Developing Recommendations to Guide Future Evidence Generation, Evidence Synthesis, and Knowledge Translation for Rare Diseases

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Dissertation abstract

Introduction: The scarcity of rigorous evidence regarding rare disease therapies contributes to uncertainty for stakeholders who make decisions about the use, prescription, or funding of such therapies. My dissertation objective was to integrate stakeholder perspectives and evidence related to how rare disease therapies are evaluated to better understand drivers of uncertainty in decision making and develop an evaluation framework for future evidence generation, synthesis, and decision support.

Methods: To better understand the perceived challenges in generating robust treatment effectiveness evidence, and describe various methods for mitigating these challenges, I used a meta-narrative literature review. I also conducted focus group interviews with key rare disease stakeholders (patients/caregivers, physicians, and policy advisors) to elicit different perspectives on how evidence is generated, evaluated, and synthesized in the context of health care decision making, both at a personal and population level. Finally, I integrated the focus group findings with a targeted literature review to identify characteristics of rare diseases and their candidate therapies that may warrant special consideration in health technology assessment (HTA) and health care decision making.

Findings: My dissertation data revealed three fundamental challenges in generating robust treatment effectiveness evidence for rare diseases: limitations in recruiting a sufficient sample; inability to account for clinical heterogeneity; and reliance on outcomes with unclear clinical relevance. Several methodological solutions have been proposed to overcome these challenges. In addition, study participants described different perspectives on how they choose to participate in and use research in their roles as health care users, care providers, and policy advisors.

Notably, conventional wisdom that patients/caregivers participate in clinical research studies because of therapeutic misconception was not supported. Finally, focus group and literature review findings identified information that potentially warrants special consideration in future HTA specific to rare diseases, including characteristics of the disease, understanding of causal hypotheses relevant to the therapy, and complexities of cost-effectiveness given the high price of many rare disease therapies.

Discussion: Together, the findings from this dissertation support an evaluation framework with eight key principles that aim to mitigate important aspects of uncertainty from various stakeholder perspectives and promote evidence-informed decision making about rare disease therapies.

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In closing, I would like to dedicate this dissertation to my dad. Even though he is not here to see me reach this milestone, I know that he would be beaming with pride.

Citations for published manuscripts

Chapter 2

Tingley K, Coyle D, Graham ID, Sikora L, Chakraborty P, Wilson K, Mitchell JJ, Sockler-Ipsiroglu S, Potter BK, in collaboration with the Canadian Inherited Metabolic Diseases Research Network. Using a meta-narrative literature review and focus groups with key stakeholders to identify perceived challenges and solutions for generating robust evidence on the effectiveness of treatments for rare diseases. Orphanet J Rare Dis. 2018;13:104.

Chapter 3

Tingley K, Coyle D, Graham ID, Chakraborty P, Wilson K, and Potter BK, in collaboration with the Canadian Inherited Metabolic Diseases Research Network. Stakeholder perspectives on clinical research related to therapies for rare diseases: Therapeutic misconception and the value of research. Orphanet J Rare Dis. 2021;16:26.

Contribution of authors

Chapter 2: KT led the study design, developed the protocol for the meta-narrative review, developed the interview guide for the focus group interviews, conducted all focus group interviews, conducted all data analysis and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. LS contributed to the design of the meta-narrative review, critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. JJM and SS contributed to the critical review of the findings and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol for the meta-narrative review, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript.

Chapter 3: KT led the study design, developed the interview guide for the focus group interviews, conducted all focus group interviews, conducted all data analysis and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript.

Chapter 4: KT led the study design, developed the interview guide for the focus group interviews, conducted all focus group interviews, the literature review, and all data analyses and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript.

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List of acronyms and abbreviations

6MWT: six-minute walk test

cmRCT: cohort multiple randomized controlled trial

HST: highly specialized technology

HTA: health technology assessment

IKT: integrated knowledge translation

IMD: inherited metabolic disease

KT: knowledge translation

MeSH: medical subject heading

MPS: mucopolysaccharidoses

NICE: The National Institute for Health and Care Excellence

RCT: randomized controlled trial

1 Introduction

Despite their individually low prevalence, collectively, rare diseases represent a significant population health burden and have a substantial impact on our healthcare system [1]. Strengthening healthcare for those with a rare disease, as for those with more common conditions, requires a 'Triple Aim' approach: simultaneous improvement in the patient experience with care and overall health of the population, while managing the cost to our healthcare system [2,3]. Realizing the Triple Aim for rare diseases requires research to support health care decision-makers (patients and their families, health care providers, policy-makers), including the generation and synthesis of high quality evidence to (1) better understand the epidemiology and natural history of these disorders, and (2) support the development and evaluation of new or re-purposed therapies for patients [3]. Over the last 30 years, legislation in many jurisdictions (e.g., Orphan Drug Act in the United States) has provided incentives for industry to develop novel therapies for patients with rare diseases [4,5]. These incentives, coupled with prioritization of rare disease research at an international level [6], have resulted in the rapid emergence of numerous therapies for rare diseases and policy decision makers expect these new therapies to be rigorously evaluated and reviewed to support decisions about their implementation [7]. However, it has been well established that achieving rigorous evaluation of healthcare interventions is challenging in the context of rare diseases [1,8–10]. This dissertation seeks to describe the key challenges associated with both executing and evaluating clinical research for rare disease therapies from multiple stakeholder perspectives, and make suggestions to guide future evidence generation, synthesis, and knowledge translation to help manage scientific, personal, and practical uncertainty in this context. For the purposes of this dissertation, we define 'stakeholder' as a person who has a specific interest in a clinical or health policy

decision regarding a rare disease therapy or the evidence that supports that decision (i.e., patients, family members, clinicians, and health care policy advisors).

1.1 Defining rare diseases

According to a recent analysis of the Orphanet database, a 37-country network that curates epidemiological information related to rare diseases [11], over 5000 rare diseases have been described to-date based on point prevalence estimates ≤5/10,000, not including disorders that are defined by incidence, such as rare cancers, infections, and poisonings [12]. That said, there is no consensus definition of what is considered 'rare' and definitions vary widely among jurisdictions/organizations [13]. For example, some liberally define rare diseases as 150 cases per 100,000 people, while others use a much stricter definition of 1 case per 1,000,000 people [13]. The variability among these definitions contributes to difficulty in developing and applying consistent health policies pertaining to the development, use, and reimbursement of rare disease therapies across and, sometimes, within jurisdictions.

The definition of 'rare' becomes particularly important when considering knowledge user expectations for robust evidence generation that will inform health policy decision making concerning rare disease therapies. A rare disease that has a birth prevalence of 1 in 2000 does not necessarily compromise investigators' ability to conduct high quality research according to conventional standards (e.g., does not preclude recruitment of adequate sample sizes to achieve planned statistical power within clinical studies) [14]. However, conducting robust clinical research becomes increasingly challenging for those diseases whose birth prevalence is much lower [14–16]. With this in mind, it is important to distinguish between rare diseases with such low prevalence that it becomes impractical to conduct clinical research according to conventional standards from those diseases that are simply uncommon [17]. To differentiate between the two,

some have used the term ‘ultra rare’ to define those diseases that have an exceptionally low birth prevalence [13,15,18], thus may require special evidentiary considerations or specific methodological strategies to reduce risk of bias and confounding when evaluating rare disease treatments. For example, the Ontario Drugs for Rare Diseases Working Group uses a birth prevalence of less than 1 case per 150,000 births as a threshold to define whether a particular rare disease and its candidate therapy warrant special attention when reviewing the clinical evidence for reimbursement purposes [17]. Given ongoing inconsistency in defining rare diseases in the literature and among stakeholders, we did not apply a specific definition or a prevalence cut-off to define rarity for the purposes of the research in this dissertation. However, this dissertation focuses primarily on issues and challenges related to clinical evaluation or review of rare disease therapies for rare diseases with particularly low birth prevalence.

1.2 The challenges of evidence generation for rare diseases

Evidence generation regarding both treatment *efficacy* (i.e., performance under ideal/strict conditions) and treatment *effectiveness* (i.e., performance in ‘real world’ conditions) [19] in the context of rare diseases, particularly ultra rare diseases as mentioned above, is often constrained because of the small number of patients available for study [8]. Clinical heterogeneity, an often wide geographic dispersion of patients, lack of validated measures of disease progression, and various resource constraints also contribute to the complexities of studying rare diseases [8,20,21]. These inherent limitations impact researchers’ ability to conduct robust randomized controlled trials (RCTs), the gold standard for determining clinical efficacy [22], and sometimes also preclude large cohort/case-control studies, forcing rare disease researchers to rely on alternative study designs that are more prone to bias (i.e., uncontrolled trials, case series) when studying clinical efficacy/effectiveness [23]. As a result of these limitations, much of the clinical

evidence that exists for many rare and ultra rare diseases falls in the bottom half of the conventional evidence hierarchy [24,25] (i.e., case series, case reports) or is methodologically flawed [23,26]. For example, a systematic review of available evidence for 11 rare disease pharmacotherapies found that case studies represented the largest proportion (140/338; 41%) of study designs used to determine clinical effectiveness of the therapy, while only 7% (14/338) of studies were considered to be double-blind, placebo-controlled RCTs [23]. In response to inherent methodological challenges associated with evaluating rare disease therapies, some authors have suggested the use of innovative methods, such as n-of-1 (single participant) studies to overcome challenges related to sample size and heterogeneity [10]; however, there seems to be limited application of these designs in practice. Given the paucity of high quality evidence for many rare diseases, patients, care providers, and policy advisors are often faced with the difficulty of having to make medical and/or policy recommendations or decisions, particularly those related to treatment effectiveness, in the context of uncertainty [26–28].

1.3 Decision making for rare disease therapies

Decision making regarding rare disease therapies is a complex process that involves many factors that broadly include evidence, stakeholders' beliefs and values, and the institutional and political landscape surrounding the decision (Figure 1-1) [29]. According to Lomas, there is an 'institutional structure for decision making' that involves a variety of *formal* and *informal* actors who have unique perspectives and influences over decision making processes (Figure 1-1) [29]. Formal actors include those who directly participate in decision making (e.g., executives, government officials), while informal actors include those stakeholders, such as patients and family members, clinicians, and policy advisors, who have more of an indirect influence over decision making [29]. Within this model, policy decisions result from the interaction and

interpretation of *information* (i.e., knowledge derived from evidence, anecdote, experience, media) with *values* (i.e., ideologies, beliefs, interests) that are upheld by the various actors involved (Figure 1-1) [29]. In the case of decision making for rare disease therapies, the quality of *information*, particularly the available clinical evidence, is often poor and this can become a dominant point of contention that influences which decisions are made. Furthermore, the interpretation of an evidence base that is not definitive may be more susceptible to being influenced by differing *values* among stakeholders. With uncertainty or a lack of consensus regarding the evidence base, the effectiveness of an intervention becomes more "arguable" and disagreement arises among stakeholders about health care and policy decisions concerning rare disease therapies [30].

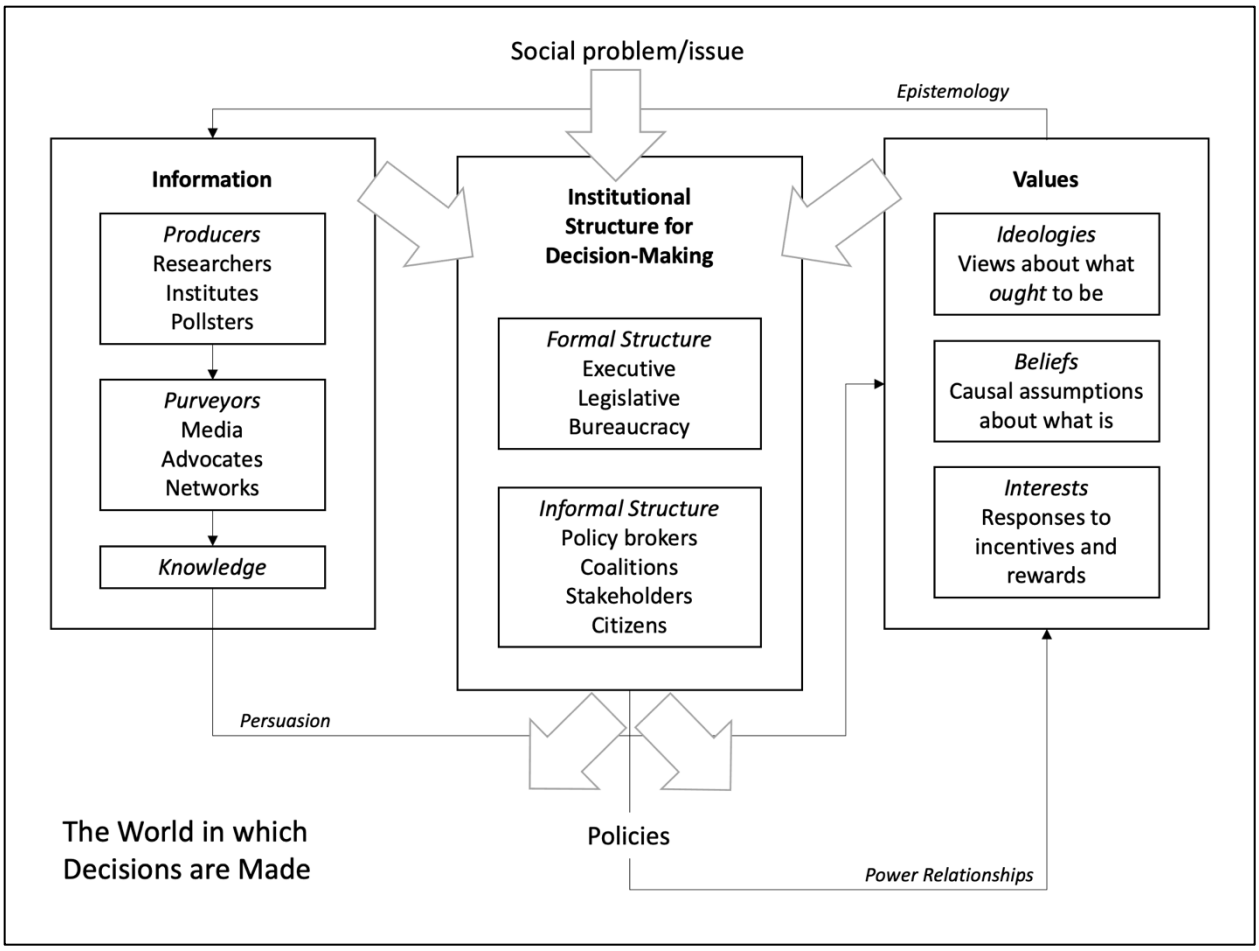

Figure 1-1. Lomas framework for understanding the context of decision making [29].

Disagreements about the evidence base arise from differences in stakeholder views about factors such as what constitutes an appropriate outcome (e.g., are biomarkers acceptable 'final' endpoints?); what is the minimal clinically important difference; and appropriateness of study design, among others [30,31]. For instance, clinicians might cite a case study as evidence supporting their decision to prescribe a novel therapy, but policy advisors are generally unlikely to consider that type of evidence as support for reimbursement of that same novel therapy. Rosenberg-Yunger and colleagues interviewed stakeholders, including patients, manufacturers,

and members of reimbursement recommendation committees, in an effort to better understand their perspectives on priority setting for rare disease therapies in Canada, Australia, and Israel [32]. Results from their qualitative study suggested that committee members placed a high value on robust clinical and cost-effectiveness evidence when making reimbursement decisions, but patients felt that evidence should not necessarily be the deciding factor in a committee's recommendation [32]. These findings highlight that it is essential to take into consideration different stakeholders' needs with respect to evidence generation and synthesis for rare disease therapies that will inform health care decision making both at an individual- and population-level. A key consideration in arriving at a better understanding of the needs of different stakeholders in order to improve decision making is determining the role of uncertainty.

1.4 Types and sources of uncertainty

The difficulty of decision making when there is imprecise, sometimes conflicting, clinical evidence concerning rare disease therapies has long been recognized [8,9,16] but has not been sufficiently dealt with. Currently, little guidance is available that addresses different stakeholder needs for managing uncertainty in context of decision making about rare disease therapies. When developing an acceptable strategy to manage uncertainty, it is first important to characterize the types and sources of uncertainty experienced by various stakeholders involved in health care decision making [33]. Han and colleagues developed an integrative taxonomy that classifies medical-related uncertainty into three broad categories, scientific uncertainty, practical uncertainty, and personal uncertainty [33], all of which warrant consideration within the evidence-based medicine paradigm. *Scientific uncertainty* is data-centred and encompasses issues that are primarily dealt with in clinical evaluative studies (e.g., causal mechanisms and natural history of disease, treatment efficacy and effectiveness) [33]. *Practical uncertainty* is

health system-centred and focuses on uncertainties about the structures and processes of health care (e.g., whether implementation of a therapy is feasible within the current system of care) [33]. Finally, *personal uncertainty* is focused on concerns that are patient-centred, comprising both psychosocial and existential elements related to health care (e.g., how a therapy may impact one's quality of life or personal relationships) [33].

Scientific uncertainty regarding the efficacy and effectiveness of rare disease therapies is a recognized challenge and a clear factor that frames debates about the availability, funding, and use of such therapies. However, aspects of *personal* and *practical uncertainty* are also likely to be experienced and considered by stakeholders, even if less formally, and may be connected to their information needs as well as their values. Thus, it is important to further investigate differing perspectives on the evidence base itself and the contribution that evidence makes, while recognizing that doing so may not lead to consensus about a policy decision (since factors aside from evidence contribute to views about such decisions). For example, demonstration of adequate safety and efficacy is required by regulatory authorities to inform decision making about availability of these rare disease therapies, but patients and families may also be concerned about additional adverse effects/harms (e.g., time away from school to receive infusion therapy at hospital) that may warrant consideration in their own personal health decision making processes. Stakeholder engagement to better understand the drivers behind disagreements (e.g., uncertain information, conflicting values) could improve the quality of decision-making regarding the development, use, and reimbursement of treatments for rare diseases.

1.5 Research objectives

The overall goal of this dissertation was to integrate stakeholder perspectives and evidence related to how rare disease therapies are evaluated to better understand key drivers of uncertainty

in decision making and make suggestions to guide future evidence generation, synthesis, and knowledge translation in order to help manage this uncertainty. Specifically, I aimed to:

i) Investigate the perceived challenges and proposed methodological approaches to research regarding the efficacy and effectiveness of clinical interventions for rare diseases (Chapter 2);

ii) Develop a deeper understanding of why and how patients and families, health care providers, and health policy advisors choose whether to participate in trials or other types of research, and how they use and value research findings to support decision making at both an individual and population level (Chapter 3);

iii) Describe stakeholder perspectives on the challenges associated with evaluating rare disease therapies from a health system perspective, focusing on the characteristics of rare diseases that may warrant special consideration in HTA and health policy decision making (Chapter 4); and,

iv) Provide an evaluation framework that will guide future evidence generation, evidence synthesis, and knowledge translation concerning treatments for rare diseases that address important aspects of uncertainty (scientific, practical, and personal) among different stakeholders in their various roles as patients, family members, health care providers, and policy makers (Chapter 5).

