fits all" (Patient 5, Workshop 1).* Patients with different lifestyles may have very different ideas about what they consider to be a beneficial treatment outcome. As one participant said:

"You're dealing with all ages, you're dealing with different responses to treatment, different lifestyle… at least in our area I would feel very bad as a patient representative to be the only one saying what I think are the right outcomes." – Patient 1, Workshop 2

These varied benefits that patients consider to be important are often also not captured in trials and real-world studies on orphan drugs as the outcome measures are inadequate for capturing the benefits that individual patients experience in their day-to-day lives.

In participants' discussions on the uniqueness of individual rare disease patients and the challenges associated with this, 3 uncertainties were revealed: does the treatment work (clinical benefit), does the treatment represent good value for money, and who will be eligible for the treatment (adoption/diffusion)? Again, decision-makers are concerned with avoiding waste and providing a treatment that is truly effective to the appropriate patient population. However, patients are also highly motivated to ensure that sufficient data is collected on outcome measures that are meaningful to them to demonstrate the true clinical benefit of the drug.

There are weaknesses in the existing health care system that affect the orphan drug lifecycle

Participants felt that there are weaknesses in the existing health care system that directly impact different stages of the orphan drug lifecycle. While the participants described how these weaknesses impact orphan drugs, they did not focus on solutions.

Participants expressed frustration with the lack of transparency in drug pricing and coverage decision-making:

> *"Why don't they have accountability? Why is there no transparency there? I don't get that." – Patient 6, Workshop 1*

In their view, patients and caregivers are purposefully kept in the dark about decision-making processes by decision-makers who *"don't want [them] to know" (Patient 1, Workshop 1)* how decisions are made.

They lamented about the difficulties the government has faced in implementing a unified electronic medical record (EMR) system, a tool they felt would be highly useful in collecting data on patients and ensuring continuity of care. As one participant said:

> *"I wish the government would have taken the entire control…you know, done a debate and come up with one [system] and it was mandatory for everybody. Could you imagine the data collection?" – Patient 5, Workshop 1*

They described their frustrations (*"god forbid you're accountable!" – Patient 6, Workshop 1*) with physicians who have been resistant towards EMRs as well as their concerns over the ownership of their records, which they believed they should have easier access to than they currently do (*"I've never signed a document to say the doctor is the only person that can keep my records." – Patient 7, Workshop 1*).

Participants frequently referred to difficulties they face in accessing orphan drugs. They discussed how coverage decision-making on orphan drugs is complicated by the significant uncertainties that often exist around clinical effectiveness of orphan drugs where you're *"not quite sure how it's going to be used and what the outcomes will be…" (Patient 1, Workshop 2)*. Participants described their frustration with the existing coverage decision-making process, in which specialists with an expertise in the rare disease in question were not always involved in the decision:

> *"…a big enhancement is that we're actually going to bring in some people who know something about the disease and the drug and ask them to comment on this…like really?" – Caregiver 1, Workshop 2*

They also cited the high cost of orphan drugs as a deterrent to decision-makers. Participants brought up the influence of public outcry on decision-making processes after negative funding

decisions are made. They discussed examples where patients with no other alternatives were desperate to receive access to a treatment for which there was *"no data to support [it] whatsoever…" (Patient 4, Workshop 1).*

Participants discussed the impact of Canada's lack of a national health care system.

"So this is where I come in and say we've got inequality across Canada." – Patient 7, Workshop 1

They believed that, because the provinces control their own budgets it is difficult to effectively implement nation-wide programs, such as the pan-Canadian Pricing Alliance, that could directly affect access to orphan drugs. They expressed deep frustration with the inequalities that patients experience in accessing orphan drugs across the country due to this balkanized system.

Finally, participants discussed Canada's small drug market and how they believe it discourages pharmaceutical companies from attempting to bring their orphan drugs to Canada as they do not expect to make a profit.

"Canada is not a friendly place for them to come to." – Patient 8, Workshop 1

Participants emphasized the importance of negotiations between the government and pharmaceutical companies to bring new orphan drugs into Canada by ensuring the companies some security.

"If they don't have some security around how long they have to recoup that money, why would they come to Canada?" – Patient 8, Workshop 1

For example, they could negotiate a lower price by agreeing not to purchase from other companies.

The weaknesses in the existing health system that participants discussed highlight a number of uncertainties around orphan drugs: does it work (clinical benefit), does it represent good value for money, who will be eligible for it (adoption/diffusion), and can the system afford it (affordability)? They also revealed uncertainties that patients have around the availability of new therapies in Canada and whether or not they will be able to access them. While participants did not focus on ways they can be involved in improving the system, their willingness to contribute their data into EMRs may help to reduce some of the uncertainties that result (e.g. clinical effectiveness).

Research on rare diseases and orphan drugs is challenging

Participants felt that there are significant challenges in conducting research on rare diseases and orphan drugs.

> *"If we don't have that, if we don't have enough patients to do that, if we can't validate that, does that mean then that we aren't going to get anything?" – Caregiver 1, Workshop 2*

They discussed the poorly understood natural histories of rare diseases ("*Well finally, at least we know I'm not the only one…" – Patient 8, Workshop 2*) and how this impacts the discovery of effective therapies. They emphasized the importance of ongoing collection of natural history and clinical outcomes data, but suggested that registries are not always a feasible option for rare disease patient populations:

> *"…if we propose full blown managed access schemes but all would need patient registries and have validated quality of life indicators and patient input and all that… it's not going to happen." – Caregiver 1, Workshop 2*

Participants described the difficulties of conducting clinical trials on orphan drugs. In their view, clinical trials are *"not likely to be happening in Canada" (Patient 6, Workshop 2)*, limiting Canadian patients' from obtaining early access to new therapies. Trials that do take place, in Canada or elsewhere, are limited by small patient sample sizes and a lack of validated outcome measures.

> *"Finally they came back and said we'd have to have 99 patients. Well we didn't have 99 patients that we're going to enroll." – Caregiver 1, Workshop 2*

The research challenges identified by participants illustrated the difficulty in collecting high quality information on rare disease populations and orphan drugs, resulting in uncertainties around clinical benefit and adoption/diffusion at the point of decision-making. They also revealed the uncertainties patients experience around whether or not they will be able to access new therapies in Canada.

Table 3-1. Notions behind a MAP mapped onto the types of uncertainty.

Statements and sub-themes	Uncertainties: Clinical benefit	Value for money	Adoption/ diffusion	Affordability	Availability	Access
All stakeholders have roles and responsibilities within the orphan drug lifecycle						
Expectations of stakeholders						
Patients are responsible for deciding how to approach their care	■					
Patients are responsible for getting more involved in the lifecycle	■					
Patients who become more involved must share their knowledge with their disease community	■					
Family members and/or caregivers should help patients with treatment decisions when necessary	■					
Patient organizations are responsible for identifying and informing patients about opportunities to be involved	■		■	■		
Patient organizations are responsible for managing patients' expectations	■					
Patient organizations are responsible for educating patient and physicians through decision-making tools and educational materials	■					
Physicians must inform patients about all available treatments, regardless of cost	■	■	■			
Physicians must inform patient about all opportunities to be involved in the lifecycle						
Unique stakeholder expertise						
Patients and their caregivers are disease experts	■	■				
Patient organizations know the disease community & patients within it the best			■			
Challenges face in fulfilling roles and responsibilities						
Patients face physical, mental, and emotional barriers to involvement	■					
Physicians do not respect patients' expertise	■					
Patient organizations have a limited capacity to advocate effectively and struggle to maintain member support	■		■			
Rare disease communities receive less support because they are lesser known to the general population	■		■			
General practitioners are not always familiar with rare diseases and their treatments	■		■			■
Family members are not always familiar with the disease and treatment protocols						
All patients are unique						
Patients experience their diseases very differently						
Patients with the same disease respond differently to the same treatment	■		■			
Rare diseases are highly heterogeneous in how they manifest	■		■			
Patients have different values than each other and other stakeholders						
Outcome measures and stopping criteria often do not capture the benefits that patients feel they experience	■	■				

Table 3-1. Notions behind a MAP mapped onto the types of uncertainty.