While much of this dissertation focuses on contention around the quality and uncertainty associated with *information* regarding rare disease therapies, I also recognized that *values* upheld by different stakeholders were likely connected to how they prioritized types of uncertainty. Thus, I include discussion of values alongside information throughout this dissertation.

1.6 Organization of dissertation

This manuscript-based thesis contains 3 substantive chapters that have each been formatted as manuscripts for publication. Chapter 2 describes a meta-narrative literature review and qualitative focus group interview study that focused on identifying challenges and proposed methodological solutions for clinical research for interventions for rare diseases. Chapter 3 describes stakeholder perspectives pertaining to participation in research and why and how research findings are used in decision making. Chapter 4 combines qualitative focus group interview results with a targeted literature review to describe characteristics of rare diseases that may warrant special consideration in health policy decision making. Finally, Chapter 5 draws upon the findings from the earlier three chapters and presents an integrated discussion of the key findings and conclusions of the thesis, including an evaluation framework comprising eight principles to guide future evidence generation, synthesis and knowledge translation for rare diseases. Each chapter is introduced by a brief preface specifying its objective(s), the contributions of each co-author, any related appendices, and details for any ethics approvals that were received. Citation details for published articles are also included where applicable.

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2 Using a meta-narrative literature review and focus groups with key stakeholders to identify perceived challenges and solutions for generating robust evidence on the effectiveness of treatments for rare diseases

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2.1 Preface

This published manuscript presents the findings from a meta narrative literature review and focus group interview study that addresses the first aim of my dissertation: to investigate the perceived challenges and proposed methodological approaches to research regarding the efficacy and effectiveness of clinical interventions for rare diseases. KT led the the study design, developed the protocol for the meta-narrative review, developed the interview guide for the focus group interviews, conducted all focus group interviews, conducted all data analysis and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. LS contributed to the design of the meta-narrative review, critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. JJM and SS contributed to the critical review of the findings and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol for the meta-narrative review, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript. All authors have read and approved the final manuscript, which was published in the journal *Orphanet Journal of Rare Diseases* in 2018.

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Ethics approval: Ethics approval for this study was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board, the Ottawa Health Science Research Network Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

2.2 Abstract

Introduction: For many rare diseases, strong analytic study designs for evaluating the efficacy and effectiveness of interventions are challenging to implement because of small, geographically dispersed patient populations and underlying clinical heterogeneity. The objective of this study was to integrate perspectives from published literature and key rare disease stakeholders to better understand the perceived challenges and proposed methodological approaches to research on clinical interventions for rare diseases.

Methods: We used a meta-narrative literature review and focus groups with key rare disease stakeholders to better understand the perceived challenges in generating and synthesizing treatment effectiveness evidence, and to describe various research methods for mitigating these identified challenges. Data from both components of this study were synthesized narratively according to research paradigms that emerged from our data.

Results: Results from our meta-narrative literature review and focus group interviews revealed three fundamental challenges in generating robust treatment effectiveness evidence for rare diseases: i) limitations in recruiting a sufficient sample size to achieve planned statistical power; ii) inability to account for clinical heterogeneity and assess treatment effects across a clinical spectrum; and iii) reliance on short-term, surrogate outcomes whose clinical relevance is often unclear. We mapped these challenges and associated solutions to three interrelated research paradigms: i) explanatory evidence generation; ii) comparative effectiveness/pragmatic evidence generation; and iii) patient-oriented evidence generation. Within each research paradigm, numerous criticisms and potential solutions have been described with respect to overcoming these challenges from a research study design perspective.

Conclusions: Several methodological approaches to overcome challenges related to explanatory evidence generation have been suggested. Over time, there has been increased recognition in the literature of the importance of pragmatic and patient-oriented evidence generation for the evaluation of rare disease therapies.

2.3 Background

For many rare diseases, strong analytic study designs for evaluating the *efficacy* (does intervention X work under *ideal conditions*?) and *effectiveness* (does intervention X work in *real-world practice*?) [1] of interventions are challenging to implement because of small, geographically dispersed patient populations and characteristically high clinical heterogeneity [2]. A poor understanding of natural history for many rare diseases, scarcity of validated measures of disease progression, and various financial constraints (e.g., limited availability of research funding, high costs of trials for rare diseases) also add to the complexity of evaluating treatments for rare diseases [2–4]. As a result of these limitations, it is often not feasible to conduct conventional randomized controlled trials (RCTs), the gold standard for determining treatment efficacy [5]. Thus, rare disease researchers must often rely on other study designs that are more prone to bias when evaluating interventions, such as open label or uncontrolled trials, observational studies, and case reports. [6, 7]

The evidence that exists for clinical interventions for rare diseases therefore typically falls in the bottom half of the traditional evidence hierarchy [7, 8] and is methodologically flawed [6, 9]. For example, a recent systematic review of available evidence for 11 orphan medicines found that case studies represented the largest proportion (140/338; 41%) of study designs used to determine clinical effectiveness, while only 7% (14/338) of studies were double-blind, placebo-controlled RCTs [6]. Studies that have reviewed the evidence for clinical interventions for rare diseases that is submitted to regulatory agencies in support of marketing authorization have also found limited RCT evidence [10–12]. A recent analysis of ClinicalTrials.gov comparing characteristics of completed or on-going trials for rare and non-rare disease treatments demonstrated that trials for rare disease therapies are likely to enroll fewer participants, be single

arm, non-randomized, and open label [13], all of which can compromise the internal validity of a study.

The lack of high quality evidence and the typically high cost of clinical interventions for rare diseases commonly result in debates about the efficacy and effectiveness of these interventions among stakeholders [14, 15]. Disagreements about the evidence arise from differing views about the methodological rigour of the study design; what constitutes a meaningful outcome; and the minimal clinically important difference for a relevant outcome [16]. Disputes among stakeholders are further fueled by differing values and the institutional/political landscape surrounding decision-making processes about interventions for rare diseases [16, 17]. As a result, health policy recommendations, such as those concerning reimbursement for some clinical interventions for rare diseases, are variable across jurisdictions [18, 19].

The objective of this study was to integrate perspectives from published literature and key rare disease stakeholders to better understand the challenges and approaches to research for clinical interventions for rare diseases. More specifically, we sought to:

(1) identify perceived challenges in generating robust evidence for establishing treatment efficacy and effectiveness in the context of rare diseases; and
(2) describe various clinical evaluative research methods that have been suggested for mitigating the identified challenges in generating robust evidence, focusing on the perceived strengths and limitations specific to each.

2.4 Methods

2.4.1 Meta-narrative literature review

2.4.1.1 Meta-narrative approach

An initial scoping of the literature regarding our research topic revealed diverse perspectives on generating evidence for efficacy and effectiveness of treatments for rare diseases. We therefore chose to use an adaptation of the meta-narrative approach developed by Greenhalgh and colleagues specifically for systematically reviewing the literature on complex topics that have been conceptualized and studied differently among researchers [20]. Meta-narrative reviews encompass six main principles: (1) *pragmatism*, the included information should be driven by usefulness to the intended audience; (2) *pluralism*, the topic should be considered from multiple perspectives; (3) *historicity*, the included information should be presented according to its development over time; (4) *contestation*, any conflicting information should be used to generate higher-order insights; (5) *reflexivity*, there should be continual reflection on the review findings; and (6) *peer review*, the review findings should be presented to an external audience for feedback [20, 21]. Below we describe the methods for each phase of our review separately and sequentially, while recognizing that the phases overlap with each other [20].

2.4.1.2 Planning and search phases

Our interdisciplinary study team has expertise in epidemiology, health services research, health economics, and information science. We held a series of meetings to discuss the emerging findings from the literature and provide direction as the project progressed. We also agreed that the outputs from this review would include a summary of current knowledge across research paradigms on the topic of establishing efficacy or effectiveness for clinical interventions for rare diseases, and a framework to guide future evidence generation and syntheses in this field (see Chapter 5).

We used an initial exploratory search (snowball sampling and citation-searching) to identify important sources of information relevant to our study objectives, and in turn, developed a

formal search strategy comprised of Medical Subject Heading (MeSH) terms and keywords. Our search strategy was developed iteratively (by LS and KT) and was not meant to be exhaustive, but was designed to identify *key* sources of scholarly information. Three electronic databases were searched: MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to June 21, 2017), EMBASE (Embase Classic + Embase 1947 to June 21, 2017), and PubMed. Search strategies for each database can be found in Supplemental File 1. We also scanned reference lists from included studies for any additional citations.

All citations returned from the searches were reviewed using a two-stage approach. During the first stage, one member of the study team (KT) scanned titles and abstracts of all citations to identify potentially relevant records. For the second stage, full-text articles were retrieved for all citations identified during stage one, and one member of the study team (KT) reviewed the articles to determine final inclusion/exclusion. Given that the purpose of the search and screening phases was to identify *key* sources of information rather than to be exhaustive, and that the meta-narrative approach is reflexive by design, having only one member of the team screen citations and papers for eligibility was deemed appropriate. To help mitigate bias in selecting studies, we established the following inclusion criteria: (i) relevant to rare diseases or orphan medicines; and (ii) describes methods used to overcome challenges for establishing efficacy or effectiveness of clinical interventions for rare diseases. We did not limit inclusion to primary studies (i.e., review articles were included), but did exclude letters to the editor, conference abstracts, and commentaries. We also did not limit according to specific diseases or disease groups. Finally, given language constraints within the team, we excluded all articles not written in English.

2.4.1.3 Mapping, appraisal and synthesis phases

A fundamental aspect of the meta-narrative approach is constructing a story about how research on a given topic has unfolded over time [20, 21]. To this end, we abstracted information from each report to identify key people, events, research questions, conceptual and theoretical issues, research findings, and areas of debate or disagreement. Data abstracted from each study included (if applicable): bibliographic characteristics (publication date, author(s), geographical location), sponsorship/declared conflicts of interest, and report characteristics (type of study, disease(s) of interest, study objectives, main findings/conclusions, etc.). Additionally, we used the following guiding questions to abstract further information to describe the different perspectives:

1. What study designs have been described for studying the efficacy or effectiveness of treatments for rare diseases?
2. What strengths, weaknesses, and risks of bias are reported as important for each study design?
3. What are the described tradeoffs in risk of bias among the study designs?
4. Is the choice of outcome(s) reported as an influence on the quality of evidence?

Data were abstracted from each report by a single reviewer (KT) and emerging findings were reviewed and discussed at team meetings. Bibliographic and report characteristics were synthesized descriptively, and all other study findings were synthesized narratively.

2.4.2 Focus group interviews with stakeholders

2.4.2.1 Design, sampling, recruitment, and participants

In parallel with the meta-narrative review, we conducted focus group interviews with three stakeholder groups to better understand their perspectives on generating evidence for clinical

interventions for rare diseases. We recruited a convenience sample from three groups who could speak knowledgeably (based on formal knowledge or experience) about evidence for interventions for rare diseases, including: physicians, policy advisors, and rare disease patients or caregivers. To facilitate the focus group discussions with physicians and patients/caregivers, we chose rare inherited metabolic diseases as a case study. For the patients/caregivers, we further narrowed the selection to mucopolysaccharidoses (MPS), a group of rare metabolic conditions; this restriction supported an in-person discussion with patients/caregivers as we could meet with that group as part of an annual event (described below). We sought between five and eight participants per focus group, based on standard focus group interview methodology [22]. Individuals were eligible to participate if they had experience with the care of those diagnosed with a rare inherited metabolic disease (metabolic physicians), if they had experience in evidence review activities that result in recommendations being made about the development, use, and/or reimbursement of interventions for rare diseases (policy advisors) or if they were adults diagnosed with MPS or a related disease, or were the caregiver (i.e., parent/guardian) of someone diagnosed with MPS or a related disease.

Recruitment invitations were distributed by email to physician members of the Garrod Association (a professional association whose members are involved in caring for patients with inherited metabolic diseases), to policy advisors by a member of their professional network (using publicly available contact information), and to patients/caregivers attending the Canadian MPS Society's 2017 Annual Family Meeting. Individuals interested in participating were instructed to contact a member of the research team (KT), and eligible respondents were asked to provide signed, informed consent to participate in the study. Focus group interviews were conducted by telephone with the physicians and policy advisors, and in-person with the

patients/caregivers in conjunction with the Canadian MPS Society's 2017 Annual Family Meeting held in Montreal, QC, Canada. The study protocol was approved by the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario Research Ethics Board (physicians and policy advisors), and the University of Ottawa Health Sciences and Sciences Research Ethics Board (patients/caregivers).

2.4.2.2 Data collection

Focus group interviews were conducted by a single member of the study team (KT) using a semi-structured interview guide and were attended by a second member of the team as an observer (BKP or JJM). The interview guide was tailored to the specific stakeholder group. The interview guide addressed general perspectives on the challenges of rare disease research, and more specific topics including generation and synthesis of evidence to establish treatment efficacy or effectiveness, and outcomes used in clinical evaluative studies. All interviews were audio-recorded with participants' consent and subsequently transcribed.

2.4.2.3 Data analysis

Each focus group transcript was analyzed using a qualitative descriptive approach that is aimed at *"obtaining straight and largely unadorned (i.e., minimally theorized or otherwise transformed or spun) answers to questions of special relevance to practitioners and policy makers"* [23]. Four members of the study team (KT, BP, DC, IG) met to identify the key concepts and themes that were present in the focus group data. These concepts/themes were organized into a coding system that was applied by one study team member (KT) using NVivo 10 Software (QSR International Pty Ltd.) and reviewed by a second member (BP) for credibility and trustworthiness [24].

2.5 Results

2.5.1 Search & screening results

Electronic database searches returned 2871 records after removal of duplicates, of which 161 records were identified as potentially relevant based on the title and abstract scan. An additional 14 titles were identified as potentially relevant from scanning reference lists of included studies. Full text articles were successfully obtained for 172/175 records. Of the 172 full-text articles reviewed, 60 articles were included in this review (Figure 2-1) [25].

2.5.2 Descriptive study characteristics

Of the 60 articles we reviewed, 57 (95%) were published after 2000 (Table 2-1; Figure 2-2). Based on the location of the corresponding author address, 27/60 articles (45%) were written by authors from the United States, 8 (13%) from authors in Canada, 5 (8%) from authors in the United Kingdom, and the remaining articles were written by authors across Europe and Australia (Table 2-1). Sixteen (27%) articles explicitly reported that their study was sponsored by industry or had some affiliation with industry, while conflicts of interest/study sponsorship were not explicitly reported for a further 14 (23%). Over half of the included studies (33/60; 55%) reported on rare diseases in general, while the remaining articles focused on a specific disease or group of diseases. A majority of the articles included were review articles of research methods used to evaluate efficacy or effectiveness of interventions for rare diseases (39/60; 65%); however, 28% (17/60) described the application of a specific research method in the rare disease context (Table 2-1). While most of the articles reviewing methods were focused on rare diseases generally (26/39, 67%), many of the applied studies were specific to single diseases (13/17, 76%). A list of the included articles can be found in Supplemental File 2.

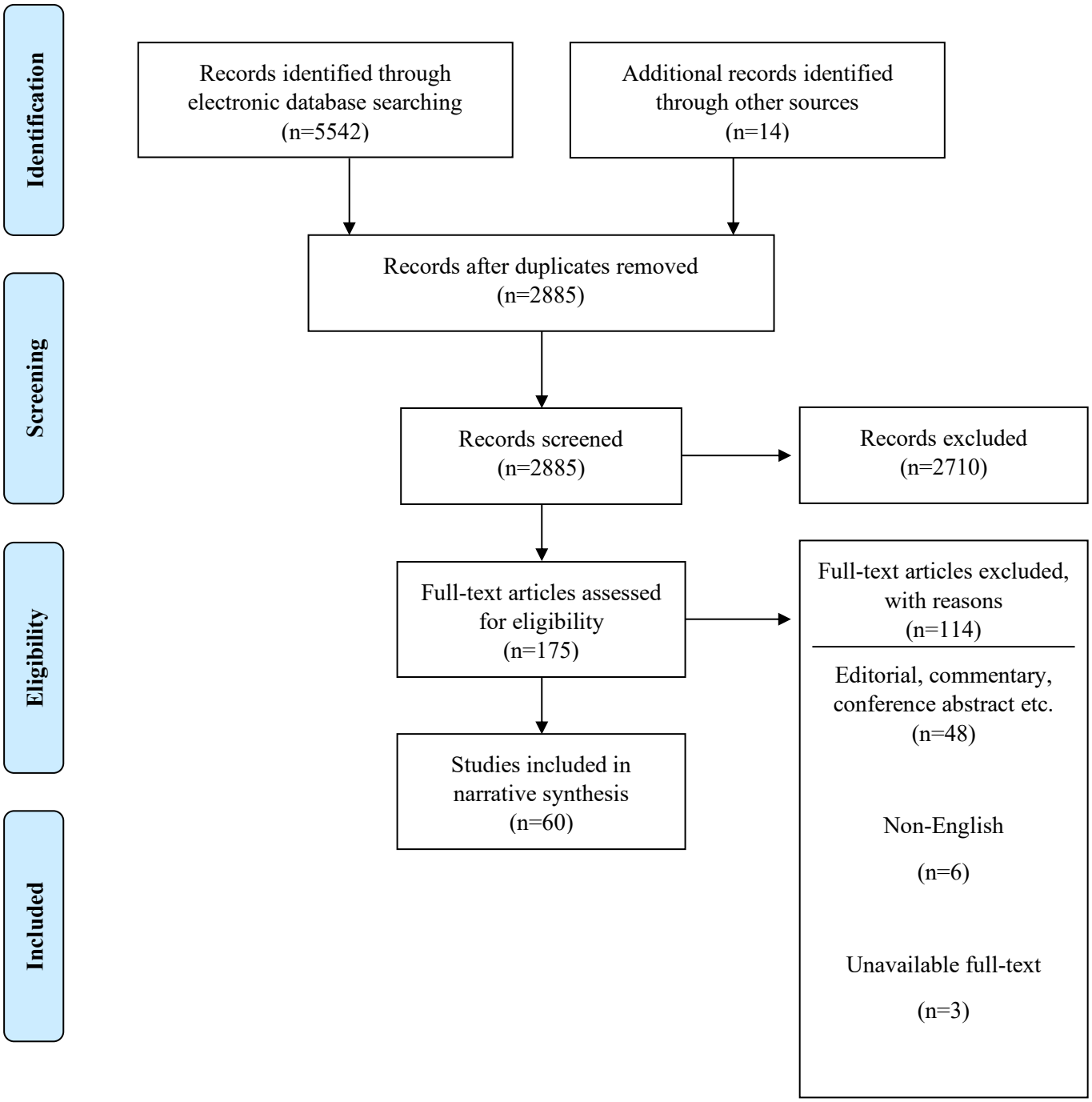

Figure 2-1. PRISMA flow diagram outlining results from search and screening process. (Adapted from: Liberati et al. 2009) [25]

Table 2-1. Descriptive characteristics of included studies (n=60).