	Uncertainties					
Statements and sub-themes	**Clinical benefit**	**Value for money**	**Adoption/ diffusion**	**Affordability**	**Availability**	**Access**
Patients have different interpretations of meaningful benefits	■	■				
There are weaknesses in the existing health care system						
Lack of transparency						
Drug pricing negotiations are done in secret		■		■	■	■
Patients, caregivers, and physicians are now well-informed on decision-making processes						■
Patients and caregivers do not trust decision-makers to be transparent						■
Access to orphan drugs						
Public outcry is used to obtain access to drugs that are not necessarily effective	■					
Orphan drugs are expensive		■		■		
Greater uncertainty around clinical effectiveness	■					
Coverage decision-making does not always involve disease experts	■					
No national health care system						
Inequality in drug access across the provinces						■
Provinces control their own budget						■
Issues with use of electronic medical records						
No unified EMR system	■					■
Resistance from physicians to EMR use	■					■
Patient frustration over EMR ownership	■					■
Canada's small drug market is less attractive to pharmaceutical companies					■	
Research on rare diseases and orphan drugs is challenging						
Research on orphan drugs						
Trials are limited by small sample sizes	■					
Treatment registries are often infeasible	■					
Lack of validated outcome measures	■					
Fewer clinical trials in Canada	■				■	■
Research on rare diseases						
Natural histories of rare diseases are often poorly understood			■			
Natural history registries are often infeasible			■			

Best practice for an ideal MAP

Participants identified 7 aspects of an ideal MAP: program goals, disease/drug priorities, program-specific committee, individual patient input, learning from other countries, ongoing monitoring and registries, and outcome measures and stopping criteria. These aspects were organized into 3 categories: system-level, organizational, and study design [197]. Each of these aspects is described in detail below. These aspects were also used to create an "Ideal MAP" checklist (Table 3-2).

<u>System-level Aspects</u>

System-level aspects are those related to issues between the MAP and the health system in which it exists [197].

Program Goals

Ultimately, participants wanted MAPs to be used only in situations for which they were truly appropriate.

> *"Quite frankly it goes back to what you're saying here, you gotta choose the right scheme though for the right purpose." – Caregiver 1, Workshop 2*

They emphasized that the MAP must be able to answer the question at hand, otherwise it is a waste of time and money. Participants believed that in an ideal MAP, all patients will have the opportunity to try the drug in an individualized treatment protocol in order to identify the right dose of the right drug for the right patient.

> *"So for me… and again [it's] an obvious fact that we should be trying it on each individual patient and seeing if it's working for them or not."—Caregiver 3; Workshop 2*

They also saw MAPs as a way of ensuring earlier access to potentially effective therapies before a patient's disease has had the opportunity to progress.

> *"The failure is that if it causes the patient to have to trial this [existing] medication and fail and within that time they lost their kidneys where you could have started them on this [new] drug and they could have saved their kidneys…" – Patient 8, Workshop 1*

Finally, participants wanted the entire MAP to be transparent in order improve patients' acceptance of funding decisions by educating them on the decision-making process.

> *"It really took the sting out of why I can't get my medication because I understood the process a little more." – Patient 4, Workshop 1*

Disease/Drug Priorities

Participants felt that disease prevalence alone is an insufficient criterion to decide for which treatments a MAP should be used.

> *"I think what you just said, [a life threatening or chronically debilitating condition], nailed it." – Patient 2, Workshop 1*

They emphasized the use of 2 additional criteria: 1) drugs that treat life-threatening or chronically debilitating conditions, and 2) drugs for which there are no other legitimate alternatives. The term "legitimate alternatives" arose when participants indicated that sometimes an alternative exists, but is still not an option for all patients. It may be unaffordable or patients may fail on it or experience intolerance. For this reason, they suggested that patient input on drug priorities for MAPs is essential. Some additional criteria were suggested, including drugs that are innovative (e.g. have a new mechanism of action) and expensive orphan drugs. There was no disagreement with these criteria; however, participants did not respond as strongly to them.

Participants wondered whether using MAPs for all drugs might help to make the health care system more efficient.

"I don't really see why we have these exclusions or are even thinking about excluding stuff." – Patient 4, Workshop 1

After further discussion, it was agreed that prioritizing drugs that meet certain criteria would help to make the introduction of MAPs more manageable. With this in mind, they suggested that drugs with greater uncertainty around clinical benefit might be most appropriate for MAPs.

Organizational Aspects

Organizational aspects are related to the governance and financing of MAPs [197]. Participants did not discuss program financing.

Program-Specific Committee

Participants felt that MAPs should be guided by a program-specific committee with 3 patient members who meet a minimum level of experience with the health care system, have a meaningful role on the committee, and are accountable back to the community they represent to avoid any bias.

"So when you have these committees that fall together, there needs to be a stipulation that there's patient representative…representation on that board." – Patient 9, Workshop 1

Participants also saw a role for patient organizations within this committee as the party responsible for selecting patient committee members to represent them.

"We all agree that [patient name] go for us and speak on…like do we all, do you think she understands all our needs and all our…everything and she can go on our behalf?" – Patient 3, Workshop 1

Participants saw the need for a physician committee member on the committee, preferably one who specializes in the specific rare disease. They also agreed with a suggestion that the expert should be selected by the patient community to ensure they are a true expert

"...somebody in the medical field who understands..." – Patient 4, Workshop 1

Having all committee meetings open, with all patients and caregivers are permitted to attend, was also important to participants.

"I think it should always be open to anybody if they wanted to attend." – Patient 7, Workshop 1

They saw this as an opportunity for patients who are not on the committee to provide individual input into the program. This is discussed further below.

Individual Patient Input

Participants believed that individual patient input from a broad range of patients is essential to developing an appropriate MAP.

"...I think that the patient, in whatever format, deserves a voice." – Patient 2, Workshop 1

They also felt that this input must be collected through a process that is quick, efficient, and, most importantly, accessible. To ensure that all patients have the opportunity to provide input, participants discussed a number of different ways in which their feedback could be collected: online surveys, written documents, videos, or face-to-face interviews with the committee. They also suggested that input be collected and synthesized by patient organizations for submission to the committee.

"Like gather up all the information and it's the one voice?" – Patient 4, Workshop 1

Most participants agreed that online surveys would be a highly effective way to gather input from as many patients as possible, but some still wanted the opportunity to present their views in person. They felt that having open committee meetings would provide patients with this opportunity. Participants emphasized the need for these input processes to be transparent with patients made well aware of opportunities to be involved.

"…so when this is happening, again it comes with transparency, because we don't know when these things happen, right?" – Patient 6, Workshop 1

International Collaboration

Participants felt that to develop an ideal MAP, it is helpful to reach out to other countries to collaborate with and learn from. When discussing the limited number of trials that take place in Canada, participants suggested collaborating with countries like the United States in order to conduct trials.

"…is it possible to have something, there are trials in the States going on that we know about, so that maybe we could get some Canadian patients matched with a Canadian physician that could be part of the trial in the States." – Patient 6, Workshop 2

They also recommended reaching out to countries with greater experience in conducting MAPs to learn from their successes and failures in designed MAPs for Canada.

"…why can't we follow or adopt one of those systems?" – Patient 1, Workshop 1

Participants also saw these collaborations with other countries as an opportunity to educate Canadian physicians on rare diseases that they are unfamiliar with.

"And so that you get learning in Canada for the physician in a rare disease or ultra-rare disease…" – Patient 6, Workshop 2

Study Design Aspects

Study design aspects relate to the operational components of the MAPs [197].

Ongoing Monitoring and Registries

Participants believed that MAPs require ongoing monitoring with an engaged physician and good documentation.

> *"Part of managed access is to have a documentation process in place for when you're doing these things so that it's captured." – Patient 5, Workshop 2*

They felt that data collection should begin through registries before treatment begins (i.e. natural history data) and include the collection of qualitative data in addition to clinical outcomes.

> *"Map out for each one…that disease, what are the stages of that patient journey, what are the progressions…" – Caregiver 1, Workshop 2*

In spite of the challenges faced in introducing EMRs in the past, a number of participants strongly believed that electronic medical records (EMRs) could be an efficient way to consistently follow-up with patients, provide continuity of care and collect large amounts of data.

> *"…you know, done a debate and come up with one [electronic medical record system] and it was mandatory for everybody. Could you imagine the data collection?" – Patient 5, Workshop 1*

Outcome Measures and Stopping Criteria

The outcome measures collected in MAPs and used as stopping criteria should be meaningful and accurately capture patients' experiences.

> *"… ask us what outcomes we're looking for is the first thing and, you know, fairly easy as long as you know who the patients are..." – Patient 1, Workshop 2*

To this end, participants felt that MAPs require patient input on meaningful outcome measures and stopping criteria.

> *"Here's what we're thinking in terms of outcomes, what do you think? What else can you tell us?" – Caregiver 1, Workshop 2*

Additionally, they believed it is important to involve patients earlier on in the lifecycle (e.g. during clinical trials) to get input on outcome measures before trials and MAPs begin. The participants also believed that instead of set stopping criteria, decisions to continue or discontinue a therapy should be made through a conversation between patients and their physicians.

> *"…like we always talk about…okay this is what it's supposed to do… if it doesn't work after this amount of time we'll try and up the dose but we can only go up to this amount of medications and after this point…" – Patient 6, Workshop 2*

However, they believed that harms are clear stopping criteria. Finally, participants stressed the need for follow-through on the results of a MAP.

> *"A smart question and you act on the answer." – Patient 1, Workshop 2*

If the treatment is found to be ineffective for a patient based on the agreed upon outcome measures, the patient must discontinue treatment. They also emphasized the need for decision-makers to enforce the follow-through.

Table 3-2. Checklist for the characteristics of an Ideal MAP.

System Level Aspects		
Program Goals		
• Is the MAP appropriate for the question at hand?	☐ Yes	☐ No
• Will the patients receive earlier access to the drug?	☐ Yes	☐ No
• Will the treatment be individualized in order to find the right drug for the right patient?	☐ Yes	☐ No
• Will all of the processes within the program (e.g. decision-making) be transparent to ensure greater buy-in?	☐ Yes	☐ No
Disease/Drug Priorities		
• Will patient input be used to identify appropriate diseases/drugs for MAPs?	☐ Yes	☐ No
• Will criteria be used beyond prevalence to prioritize drugs for MAPs?	☐ Yes	☐ No
• No legitimate alternatives?	☐ Yes	☐ No
• Drugs that treat life-threatening or chronically debilitating conditions?	☐ Yes	☐ No
• Innovative?	☐ Yes	☐ No
• Expensive orphan drugs?	☐ Yes	☐ No
• Greater uncertainty in clinical benefit?	☐ Yes	☐ No
Organizational Aspects		
Program-Specific Committee		
• Will there be a program-specific committee established to guide the MAP?	☐ Yes	☐ No
• Will there be 3 patient members on the committee?	☐ Yes	☐ No
• Will the patient members meet the follow criteria:		
• Meet a minimum level of experience with the health care system	☐ Yes	☐ No
• Have a meaningful role on the committee?	☐ Yes	☐ No
• Are accountable back to the disease community that they represent?	☐ Yes	☐ No
• Will patient organizations select the patient members?	☐ Yes	☐ No
• Will there be a physician committee member?	☐ Yes	☐ No
• Will they be an expert in the rare disease?	☐ Yes	☐ No
• Will patient organizations select the physician member?	☐ Yes	☐ No
• Will the committee meetings be open to all patients and caregivers who wish to attend?	☐ Yes	☐ No
Individual Patient Input		
• Will individual input from a broad range of patients be collected to develop the MAP?	☐ Yes	☐ No
• Will the process be quick and efficient?	☐ Yes	☐ No
• Will there be a variety of ways for patients to provide input?	☐ Yes	☐ No
• Will the input processes be transparent and patients well informed of the opportunity?	☐ Yes	☐ No
International Collaboration		
• Will there be collaboration with other countries to learn from their experiences with MAPs?	☐ Yes	☐ No
• Will there be collaboration with other countries to conduct trials (if necessary)?	☐ Yes	☐ No
• Will there be collaboration with experts in other countries to educate Canadian physicians on the rare disease?	☐ Yes	☐ No
Study Design Aspects		
Ongoing Monitoring and Registries		
• Will there be ongoing monitoring with an engaged physician and good documentation (e.g. through EMRs)?	☐ Yes	☐ No
• Will the following information be collected:	☐ Yes	☐ No
• Natural history data?	☐ Yes	☐ No
• Qualitative data?	☐ Yes	☐ No
• Clinical outcomes?	☐ Yes	☐ No
Outcome Measures and Stopping Criteria		
• Will the outcome measures used be meaningful to patients and adequately capture their experiences?	☐ Yes	☐ No
• Will patients provide input on meaningful outcome measures?	☐ Yes	☐ No
• Will decisions to continue/discontinue therapy be made between physicians and patients without the use of set stopping criteria?	☐ Yes	☐ No
• Will there be follow-through on the results of the MAP?	☐ Yes	☐ No

Discussion

Motivating factors behind the use of MAPs

While the research question driving the workshops was centered on what an ideal MAP should look like, a significant proportion of the commentary made by participants focused on the current context of orphan drug access, the challenges that patients and caregivers face, and, ultimately, why MAPs might be an appropriate solution. Throughout the discussions, 3 themes emerged driving participants' belief that MAPs should be used to improve orphan drug access and why they want to be involved: a lack of trust in decision-makers and physicians to ensure that patients are able to access truly effective therapies, desperation for access when no other alternatives exist, and hope that access to orphan drugs can be improved. The literature provides support for the idea that these emotions – lack of trust, desperation, and hope – motivate action in patients [198-200]. A study on patient participation in decision-making found that patients with lower levels of trust in their physician are more likely to want an autonomous role in treatment decision-making [198]. Another study into the meaning of hope to patients found that hope often served as a justification for action by the patients [199]. A third study into the growing popularity of stem cell tourism found that a combination of patient desperation and hope helps motivates patients with untreatable disease to take such measures [200].

Notions behind an ideal MAP

Four themes were identified that captured the notions behind what participants considered to be an ideal MAP: stakeholder roles and responsibilities, uniqueness of patients, weaknesses of the existing health care system, and the challenges behind conducting research on rare diseases and orphan drugs. Discussions around these notions highlighted the existing uncertainties around orphan drugs that decision-makers face in clinical benefit, value for money, adoption/diffusion, and affordability. It was revealed that patients are also concerned with addressing these

uncertainties. They were also concerned with 2 additional uncertainties: will the drug be available in Canada and, if so, will they be able to get access? Participants also identified how they may be involved to help reduce these uncertainties and demonstrated an eagerness to take part. This is consistent with the literature, which has reported a wide variety of opportunities for patient involvement in the orphan drug lifecycle and the willingness of patients, caregivers, and patient organizations to take part in these opportunities to help reduce the uncertainties that decision-makers face [175;189].

An ideal framework for MAPs

Participants identified 7 aspects of an ideal MAP that fell into 3 categories. System level aspects (program goals, disease/drug priorities), organizational aspects (governance by a program-specific committee, individual patient input into program governance, and international collaboration), and study design aspects (ongoing monitoring and registries, appropriate outcome measures and stopping criteria). Of particular importance to participants was patient involvement. Participants felt that, not only should patients serve on a program-specific committee to govern the program, but that all patients should have the opportunity to provide input into the program design. In particular, participants wanted patients to be able to provide input on drug priorities for the programs and on the outcome measures that would be used. Participants also emphasized the importance of transparency throughout all aspects of the program, particularly in processes to collect input from individual patients and to select outcome measures. Previous research has demonstrated a lack of transparency in reporting on MAPs [6]. Transparency has been identified as a critical aspect in other decision-making processes [201;202].

Potential weaknesses of the study

Participants were recruited for this study through convenience sampling by hosting the discussions at events hosted by the CORD. It is possible that people who choose to actively

participate in these events differ from those who do not and so are not representative of the whole Canadian rare disease population. However, CORD is comprised of more than 80 different rare disease patient organizations and provides funding for travel costs to facilitate attendance of patients and caregivers from all rare disease communities at their events, reducing the likelihood of a biased sample. Additionally, the population of focus in this study was patients and caregivers who are highly motivated to gain access to therapies for rare diseases and these individuals are more likely to attend CORD events. As such, these participants are likely representative of the population under study.

A second limitation of the study is that a single researcher coded the workshop transcripts. However, the results of the analysis were reviewed by two additional researchers who facilitated the workshops.

Opportunities for future research

Participants were explicit in the ways in which they felt patients should be involved in MAPs, beyond receiving access to the drugs. While they also recognized that disease specialist involvement is also essential, they did not go into great detail about their possible role. Additionally, they did not discuss the role that the government and pharmaceutical companies would play. Successful MAPs require involvement from all stakeholders [197]. This framework could benefit from review by other stakeholders to gain their feedback on its feasibility and how they see themselves involved.

Conclusion

Patient and caregiver interest in MAPs and their willingness to be involved is motivated by a lack of trust in decision-makers and physicians to ensure their access to effective orphan drugs, desperation to gain access to a potentially effective drug when they have no alternatives, and

hope that access to effective orphan drugs can be improved. Their ideal MAP is built upon patient involvement and transparency in all aspects of the program. Future research is needed to examine the feasibility of this framework and the roles for other stakeholders in the program.

Figure 3-3. Thematic Network 1: all stakeholders have roles and responsibilities.