Study characteristic	Number of studies (%)
Year of publication	
1990-1994	1 (2)
1995-1999	2 (3)
2000-2004	3 (5)
2005-2009	7 (12)
2010-2014	39 (65)
2015-present (June 21, 2017)	8 (13)
Country (corresponding author address)	
United States	27 (45)
United Kingdom	5 (8)
Canada	8 (13)
France	4 (7)
The Netherlands	6 (10)
Germany	3 (5)
Italy	4 (7)
Belgium	1 (2)
Ireland	1 (2)
Australia	1 (2)
Sponsorship	
Industry affiliations	16 (27)
None (no conflicts of interest declared)	24 (40)
Other (e.g., government funding)	6 (10)
Not explicitly reported	14 (23)
Disease/disease group of focus	
Rare diseases in general	33 (55)
Disease groups:	
Inherited metabolic diseases	2 (3)
Lysosomal storage disorders	3 (5)
Pediatric rheumatic diseases	1 (2)
Rare lung diseases	2 (3)
Rare neonatal diseases	1 (2)
Rare neurodegenerative diseases	1 (2)
Rare renal diseases	1 (2)
Individual disease(s):	
Alpha1-antitrypsin deficiency & pulmonary alveolar proteinosis	1 (2)
Batten Disease	1 (2)

Childhood polyarteritis nodosa	2 (3)
Duchenne muscular dystrophy	1 (2)
Familial hypercholesterolemia	1 (2)
Familial Mediterranean fever	1 (2)
Gaucher disease	1 (2)
Hemophilia A	1 (2)
Late-onset Pompe disease	1 (2)
Non-dystrophic mytonia	1 (2)
Pediatric multiple sclerosis & Creutzfeldt-Jakob disease	1 (2)
Primary sclerosing cholangitis	1 (2)
Scleroderma	2 (3)
Vasculitis (rare form)	1 (2)
Types of studies	
Review article of multiple research methods	28 (47)
Review article of a single research method	11 (18)
Application/case example of research method	17 (28)
Key article that operationalized steps for the research method	3 (5)
Other	1 (2)
Research paradigm discussed*	
Explanatory evidence generation	35 (58)
Comparative effectiveness/pragmatic evidence generation	30 (50)
Patient-oriented evidence generation	15 (25)

*not mutually exclusive as some studies discussed more than one research paradigm

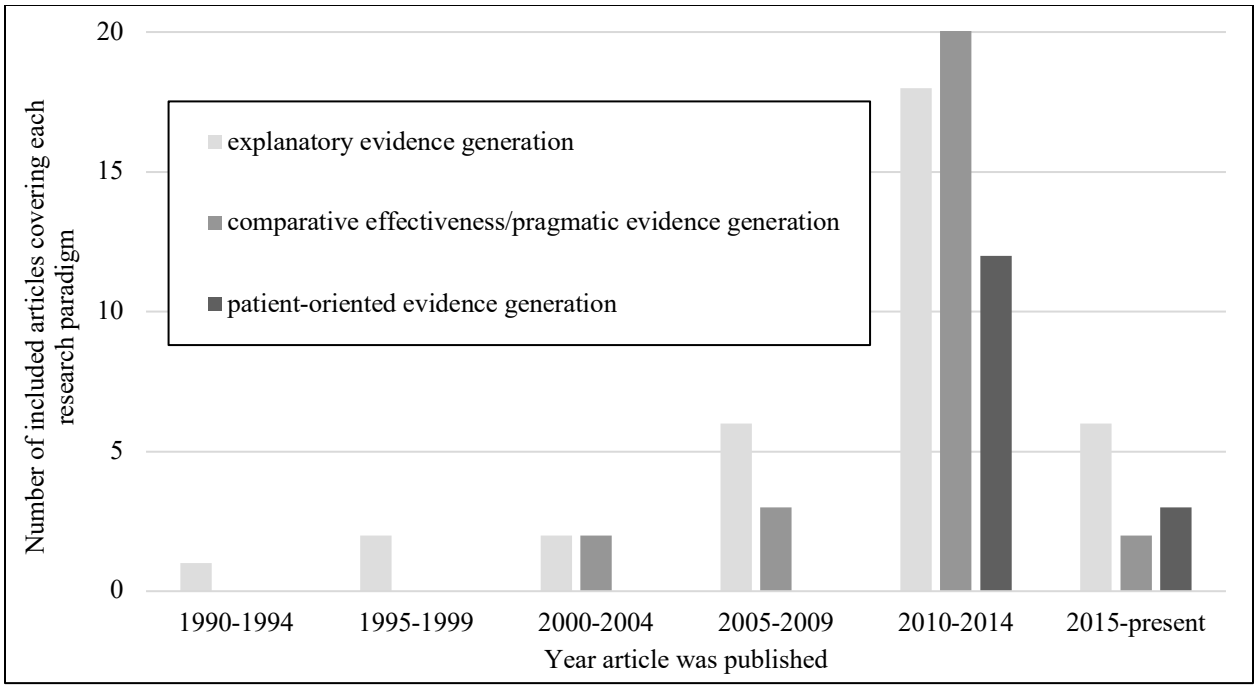

Figure 2-2. Research paradigms discussed by year of publication (note: research paradigms are not mutually exclusive). Note: the last time period only includes 2.5 years (2015-June 21, 2017) rather than a full 5 years, which contributes to the decline in the number of articles compared to 2010-2014.

2.5.3 Description of focus group participants

We held three focus group interviews with 13 participants in total (physicians n=6; policy advisors n=3; patients/caregivers n=4). Across the three groups there were 9 women and 4 men. Participants were from 5 provinces in Canada: British Columbia, Alberta, Ontario, Quebec, and Newfoundland and Labrador.

2.5.4 Research paradigms in establishing efficacy or effectiveness of clinical interventions for rare diseases

Three overlapping research paradigms through which stakeholders view the challenges and prioritize potential solutions for establishing efficacy or effectiveness of clinical interventions for rare diseases emerged from our data: (1) explanatory evidence generation, (2) comparative effectiveness/pragmatic evidence generation, and (3) patient-oriented evidence generation. The findings from our literature review and focus group interviews are discussed according to each of these paradigms. While each research paradigm is discussed separately, they are not mutually exclusive. A summary of perspectives across the three research paradigms is provided in Table 2-2.

Table 2-2. Summary of findings according to each research paradigm.

Key research paradigms	Main perspectives from the literature	Main perspectives from focus group participants
Explanatory evidence generation	- internal validity for conventional RCTs in rare diseases is threatened because of the small and often heterogeneous patient population - with small numbers of participants, there is potential for unbalanced confounders across groups despite randomization, and poor statistical power to detect treatment effects - modifications to conventional RCTs have been proposed to help maximize internal validity (e.g., adaptive trials, application of Bayesian statistics) - lack of patient/family/clinician acceptance to the possibility of being randomized to a placebo group, study designs that make participation more appealing by maximizing time spent on- or guaranteeing provision of- the new treatment have been suggested (e.g., crossover trials, N-of-1 studies)	- challenging to evaluate evidence with small sample sizes and short duration of follow-up *"I do find it quite difficult when the clinical trials are very short, very small numbers, and the endpoints are something like the six minute walk test in regards to really being confident that that is going to be an effective treatment for the patients that I'm seeing." – Physician 4* *"Well the ex-[profession] in me looks at things like, you know, the size of the study, well MPS is [laughter around the table], okay that's not going to happen. You know, so you have to, it's hard when you're looking at MPS because the things that you would normally look for in a good study aren't going to be there because of the size of the sample…" – Patient/caregiver 3*
Comparative effectiveness/pragmatic evidence generation	- external validity is threatened in rare disease research by the desire to enroll homogenous groups of participants for explanatory trials (patient population is often inherently heterogeneous) - there are also substantial differences between trial protocols and real-world clinical practice, reducing the external validity of some studies (i.e., need to account for co-interventions, less frequent follow-up visits) - several study designs have been suggested that may compromise internal validity to some extent in order to address real-world effectiveness (e.g., pragmatic trials, registry studies, hybrid study designs)	- need to address heterogeneity in treatment effect across clinical spectrum *"…the way that the trials are designed, very sub, select populations with the actual disease of concern, which is already a narrow disease as it is. It makes it very difficult for us to know where and when these therapies are going to work. And so, when we're talking about rare diseases, it really has to be linked to not just research, but effectiveness research about natural history and epidemiology. And given the wide degree of heterogeneity with the diseases that we're dealing with, we're going into this with a huge degree of uncertainty about whether or not there really is any evidence to support that these therapies are going to work." – Policy advisor 2*
Patient-oriented evidence generation	- explanatory study designs tend to rely on short-term, surrogate outcomes that are not necessarily clinically meaningful or relevant to patients and/or families - important to engage with patients and/or families throughout the research process to define important outcomes and determine minimal clinically important difference - there has been a shift/push to improve use of more patient-oriented outcomes in clinical evaluative research for rare diseases (e.g., quality of life measures, activities of daily living) - more difficult to use patient-oriented outcomes because tools have not been standardized in rare disease populations	- very important to measure outcomes that are clinically relevant *"For me I think one of the big issues is the outcome measures that we're trying to document. For instance, with the lysosomal storage diseases, what is the relevance of a 6 minute walk test? What is the clinical relevance of this type of test?" – Physician 5* *"…because yes, scientific research is important too, but it's this push-pull dichotomy between the happiness, the living life, just the simple moments, you know, going outside, sitting in the sun, that type of, going down to the beach, those things need to be equally measured… – Patient/caregiver 4*

2.5.4.1 Explanatory evidence generation

Much of the discussion in the literature and amongst focus group participants concerning evaluative clinical research in rare diseases centered on problems associated with the inherent small numbers of patients available for study and adequate recruitment for conventional RCTs, long considered the gold standard explanatory design with a low risk of bias [5].

"I do find it quite difficult when the clinical trials are very short, very small numbers, and the endpoints are something like the six minute walk test in regards to really being confident that that is going to be an effective treatment for the patients that I'm seeing." – Physician 4

"For common diseases, there's no reason for not doing a randomized controlled trial. I mean, that's one of the big points in the paper that we published a few years ago was that in order to be called rare, you should not have enough patients to confidently determine whether a treatment is efficacious or not." – Policy Advisor 1

"Well the ex-[profession] in me looks at things like, you know, the size of the study, well MPS is [laughter around the table], okay that's not going to happen. You know, so you have to, it's hard when you're looking at MPS because the things that you would normally look for in a good study aren't going to be there because of the size of the sample…" – Patient/caregiver 3

This paradigm was discussed by more than half (35/60, 58%) of the studies we reviewed, and was also the first that emerged in the literature in 1992 (Figure 2-2). Most of the reports that discussed this paradigm were methodological review articles that focused on rare diseases in general or a group of rare diseases (24/35, 68%), rather than a single specific rare disease. The first author to highlight the challenges associated with fewer participants for clinical studies was Haffner, who took the perspective of a regulatory agency responsible for reviewing the safety and efficacy of orphan medicines [26, 27]. Haffner argued that orphan medicines should be as well-scrutinized as medicines for more common diseases but recognized that conventional RCTs are not always feasible due to small numbers [26, 27]. Some alternative research methods or

design features for demonstrating safety and efficacy that may be acceptable to a regulatory agency were suggested, including the use of multicenter studies, crossover trials, randomized withdrawal trials, open label studies, open protocol studies, and incorporating historical controls or composite or surrogate endpoints [26, 27]. The discussion concerning explanatory evidence generation for clinical interventions for rare diseases continued from these early publications to the present day (Figure 2-2). Others elaborated on the issues brought forth by Haffner and offered more suggestions to overcome the challenges related to small numbers and limited feasibility of conventional RCTs, while preserving internal validity and protecting against bias and confounding [2, 4, 14, 28–57].

While participants in our focus groups did highlight the limited feasibility of conventional RCTs because of small sample sizes, there was little emphasis in the focus group discussions on specific strategies that might be used to overcome this challenge. Thus, most of the results presented under the paradigm of explanatory evidence generation are derived from our meta-narrative literature review.

In general, the research methods or study design features that have been proposed in the literature to address small numbers while retaining internal validity and thus an explanatory focus have concentrated on three overarching strategies: (i) enhancing statistical efficiency at the design phase, so that fewer participants are required to conduct a robust evaluation; (ii) using Bayesian rather than frequentist analysis methods, also to reduce the number of participants required; and (iii) making participation more appealing to patients and families by maximizing time spent on the active treatment. Several methodological reviews were published on this topic in the last decade [34, 39, 42, 43, 45, 48, 49], some of which provided more detail about the

methods described below; here we focus on the most commonly suggested research designs that focus on minimizing bias to maximize internal validity and explanatory power.

Strategies that have been proposed for enhancing statistical efficiency at the design phase for clinical evaluative studies of rare disease treatments include factorial trials and adaptive designs. Factorial trials are designed to test multiple treatments simultaneously using the same study population, thus reducing the overall number of participants needed [2, 30, 36, 42, 43, 49, 52, 55]. For example, in a 2x2 factorial design participants are randomized to either treatment A or control group A, and then randomized again to treatment B or control group B, which effectively reduces the sample size needed to test these two treatments by 50% because the same participants are being randomized [43]. However, authors have pointed out that this reduction in sample size only holds assuming there is no interaction between the treatments being administered concurrently; otherwise, statistical efficiency is lost [43]. Adaptive designs allow flexibility in trial procedures such that changes ("adaptations") based on interim analyses can be made after trial initiation without undermining the validity of the trial [32]. Two commonly discussed adaptive trial strategies are response-adaptive randomization and group sequential design [32, 34, 39, 43, 49, 55]. Response-adaptive randomization involves modifying treatment assignment probabilities with the accrual of data so that the number of participants randomized to the best-performing treatment arm ("play-the-winner") is increased and overall sample size is decreased [32]. Group sequential designs do not have a predetermined sample size, rather, small groups of participants are recruited over several phases and data are analyzed at the end of each phase to assess safety, futility, efficacy, or a combination of these until enough data have been accrued to justify study termination [32, 34]. Simulation studies have shown that sequential design approaches may, but do not always, reduce the eventual sample size compared to fixed

sample size designs [38, 55, 58]. While adaptive trial strategies are often reported as a means to enhance statistical efficiency, some authors have questioned their usefulness based on the paucity of published practical application in the context of rare diseases [32, 43].

For conventional RCTs with small sample sizes, achieving sufficient statistical power to detect differences in treatment effects, especially when the treatment effect is expected to be modest, is challenging [28]. Several authors have argued (as early as 1995) that Bayesian techniques would be better suited in this context relative to standard frequentist approaches to analysis, because a Bayesian analysis is not as compromised by small numbers and offers more direct conclusions [28, 35, 37, 44, 47, 48, 51, 53, 54]. In such approaches, previously collected data or expert opinion is used to generate a prior probability (posterior) distribution for the unknown treatment effect, and Bayes theorem is applied as new data are accumulated to update the posterior distribution for the new treatment and inform clinical practice [28, 51]. As an example, Johnson and colleagues reanalyzed data from an RCT of methotrexate versus placebo in 73 patients with scleroderma, and demonstrated that methotrexate had more favorable odds of being beneficial for patients when a Bayesian approach was applied compared to the non-statistically significant findings obtained through a frequentist approach [35]. While several authors argued that Bayesian statistics offer an alternative approach to the analysis of small numbers of participants, some criticized the subjectivity in establishing prior distributions and were skeptical of the acceptance of results obtained using Bayesian statistics at the regulatory level [37, 39, 48, 51].

It was reported in the literature and in our focus group discussions that there can be a lack of patient/family/clinician acceptance of the possibility of being randomized to a control group, particularly for placebo-controlled studies of treatments for rare diseases where few treatment alternatives exist. Therefore, study designs that make participation more appealing by

maximizing time spent on- or guaranteeing provision of- the active treatment have been suggested [4, 29, 30, 33, 36, 39, 41–45, 47–50, 52, 54].

> *"I agree with [name]'s comments that it's hard to have a placebo-controlled trial. I mean, certainly there has been trials to try to do that. …however, they're very short and really with these, like almost, like even to encounter, to have families agreeable to participate being a placebo for long-term, I think would be very difficult. I think for the short-term, for a few months or a year, families are agreeable, but after that I don't think they would be agreeable."* – Physician 2

The randomized placebo-phase design has the same design features of a conventional RCT, except that the time from enrollment in the study to the start of the experimental treatment is randomized for all participants [29]. All participants eventually receive the experimental treatment, and effectiveness is determined based on whether a response is observed sooner among those that received the treatment earlier [29]. Similarly, randomized withdrawal, early escape, and stepped wedge trials reduce time spent in a control arm or ensure that all participants eventually receive the intervention being studied, and have been proposed as alternative approaches to evaluate clinical interventions for rare diseases [43]. Crossover trials and n-of-1 trials also guarantee that participants receive the active treatment, but are different than conventional RCTs in that the treatment sequence is randomized with a washout period in between treatment regimens, such that each participant acts as his or her own control [2, 30, 39, 44, 55]. As some authors reported, n-of-1 trials are often embedded in clinical practice to help healthcare providers determine the best treatments for their patients [2, 30, 39]. While several authors have examined the advantages of crossover and n-of-1 trials, others have discussed the risk of carryover and period effects between phases, and have argued that these designs are

generally not suitable for diseases that have an unstable disease course or for interventions that are not fast-acting with reversible effects [2, 14, 36, 39, 42, 47, 49, 55].

The three overarching strategies and associated research methods discussed above are not mutually exclusive, rather there is significant overlap among them in the literature. For example, in addition to being an attractive option for participants, crossover trials are also considered statistically efficient and reduce the number of participants needed because each participant acts as his or her own control [2, 14, 36, 39, 42, 43, 47, 49]. Huang and colleagues have suggested that statistical efficiency could be further enhanced in crossover trials by allowing participants to "escape early" (reducing participant exposure to ineffective treatment by allowing them to "escape" either to open therapy or, while still blinded, to the other treatment arm according to pre-specified criteria) [44]. Similarly, authors have stated that trials using adaptive randomization can be attractive to participants because the likelihood of being randomized to the less effective treatment arm is reduced over time [32, 34, 39, 43, 49, 55]. Bayesian methods are also reported as a common design feature of adaptive trials as a means of improving statistical efficiency [32, 37, 45]. They have also been proposed as a means to combine results from multiple n-of-1 trials and enhance the usability of n-of-1 trial data in answering population-level questions about treatment efficacy and effectiveness [54].

A criticism of explanatory evidence generation reported both in the literature and in focus group discussions was that studies designed to evaluate the efficacy of an intervention typically limit enrolment to a very homogenous group of participants, which strengthens the robustness of the causal interpretation of the findings, but at the expense of a reduction in the external validity or generalizability of study results [4, 14, 33, 47]. Because rare diseases typically exhibit substantial clinical heterogeneity (discussed in the following section), some authors have questioned the

suitability of the above-mentioned approaches for evaluating clinical interventions for rare diseases [4, 14, 33, 47]. Additionally, authors have argued that many conventional RCTs and other explanatory studies are short in duration, often due to resource constraints, and do not allow for adequate assessment of long term treatment effects, further compromising external validity [4, 14, 30]. Finally, some authors were concerned that unfamiliar approaches to research design, such as adaptive randomization or n-of-1 trials would not be accepted by regulatory agencies and other policy decision-making bodies [39]. Partly in response to some of these concerns, other research paradigms for evaluating clinical interventions for rare diseases have evolved.

2.5.4.2 Comparative effectiveness/pragmatic evidence generation

It is well established that there is a high degree of clinical heterogeneity among rare disease patients, such that patients with the same specific disease might have drastically different clinical manifestations based on patient characteristics such as age, disease characteristics such as residual enzyme activity levels, or for unknown reasons, and may respond differently to a given intervention [14, 45]. As several authors have discussed, this clinical heterogeneity is often not accounted for in conventional RCTs, and has raised concern among stakeholders about the applicability of study results to patients with clinical manifestations different from those included in RCTs [4, 14, 33, 47].

" And I find it frustrating in terms of research what I've found, and you guys know this, that each case is so unique and different, and so when you read a study or evidence-based research, I find that it, it's not a guarantee that it's going to directly correlate to your particular unique situation. So, you have to take that at face value and not think that 'oh because I read that study and that it is evidence based that this is exactly what's going to pertain to my situation." – Patient/caregiver 4

"…there's a huge heterogeneity of this population. There's people with very severe diseases, people with very mild disease, and this is the nature of enzyme deficiencies. There's some people that have zero and some people will have, a lot, near normal enzyme activity, so we're going to get this heterogeneity. And this is one of the big problems, like [name] mentioned, how do we apply this clinically to a larger population of these patients? Are the results, for instance, with infantile-Pompe, how do we relate that to an adult Pompe patient?" – Physician 5

"…the way that the trials are designed, very sub, select populations with the actual disease of concern, which is already a narrow disease as it is. It makes it very difficult for us to know where and when these therapies are going to work. And so, when we're talking about rare diseases, it really has to be linked to not just research, but effectiveness research about natural history and epidemiology. And given the wide degree of heterogeneity with the diseases that we're dealing with, we're going into this with a huge degree of uncertainty about whether or not there really is any evidence to support that these therapies are going to work." – Policy advisor 2

In response to concerns about the external validity of study results, several authors and focus group participants have advocated for study designs that may compromise internal validity to some extent, by shifting away from the explanatory RCT, in order to address real-world effectiveness [2, 4, 7, 14, 30, 31, 45, 47–50, 57, 59–76].

"…I think the effort like the Canadian group CIMDRN to look at long-term outcomes, where there's natural selection of various treatment groups, I think will be very helpful over the long term because of the challenges we have in doing strict study designs, and lack of financial supports for long-term studies. This effect to observational studies and looking at outcome differences in naturally, sort of, selected difference maybe as helpful in rare diseases I think as the designed studies." – Physician 1

Almost 10 years after discussions about explanatory evidence generation for clinical interventions for rare diseases emerged in the literature, the research paradigm of comparative effectiveness/pragmatic evidence generation started to develop (first discussion published in 2001). This paradigm was discussed by half (30/60, 50%) of studies included in this review, and

was first mentioned by Wilcken in 2001 [7]. Like the previous research paradigm, most of the reports that discussed this paradigm were methodological review articles that focused on rare diseases in general or a group of rare diseases (21/30, 70%), rather than a single rare disease. Wilcken suggested that for some rare diseases, conventional RCTs remained possible, but for others, observational studies with historical controls could be used to evaluate treatment effectiveness [7]. Since that initial publication, many authors have discussed research designs that take a more pragmatic approach to evaluating treatment effectiveness in rare diseases, and often explicitly attempt to include a broader patient population and longer-term observation in natural settings. These designs include: pragmatic clinical trials, observational studies (e.g., cohort studies and registries, case series, case reports), and hybrid designs that incorporate both randomization and systematic observation [2, 4, 14, 30, 31, 45, 47–50, 57, 59–76].

While participants in our focus groups questioned the suitability of explanatory RCTs for establishing effectiveness of clinical interventions for rare diseases, little of the discussion focused on specific solutions to overcome this challenge. Like the previous research paradigm, most of the results presented under the paradigm of comparative effectiveness/pragmatic evidence generation are derived from our meta-narrative literature review.

Incorporating more pragmatic features into RCTs has been suggested as a means to improve external validity while maintaining the element of randomization to help control for unmeasured confounding and maintaining other standard methodological features of explanatory RCTs, such as blinded outcome assessments [14, 30, 48]. These pragmatic RCTs feature design elements that better reflect actual clinical practice, including: enrolling participants with differing clinical presentations, taking into consideration the system of care in which the new treatment will be delivered (e.g., using standard-of-care as a comparator instead of placebo), following participants

for a longer period of time, and incorporating outcomes that are meaningful from a patient/care provider standpoint (patient-oriented research will be discussed in the following section) [14, 30, 48]. Authors have criticized pragmatic RCTs because they do still estimate average treatment effects and thus are not necessarily better suited to investigating potential heterogeneity of treatment effects relative to explanatory RCTs [14].

Among the most common observational rare disease research designs discussed in the studies we reviewed are patient registries [4, 14, 31, 45, 50, 60, 61, 63, 68–70, 73, 76] and cohort studies [64, 74]. Because these observational studies do not typically have strict inclusion or exclusion criteria for participants, nor do investigators manipulate participants' treatment(s), some authors have argued these studies better reflect real-world clinical practice and the clinical heterogeneity that typifies many rare diseases [14, 45, 63, 68]. As reported in the literature, registries have multiple purposes including: evaluating clinical- and/or cost-effectiveness of therapies; monitoring safety of new or existing therapies; evaluating diagnostic tools; monitoring quality of care; and assessing natural history over time [63]. We identified several examples of registries being used to evaluate treatment effectiveness of interventions for rare diseases, for example, enzyme replacement therapy for lysosomal storage disorders [68]. The International Collaborative Gaucher Group Registry was established in 1991 and, at the time of the publication of a paper by Jones and colleagues (2011), had collected longitudinal clinical data for almost 6000 patients [68]. Several authors stated that an additional advantage of registries is that they can be used to identify potential participants for recruitment into future research studies, including clinical trials [14, 63, 69, 72, 73]. Some authors have also suggested that observational patient registries may play an important role in post-market evaluation of interventions for rare diseases by serving as a platform to collect longitudinal clinical and quality of life data [50].

While observational patient registries are an attractive method for the evaluation of longer term outcomes in real-world settings, some authors reported that results remain prone to residual confounding in the absence of randomization, especially confounding by indication (when patient characteristics influencing the choice of treatment also influence the outcome) [14, 47]. A few authors discussed variability in the quality of registry data, as observational patient registries tend to be heterogeneous in the depth of data collection and the definitions applied to included data elements, particularly in the context of the multi-center and sometimes multi-national nature of rare disease research [45, 61]. In addition, some authors described the potentially important influence of complete case ascertainment and data collection on the accuracy of study results, particularly given that registry participation may be associated with receipt of particular treatments or lead to different investigations [63, 69, 77].

In recent years (since 2009), some authors have suggested that elements of both explanatory and observational studies can be combined into "hybrid" study designs that attempt to mitigate challenges faced by both approaches [14, 59, 71]. For example, Vickers and colleagues suggested that the "clinically-integrated randomized trial," which seeks to integrate randomization into standard clinical care, would be suitable for rare disease research, addressing the threat of confounding while maintaining an element of pragmatism and enhancing generalizability [59]. The key feature of the clinically-integrated randomized trial is that there is no difference between the care a patient routinely receives, follow-up, payment, or documentation (e.g., charting), other than the fact that treatment was assigned randomly with informed consent from participants [59]. In the context of rare diseases, the authors argued that the clinically-integrated randomized trial is attractive because there is often considerable uncertainty about the most effective course of treatment for patients and that trials could easily

be conducted worldwide to maximize the number of participants [59]. Another design that incorporates elements of both explanatory and observational approaches and has been suggested in the context of rare diseases is the "cohort multiple randomized controlled trial (cmRCT)" [71]. The cmRCT seeks to enroll an observational cohort of patients, with participants routinely reporting on a minimum set of core outcomes [71, 78]. At the time of enrollment in the cohort, participants give their consent for 1) their longitudinal data to be used in aggregate; and 2) to be randomly selected to participate in potential RCTs of new or existing interventions with the understanding that only those who have been selected to be offered the intervention under study will be contacted [71, 78]. Those who are eligible for the RCT, but who were not randomly selected to be offered the intervention serve as the control group and are not contacted about the study [71, 78]. According to the literature, launching RCTs using this design increases the efficiency of research by accommodating multiple trials and comparison of multiple treatments, allows for longer follow-up of participants, provides pragmatic/real-world evidence, and accommodates clinical heterogeneity by enrolling participants across the clinical spectrum [14, 71, 78]. Concerns that have been raised with these "hybrid" study designs include: potential for confounding and bias in the observational component of the study, and the feasibility of implementing such a study design [14, 71, 78]. Some critiques published after our search have been raised with respect to statistical power, sample size, and treatment effect estimation, namely intention-to-treat estimates [79].

Finally, there is discussion in this literature about other observational designs such as case-control studies, small case series and case reports; however, these approaches are not commonly suggested as potential solutions for improving pragmatic evidence generation for establishing effectiveness of treatments for rare diseases. Some authors have suggested that case-control

designs, where individuals who have experienced a certain outcome (cases) are matched to and compared with individuals who have not experienced the outcome of interest (controls), are well suited for studying rare diseases, particularly in instances where there could be a long lag time between the treatment and outcome of interest [2,76]. However, there are concerns about the potential for introducing selection bias in choosing controls [2]. Other authors have argued the importance of case series and case reports in the context of establishing treatment effectiveness for rare diseases [50,62]. Case series and case reports typically include in-depth information related to clinical manifestations of disease, treatment, and follow-up for a single patient or small group of patients [50,62]. While authors have acknowledged there are clear limitations in terms of establishing treatment effectiveness, they have argued that this evidence can provide a better understanding of natural history for many rare diseases, and can identify unexpected harms or benefits of treatments, which could be of particular importance for diseases considered "ultra-rare" [50,62]. Similar to the concept of using case reports as pragmatic evidence, several focus group participants reported relying on some anecdotal evidence to help inform medical-decision making:

> *"I think all of the different information is important, and including anecdotal, right? Because we deal with very rare disorders sometimes, and you often go to clinicians who have seen these conditions and have treated them, and may take their point of view about a certain treatment. So, you may say that's anecdotal, but it may be extremely valuable if there's only a handful of patients who have received that treatment. So, I think all of the studies and designs, including anecdotal evidence, I personally use that in determining whether I think about a treatment for a patient."* – Physician 1

> *"…sometimes it all depends on the experience of what other people lived. Sometimes people tell you not to go there because they've has a bad experience. So, I like to have the bad and the good ones too, and then make my mind and take better decisions."* – Patient 2

The main criticism in the literature for comparative effectiveness/pragmatic evidence generation is the inherent risk for bias and confounding because of the lack of randomization; however, there have been efforts made to mitigate this risk. As previously discussed, some authors have suggested incorporating pragmatic elements into RCTs [14,30,48], while others have proposed methods to overcome challenges in non-randomized studies. For example, Cole and colleagues demonstrated the use of case-control matching using the risk-set method for participants enrolled in the International Collaborative Gaucher Group Registry [65]. The authors applied this method to balance "cases", i.e., Gaucher patients with skeletal avascular necrosis, and controls according to demographic and clinical factors [65]. Use of propensity scores to match participants has also been suggested as a means of reducing the risk of bias in observational studies of rare diseases [47].

2.5.4.3 Patient-oriented evidence generation

One of the main criticisms, both in the literature and by focus group participants, of highly internally valid, explanatory study designs is their tendency to rely on short-term, and often surrogate, outcomes that are not necessarily clinically meaningful [9].

"Most of the time study with rare diseases rely on surrogates and the surrogates are selected usually on the basis of biochemical indicators of some biological activity of the treatment. And so, for enzyme replacement therapy, the reduction in the concentration of a substrate in urine or blood is regarded as evidence of a biological pivot, a biological activity, but there's far too many examples where a surrogate, such as the one I've just described, are really, there's no relationship to what the clinical outcomes are." – Policy Advisor 1

"…I have a concern that sometimes outcome measures are defined by what funding and drug approval [agencies] like FDA want to see, right? [chuckles].

Rather than what the clinician may feel for a particular rare disease is far more important. …it becomes challenging to design appropriate studies and pharma is at the end of the day interested in getting approval and funding approval, and may target outcome measures that are demanded by various bodies rather than perhaps going for the most clinically appropriate outcome measures." – Physician 1

Only in the last decade (Figure 2-2) has a discussion in the literature emerged regarding the importance of patient-oriented evidence generation in rare diseases (the first appearing in 2010). This discussion emphasizes the need for outcomes that are of direct importance to patients and caregivers. Fifteen of 60 reports (15/60, 25%) discussed issues related to the paradigm of patient-oriented evidence generation, making it the research paradigm with the smallest proportion of literature. The majority of reports that discussed this paradigm were again methodological review articles (13/15, 87%), and the remaining two articles described case examples specific to one rare disease.

Connected to the paradigm of explanatory evidence generation, some authors have suggested the use of surrogate outcomes as proxies for patient-oriented outcomes such as survival or quality of life because they can be measured relatively quickly and require fewer participants to reach statistical efficiency [36,80–82]. For example, in 2010, Kinder and colleagues reported that functional outcomes such as exercise tolerance, survival, and quality of life were the most salient outcomes to consider for rare lung disease studies because they have undeniable meaning for patients; however, the authors also described the limited feasibility of conducting explanatory RCTs that include these outcomes and argued that surrogate outcomes could therefore be developed and used as proxies for patient-oriented outcomes [36]. Several authors and focus group participants expressed concern about the lack of validation of surrogate outcomes; a clear understanding of the natural history of disease and proposed causal mechanism of a treatment in

relation to the disease is needed in order to establish, with reasonable certainty, the relationship between surrogate and patient-oriented outcomes [36,66,69,82,83].

> *"…in order to identify reasonable outcomes measures for any clinical trial, one has to know the what the natural history of the disease is. So, those are major challenges, and what we're faced with in the pharmaceutical industry, who are anxious to do as short a study as possible, for rare disease almost always use surrogate markers as evidence of effectiveness and the relationship between the surrogate marker and clinical outcome is often completely unknown."* – Policy Advisor 1

For example, the six-minute walk test (6MWT) is a common surrogate outcome measure used in clinical evaluative studies for many rare diseases [80,81,84]. The 6MWT was originally developed for patients with moderate to severe lung disease as a means of assessing overall functional status and as a predictor of morbidity and mortality [85] but has since been used in studies of many rare diseases, including late-onset Pompe disease and Duchenne muscular dystrophy, among others [81,84]. An important criticism of this extension of its use is the lack of adequate validation to determine if observed changes in the 6MWT reflect meaningful changes for patients [80,81,84].

> *"For me I think one of the big issues is the outcome measures that we're trying to document. For instance, with the lysosomal storage diseases, what is the relevance of a 6 minute walk test? What is the clinical relevance of this type of test?"* – Physician 5

Partly in response to concerns about the relevance and validity of surrogate outcomes being used in clinical research for interventions for rare diseases, there has been a shift towards incorporating patient-oriented outcomes in clinical research [4,45,48,70,86].

"…because yes, scientific research is important too, but it's this push-pull dichotomy between the happiness, the living life, just the simple moments, you know, going outside, sitting in the sun, that type of, going down to the beach, those things need to be equally measured… – Patient/caregiver 4

"We need to know more what's going to happen in terms of lifespan, in terms of morbidity, in terms of the operations these patients are getting, in terms of growth as well. Is this something that we're seeing improvement?" – Physician 5

"I think that [name] made reference to this earlier about the importance of evaluating quality of life. And unfortunately, this is not really done. I don't know of a single study that has done this rigorously for the diseases that I happen to be involved with or have been. And so, for example, the fact that a child may require an intravenous infusion of some medication that takes six hours of infusion and needs it every week. They're missing a day of school every week. That's twenty percent of their schooling! This is never, in my experience, never evaluated. Now that's not a direct measure of quality of life, but you could easily imagine that it would have a significant indirect impact on quality of life." – Policy Advisor 1

In the literature and among our focus group participants, much of the discussion regarding patient-oriented outcomes has focused on developing outcomes that are meaningful based on the lived experiences of patients and their caregivers [14,45,70,86]. Tudur Smith and colleagues used the example of juvenile idiopathic arthritis to demonstrate that clinical research initially focused on outcomes related to clinical disease activity and disease damage, but more recently has shifted to identifying and validating outcomes that are most important to patients and parents, such as health related quality of life, functional assessments, and pain assessments [48]. Basch and Bennett advocated for the use of patient-reported outcomes in clinical studies for interventions for rare disease as the best measurement tools for how a patient feels and functions [86]. Participants in our focus groups also expressed a desire for researchers to incorporate outcomes beyond those directly related to the patient, including parent- and family-related outcomes.

"One quick comment about the whole family because I know, obviously, a lot of this is directed towards the patient, the person with [disease], but it's, you know, so linked and so connected, that I find there's a direct, you know, effect on the child through the parents, so I'd like to see more supports, research for the parents that are also kind of surviving through this…" – Patient/caregiver 4

A common criticism is that many outcome measures, including patient-oriented outcome measures, have not been validated or standardized for the population of interest, leading to questions about the applicability of study results [4,45,66].

"… we know that some of these tests or some of the questionnaires have not been standardized for these particular populations, and we're faced with always the question is it clinically relevant for these patients? I think overall, there's agreement that they are, but we run into this problem all the time with, you know, Pompe or the different MPS' because there hasn't been long enough natural history studies, there has not been standardization of these tests, so we're choosing these measuring tools for these particular studies without really knowing if they're the best tools. And this is very relevant for the quality of life questionnaires, we sometimes use the SF36 or we use specific pain criteria, APPT or something like that, but we haven't actually standardized this for these populations, so we don't actually know if what we're measuring is clinically relevant." – Physician 5

In response to this criticism, some researchers have begun to identify/develop and validate standard sets of outcome measures that can be used in clinical research evaluating treatment effectiveness in their populations [4,48,72]. Another concern that has been raised with respect to outcomes is that it may not be possible to use the same outcome measure within the same disease if there is substantial clinical heterogeneity among patients [4,45,48,81,86]. Some authors and focus group participants also noted that clinical heterogeneity has implications for identifying the minimal clinically important difference [45].