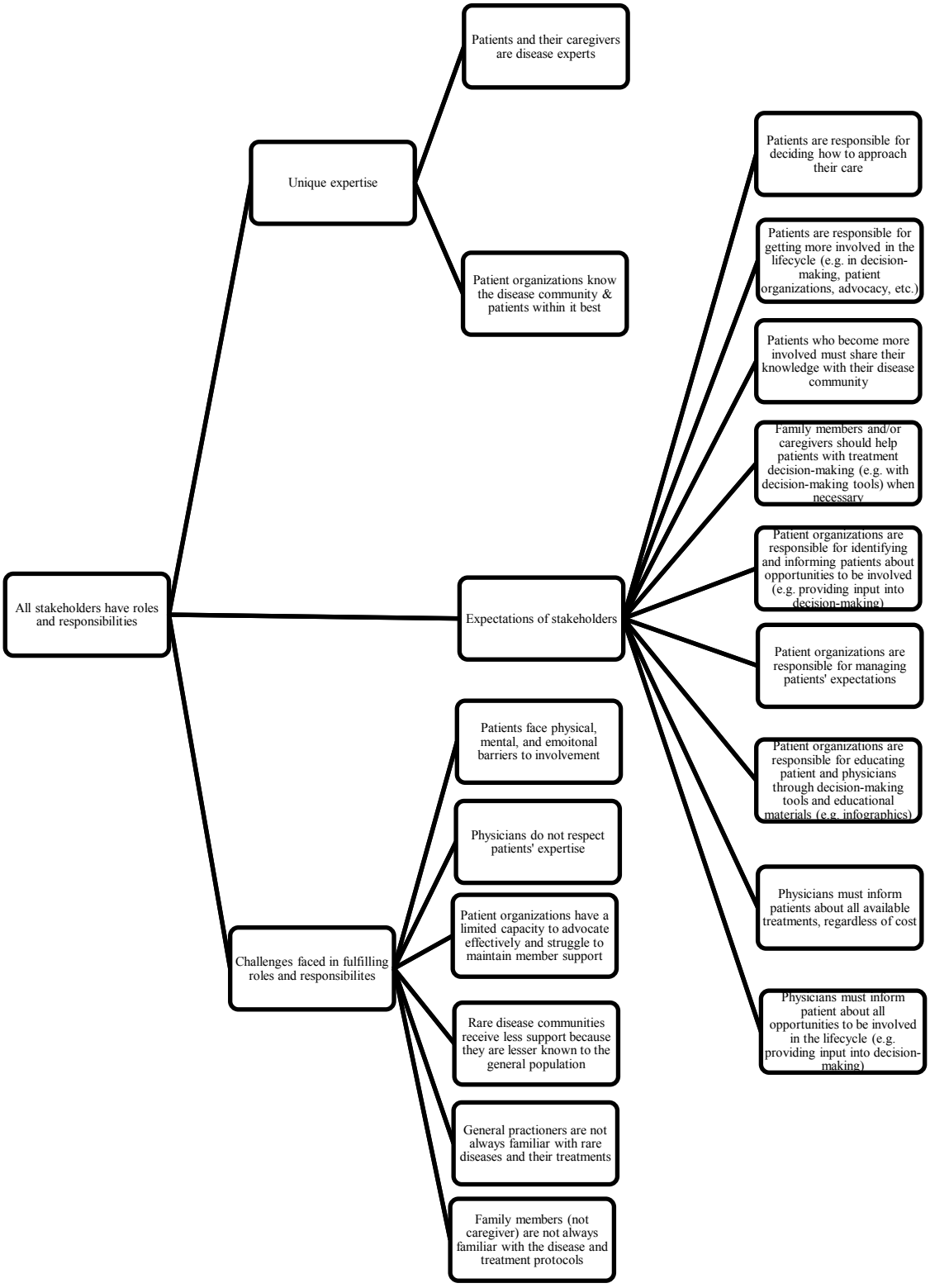


Figure 3-4. Thematic Network 2: all patients are unique.

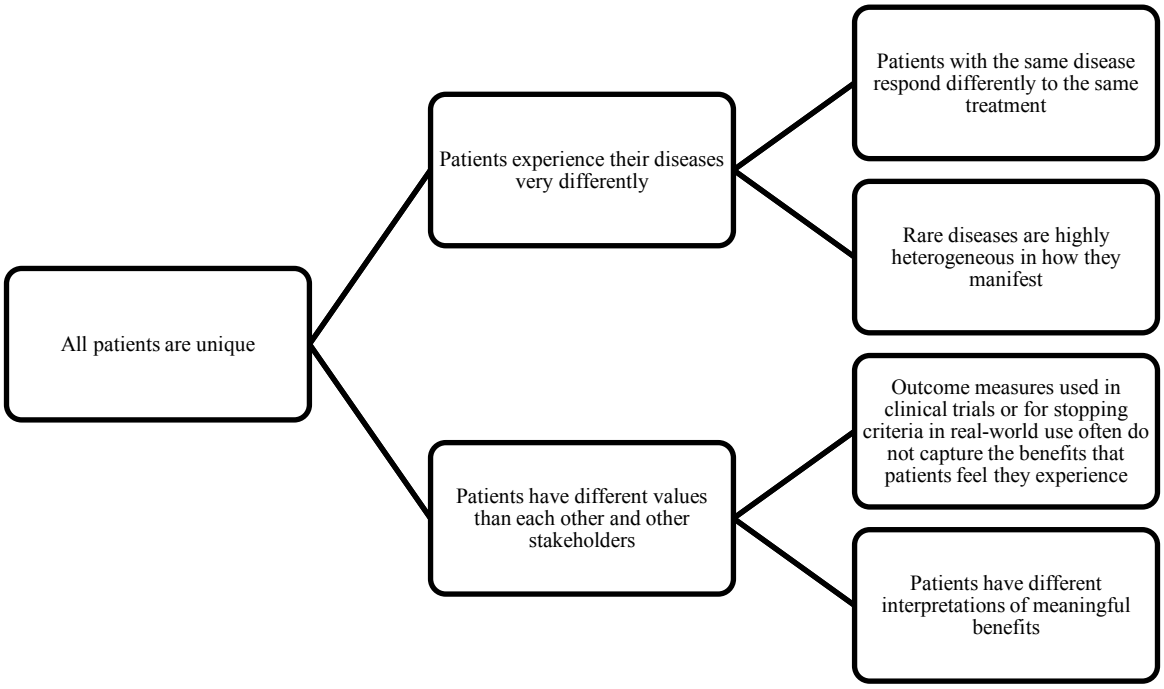


Figure 3-5. Thematic Network 3: there are weaknesses in the existing health care system.

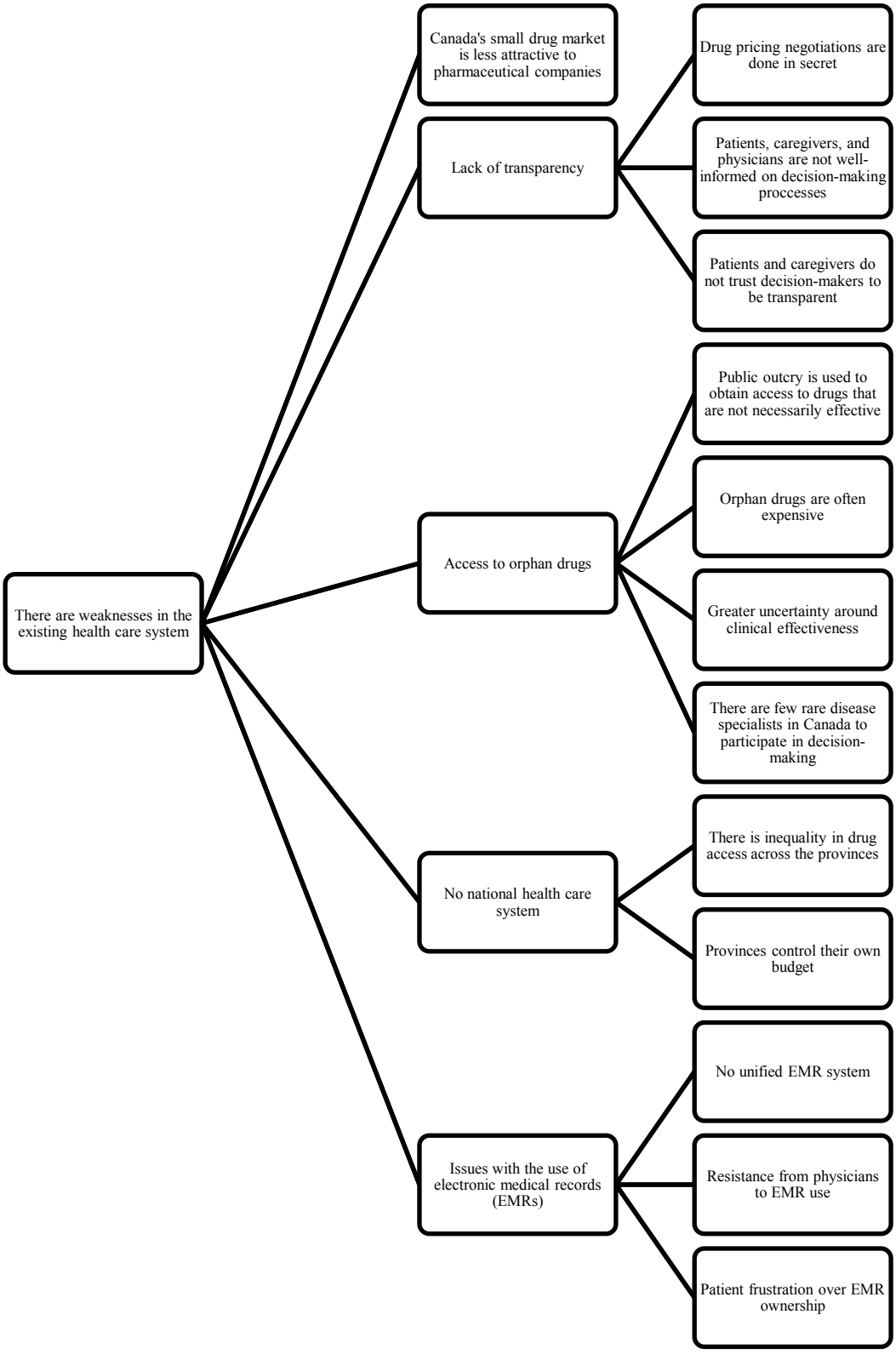


Figure 3-6. Thematic Network 4: research on rare diseases and orphan drugs is challenging.

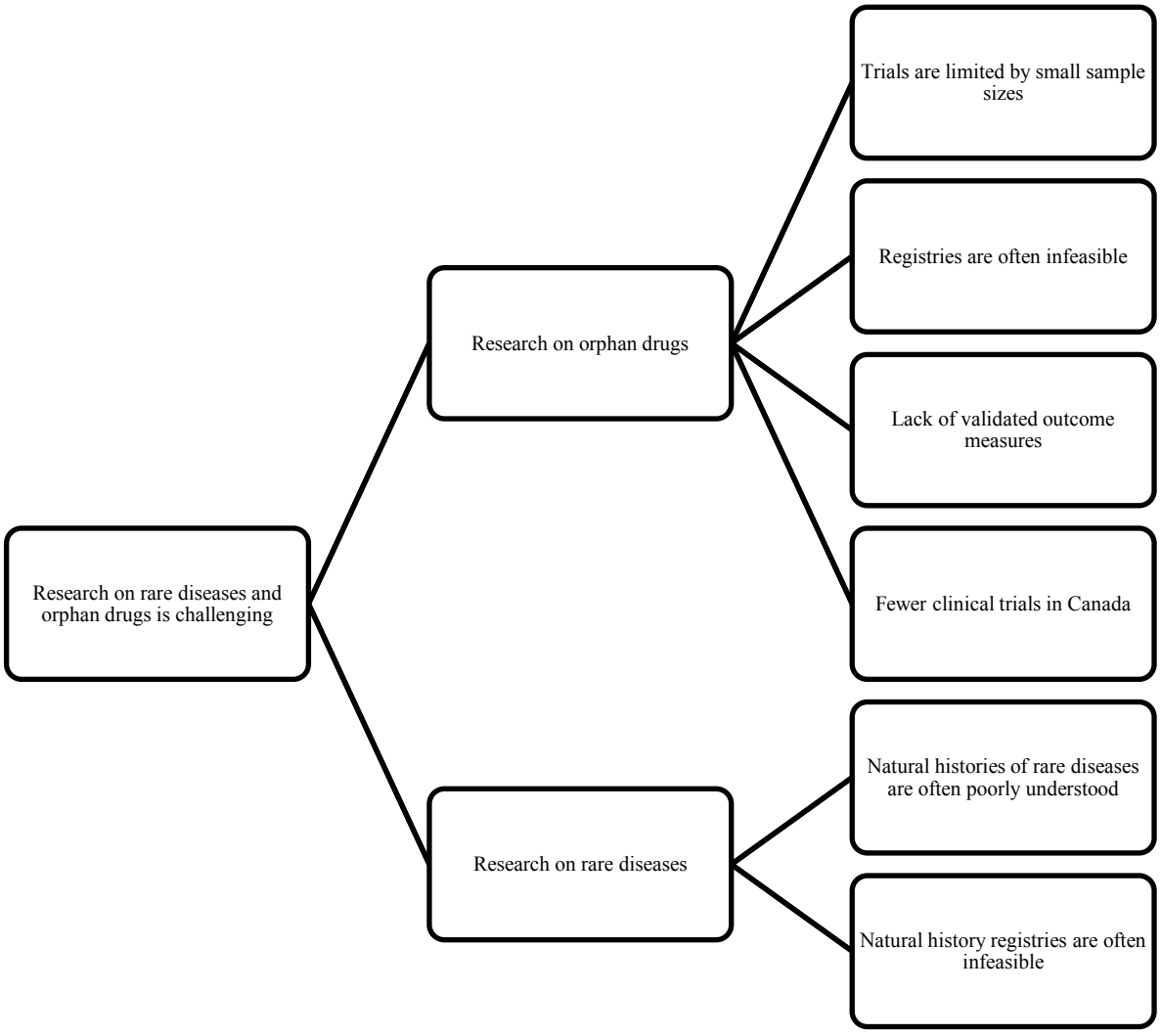


Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
All stakeholders have certain roles and responsibilities within the orphan drug lifecycle				
1	Patients and families know the patients' experiences best	Patients and their families are disease experts	*"I'm living with that body. I know me."*	Unique expertise
2	Patients and families know which outcomes matter most			
2	Patient organizations know the patients	Patient organizations are most familiar with the disease community and the patients involved in it	*"…And that's what I tell patients to ask the physicians to do, to call, for example, [patient organization] where we see hundreds of these patients as one physician in Quebec may see…"* *"They may have already had the experience and know what to do."*	
1, 2	Patient autonomy in decision-making	Patients are responsible for deciding how to approach their care and which treatments to take	*"And it's totally the patients who will take themselves off the drugs because it is not worth it whatsoever."* *"…and I make corrections to the medication…"*	Expectations of stakeholders
1, 2	Patients are responsible for managing their own care			
1	Patients are responsible for getting involved	Patients are responsible for getting more involved throughout the orphan drug lifecycle (e.g. advocacy; decision-making processes, etc.)	*"All the people at home are saying I don't have to because somebody is going to do it for me, somebody's going to do it for me, somebody's going to do it for me. And then, they've lost their right. I'm sorry, it's like if you don't go to vote, you can't complain!"*	
1	Involved patients are responsible back to disease community	Patients who become more involved are responsible for sharing their knowledge with the rest of the disease community	*"And that's where I think it's important that the rest of us are there for those voices so that we can go back to the community, can go back to these people and say…"* *"I'm going to give you this information and what you do with it is up to you, kind of thing."* *"In your case you've got this great organization now. You can bring it back to there and then it's up to these people to take that information and do whatever they want with it."*	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
1	Family members and/or caregivers should help patients with their treatment decision-making when necessary (e.g. walking them through decision-making tools)	Family members and/or caregivers should help patients with their treatment decision-making when necessary (e.g. walking them through decision-making tools)	*"I can see that coming in handy like if you take a look at how long you need and I can only speak from my own situation, I'm the only person who knows my son. I'm the only one who knows all of his medications. Everything from head to toe, inside and outside. God forbid something should ever happen to me, there would be this that his sister could go "I recognize this, I didn't know that."*	
1	Patient organizations are responsible for identifying patients and informing them of opportunities to be involved	Patient organizations are responsible for identifying and informing patients about opportunities to be involved (e.g. in decision-making processes)	*"Through the support groups."* *"Could you do it through patient support groups?"*	
1	Patient organizations are responsible for managing patients' expectations	Patient organizations are responsible for managing patients' expectations of new orphan drugs	***"Do you think there's a role for patient organizations in helping patients to figure out what would be reasonable to push for or not?"*** *"Absolutely."*	
1	Patient organizations are responsible for educating their patients	Patient organizations are responsible for educating patients and physicians through decision-making tools and educational documents (e.g. infographics)	*"So, yeah I do believe that there's a responsibility of the patient group to educate."*	
1	Patient organizations educate through decision-making tools			
1	Improving patient care through education/decision-making tools			
1	Patient organizations should educate physicians			
1	Patient organizations educate through educational documents			
1	Physicians are responsible for informing patients of opportunities to be involved	Physicians are responsible for informing patients about all opportunities to be involved (e.g. in decision-making processes)	*"Through the physicians, through the clinics, through support groups, through foundations."*	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
1	Physicians are responsible for informing patients about all available drugs	Physicians are responsible for informing their patients about all drugs that are available, regardless of their price	*"We're developing it because we want our physicians to know, because we know so many of our physicians are making treatment decisions based on cost of the drug."* *"They won't prescribe this medication…'I won't even mention it to them because they can't afford it'."*	
1	Lack of support due to unfamiliarity with rare diseases (e.g. in charity runs)	Rare diseases receive less support because they are unknown to the general population	*"But every disease needs support."*	Barriers faced in fulfilling roles and responsibilities
1	Patients face different barriers to involvement (mental, physical, emotional)	Patient involvement in the lifecycle is limited by a number of different barriers (e.g. physical, mental, emotional)	*"If you're not capable, if you're not cognitively able to do it…"* *"But on the other side of it, like when I said that the majority of our patients can't help they need help. And that is true."* *"The majority need help. And so I don't want anyone…like where do you start judging where we are accountable and that…"* *"But at the same time, at the end of the day, the patient is a patient. So when you have 2 or 3, you still have to expect sometimes one of these are not going to be feeling well. And you know, like it's…that's part of their lives."*	
2	Physicians are not open to patients' expertise	Physicians are not open to patients' expertise	*"They're not open."*	
1	Some family members lack knowledge about the disease and treatments	Not all familiar members are familiar with rare diseases and the treatment protocols	*"…but nobody knows what she's dying of or what's really going on."* *"Like what she's taking or what she's…anything."*	
1	Patient organizations have a limited capacity to advocate properly	Patient organizations have a limited capacity to advocate properly and often struggle to maintain member support	*"…I'd always get the ones where somebody just died, somebody just got diagnosed…there out there that first year running for Aunt May and 'I'm gonna do this' and then after their mourning process is done, they're gone!"*	
1	Patient organizations taking on too much			
1	Patient organizations struggle to maintain member support			
2	General practitioners are not always familiar with rare diseases and their treatments	General practitioners are not always familiar with rare diseases and their treatments	*"…and what happened was they spent hours in meetings where the [general practitioners] and the other physicians were questioning the*	
2	Some physicians are unfamiliar with rare			