"…the main trial showed an improvement of 22.5 meters after 6 months in the six-minute walk test, which there's quite a variability in outcomes depending on which patients you're looking at, but that the average improvement. What does that really mean is a very difficult decision because for somebody that is walking perhaps 300 meters in six minutes and improves by 22.5 meters, that's probably not clinically significant, if we're just looking at a six-minute walk test. But, if someone is not very mobile at all and has that improvement, we might actually have a more clinically significant impact with that treatment." – Physician 5

Finally, some focus group participants expressed concern about balancing subjective outcomes (e.g., patient-reported quality of life) with more objective outcomes (e.g., biomarkers of disease progression) because of possible placebo effects with patient-reported outcomes.

"I think there needs to be a combination of objective and subjective outcome measures and quality of life measures because, certainly, quality of life is extremely important, but my sense is that it's a lot more vulnerable to placebo effect. As well, just in the sense that a lot of these families are extremely invested in being on their therapy because it is their only therapeutic option. And so by relying on quality of life measures very heavily, I think we can end up advocating for treatment for patients that aren't really clinically benefitting." – Physician 6

2.6 Discussion

Randomized controlled trials have long been considered the 'gold standard' in evidence-based medicine due to their superior ability to maximize internal validity [5]. However, our review and focus group findings describe criticisms of conventional explanatory RCTs to establish treatment effectiveness for rare disease therapies. There was agreement across the focus group interviews and with the literature we reviewed that the main challenges in generating robust treatment efficacy and effectiveness evidence for rare diseases include: i) limitations in recruiting a sufficient sample size to achieve planned statistical power (due to low disease prevalence,

geographical dispersion of potential participants); ii) difficulties in accounting for characteristic clinical heterogeneity of many rare diseases; and iii) frequent reliance on short-term, surrogate outcomes whose clinical relevance is often unclear. We mapped these three perceived challenges and associated methodological solutions to three interrelated research paradigms that emerged from our data: i) explanatory evidence generation, ii) comparative effectiveness/pragmatic evidence generation, and iii) patient-oriented evidence generation. Discussions related to explanatory evidence generation were the first to arise in the rare disease literature (in 1992) and have persisted, with 58% (35/60) of the reports we reviewed examining this research paradigm. The paradigm of comparative effectiveness/pragmatic evidence generation, which was discussed in 50% (30/60) of reports, emerged in the literature in the early 2000s and has also persisted, with a substantial increase in the number of reports in the literature over the last decade. The paradigm of patient-oriented evidence generation developed more recently in the literature (beginning in 2010) and has been discussed in 25% (15/60) of reports included in this review. Based on the year of publication for the included studies, there appears to be a shift in perspectives over time with increased criticism of conventional explanatory RCTs and associated recognition of the importance of pragmatic and patient-oriented evidence generation in the context of establishing treatment effectiveness for rare diseases.

Several methodological solutions have been suggested within each research paradigm to address the perceived challenges that were identified both in the literature and by our focus group participants. For explanatory evidence generation, the potential solutions include: study designs that incorporate elements to improve statistical efficiency and reduce the required sample size (e.g., factorial trials, adaptive designs, applying Bayesian statistical methods), and study designs that ensure receipt of or maximize time spent on active treatment to help boost participation (e.g.,

randomized placebo-phase designs, crossover/N-of-1 trials). For comparative effectiveness/pragmatic evidence generation, study designs or features that have been proposed to improve the external validity of study results include: incorporating pragmatic elements into conventional RCTs, registries/cohort studies, and hybrid designs such as cmRCTs. For patient-oriented evidence generation, authors and focus group participants suggested that incorporating outcomes that are considered important by patients and their caregivers (e.g., health-related quality of life) is critical to improve the applicability of study results.

Notably, though numerous non-conventional study designs were described in the literature we reviewed, few of the suggested approaches appear to have been applied successfully in the context of rare diseases. Only 28% (17/60) reports included in this review were considered applications or case examples of a specific research method. As suggested by Gupta and colleagues, the paucity of real-world application of these designs, particularly the non-conventional explanatory RCT designs, may be related to a lack of acceptance of unfamiliar study designs [39]. New therapies for many rare diseases are rapidly developing, so there is an increasing opportunity to apply some of these non-conventional study design strategies to evaluate efficacy and effectiveness of emerging treatments for rare diseases [87].

Among the suggested methodological strategies, there are tradeoffs with respect to internal and external validity, some of which may be exacerbated in the context of rare diseases. For example, external validity is compromised in many explanatory RCTs in favour of maintaining strong internal validity to reduce potential bias and confounding. In addition, because of the small number of individuals available to participate in research, relying on randomization procedures to balance patient characteristics (both known and unknown) will not always be successful. By contrast, study designs that can better accommodate clinical heterogeneity and enhance external

validity may introduce a risk of confounding and bias. And while external validity can be compromised if the outcomes(s) included in a study are not considered important by clinicians and patients, many patient-oriented outcome measures require additional validation and long-term follow-up. With these tradeoffs in mind, strategies for both comparative effectiveness/pragmatic and patient-oriented evidence generation are increasingly being recognized as important for investigating the effectiveness of treatments for rare diseases, with explanatory RCTs becoming less dominant in the literature in recent years.

The results of our meta-narrative review corroborate the conclusions of methodological reviews that have focused on approaches to generating evidence for interventions for rare diseases [39,42,43,45,48,49]. To our knowledge, our study is the first to incorporate stakeholder perspectives in addition to data from the published literature and to include a description of how perspectives have evolved over time using a meta-narrative review. Many of the approaches described in previously published reviews are specific to explanatory evidence generation. For example, both Gupta and colleagues and Cornu and colleagues provide algorithms that could be used by researchers to facilitate decision-making about which explanatory trial design to apply for a particular rare disease research question [39,43]. Previous reviews included limited discussion of pragmatic evidence generation, with the exception of observational methods such as registries or cohort studies [45,49]. Gagne and colleagues were the only authors among our reviewed studies to include an in-depth discussion about strategies that could be used to mitigate bias and confounding in observational studies of interventions for rare diseases [49]. Previously published reviews rarely mentioned patient-oriented outcomes in the context of evidence generation related to rare diseases.

Our work is not without limitations. The search strategy that was developed for the meta-narrative portion of this study was not exhaustive, so there is a possibility that some literature may have been missed. However, our intention was to identify key literature on this topic. In addition, we only had a single reviewer (KT) who determined study eligibility, which could have led to selection bias in the articles chosen; however, clear inclusion and exclusion criteria were used and the study team met several times to review selected literature and discuss emerging findings. We only conducted three focus group interviews with a relatively small, convenience sample of participants; consequently, we may have missed some perspectives. Our patient/caregiver focus group was particularly narrow in its focus on a single group of rare diseases. Because we were able to leverage an existing meeting of an otherwise geographically dispersed group of patients and families with MPS, an advantage of our approach was the ability to conduct an in-person focus group interview and thus ascertain the views of the participants more fully. However, some of the perspectives may have been specific to that disease group and future research could explore the perspectives of patients and families with other rare diseases.

2.7 Conclusions and future directions

Through our meta-narrative literature review and focus group interviews we identified several perceived challenges and potential solutions for generating robust treatment effectiveness evidence for rare diseases according to three interrelated research paradigms: explanatory, comparative effectiveness/pragmatic, and patient-oriented evidence generation. Over time, there has been more recognition that observational studies, such as patient registries and cohort studies, are important approaches for clinical evaluative research in the context of rare diseases to address gaps in comparative effectiveness/pragmatic and patient-oriented evidence generation. Developing better methods to mitigate potential bias and confounding would increase the value

of these approaches for establishing treatment effectiveness in the rare disease context. From a policy perspective, there is a need for inclusive discussions amongst patients and their families, clinicians, and policy advisors, including those involved in regulatory and reimbursement decision-making about interventions for rare diseases, in order to identify solutions that meet the needs of all stakeholder groups. Finally, little research has been done with respect to developing knowledge synthesis methods that consider the challenges faced in generating robust evidence for rare diseases. Future directions for our work include developing a framework to expand current evidence synthesis practices to take into consideration many of the concepts discussed in this paper.

2.8 Declarations

Ethics approval and consent to participate

Ethics approval for this study was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board, the Ottawa Health Science Research Network Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during and/or analysed during the meta-narrative portion of this study are available from the corresponding author upon reasonable request. The datasets generated during and/or analysed during the focus group portion this study are not publicly available to protect the privacy of the participants.

Competing interests

The authors have no competing interests to disclose.

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2.9 List of supplemental files

The following can be found in the supplemental information for Chapter 2:

- Search strategies for electronic databases
- List of articles included in meta-narrative literature review
- Ethics approval letters
- Reprint of published article from *Orphanet Journal of Rare Diseases*

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3 Stakeholder perspectives on clinical research related to therapies for rare diseases: Therapeutic misconception and the value of research

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3.1 Preface

This published manuscript presents the findings from a qualitative focus group interview study that addresses the second aim of my dissertation: to develop a deeper understanding of why and how patients and families, health care providers, and health policy advisors choose whether to participate in trials or other types of research, and how they use and value research findings to support decision making at both an individual- and population- level.

KT led the study design, developed the interview guide for the focus group interviews, conducted all focus group interviews, conducted all data analysis and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript. All authors have read and approved the final manuscript, which was accepted for publication in the journal *Orphanet Journal of Rare Diseases* in 2020.

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3.2 Abstract

Background: For many rare diseases, few treatments are supported by strong evidence. Patients, family members, health care providers, and policy-makers thus have to consider whether to accept, recommend, or fund treatments with uncertain clinical effectiveness. They must also consider whether and how to contribute to clinical research that may involve receiving or providing the therapy being evaluated.

Objective: To understand why and how patients and families with rare metabolic diseases, specialist metabolic physicians, and health policy advisors choose whether to participate in studies and how they use and value research.

Methods: We conducted separate focus group interviews with each stakeholder group (three groups in total); two groups were conducted by telephone and the third was held in-person. Participants were recruited using purposive sampling. We analyzed each interview transcript sequentially using a qualitative description approach to inductively identify key themes. Several strategies to ensure credibility and trustworthiness were used including debriefing sessions after each focus group and having multiple team members review transcripts.

Results: Four patients/caregivers, six physicians, and three policy advisors participated. Our findings did not support conventional perspectives that therapeutic misconception (gaining access to treatment) is the main motivating factor for patients/caregivers to participate in clinical research. Rather, patients'/caregivers' expressed reasons for participating in research included advancing science for the next generation and having an opportunity to share their experiences. Patients/caregivers and physicians described the difficulties in weighing harms versus benefits of accepting treatments not well-supported by evidence. Physicians also reported feeling conflicted in their dual role as patient advisor/advocate and evaluator of the evidence. Policy advisors were

primarily focused on critically appraising the evidence to make recommendations for the health system.

Conclusions: Stakeholders differ in their perspectives on rare disease research but share concerns about the harms versus benefits of therapies when making individual- and population-level decisions.

3.3 Background

For many rare diseases, there are few or no established treatments supported by strong evidence that the intervention alters the natural history of illness [1,2]. This paucity of proven effective treatment options requires patients, caregivers, health care providers, and policy advisors to consider whether to accept, recommend, or fund emerging or controversial treatments where there is substantial uncertainty about potential benefits and harms, decisions which may be particularly difficult for diseases which are progressive and life-shortening [3–5]. Several authors have reported that patients and care providers demonstrate a willingness to try treatments without existing evidence because of a hoped-for or even expected clinical benefit over supportive care or no treatment [3,4,6–8]. This expectation of benefit conflicts with one of the central tenets of conducting research to establish the effectiveness of a new or existing intervention, which is the concept of *clinical equipoise* [9].

Clinical equipoise, the presence of uncertainty or disagreement in the expert medical community about the comparative benefits or harms for a given intervention [10], provides the ethical basis for assigning study participants to different treatment groups in a clinical research study [9,11]. Pai et al. reported that one of the barriers to conducting clinical research for rare diseases is the perceived lack of clinical equipoise among patients, caregivers, and health care providers [4]. If patients and/or care providers choose to participate in a trial to gain access to an intervention they already believe to be effective, then there is no clinical equipoise from their perspective [12]. This phenomenon is known as *therapeutic misconception,* which exists when clinical trial participants believe that the purpose of research is to benefit the individual rather than to generate generalizable knowledge to advance science [13,14]. Therapeutic misconception leads to a reluctance among some patients and caregivers to participate in studies where there is a

chance they will be assigned to a placebo or control group rather than the new treatment group [12,15]. Coupled with small, geographically dispersed patient populations and characteristic clinical heterogeneity for many rare diseases [12,16], this reluctance among patients and caregivers to participate may exacerbate challenges faced by researchers to recruit adequate sample sizes for rare disease clinical studies and thus limit the conclusions that can be drawn [17].

Recognizing that it is challenging to recruit a sufficient number of participants for clinical trials related to rare diseases, several alternative study designs have been proposed to make participation more attractive to patients and families by maximizing the time spent on- or guaranteeing the provision of- the experimental treatment [18,19]. For example, in crossover and n-of-1 trials each participant receives both the control and experimental treatments, but the order in which each treatment is delivered is randomized [20,21]. Using adaptive randomization procedures to reduce the likelihood of being assigned to the less effective treatment group over time may also make participation in clinical research studies more appealing [20,22]. While these alternative designs may improve participant recruitment, there remains a need to consider how to reconcile the scientific and ethical concept of clinical equipoise with the potential therapeutic misconception experienced by patients or families when choosing to participate in clinical research.

As part of a larger project that seeks to develop specific guidance for the evaluation and synthesis of evidence for treatments for rare diseases, the objective of this paper is to describe different stakeholder perspectives on the role of research related to the development and evaluation of treatments for rare diseases. Specifically, we were interested in developing a deeper understanding of why and how patients and families, health care providers, and health

policy advisors choose whether to participate in trials or other types of research, and how they use research findings to support decision-making at both an individual- and population- level.

3.4 Methods

This study is described according to the Standards for Reporting Qualitative Research reporting guidelines [23].

3.4.1 Qualitative approach

Recognizing that there were likely to be differing perspectives among stakeholders on the generation and evaluation of evidence for clinical interventions for rare diseases, we chose to conduct a series of focus group interviews to better understand the factors that stakeholders take into consideration when making decisions about research related to clinical interventions. Our study was conducted from an interpretivist point of view using a qualitative description approach, designed to allow researchers to develop a deep understanding of and describe a particular phenomenon based on participants' experiential knowledge [24,25].

3.4.2 Sampling and recruitment strategy

We recruited participants using purposive sampling, a deliberate, non-probability sampling method used to select participants who can provide rich data related to the research topic [26,27] comprising three groups of stakeholders: rare disease patients or caregivers, physicians, and policy advisors. Each group was chosen because they had formal knowledge and/or lived experience related to the research topic. To facilitate the focus group interviews, we chose rare inherited metabolic diseases (IMD) as a case study. For the patients and caregivers, we further narrowed the selection to those diagnosed with mucopolysaccharidoses (MPS), a group of IMD with several characteristics that typify many rare diseases (e.g., significant clinical heterogeneity; see Box 3-1 for description of MPS).

Box 1 – Brief description of mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a group of seven heritable conditions that have an autosomal recessive inheritance pattern, except for MPS II which is X-linked.[28] Overall birth prevalence estimates for MPS vary by country/region and range from 1.04 to 4.8 per 100,000 live births.[29] These disorders are characterized by specific enzyme deficiencies that cause an accumulation of glycosaminoglycans (GAG) in the lysosomes of most cells.[28,30] This buildup of GAG results in a wide spectrum of cell, tissue, and organ damage. The clinical manifestations of MPS begin early in life and are chronic, progressive, and typically involve multiple organ systems. Common clinical symptoms include: vision, hearing, cardiovascular, airway, and joint problems, organomegaly, musculoskeletal and facial abnormalities, among others.[28,30] Similar to many other rare diseases, there is substantial clinical heterogeneity both between different MPS and within the same MPS.[28,30] The spectrum ranges from mildly affected to severely affected. In addition to other symptoms, severely affected individuals may also experience neurocognitive deficits that are not present in more attenuated forms of the diseases.[28,30] Currently, transformative treatments are limited for MPS, so care is generally supportive to help manage various symptoms.[30] For those with severe MPS I, early hematopoietic stem cell transplantation is recommended as standard of care to slow the progression of symptoms, particularly neurocognitive impairments.[30] In addition, enzyme replacement therapy, an expensive orphan drug, is available for MPS I, II, and VI[31,32]; however, the extent of its efficacy is debated in the literature.

Individuals were eligible to participate if they were adults diagnosed with MPS or were the adult caregiver (i.e., parent/guardian) of someone diagnosed with MPS, if they were a physician

providing health care to those diagnosed with rare IMD, or if they had experience in evidence review activities that resulted in recommendations for the development, use, or reimbursement of interventions for rare diseases (policy advisors). Between five and eight individuals were sought for each focus group according to established focus group methodology in order to facilitate discussion while allowing each participant to be heard [26].

We distributed recruitment invitations by email to physician members of the Garrod Association (a professional organization whose members are involved in caring for children with IMD), to policy advisors by a member of their professional network using publicly available contact information, and to patients/caregivers attending the Canadian MPS's Society's 2017 annual Family Meeting. Individuals interested in participating in the focus groups contacted the lead author (KT) for more information and to confirm eligibility. Eligible respondents were asked to provide signed informed consent to participate in the study.

3.4.3 Data collection

Focus groups were held separately for each stakeholder group; the patient and family focus group was conducted in person in conjunction with the Canadian MPS Society's 2017 Annual Family Meeting, while focus groups with physicians and health policy advisors were conducted via teleconference. We conducted two focus groups by telephone in order to reach a geographically dispersed group of people across Canada who would otherwise be unable to gather in-person [33]. We reasoned physicians and policy advisors would likely have greater familiarity with the topic, thus may be comfortable convening via teleconference, whereas an in-person focus group may be important for patients and families.

We developed a semi-structured interview guide for each focus group that included questions related to the generation and evaluation of evidence for clinical interventions for rare diseases.

Topics included: general perspectives on rare disease research, reasons for participating in research activities, outcomes used in clinical studies, and challenges in establishing treatment efficacy and effectiveness. The interview guide was reviewed by all members of the research team and by a representative from the Canadian MPS Society. One team member (KT) conducted all three focus group interviews, with at least one additional team member attending as an observer.

3.4.4 Data processing and analysis

Each interview was audio-recorded with participants' consent and transcribed for data analysis. The transcripts were analyzed sequentially using thematic analysis [34], which involved generating a set of initial codes based on interesting features of the data and then organizing those codes into key themes related to the research topic. To do this, a series of research team meetings were held to review the transcripts and inductively identify emerging concepts from each interview. Key concepts that were identified in the focus group data were organized into a coding system that was applied by one member of the study team (KT) using NVivo 10 software (QSR International Pty Ltd.) across the entire data set. Coded transcripts were reviewed and verified by a second team member (BP) to confirm all codes had been applied appropriately and that no themes had been overlooked. We used several strategies to ensure credibility and trustworthiness of our data [35], including: debriefing sessions after each focus group to identify key perspectives, multiple research team members reviewing transcripts, multiple team discussions to identify themes, and transcript coding verification by a second team member.