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
	diseases		*basic principles and measures and indicators of this 60 year old disease. So it was a very bad experience for these medical geneticists that treat at the [disease] clinic and that know…"* *"He didn't read the literature. Next going into hypoglycemic shock and nobody's picking up on it."* *"So some physicians could be very uncomfortable with dealing with these one-on-one personalized cases with treatments."*	
All patients are unique and cannot be represented by one individual				
1, 2	Patients respond differently to treatments	Patients with the same disease respond differently to treatments	*"…we're not having the same bodies. We don't have the same ways [of] metabolizing."* *"A one size decision does not fit all in many of these cases…"*	Patients have very different experiences with their diseases
2	Rare diseases are heterogeneous	Rare diseases are highly heterogeneous	*"Everybody's different."* *"…and I learn so much from everybody else too, because we're not just one experience. Everyone is unique."*	
2	Rare diseases vary in severity			
2	Rare diseases manifest differently in different patients			
1	Patients at different stages of progressive diseases			
1	Inappropriate stopping criteria	Outcome measures used in clinical trials or for stopping criteria in real-world studies often do not capture the benefits that patients experience	*"You can't do a one size fits all."*	Patients have different values
2	Clinical outcome measures do not capture treatment benefits that patients experience			
2	Patients have different ideas of what is a meaningful benefit	Patients have different interpretations of what is a meaningful benefit	*"You're dealing with all ages, you're dealing with different response to treatment, different lifestyle…at least in our area I would feel very bad as a patient representative to be the only one saying what I think are the right outcomes."*	
There are weaknesses in the existing health care system that affect the orphan drug lifecycle				
1	Drug pricing is done through secret negotiations	Drug pricing is done through secret negotiations	*"It's true. Secret negotiations with the drug companies…"* *"Why don't they have accountability? Why is there no transparency there? I don't get that."*	Lack of transparency

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			"We never know what the deal is."	
1	Patients and family members are unaware of the system, how decisions are made and opportunities for involvement within it	Patients, families, and physicians are unfamiliar with the decision-making processes in the orphan drug lifecycle	*"I didn't even…I'm a nurse and I didn't even know about this."*	
1	Physicians are unfamiliar with the system and how decisions are made		*"I've learned so much in these two days about these processes but like these three people who would represent whatever…"* *"So they didn't know what the system is."* *"They don't. My doctor, she couldn't tell me *unintelligible* all I know that it's going to be way more expensive than growth hormone."* *"And they simply don't know…so…"*	
1	Belief that other stakeholders want patients in the dark on decision-making processes	Belief that other stakeholders want patients in the dark on decision-making processes	*"Maybe they don't want us to know."* *"No, they don't! They don't want us to know."*	
1	Good follow-up through EMRs	If EMRs could be successfully implemented they would be helpful in providing continuity of care and good data collection	*"Could you imagine the access to records?"* *"You can go into anyone of the hospitals and they can pull up your file, your last week in endocrinology, they can pull up your neurosurgery…"* *"Everything? Could you imagine one system? Fantastic!"* *"You know, done a debate and come up with one and it was mandatory for everybody. Could you imagine the data collection?"*	Challenges in implementing EMRs
1	Continuity of care through EMRs			
1	Unified EMR system			
1	Good data collection through EMRs			
1	Resistance to EMRs from physicians	Challenges of ongoing monitoring include issues around EMRs (e.g. resistance from physicians; ownership disagreements) and the feasibility of establishing registries	***"…a lot of the push back came from clinicians. They perceived it as other people more easily checking on…"*** *"Big brothers watching you."* *"God forbid you're accountable."*	
1	Access to/ownership of EMRs		*"I've never signed a document to say that the*	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			doctor is the only person that can keep my records."	
2	Feasibility of registries is an issue		*"What would be doable because if we propose full blown managed access schemes but all would need patient registries and have validated quality of life indicators and patient input and all that…it's not going to happen."*	
1	Public outcry, particularly through social media, demanding access to drugs that are not necessarily effective	Public outcry is used to obtain access to orphan drugs that are not necessarily effective	*"…no data to support this whatsoever and yet it was, you know, huge public outcry about it."*	Challenges in accessing orphan drugs
2	Orphan drugs are usually more expensive	Orphan drugs are often expensive	*"…the drugs that are coming in as orphan in our experience are all very expensive drugs..."*	
2	Greater uncertainty around clinical effectiveness	There is greater uncertainty around the clinical effectiveness of orphan drugs	*"So you're not quite sure how it's going to be used and what the outcomes will be depending on the way it's used."*	
2	Existing coverage review and decision-making processes do not necessarily involve true disease experts	Existing coverage review and decision-making processes do not necessarily involve true disease experts	*"…a big enhancement is that we're actually going to bring in some people who know something about the disease and the drug and ask them to comment on this… like really?"*	
1	Provincial inequalities in drug access	Provincial inequalities in drug access	*"So this is where I come in and say we've got inequality across Canada."* *"It's awful. It has to be one."*	No national health care system
1	Provinces have their own budget	Provinces have their own budget	*"The problem is the provinces have all their own money."*	
1	Small Canadian drug market	Small Canadian drug market	*"Because we need these companies to bring the drugs to Canada. Like why do you think we only have one treatment right now or one special access? Canada is not a friendly place for them to come to. If they don't have some security around how long they have to recoup that money, why would they come to Canada?"*	Small Canadian drug market
There are greater challenges associated with orphan drug lifecycle				
2	Lack of validated outcome measures	There are a lack of validated outcome measures for rare diseases	*"What would be doable because if we propose full blown managed access schemes but all would need patient registries and have validated quality of life indicators and patient input and all that…it's not going to happen."*	Orphan drug research

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
2	Small sample sizes	Clinical trials on orphan drugs are often limited by small patient sample sizes	*"If we don't have that, if we don't have enough patients to do that, if we can't validate that, does that mean then that we aren't going to get anything?"* *"Finally they came back and said we'd have to have 99 patients. Well we didn't have 99 patients that we're going to enroll."*	
2	Clinical trials are less likely to take place in Canada	Clinical trials do not frequently take place in Canada for orphan drugs	*"Thinking of that from an ultra-rare disease perspective where the clinical trials are not likely to be happening in Canada…"*	
2	Registries are often infeasible	Registries are often infeasible	*"What would be doable because if we propose full blown managed access schemes but all would need patient registries and have validated quality of life indicators and patient input and all that…it's not going to happen."*	
2	The natural histories of rare diseases are often poorly understood	The natural histories of rare diseases are often poorly understood	*"And now, 10 years later we know other patients having that."* *"I was afraid, I was scared of like everything."*	Rare disease research
2	Registries are often infeasible	Registries are often infeasible	*"What would be doable because if we propose full blown managed access schemes but all would need patient registries and have validated quality of life indicators and patient input and all that…it's not going to happen."*	
Best practice – what does an ideal managed access program look like?				
1	Right drug for the right patient	Individualized treatment to identify the right drug for the right patient	*"… does a patient need all 15 of these medications?… It's in my blister pack, I don't know. Right? And it's like…you probably don't actually need it."* *"So for me, and again an obvious fact, that we should be trying it on each individual patient and seeing if it's working or not for them."* *"So that patient should at least try it. So that's what I mean also. It's not just the validity of the test and the other ones who walk less should also be trying it also in case, you*	Goals
2	Appropriate dose			
2	All patients should try			
2	Let all patients try to identify those for whom it will work			
2	Individualized treatment			