3.5 Results

3.5.1 Focus group characteristics

We completed three focus group interviews with a total of 13 participants (physicians n=6; policy advisors n=3; patients/caregivers n=4). Each focus group interview lasted between 45 and 75 minutes. Across the three groups there were nine women and four men. Participants were from five provinces in Canada: British Columbia, Alberta, Ontario, Quebec, and Newfoundland and Labrador. Regardless of group size, all participants were engaged throughout the discussion with very little prompting from the moderator. Data from our focus group interviews revealed several key themes related to therapeutic misconception, reasons for participation in research activities, and how stakeholders value research.

3.5.2 Making choices about participation in research

Given their role in the health system, policy advisors are typically not directly involved in clinical research, so results related to participation in research are derived from focus groups with patients, caregivers, and physicians. Both patients/caregivers and physicians identified several reasons for participating in studies that seek to evaluate therapies for rare diseases. Some of their perspectives overlapped and others were unique to a single group (Figure 3-1).

For example, some members of the physician group described their perception that patients and families often participate in clinical research, and even believe they are benefitting, out of a sense of desperation or willingness to try anything, especially when treatment options are limited.

> *"...you have patients or families that are experiencing a devastating condition and they want to try anything."* – Physician 4

> *"... a lot of these families are extremely invested in being on this therapy because it's their only therapeutic option."* – Physician 6

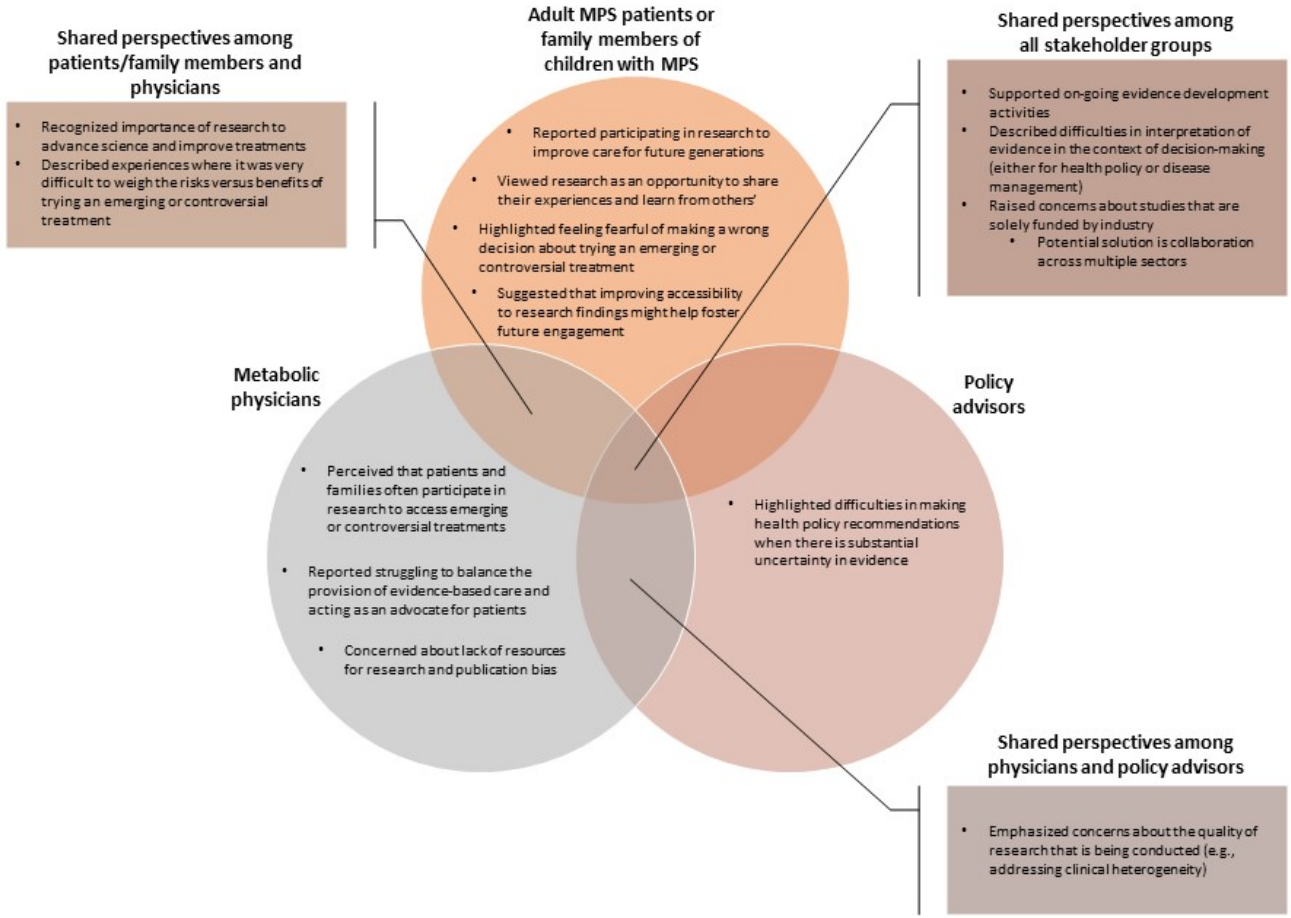

Figure 3-1. Shared and unique perspectives among focus group participants about participation in clinical research and the value of clinical research.

Contrary to this view, patients and caregivers more frequently reported other reasons for choosing to participate in research activities and did not explicitly mention choosing to participate based on gaining access to treatment. For example, participants viewed involvement in research activities as a form of advancing science and an act of altruism of potential benefit to the next generation of individuals affected by the disease, understanding that they or their family members may be unlikely to personally benefit.

"…I think research of any kind is always useful for progressing science, and I've been involved in a number of different kinds of research studies over the years." – Patient/caregiver 3

"I find it's hard because research takes so long [murmurs of agreement from the group]. It's like, when you start off with this and talk about research and all this stuff, you have a lot of hope, as in wow it's going to be done in no time, but then living with it, you think, you know what, maybe in somebody else's lifetime, but it won't be in our child's lifetime. But you have to keep researching because if you stop, well it will be in nobody's lifetime." – Patient/caregiver 1

"…participating in research is really important, especially with such a complex and ever-changing environment with rare diseases and particularly MPS. Yeah, so just for the learning and for sharing information." – Patient/caregiver 4

Patients and/or caregivers also described approaching research as an opportunity to share their own experiences and in turn to benefit from research findings that describe a broad range of experiences of other patients and families, to help inform decision-making.

"I think it's important to have a lot of information because nobody has the same thoughts. I know from experience, your thoughts change from early diagnosis from like 13 years ago to now. I have a totally different way of thinking about the medication, the outcome, the whole thing." – Patient/caregiver 1

"I think it's important because sometimes it all depends on the experience of what other people lived sometimes people tell you not to go there because they've had a bad experience. So, I like having the bad and the good ones too and then make up my mind and take better decisions." – Patient/caregiver 2

Some physician participants had similar views on the importance of research for furthering the development and improvement of rare disease therapies.

"…you're advocating for your patient and if these treatments don't ever happen, then they'll never evolve, so that we won't then get on to a better treatment. So, I think it's extremely important that these treatments do develop, but it's just tricky, sort of, coming up with the new treatments." – Physician 4

It was clear that not all patients and caregivers found it easy to make the decision to participate in a research study or to try a new therapy. Participants described being fearful of making the wrong decision in choosing whether to participate.

"For parents, it's scary because if you say, okay we'll try this, but what if you made the wrong decision [agreement from others]. That's what always goes around in my head, what if I did it wrong? And usually we talk about it, my husband and I, but it seems to be like okay, mom you make the decision, but I don't want to make it all by myself. What if I'm wrong?"
– Patient/caregiver 1

Patients and their caregivers also reported difficulty with weighing the harms versus benefits of trying a new therapy and spoke about uncertainty about whether it would be "worth it".

"P1: But it's scary to try other things. After one thing fails, it's like okay, we could do this, but it sounds a little drastic. P4: I know, but what do we have to lose? P1: So what if it harms your child more than… P4: I know. P1: Sometimes you're so afraid that you just don't want to do anything. P4: Yup."
–Patient/caregiver 1 & 4

"I think it depends too on what you have to do to get that little bit of change. Is it going to cost a lot of pain and anxiety and for just a little bit? It's not really worth it because all that time spent could have been quality time spent doing, oh let's go out and just sit in the sun…" –Patient/caregiver 1

Similarly, one of the participants from the physician group described an experience of having to weigh harms versus benefits and wondering whether trying an experimental treatment was the right decision for their patients.

"I was involved with two babies with [severe inherited metabolic disease] quite early when [treatment] was just first available… and in retrospect, now that we have more knowledge about who is going to respond to [treatment], you know, I think it may have been that there was some harm done for those families, they could have had better quality of life. Both babies died, but you know, I think we were very optimistic at the time based on the publication of the studies, and you do wonder at the end of the day did I, was it more harmful for those families in regard to taking away quality time they could have spent with the baby and the family versus being back and forth in the hospital?" – Physician 4

Despite the difficulties and uncertainty in making decisions to participate in clinical research or to try an experimental treatment, one caregiver highlighted the importance of being persistent and continuing to ask questions and do research.

"You always have to push. You can't sit back and just accept things sometimes. It's like, I know [name]'s situation came to a halt, but still kind of want to know why? And yeah, keep pushing and find out why does something happen? Why does it stop? And it's always, you got to keep push, push, push, push. No matter who and how, you just have to keep asking questions." – Patient/caregiver 1

Lastly related to participation in research activities, patients or caregivers expressed a desire for research to be more accessible and noted that sharing findings from research in which they've directly participated may help encourage further research engagement.

> *"I find that when I read studies, I like the introduction and the conclusion, because the middle stuff is so scientific that even the ex-[profession] in me can't understand it."* – Patient/caregiver 3
>
> *"…user-friendly for the non-scientist parent. If it's too overwhelming then you don't really grasp. It could be sort of coded in a way that is easy for a tired parent."* – Patient/caregiver 4
>
> *"…I think that's a really important piece to keep people motivated to participate in these things is to at least have some sort of follow through that allows us to see if what we shared made any kind of a difference. So that would be one thing that I'd like to see…"* – Patient/caregiver 4

3.5.3 Perspectives on the value of research

There was general agreement among participants in all three groups about the importance of supporting evidence development for new or existing therapies for rare diseases (Figure 3-1). However, given their diverse backgrounds, there were differences across groups in how participants reported using research findings, the specific concerns they had with respect to the quality of clinical research, and the value of research to them in their roles as providers, evaluators, and users of care (Figure 3-1).

For example, participants in both the physician and policy advisor groups were largely critical of the quality of research that is conducted for many rare disease therapies. They described difficulties in interpreting the available clinical evidence with respect to its value for informing

decisions about real-world patient care, particularly for rare diseases characterized by important clinical heterogeneity.

> *"…this is a huge problem in terms of trying to interpret information from clinical studies, from treatment outcomes. How do we look at clinical trials versus actual clinical work that we do, which is much longer term than that of short clinical trials? How do we deal with some of the heterogeneity of the lysosomal storage diseases?"* – Physician 5

> *"And given the wide degree of heterogeneity with the drugs that we're dealing with or the diseases that we're dealing with, we know we're going into this with a huge degree of uncertainty about whether or not there really is any evidence to support these therapies are going to work".* – Policy advisor 2

Physician participants also reported that when considering how to use research findings, they struggled between providing care that is evidence-based, which requires a critical evaluation of research, and wanting to be an advocate for their patients, especially when their patients have limited treatment options.

> *"…most of the clinical trials are with few patients and are relatively short-term, so there's always this conflict I think for clinicians between the short-term outcome measures and also our role as advocates for patients and families that may be very interested in pursuing these treatments, these very expensive treatments... you want to be an advocate but you [are] also a scientist and, you know, you may not be impressed by the outcomes or sometimes even study designs…."* – Physician 4

In considering how to best use evidence to inform routine patient care, one physician expressed concern about interpreting findings that show improved outcomes because of frequent interactions with the healthcare system as a result of being involved in a research study.

"One of the issues that's been brought up by some of these studies as well is that when these patients are getting [treatment], they're generally seeing the physician more frequently as well, and this is always a complicating factor in terms of treatment benefit. When they're seeing the physician more frequently, they're more likely to get interventions that are unrelated to the [treatment] because they're there at that time and they're complaining about X and Y, and they're more likely to get treated earlier on, as opposed to patients who have had no therapy, and might only see the doctor one a year." – Physician 1

Another concern included potential publication bias in the context of rare diseases in that study designs that are conventionally considered low quality are more difficult to get published.

"The problem is that it's often very difficult to get [observational] studies published, right? Even in journals dealing with rare disorders…" –Physician 1

Finally, one concern that was raised in all three groups with respect to the quality of research was the difficulty of conducting high quality rare disease studies due to limited resources. In addition, participants across groups were concerned about potential bias in studies that are solely funded by pharmaceutical companies.

"And I think the conspiracy theorist in me wonders about who funds the research? Where is the funding coming from and what are their interests?" – Patient/caregiver 4

"I have to say that there are concerns about the [name of research study] as well because, I mean, difficulties in obtaining funds continuously for a long period of time because it's not pharma funded and also just because of the resources. …there's still problems with that study because we just don't have the manpower to properly run a study and design it properly etcetera." – Physician 1

"I think in a sense we are stuck with nobody having large enough pockets to fund a study looking at whether it's [treatment] or whether it's [treatment], we

just don't have the funding to do that without pharma. So, you're between a rock and a hard place." – Physician 5

Some participants suggested that one way to overcome this would be to approach research in a more collaborative way that involves individuals from across sectors (e.g., health technology assessment agencies, health policy decision makers, and academic researchers as well as industry).

"…perhaps having partnerships between pharmaceutical companies, governments, and clinicians to ensure that we do get appropriate long-term follow-up is going to help us get that data and again, improve treatments." – Physician 6

3.6 Discussion

We identified several themes from our focus group data related to why individuals choose to participate in research activities and how different stakeholders value and use research in their roles as evaluators, care providers, and recipients of care. Patients, caregivers, and physicians that participated in our focus group interviews shared the understanding that research is important for the development and improvement of treatments; however, physicians discussed concerns that rare disease patients and families often participate in clinical research studies because of potential therapeutic misconception and, as a result, patients may be unwilling to accept assignment to a placebo or comparator group. Previous discussions in the literature have also posited that patients and families choose to participate in clinical research studies because of desperation and that the expectation of personal benefit can threaten clinical equipoise [3,4,6,7]. In contrast, patients and caregivers who contributed to our study had more nuanced views about participating in clinical research which extended beyond gaining access to a potential therapy, raising questions about the influence of therapeutic misconception in their decision-making

about participating. Individuals in our study reported participating in clinical research studies to advance knowledge for future generations affected by the disease, to share personal experiences, and as an opportunity to learn from experiences of others. A survey of more than 3000 people affected by a rare disease conducted by the European Organization for Rare Disorders similarly found that the main motivation for respondents to participate in research was to help the community and make scientific advancements rather than gaining access to new treatment options [36]. These findings suggest patients and caregivers understand that participating in research has implications beyond accessing potential treatments and that those implications play a role in decisions about taking part.

Patients, caregivers and some physicians did speak extensively about the difficulty of weighing the personal benefits and harms, including opportunity costs to patients, of participating in a clinical study or accepting a treatment that is not well-supported by evidence. This finding indicates that these stakeholder groups do consider the individual implications of participating in research but, again in contrast to the therapeutic misconception, it suggests that they recognize that experimental therapies may carry personal risk or may not be effective. This perspective demonstrates that clinical equipoise may not be significantly compromised among this stakeholder group. While our work demonstrated that patients, caregivers, and health care providers valued research, it remains important to manage expectations of personal benefit and possible harms when strong evidence regarding an emerging intervention is unclear or not yet available.

Given their different roles in the health system as evaluators, care providers, and recipients of care, the ways in which participants from each group used and valued research findings differed. As described, patients, caregivers and physicians described potential personal benefits and harms

of using treatments in the absence of strong evidence. Physicians also reported being conflicted in their role as both advocate/advisor for their patients and as an evaluator of the evidence base, suggesting that their priorities relate to whether there is sufficient evidence to support recommending a particular treatment and how to balance that evidence with patient and caregiver preferences. Policy advisor participants were primarily concerned about the quality of research that is being conducted. Policy advisors did not share the perspectives of patients or caregivers beyond the broad theme that uncertainty makes decision-making more difficult. This is perhaps not surprising given that the role of policy advisors is to critically appraise research and recommend if a treatment should be made available and/or reimbursed in the health system. Together, these findings suggest it is important to consider different roles and evidence needs among stakeholders when developing clinical research studies, approaching potential study participants, defining and prioritizing outcomes, and/or conducting evidence syntheses to ensure that scientific research is relevant and meaningful.

To our knowledge, there are few published studies discussing how different stakeholders value and engage with research in the context of rare diseases. Kesselheim and colleagues conducted a focus group interview study with patients, caregivers, and patient advocates; some similar themes emerged from their data including that participants reported experiencing difficulties in weighing the potential harms and benefits of accepting a controversial therapy. Some findings conflicted with the results from our study, namely our patient and caregiver participants did not report feeling desperate to try anything and did not discuss feeling uncomfortable in participating in a study with the potential to be randomized to a control group [37]. A focus group study with parents and clinicians of individuals with Duchenne muscular dystrophy regarding participation in research touched on similar themes of parents and clinicians finding it difficult to make

decisions to participate in research when there is such a limited evidence base [38]. Regarding the themes we identified concerning the quality of research, it is established in the literature that the small, geographically-dispersed, and clinically heterogeneous patient populations that typify many rare diseases present challenges for meeting conventional evidence standards for establishing treatment effectiveness (e.g., there are few or no randomized controlled trials for many rare disease therapies) [18,39].

While there is little published empirical research regarding stakeholder attitudes toward participation in rare disease clinical research, there is a rich literature discussing motivations for participating in research in other disease areas. For example, Dupont and colleagues discuss ethical aspects of the participation of pediatric cancer patients in clinical trials [40]. Similar to our findings, the authors highlight that there is a complex harm-benefit judgment entailed in families' decision-making about whether to participate in clinical research and that patient and family preferences should be carefully considered [40]. While there are key differences between pediatric cancers and rare genetic diseases (e.g., cancers are defined by incidence whereas rare genetic diseases are defined by prevalence, disease course may be very different), the challenges for clinical research are similar in many ways, especially given the relatively low incidence of pediatric cancer and the uncertainties surrounding potential therapeutic options [41,42].

Though it was not discussed extensively by the participants in our study, some literature has shown therapeutic misconception as a strong motivating factor when choosing to participate in research [13,14,43,44]. For example, Hendersen et al. demonstrated in their study of early phase gene therapy that while some participants may understand they are in a research study to generate generalizable knowledge, they may still have unrealistic expectations about the direct benefit of the therapy under study [43]. A recent survey of health care professionals working in

pediatric cancer centres also demonstrated similar results to ours in that the majority of health care professionals surveyed believed perception of medical benefit for the child was a primary motivating factor for parents' consent for participation in early-phase clinical trials [45]. Therapeutic misconception is a complex concept that warrants further investigation in the field of rare diseases.

An important strength of our study is the in-depth insights generated about participating in clinical research studies and the perceived value of research in supporting health care decision-making. Using focus group methodology allowed participants to compare and contrast their perspectives with those described by others in the group and to build on others' ideas. Another strength of our study is the use of multiple methods to ensure credibility and trustworthiness of our data [35]. While the preferred sample size for focus group interviews is between five and eight individuals, we only recruited three and four participants to the policy advisor and patient/caregiver focus groups, respectively. In addition, conducting two focus group interviews via teleconference may have reduced the interactions between participants and in turn, limited the richness of our data set [33]. Despite the small number of participants in these groups and the inclusion of telephone focus group interviews, there was still a lively discussion in each group. The small number of people in each group also allowed each participant ample time to speak and fostered a very in-depth discussion of the research topic. Thus, we do not feel that these factors substantially reduced the richness of the data collected. In future focus group studies, adding a webinar option could provide a good alternative to in-person focus groups [46]. We did not formally assess data saturation, so it is possible that we have not identified an exhaustive set of themes; however, the literature suggests that three focus group interviews is enough to identify the most prevalent themes in a dataset and approximately 80% of all possible themes [47].

Transferability of the results to the broader rare disease community may be limited given that we recruited a purposive sample of metabolic physicians and MPS patients and caregivers. In addition, patients and caregivers were recruited from a list of attendees at a national meeting for MPS patients and families which may have restricted the variation in perspectives. However, inherited metabolic diseases and specifically MPS, do exemplify some of the typical characteristics of rare diseases, including small patient populations, significant clinical heterogeneity, and few available treatment options; thus, it is likely that many of the themes identified in this work could be transferable to other rare diseases. Future work could explore perspectives among different rare disease groups to understand if their views align with our study. Additional work among other rare disease groups would also enable a more in-depth investigation of how disease progression/severity, timing, and other factors affect decision making regarding participation in research (e.g., is there less willingness to participate in clinical research studies among patients/families if the manifestations of the disease are less severe?).

3.7 Conclusion

In the context of rare diseases, health care decision-making (individual- and population- level) and clinical research are often intertwined, and the lines between individual care and participation in clinical studies are sometimes blurred. Our study identified different perspectives on how diverse stakeholders choose to participate in and use research in their roles as health care users, care providers, and policy advisors. Notably, the conventional wisdom that patients and family members participate in clinical research studies because of therapeutic misconception was not supported. We believe there is an opportunity to further investigate this finding in other rare disease populations and assess whether there is heterogeneity in opinions held among rare disease stakeholders from other jurisdictions as well. Overall, we found that stakeholders differ

in their perspectives on rare disease research but share concerns about the harms versus benefits of therapies when making individual- and population-level decisions. This shared perspective provides opportunities for engaging all stakeholders toward collaborative approaches to the design, conduct, and use of research to evaluate care. Developing a deeper understanding of why stakeholders choose to participate in research activities and how they value research will inform the design of future clinical research studies and ensure that results are meaningful.

3.8 Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ottawa Health Science Network Research Ethics Board, the Children's Hospital of Eastern Ontario Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

Consent for publication

Not applicable.

Availability of data and material

In order to protect the privacy of our study participants, research data are not publicly available.

Competing interests

None to declare.

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Author Contributions (using CRediT)

Kylie Tingley: Conceptualization (equal); methodology (equal); investigation (lead); formal analysis (lead); writing – original draft preparation (lead); writing – reviewing & editing (equal). **Doug Coyle:** Conceptualization (equal) methodology (equal); formal analysis (supporting); writing – reviewing & editing (equal); supervision (co-lead). **Ian D. Graham:** Conceptualization (supporting); formal analysis (supporting); writing – reviewing & editing (equal); supervision (supporting). **Pranesh Chakraborty:** Conceptualization (supporting); writing – reviewing & editing (equal); supervision (supporting). **Kumanan Wilson:** Conceptualization (supporting); writing – reviewing & editing (equal); supervision (supporting). **Beth K. Potter:** Conceptualization (equal); methodology (equal); investigation (supporting); formal analysis (supporting); writing – original draft (supporting); writing – reviewing & editing (equal); supervision (co-lead).

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3.9 List of supplemental files

The following can be found in the supplemental information for Chapter 3:

- Focus group interview guide

- Reprint of published article from *Orphanet Journal of Rare Diseases*
- Ethics approval letters (see Supplemental File 2-3)

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4 Canadian health system stakeholder perspectives regarding evidence use in health technology assessment and health policy decision making for rare disease therapies: A focus group and targeted literature review study

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4.1 Preface

This article presents the findings from a qualitative focus group interview and targeted literature review study that addresses the third aim of my dissertation: to describe stakeholder perspectives on the challenges associated with evaluating rare disease therapies from a health system perspective, focusing on the characteristics of rare diseases that may warrant special consideration in HTA and health policy decision making.

KT led the study design, developed the interview guide for the focus group interviews, conducted all focus group interviews, conducted all data analysis and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript. All authors have read and approved the final manuscript.

Manuscript status: In preparation

Ethics approval: Ethics approval for this study was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board, the Ottawa Health Science Research Network Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

4.2 Abstract

Introduction: Health technology assessment (HTA) of rare disease therapies has been controversial. Our objective was to better understand health system stakeholders' perspectives regarding characteristics of rare diseases that may warrant special consideration in HTA and health policy decision making.

Methods: We used a qualitative focus group interview study with metabolic physicians and policy advisors, as well as a targeted literature review to identify whether specific HTA and/or health policy decision making strategies for rare diseases have been discussed or implemented across jurisdictions. Participants were recruited using purposive sampling and the interviews were held by telephone. Each interview transcript was analyzed using a qualitative description approach to inductively identify key themes. For our literature review, we used a combination of keywords and medical subject headings to search MEDLINE for potential articles. One team member reviewed all citations for relevance and abstracted data accordingly. Information from included articles was synthesized narratively and integrated with focus group findings.

Results: Six physicians and three policy advisors participated in the focus group interviews. Our literature search yielded 258 citations, with 25 articles deemed eligible for inclusion. Stakeholders in our study agreed that there is an opportunity to improve upon the mechanisms by which rare disease therapies are currently reviewed, proposing that additional measures be taken to ensure significant uncertainties regarding the disease and candidate therapy are addressed (e.g., a rare disease specific evaluation framework). Some jurisdiction-specific HTA strategies for disease therapies have been proposed or implemented according to the literature. Study participants also identified information that potentially warrants special consideration in future HTA specific to rare disease, including characteristics of the disease (e.g., severity and stability),

understanding of the potential biological mechanism or other causal hypotheses relevant to the therapy, and complexities of cost-effectiveness given the high price of many rare disease therapies. Some of these considerations have been included in proposed HTA strategies reported in the literature.

Conclusion: Some rare disease specific processes have been implemented, but further optimization of HTA to address practical uncertainties and improve rare disease health policy is needed.

4.3 Background

Across many countries policy decisions concerning the availability and funding of health technologies (i.e., drugs, devices, diagnostic procedures) are informed by formal health technology assessments (HTA) [1–3]. The purpose of HTA is to systematically evaluate a health technology in terms of clinical efficacy and effectiveness, cost-effectiveness, and organizational, social, and ethical issues [4,5]. Ideally, information produced through HTA enables health policy decision makers or their advisors to make evidence-informed recommendations or decisions about adoption, funding, appropriate use, and, when applicable, disinvestment of health technologies [6]. A current debate in the HTA literature is how to optimize the evaluation of therapies for rare diseases, which pose a series of unique challenges for HTA producers [7,8].

While definitions vary, each individual rare disease is defined by its low prevalence (e.g., <1 in 2,500 [9]), taken together, the over 6000 rare diseases currently identified affect approximately 3.5-5.9% of the population, globally [10,11]. For the vast majority of rare diseases, there are no transformative, disease modifying therapies available, producing significant unmet need for many patients and their families [12]. However, legislation in many jurisdictions has lessened barriers and provided incentives for manufacturers to develop or re-purpose medicines targeted at rare diseases [13]. This, coupled with prioritization of rare disease research on an international scale [14], has led to a significantly increased pace with which rare disease therapies are being developed, regulated, and marketed [10]. For example, Miller & Lanthier recently demonstrated that following the 1983 Orphan Drug Act in the United States, the number of orphan drug approvals rose substantially over time from two in 1983 to 77 in 2017 [15]. With this growth in production and marketing of rare disease therapies comes increased requests for HTA producers

to evaluate and make recommendations about their use and reimbursement within existing health care systems [16,17].

4.3.1 The policy problem

Evaluating rare disease therapies presents a variety of challenges for HTA producers that are often directly related to the difficulties in conducting high quality clinical research with small, clinically heterogeneous, and geographically dispersed patient populations, typical of many rare diseases [7]. The struggle to generate high quality evidence of treatment efficacy and effectiveness in the context of rare diseases is well-documented in the literature [18]. Consequently, the evidence available at the time of regulatory review or HTA for many rare disease therapies is far less mature relative to therapies for more common diseases [19–22].

Further complicating HTA and policy decision making regarding rare disease therapies is that they frequently have an exceptionally high per-patient cost. Drugs for rare diseases are among the most expensive in the world (e.g., the average price per patient per year in 2018 among the top 100 orphan drugs available was over $150,000 USD) [23]. Improving the overall health of the population may be seen as the goal of publicly funded health care systems. HTA can inform policy decisions toward this goal by establishing whether new therapies represent sufficient value for money [24]. Determining value for money in HTA is often accomplished by formally assessing cost-effectiveness for a given therapy in relation to its comparators [24]. Given the high price associated with most rare disease therapies and substantial uncertainty in the available clinical evidence, it is not surprising that these therapies often do not meet the requirements to demonstrate value for money. Thus, they frequently receive negative reimbursement recommendations on the basis of being unlikely to increase overall population health relative to alternatives. These negative recommendations acknowledge that some health care services would

need to be forgone and this funding redirected to pay for the rare disease therapy (i.e., expensive rare disease therapies have high opportunity costs) [25].

These issues related to the nature of available evidence and the costs of treatment make it difficult to apply standard HTA methods to the evaluation of rare disease therapies. This difficulty in turn contributes to substantial variability among jurisdictions in decisions taken regarding reimbursement of rare disease therapies [26–28]. For example, in a comprehensive review of recommendations made for a sample of orphan drugs among four well-established European HTA agencies, Nicod identified considerable differences in recommendations for six of the 10 drugs reviewed [28]. These cross-country differences in recommendations were related to dissimilarities in the breadth of evidence appraised by each agency as well as the interpretation of the available evidence and its associated uncertainties [28]. The differences seen in HTA recommendations for rare disease therapies call into question whether reliance on standard HTA methods is the best mechanism by which to evaluate such therapies. Developing alternative HTA processes tailored to establishing the value of rare disease therapies may reduce uncertainty among key stakeholders (e.g., health system decision makers, care providers) about whether to recommend and/or reimburse these therapies.

We sought to describe the perspectives of health care providers and policy advisors on the challenges associated with evaluating rare disease therapies from a health system perspective. We were particularly interested in their views as health system stakeholders regarding characteristics of rare diseases that may warrant special consideration in HTA and health policy decision making.

4.4 Methods

Our study was a qualitative focus group interview study that was supplemented with a targeted literature review to interrogate the specific findings from the focus groups. This study is described according to the Standards for Reporting Qualitative Research reporting guidelines [29].

4.4.1 Qualitative approach

To better understand concerns related to HTA and health policy decision making for rare disease therapies, we chose to conduct separate focus group interviews with stakeholders responsible for advising on treatment or policy decisions (i.e., health policy decision makers or their advisors; and health care providers). Our goal was to elicit stakeholders' opinions about shortcomings of current HTA processes for rare disease therapies and their ideas regarding potential ways to improve how such therapies are assessed and valued from a public payer perspective. We took an interpretivist point of view following a qualitative description approach, that would allow us to develop a deep understanding of and describe a particular phenomenon based on participants' experiential knowledge [30,31].

4.4.2 Sampling and recruitment strategy

We recruited physicians and policy advisors using purposive sampling, a deliberate, non-probability sampling method used to select participants who could provide rich data related to the research topic [32,33]. Each participant was chosen because they had formal knowledge and/or practical experience related to treatment or policy decision making regarding rare disease therapies. To facilitate the focus group interviews, we chose rare inherited metabolic diseases (IMD) as a case study because pharmacotherapies for several IMDs have become available in recent years (e.g., enzyme replacement therapies for lysosomal storage disorders) [34] and have been formally reviewed by HTA agencies and health policy decision makers in many

jurisdictions. We therefore recruited physicians providing health care to those diagnosed with rare IMD. Policy advisors were eligible to participate if they had experience in evidence review activities that resulted in recommendations for the development, use, or reimbursement of interventions for rare diseases. We sought five to eight individuals per focus group in order to facilitate an in-depth discussion and allow each participant to contribute [32].

The Garrod Association, a professional organization whose members are involved in caring for individuals with rare IMD, facilitated recruitment of metabolic physicians by sending a recruitment invitation email to its membership. Policy advisors were sent a recruitment invitation email by a member of their professional network using publicly available contact information. Individuals interested in participating in the focus groups contacted the lead author (KT) for more information and to confirm eligibility. Eligible respondents were asked to provide signed informed consent to participate in the study. The study protocol was approved by the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario Research Ethics Board.

4.4.3 Data collection

Focus groups were held separately for physicians and policy advisors and were conducted via teleconference, in order to reach a geographically dispersed group of people across Canada who would otherwise be unable to gather in-person [35]. We reasoned that both physicians and policy advisors would likely be familiar with the research topic, thus would be comfortable convening via teleconference. We developed a semi-structured interview guide for each focus group that included questions related to the generation and evaluation of evidence for clinical interventions for rare diseases. The interview guide covered current methods for conducting HTA to inform treatment and policy decisions about rare disease therapies and potential areas for improvement.

The interview guide was reviewed by all members of the research team. One team member (KT) conducted both focus group interviews, with at least one additional team member attending as an observer.

4.4.4 Data processing and analysis

Each interview was audio-recorded with participants' consent and transcribed for data analysis. The transcripts were analyzed using thematic analysis [36], which involved generating a set of initial codes based on interesting features of the data and then organizing those codes into key themes related to the research topic. To do this, a series of research team meetings were held to review the transcripts and inductively identify emerging concepts from each focus group interview. Key concepts that were identified in the focus group data were organized into a coding system that was applied by one member of the study team (KT) using NVivo 10 software (QSR International Pty Ltd.) across the entire data set. Coded transcripts were reviewed and verified by a second team member (BP) to confirm all codes had been applied appropriately and that no themes had been overlooked. To ensure credibility and trustworthiness [37], we used several approaches including: debriefing sessions after each focus group to identify key perspectives, multiple research team members reviewing transcripts, multiple team discussions to identify themes, and transcript coding verification by a second team member. In addition, we corroborated our focus group findings with a targeted literature review as described below.

4.4.5 Targeted literature review

To interrogate and contextualize the focus group interview findings, we conducted a targeted literature review to identify whether specific strategies discussed by focus group participants to improve HTA and/or the determination of value for money for rare disease therapies have been implemented across some jurisdictions or recommended in the literature. In particular, we were

interested in identifying what, if any, strategies are currently being used/proposed to ensure ongoing evidence generation after initial market authorization for rare disease therapies; what criteria/guidance are included if rare-disease specific strategies for HTA are in place; and, what accommodations are made/proposed in the context of rare diseases (e.g., nature of the condition). We were also interested in strategies discussed in the literature that were not mentioned in the focus group interviews. Using keywords, including "health technology assessment", "health policy," "rare diseases," and "orphan drugs" and associated Medical Subject Headings (MeSH), we searched Ovid MEDLNE (R) 1946-December 20, 2019 for potentially relevant titles. Our search strategy was not meant to be exhaustive, but rather was aimed at identifying *key* data sources related to the topics covered in the focus groups. If a jurisdictional-specific HTA strategy was mentioned in an eligible published article, we relied on publicly available information from that HTA organization website for further information about their specific strategy(ies).

One research team member (KT) reviewed titles and abstracts for all records retrieved in the search for relevance to the research topic. A publication was potentially eligible for inclusion if the article was: i) focused on rare diseases, ii) included details about specific processes or recommendations for conducting HTA and/or making reimbursement decisions in the context of rare diseases, and iii) was written in English. Full texts of all potentially eligible articles were reviewed and an article was selected for inclusion in the final analysis if the above criteria held true upon its full review. Information from included articles was synthesized narratively and integrated with focus group findings.

4.5 Results

We conducted two focus groups with a total of 9 participants (metabolic physicians n=6; policy advisors n=3). There were five women and four men. Participants were residents of one of four Canadian provinces: Alberta, Ontario, Quebec, Newfoundland and Labrador. Focus group interviews lasted 60 minutes (policy advisors) or 75 minutes (physicians).

Our electronic database search in MEDLINE yielded 258 citations, from which 25 articles were deemed eligible for inclusion as they specified different strategies taken to systematically evaluate therapies for rare diseases and/or make funding decisions (see Supplemental File 4-1: list of included articles & Supplemental File 4-2: flow chart describing results from search and screening process). Of these, 10 included details about rare disease therapy-specific HTA processes or recommendations, 10 described strategies related to making funding decisions, and 5 included discussion on both topics.

4.5.1 Theme 1: Corroborating the policy problem

Focus group participants noted that evidence synthesis to support decision-making is challenging because for many rare disease therapies there are few primary studies that meet the usual criteria for inclusion in a review, for example, the use of specific study designs like randomized controlled trials or studies with adequate statistical power to generate reliable results.

"[Systematic reviews] often don't work very well [chuckles] in rare disorders just because of small numbers and the way they evaluate studies are often based on having adequate power, and larger numbers, and randomized placebo controlled, and for the reasons we've already, people have already been mentioning, that is a challenge when it comes to rare diseases and orphan drugs." – Physician 6

"P1: Yes, I've very rarely seen Cochrane reviews for inherited metabolic diseases. I: Yeah. P6: They've done a few, like for McArdle, but they usually

end up coming up with, there's no real benefit for any of the interventions tried, that's their conclusion." – Physicians 1 & 6

Participants also indicated that the clinical evidence that is available is often underpinned by substantial scientific uncertainty, which makes it especially difficult to interpret, even with modelling approaches that attempt at prediction.