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			know…" *"Because a one size decision does not fit all in many of these cases…"*	
1	Avoiding disease progression due to slow access	Early access	*"The failure is that if it causes the patient to have to trial this medication and fail and within that time they lost their kidneys where you could have started them on this drug and they could have saved their kidneys…we don't want that either, right?"*	
2	Right scheme for the right purpose	Program appropriateness	*"Quite frankly, it goes back to what you're saying here, you gotta choose the right scheme though for the right purpose."* *"The scheme has got to be designed for the purpose."* *"There's no hope in hell of getting that. So you set that basis of the study in a way, you're never…and then they abandoned the study after 3 years, 6 years…whatever you want to call it."* *"Nobody is willing to go there so you do have to set schemes up in such a way (1) in hope of getting an answer and (2) that you're going to act on the results in a reasonable kind of way."* *"I like your question…not a stupid question but a smart question…"*	
2	Program appropriateness			
2	Program appropriateness for question at hand			
1	Transparent program	A transparent program that improves the acceptance of decisions by educating patients on the decision-making process	*"It really took the sting out of why I can't get my medication because I understood the process a little more."* *"That was a huge lesson I'm going home with. Has it changed my mind? No, but do I have a much better understanding? Absolutely."*	
1	Improving acceptance of decisions through education on decision-making process			
1, 2	All drugs/diseases to improve system efficiency	While putting all drugs through a MAP may improve system efficiency, prioritizing	*"So if they save a lot of money there, they have a lot more money available for rare*	Drug/disease priorities

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
1	Prioritize certain drugs to make MAPs more manageable	certain drugs will make the introduction of MAPs more manageable and avoid an overwhelming burden/cost of too many MAPs	*disease."* *"I don't really see why we have these exclusions or are even thinking about excluding stuff."* ***"I think just to make it more manageable. To say okay let's try and bite off this piece first."***	
1	Prioritize certain drugs because of the associated burden/cost of MAPs			
1	Life-threatening or chronically debilitating	Drugs that treat life-threatening or chronically debilitating diseases	*"It also has to be a life threatening or chronically debilitating condition."*	
1	Not just prevalence	Criteria beyond prevalence	***"But then there's others, like the Netherlands or Belgium, where it's not just prevalence."***	
1, 2	No alternatives	No legitimate alternatives	*"There might be a disease modifying kind of thing but what if it's really either very expensive also…"* *"…or really hard to adhere to or there's other problems with it."* *"…because technically there's something out there but in real life…if you could use it or…"* *"Okay, so something around those two criteria and figuring out a way to talk about an alternative that is actually a legitimate alternative."* *"That's intolerance. I think we need to say failure or intolerance."* ***"…you can't say that supportive care is the equivalent of having an option."***	
1	No affordable alternative			
1	No manageable alternative			
1	Supportive care is not an alternative			
1	Failure on alternatives			
1	Intolerance to alternatives			
1	No legitimate alternative			
2	New mechanism of action	Innovative drugs	*"Well my first one would be when the drug is somewhat innovative and it works in a different way, either in terms of how it's prescribed."* *"Well in the case that I'm thinking about, it's not a different mechanism but it's a different*	
2	Different half life			

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			half-life."	
2	Expensive orphan drugs	Expensive orphan drugs	*"And that was my question because not all orphan drugs are necessarily expensive so, you know, that's a factor when you think of the burden…it shouldn't be all drugs."* *"If it's a really cheap therapy and it's going to cost more to do an access scheme than it is to basically, you know, give the drug then follow the drug…yeah, why bother?"*	
2	Drugs with greater uncertainties in clinical benefit	Drugs with greater uncertainty in clinical benefit	*"…if it's straightforward, we know what the outcomes are going to be, we know what patients should be on it or at least reasonably…if it's a really cheap therapy and it's going to cost more to do an access scheme than it is to basically, you know, give the drug then follow the drug…yeah, why bother?"*	
1	Patient input on drugs/diseases for MAPs	Patient input is essential to help identify appropriate diseases/drugs for MAPs	*"Proves that patient input is so important."*	
1	Patient input to ensure MAP "makes sense"	MAPs guided by a program-specific committee with 3 patient members who meet a minimum level of experience with the health care system, have a meaningful role on the committee, and are accountable back to the community they represent to avoid bias	***"And then there would have to be for each MAP, or each managed access plan, we'd have to have a way of getting the really, the important, detailed feedback on what actually makes sense or not."***	Program-specific committee
1	Patient membership on program-specific committee		*"So when you have these committees that fall together, there needs to be a stipulation that there's patient representative…representation on that board."* ***"And actually now that I'm thinking about it, do you actually need an overriding group above that? Because I don't actually think you do."***	
1, 2	Need for broad patient representation on committees		*"And then you may need within that, maybe you do want someone who has had a transplant, may you do want someone who has…you know, I think you've gotta be…you can't do a one size fits all."*	
1	Multiple patient representatives on committee with set term		*"What I would suggest is that you would have more than one patient and of course they*	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			would have like a term."	
1	"Real" patients on the committee		*"But when I mention that by saying the consumer, we actually have to specify that it's a patient. Someone who has life dependency on this medication."*	
1	Patient committee member needs to have a certain level of experience with the health care system			
1	"Informed" patient committee member			
1	Patient member is chronic system user		*"That's what I was trying to say, you have to like an informed patient. Someone who can actually talk on behalf or at least understand the situation."* *"And then you also want to be very sure that you have a kind of rotating person who is knowledgeable in the particular drug area or disease area that's under discussion."* *"They just have to be well educated. Self-educated."* *"It's gotta be somebody who is a chronic user of the system so they completely understand how it works."* *"There have to be criteria and that criteria has to be followed for the qualifications of the people who are on it."* *"I don't think there will be a one size fits all, that's why I am saying you have to look at what is under discussion and make sure that ask yourself what are the important criteria that we want to make sure they know."* *"I personally believe you always want somebody who uses the system all the time."*	
1	3 patient committee members		*"Well the first thing is you can never send one patient. All the research shows, actually believe it or not, the best is 3 patients. Not even 2, but 3. So I think we should start by asking for best practice, and we have that but it's to show that that's best practice."*	
1	Patient committee member responsible back to		*"You have to have at least one of those*	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
	community to avoid bias		*patients that's responsible back to the community in some way."* *"…and I prefer all three, has some accountability back to their community. So if we're not happy, you know, if you get in a situation where one person is way off in la-la-land because some drug company sent them on a trip somewhere, they are accountable back to their community. The community can say excuse me, out you go. I think you need that too."*	
1	Avoiding biased patient committee members		*"That's where my concern is and sometimes what I worry about is pharma influence. We want their support, yes we want their support, we want their help, we do want to work with them… but we want to make sure that we have an objective opinion of patients not somebody that's been influenced."*	
1	Meaningful role for committee members to avoid tokenism		*"It's totally tokenism."* *"It's a pat on the head."* *"The patient reps would sit there and say nothing and it was absolute crap."*	
1	Patient committee member selected by patient organizations	Patient committee members selected by patient organizations	*"We all agree that [patient name] go for us and speak on…like do we all, do you think she understands all our needs and all our… everything and she can go on our behalf?"*	
1	Committee meetings open for all patients to attend	Open committee meetings, which all patients and families are permitted to attend	*"I think it should always be open to anybody if they wanted to attend."* *"If I wanted to take the time, to have the option to get there, I would like that option."*	
1	Physician committee member	Physician committee member on program-specific committee	*"Do you also have your physician accompany as another representative?"* *"Well somebody who's in the medical field who understands…"*	
2	Physician committee member who is a disease specialist			

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			"…and I think it was you who first mentioned it in Toronto, is that it's also important…it's also important that patients help to identify their experts because someone had mentioned to me that in a lot of the cases for the CADTH reviews, there really is no true clinical expert representing the actual… who understands disease and on that committee…"	
1	Patient input to ensure MAP "makes sense"	Individual patient input from a broad range of patients to help develop an appropriate MAP	***"And then there would have to be for each MAP, or each managed access plan, we'd have to have a way of getting the really, the important, detailed feedback on what actually makes sense or not."*** *"A temporary portal or whatever, so that this is where you go in and fill out these answers and then that information is directly going to go into, you know, that part. Whether it goes to the patient advocate and they take it, those three patient advocates, or whether it goes straight into the session."* *"I think that there should be a patient group that represents but I think that the patient, in whatever format, deserves a voice."* *"…you can get some more individual input."* *"I think it's really important that the patient is part of all those things."* *"And so do you have to have…you don't have to have a separate process but you do have to I think… is you gotta have enough of a representation of patients that you can get that range of inputs."*	Individual patient input
1	Individual patient input			
1, 2	Need for broad individual patient input			
1	Quick & efficient patient input	Input collected through a quick and efficient process	***"Like, do you think that if they opened up some kind of web portal that you could type that in so that it would be an easy way for government to have that information when***	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			they're trying to set up…because you don't want it to be so burdensome that they take bloody well three months to get the patient input that they need in order to start this. You want it to be quick, right?"	
1	Opportunity for all patients to provide input through written document or video	Accessible ways for patients to provide individual input	*"You could also do it electronically."*	
1, 2	Opportunity to provide input through online survey		*"Yeah, is there an opportunity to have the choice of doing it in person?"*	
1	Opportunity to provide input face-to-face			
1	Accessible ways for patients to provide input		*"Like gather up all the information and it's the one voice?"*	
1	Collect broad individual patient input through patient organizations			
1	Transparent input process	Transparent	*"It's gotta come through transparency. Thinking about the people who are maybe at home with their disease and can't get to meetings, but want to have a voice and if they have a computer and a family member, they could sit beside it and put their answers in. We have this technology right, so that's an example of using it for good."*	
			"So, also…so when this is happening again it comes with transparency, because we don't know when these things happen, right?"	
2	Collaboration with other countries to conduct trials	Collaboration with other countries to conduct trials	*"Thinking of that from an ultra-rare disease perspective where the clinical trials are not likely to be happening in Canada, is it possible to have something, there are trials in the States going on that we know about, so that maybe we could get some Canadian patients matched with a Canadian physician that could be part of the trial in the States."*	International collaboration
			"Working together internationally."	
1	Learning from other countries about MAPs	Learning from other countries about MAPs	*"Have there been any other pilot programs in other countries to find out what was in their managed access systems and which countries has it worked and why can't we follow or adopt one of those systems?"*	

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
1	Collaborating with other countries to educate Canadian physicians on rare diseases	Collaborating with other countries to educate Canadian physicians on rare diseases	*"And so that you get learning in Canada for the physician in a rare disease or ultra-rare disease…"*	
2	Ongoing monitoring with engaged physician	MAPs require ongoing monitoring with an engaged physician and good documentation	*"…where I've had to take myself off the medication and go to a clinic and say, what do I do because the reactions are so bad but then the moment that happened when I call his office and say "can I get an earlier appointment, this is what happened" they try and fit me. If they can't…they still."* *"Part of managed access is to have a documentation process in place for when you're doing these things so that it's captured."*	Ongoing monitoring and registries
2	Ongoing monitoring with good documentation			
2	Collection of qualitative data	Data collection should begin before treatment (i.e. natural history data) and include the qualitative data in addition to clinical outcomes	*"You can actually get some qualitative information at the different stages of the patient journey."* *"Map out for each one… that disease, what are the stages of that patient journey, what are the progressions…"* *"Send it out there widely and ask people to respond to it and grow that database."*	
2	Natural history registries			
1	Good follow-up through EMRs	Using EMRs to consistently follow-up on patients, providing continuity of care and good data collection	*"Could you imagine the access to records?"* *"You can go into anyone of the hospitals and they can pull up your file, your last week in endocrinology, they can pull up your neurosurgery…"* *"Everything? Could you imagine one system? Fantastic!"* *"You know, done a debate and come up with one and it was mandatory for everybody. Could you imagine the data collection?"*	
1	Continuity of care through EMRs			
1	Unified EMR system			
1	Good data collection through EMRs			
2	Collecting meaningful outcome measures	Collect meaningful outcome measures that capture the patients' experiences	*"…ask us what outcomes we're looking for is the first thing and, you know, fairly easy as*	Outcome measures and stopping criteria
2	Outcomes that capture patients' experiences			

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			long as you know who the patients are, it's fairly easy to ask them what they would see as success." *"Here's what we're thinking in terms of outcomes, what do you think?"*	
2	Patient input on meaningful outcome measures	Patient input on meaningful outcome measures and stopping criteria	*"Here's what we're thinking in terms of outcomes, what do you think? What else can you tell us? Because quite frankly if you don't do that, you're going to build this program and at the end of the day everybody is going to say 'well, that kind of sucks, we don't wanna but into that.'"* *"That's where patient input is very important on…so for…reconsidering."* *"Because a one size decision does not fit all in many of these cases…"* *"Ideally the patients will come in at the clinical trial stage, I mean, and that clinical trial input would actually lead over into regulatory approvals."*	
2	Patient input on stopping criteria			
2	Early involvement in the lifecycle to get input on outcome measures			
2	Harms are clear stopping criteria	Harms are clear stopping criteria	*"Yeah, if you get an adverse effect, if you get a harm. Yeah, those may be worth stopping for them."*	
2	Consider other factors (e.g. inappropriate dosing) before stopping	Instead of stopping criteria, decisions to continue on with a therapy should be made through a conversation between physicians and patients	*"The question might be do I need to up the dosage? Do I need to make it more frequent? Do I need to do more in order to get the impact?"* *"I can continue with observation for another period of time. Or I can up the dosage. Or I can add something else. You know, I think we need to be clear, what are the options there?"* *"…like we always talk about, okay this is what it's supposed to do…if it doesn't work after this amount of time, we'll try and up the dose*	
2	Decision points (i.e. a conversation between physician and patient) instead of set stopping criteria			

Table 3-3. Basic, organizing, and global themes identified in the thematic network analysis.

FG	Codes	Basic Themes	Quotes	Organizing Themes
			but we can only go up to this amount of medications and after this point… and we have to try and move on to something else…and these are the types of side-effects and if the side-effects are too much, then I go right back say 'listen, this is too great.'"	
2	Follow-through on results of MAP	Follow-through on the results of the MAP	*"Nobody is willing to go there so you do have to set schemes up in such a way (1) in hope of getting an answer and (2) that you're going to act on the results in a reasonable kind of way."* *"A smart question and you act on the answer."*	

Note: bolded quotes are statements made by the facilitator that the participants strongly agreed with.

Conclusion

This thesis is comprised of 3 papers, beginning with the identification of opportunities for patient, caregiver, and patient organization involvement throughout the orphan drug lifecycle, followed by an examination of how patients and caregivers want to be involved, and finally, an in-depth exploration of one of their priorities for involvement, MAPs.

A scoping review revealed a number of opportunities, both existing and proposed, for patients, caregivers, and patient organizations to become involved in the orphan drug lifecycle. The majority of these opportunities were 'existing opportunities' and described involvement in research. The few proposed opportunities were primarily within regulatory and reimbursement decision-making. Consultation with patients and caregivers identified gaps in the literature, demonstrating a need for greater information sharing on examples of involvement in Canada.

Patients and caregivers displayed an eagerness to be involved in the orphan drug lifecycle but wanted to ensure that their involvement was meaningful and valued by other stakeholders. For patients and caregivers, improving coverage decision-making was a priority. They were particularly interested in MAPs as a means of reducing uncertainty in coverage decision-making while providing patients with quicker access to potentially effective orphan drugs. They recognized the need for prudent decision-making, but also that lack of evidence of effectiveness is not the same as evidence of lack of effectiveness. Therefore, MAPs were viewed as a reasonable way forward.

It was discovered that patient and caregiver interest in MAPs and their willingness to be involved is motivated by 1) lack of trust in decision-makers and physicians to ensure they receive access to effective orphan drugs, 2) desperation to gain access to a potentially effective

drug when they have no alternatives, and 3) hope that access to effective orphan drugs can be improved. As a result, it was their view that, an ideal MAP must contain two essential components: patient involvement and transparency in all aspects of the program.

Finally, the findings of this thesis also revealed several areas for future research. First, more research into the development and mobilization of non-tokenistic mechanisms of allowing patients and caregivers to become meaningfully involved in the lifecycle is needed. While the third paper sought to outline a framework for one opportunity that patients and caregivers identified as a priority (i.e. MAPs), research into the feasibility of the framework and roles for other stakeholders within the program is still required.

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