"…I think we're all kind of saying the same thing. In [province], we are specifically frustrated with modeling and predictions because really, after about six months, modeling means you're guessing about what's going to happen and so that's really saying the same thing that we need better understanding of the course of the disease, the progression, so that can be our comparator when we don't have a control group." – Policy advisor 3

As a result, participants, particularly those in the policy advisor group, reported that in practice, different approaches to synthesizing and interpreting evidence are frequently adopted out of necessity to support HTA and policy decision-making, which means that evidence standards are lower for rare disease therapies compared to therapies for more common diseases.

"I think for rare disease, we're more liberal in the evidence that we're considering, just by the nature of it. We're more inquisitive about what is going on and finding out more about the natural history. I mean, we have a completely separate process for rare diseases than we have for regular diseases, not because there's necessarily going to be a differential criteria for decision-making, though I think there is, but also just the fact that we need to have a differential approach to evaluating and weighing up the evidence." – Policy advisor 2

"I think that I would just reiterate that we know when we're reviewing medications for coverage, we see studies that involve, 40 participants worldwide. And so we have to accept that that's actually, a very reasonable sample for some of the conditions and compared to, thousands of participants in studies for cardiac medications. So I guess, it sounds negative but the bar really goes down. I mean, that sample size hardly powered to find a difference, so that's when the difficulty in interpretation comes in. I guess that's what's we

accept is that instead of just having an n of 1 at least we have an n of a reasonable sample, and companies have made the effort to try to gather as many [participants] as they can." – Policy advisor 3

Participants discussed that the paucity of clinical evidence necessitates consideration of all available information, possibly even including case studies, because so little is known about many rare diseases.

"I mean, this is such a difficult population to get any information on that anything that is data is an evidence base. Just to give us more pictures of how the disease progresses, what the natural history is, but also what's the variability in them, so we've looked at case series, we've looked at single cases even, just to give us some more background because sometimes the evidence base is so weak that every type of evidence comes into play." – Policy advisor 2

As described in the Introduction, the challenges with HTA for rare diseases are widely acknowledged in the literature. Implicitly, the published articles and HTA websites we reviewed recognized these challenges by virtue of their development, use, or recommendations of rare disease-specific approaches for HTA [7,38–45].

4.5.2 Theme 2: Rare disease-specific approaches for the synthesis and use of evidence

In recognition of the current inadequacies regarding standard HTA and policy decision making processes for rare disease therapies, focus group participants suggested that there would be value in having a more formalized strategy to evaluate the evidence and make recommendations or decisions about these therapies that would reduce some of the most salient uncertainties.

"I think that it's basic, but evaluating treatment in rare diseases, we just don't have a framework that is very good. I don't feel that I have enough knowledge in regards to expertise in that area, but I think there needs to be a whole different framework for evaluating treatment in rare diseases." – Physician 4

Specialized evaluation approaches for conducting HTA and value determination for rare disease therapies were commonly discussed and recommended in the literature [7,38–45]. We identified several jurisdictions that have implemented jurisdiction-specific strategies for conducting HTA and value determination for rare disease therapies or have implemented special methods related to reimbursement of these therapies. For example, the National Institute for Health and Care Excellence (NICE) in the United Kingdom has established the Highly Specialized Technologies (HST) programme that assesses drugs for "very rare conditions" [46], and the Scottish Medicines Consortium has implemented an additional process that can be requested by orphan drug manufacturers after their standard HTA is complete called the Patient and Clinician Engagement (PACE) process [47]. In Canada, some provincial health policy advisory groups, such as Ontario's Drugs for Rare Diseases Working Group, have established specific strategies to evaluate rare disease therapies and inform funding decisions from a public payer perspective [41,48].

Participants in our focus groups posited that a specific evaluation strategy for rare disease therapies might include methods to ensure ongoing evidence generation (e.g., a standard recommendation that policy decision-makers require the collection of long term follow-up data for rare disease therapies approved through a rare disease-specific process to ensure that their intended benefits are being realized), and/or developing a common set of evidence review standards to be applied for evaluating rare disease therapies. Participants also noted that because evidence generation, evidence synthesis, and policy decision making are intrinsically linked, a specific evaluation strategy for are disease therapies should be developed as a collaboration across sectors, rather than relying solely on evidence produced by industry, which may be

subject to bias. This would involve collaboration among all key stakeholders, including health system decision makers, patients and clinicians, researchers, and industry.

"I think it's more the use of the evidence rather than in terms of how the funding is put into place, and how we follow-up to determine whether or not the therapy is working in patients. That could be, I think, done better." –Policy advisor 2

"P4: I think as [name] had mentioned maybe initial trial endpoints do have to be established in terms of looking at efficacy, but then in my mind there almost needs to be a sort of phase 5 clinical trial to say okay yes, we have proven efficacy in terms of the endpoint but does that actually equate meaningful improvement in quality and duration of life? Because I think not always…." P5: Yeah, and I think that brings up a very good point as well with the sort of extension of these studies, the [research network] is a good example of a very long term. But it's quite difficult to maintain the clinical monitoring that's required to document these effects without the resources that you would have within a study trial…. We have the opportunity, as was mentioned earlier, that we have a network across Canada, and I think this is ideally what we should be aiming for but there would have to be cooperation at the government level in terms of looking at these issues in much more detail, which I think we have the ideal situation in Canada to do, but we need some resources to do that. P1: And again, could be a partnership between government and pharma. P5: Government, pharma, and us. P1: Yes, exactly. – Physicians 1, 4 & 5

"I think no biased funding, so not just relying on the pharmaceutical industry. So, investing in research, having a sort of national framework for how we're going to approach this, rather than relying on companies that come up a single drug as a cure for a certain disease, and relying on marketing and promotion in the form of evidence there." – Policy advisor 3

From our literature review, we determined that, in some jurisdictions, when rare disease therapies are not well supported by evidence or are unavailable through conventional reimbursement mechanisms, authorities have implemented alternative jusrisdiction-specific strategies that allow access [49,50]. A relatively common strategy is the execution of managed-entry agreements that include coverage with evidence development and performance-based reimbursement processes [49]. For example, in the UK, when considering a rare disease therapy

that is accompanied by substantial uncertainty in the evidence, the NICE HST Evaluation Committee may recommend a managed access arrangement that requires further generation of evidence over a specified period of time while facilitating patient access to the therapy [46]. Under such schemes, reimbursement is conditional based on a set of mutually agreed upon conditions such as which outcomes will be measured and how often, as well as treatment continuation criteria and interim funding responsibilities [46]. Using managed entry agreements or similar schemes to generate longer term, real-world effectiveness evidence is thus an existing approach that aligns with the views of our focus group participants and can be part of a separate HTA strategy for the evaluation of rare disease therapies.

4.5.3 Theme three: Factors that warrant specific consideration in HTA for rare disease therapies

Focus group participants described factors that influenced their interpretation of the evidence for rare diseases therapies and that may warrant further consideration in HTA and policy decision making. First, participants stressed the importance of considering knowledge about the natural history of a rare disease to better assess whether a treatment under review actually alters the course of disease. For example, as one participant noted, the standard of evidence required to inform decision making may depend on whether the disease has a stable versus progressive disease pattern.

> *"First of all is the determination of whether or not the drug or the disease that we're dealing with is truly a rare disease and then it's looking at the natural history and trying to work out if we can actually work out what the nature of the disease is, and sometimes we can't even get beyond that stage, when we're looking at therapies for rare diseases. If we've got no idea what the actual implications of the disease is, then how can we legitimately fund a therapy that we don't know what it's changing or how it's changing it? After that we then*

start to look at the evidence and try to weigh up whether or not there's a suggestion that the treatment can change the natural history of the disease, and from there we start to look at the likely impact of those changes." – Policy advisor 2

"So, it's hard, as you said, to really make that judgment, and that's why I don't think we necessarily can rely on those individual tests, but have to rely on the global picture and we have to be aware of what the patient is expecting and what we're expecting from this. Certainly, if it is a progressive disease and we see stability, that might be significant. If it's a disease that's not progressive, and we see improvement then that might be more significant than just stability. So it's very hard to give a concrete answer to that question because I think it's quite variable depending on the disease." – Physician 5

Second, participants discussed the importance of understanding the intended biological mechanism for a treatment and noted that there may be different standards of evidence for therapies that are considered transformative versus those that have a more incremental effect. For example, one of the policy advisor participants spoke about the desire for rigorous explanatory evidence (e.g., randomized controlled trials) to inform decisions about therapies for which there is only a modest treatment effect, highlighting the need for comparative effectiveness evidence to reduce uncertainties for such therapies. In addition, they discussed the relevance of a causal evaluation framework that allows for different kinds of evidence (e.g., regarding pharmacokinetics) that are typically not considered in HTA for therapies for more common diseases.

"My comment about, about RCTs really only applies to those areas where, in a sense, the treatment works or it doesn't, so enzyme replacement therapy is a classic example of that. In other areas, RCTs are clearly needed because we need to know what the incremental effect is when you looking at modest changes in disease or severity, then clearly RCTs are important, but a lot of the time we know that we're having to use the whole evidence base to try and weigh up not just whether or not the treatment works, which is what the trial

can tell us, but what does that actually mean in terms of what the implications to patients might be." – Policy advisor 2

"Yeah, I mean, we actually go back to think about the whole Bradford-Hill approach to looking at causality, which is not really what effectiveness is designed for because it gives us a very good clue what is the pharmacology of this drug and how is it going to work biologically? Is there any evidence of a gradient effect? All of those things really do strongly come into play because we're dealing here with in many ways hypothesis testing within the committee, rather than weighing up of evidence. So, we're looking at all the different pieces of evidence that have come in. It's almost like a sort of evidence for and against in terms of a trial in a sense, and therefore, yeah we're actually looking at all of the things like biological plausibility, which typically for drugs in other areas treatment says it works and the trial says it works, we don't really go into the pharmacokinetics of it. And this time around, we strongly do." – Policy advisor 2

Similar recommendations have been made in the literature with respect to ensuring the natural history of a disease is adequately understood such that the potential value of new rare disease therapy can be assessed [38,42]. For example, Ontario's drugs for rare diseases evaluation framework incorporates these elements by reviewing all available medical literature (including but not limited to randomized controlled trials of the intervention under review) as well as engaging with disease experts to ensure that the actual or potential health effects for a treatment are fully understood [41,48]. In addition, the evaluation framework used in Ontario makes use of an adapted set of Bradford Hill criteria [51] to screen interventions for potential causative effects in an attempt to systematically bring together pieces of evidence that may otherwise be excluded using standard HTA practices [41,48]. Other HTA authorities, including the NICE HST programme, also emphasize consideration of the nature of the condition (i.e., disease severity, morbidity) during their evaluation and interpretation of sparse clinical evidence for rare disease therapies [46,47].

Finally, focus group participants spoke about the fact that rare disease treatments are often very expensive and that their price is an important factor when it comes to HTA, determining value for money, and health policy decision-making, especially in a publicly funded system.

"Well the other thing that is always hovering in the background is the incredible cost of these treatments, and when the government agencies are assessing these medications, this is always, I think, in the background." – Physician 3

"... if you say, we don't have enough patients to judge then you're called rare, in which case the decision to reimburse, particularly when it's expensive, requires a different approach." – Policy advisor 1

Some participants in the physician group also noted that there are potentially substantial costs to the health care system and society by not funding effective treatments for rare diseases because of their high price, so continuing to ensure these factors are well integrated in HTA is important.

"So if you have a drug that's effective, but expensive, and you have a patient who could benefit from it, but it may not be available to them because of cost and government objections to paying, what are the costs to society of this patient in terms of other costs to care for this person? For example, special education, institutional care, disability and welfare payments. ...that should be taken into consideration when you compare the cost of a possible successful treatment." – Physician 3

"I think the health technology assessment kind of component, it's a bit separate from evaluating- it's related to evaluating evidence, but it also takes into account, as [name] had mentioned earlier, the costs of some of these treatments to society versus the cost of not treating individuals, and having people with poor outcomes that require more health care, social services etcetera." – Physician 6

Likewise, both direct costs to the health care system as well as opportunity costs that accompany rare disease therapies are commonly discussed in the literature, along with recommended

methods for determining value for money to inform reimbursement decision making [8,38,40–42,44,45,52–56]. Including a formal economic assessment is nearly always a requirement of the HTA process, regardless of the therapy; however, some jurisdictions have adapted their standard processes to better accommodate rare disease therapies that have significant per-patient costs [57]. For example, Australia has implemented the Life Saving Drug Program for situations when there is sufficient clinical evidence for a rare disease therapy, but its cost-effectiveness analysis results in a negative reimbursement recommendation and there is no suitable alternative treatment [39,58]. Managed entry agreements, as described above, may also include financial risk sharing conditions between payers and manufacturers [49].

4.6 Discussion

The findings from our study corroborate, from provider and policy advisor perspectives, that therapies for rare diseases often do not meet the same standard of evidence for HTA expected for therapies for more common diseases because of inherent limitations in generating strong clinical evidence. These shortcomings add further complexity to the already difficult task of determining which health interventions provide adequate value to support their use and reimbursement in a publicly funded health care system. Stakeholders in our study agreed that there is an opportunity to improve upon the mechanisms by which rare disease therapies are currently reviewed. Many of the potential solutions discussed by our study participants strongly aligned with the results from our targeted literature review, which revealed that rare disease-specific evaluation strategies and methods have been sporadically implemented by some HTA producers.

Collectively, the results from our study suggest that the uncertainties in clinical and economic evidence for rare disease therapies, which can lead to inconsistent and unpredictable policy decision-making when considered using standard HTA strategies, could be mitigated by

implementing different HTA strategies, on their own or within a jusrisdiction-specific HTA strategy. Some of these processes including facilitating the continued generation of evidence following the approval of a therapy (e.g., by providing funding approval on the condition that more data about effectiveness will be gathered [49,50]), considering a broader body of evidence than would typically be reviewed under a standard HTA strategy, including evidence from studies that describe the natural history of the disease and/or pharmacokinetics of the therapy under review [41,46], and specifically eliciting and considering perspectives from disease experts (e.g., patients, clinicians), especially when interpreting clinical evidence that is weak or limited [41,46,47].

While some of these strategies have been implemented in some HTA organizations, their use is not consistent from one HTA agency or jurisdiction to another and there remains no standard evaluation framework for HTA for rare disease therapies that is applied consistently and transparently across different jurisdictions and that considers all of the factors deemed important by our focus group participants. Thus, there is an opportunity to formally review and compare both overarching frameworks and the specific strategies and processes within those frameworks to identify potential barriers and facilitators to adopting a standardized framework that is consistent across jurisdictions, but that could be operationalized according to specific considerations within each jurisdiction. Multi-stakeholder engagement, especially with knowledge users from various HTA organizations, would be essential to ensure that all relevant inputs be considered.

Without an agreed upon evaluation framework that seeks to address and reduce the inherent uncertainties in clinical and economic evidence for rare disease therapies, decision making related to use and reimbursement will continue to be inconsistent among jurisdictions

leading to potential inequities in care for rare disease patients and families. The literature demonstrates that differing reimbursement policy decisions related to rare disease therapies likely result from how the evidence is interpreted and how much uncertainty is considered acceptable among policy advisors and decision makers [28]. This does not mean that a harmonized framework would necessarily result in universally relaxed standards for rare disease therapies. Rather, a rare disease-specific framework would provide an opportunity to not only fairly review new therapies but also to implement routine re-assessment of rare disease therapies previously approved, based on new information generated post funding approval, and to "disinvest" in therapies that are not sufficiently cost-effective and enhance sustainability of publicly funded health care systems as new therapies continue to emerge.

4.6.2 Study limitations

While our study provided important insights about HTA and health policy decision making in the context of rare diseases, it is not without limitations. First, the preferred sample size for focus group interviews is between five and eight individuals [32]; we only recruited three and six participants to the policy advisor and metabolic physician focus groups, respectively. In particular, the small number of policy advisors may limit the transferability of insights related to HTA and health policy decision making for rare disease therapies. In addition, both focus group interviews were conducted via teleconference, which may have reduced the interactions between participants and in turn, limited the richness of our data set [35]. Despite having a small number of participants who convened via teleconference, there was still a lively discussion in each group with participants comparing and debating their opinions with those described by others in the group. Having a small number of participants in each focus group also allowed each participant plenty of time to speak and fostered in-depth discussion of the research topic. Thus, we do not

expect that the richness of data collected was compromised by the small number of participants. Adding a webinar option in future focus group studies where participants are unable to convene in-person may provide a better alternative [59]. We did not formally assess data saturation, so it is possible that we have not identified an exhaustive set of themes; however, we did corroborate our focus group findings with the literature from which similar themes emerged. Transferability of the results within or beyond Canada may be limited given that we recruited a purposive sample of Canadian policy advisors and physicians; however, our sample was diverse with respect to geography, gender, and level of experience potentially mitigating some of this concern. Our results may also be limited in transferability to other rare diseases given that we focused on IMDs by involving only specialist metabolic physicians, specifically. This group of conditions do exemplify some of the typical characteristics of rare diseases, including small patient populations, significant clinical heterogeneity, and few available treatment options; thus, it is likely that many of the themes identified in this work could be transferable to other rare diseases. Future work should explore perspectives among different rare disease groups to understand if their views align with our study. In addition, engaging with a broader group of policy advisors across other jurisdictions/organizations is important towards understanding the acceptability and feasibility of developing and/or adopting rare disease specific HTA frameworks or strategies.

4.7 Conclusion

Conducting rigorous HTA for rare disease therapies to determine which therapies provide adequate value for money is especially challenging given sparse clinical and economic evidence, resulting in significant uncertainty surrounding health policy decisions such as reimbursement [7,45]. Issues that are salient among rare disease stakeholders and that potentially warrant

consideration in future HTA include bringing together evidence that adequately describes disease severity and nature of the condition (e.g., stable vs. progressive), the anticipated effect of the therapy (e.g., incremental vs. transformative), and long-term effectiveness of the therapy. Some rare disease specific frameworks or strategies have been implemented; however, these methods are not consistently and transparently applied across jurisdictions. There is an opportunity to further optimize HTA for rare disease therapies to address practical uncertainties and improve rare disease health policy decision making by formally evaluating and comparing these various evaluation frameworks. Involving multiple stakeholders and promoting better exchange between HTA organizations to develop and evaluate a common evaluation framework for rare disease therapies would ensure that information relevant to all stakeholders is considered within subsequent decision making contexts.

4.8 Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ottawa Health Science Network Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

Consent for publication

Not applicable.

Availability of data and material

In order to protect the privacy of our study participants, research data are not publicly available.

Competing interests

None to declare.

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Author Contributions (using CRediT)

Kylie Tingley: Conceptualization (equal); methodology (equal); investigation (lead); formal analysis (lead); writing – original draft preparation (lead); writing – reviewing & editing (equal). **Doug Coyle:** Conceptualization (equal) methodology (equal); formal analysis (supporting); writing – reviewing & editing (equal); supervision (co-lead). **Ian D. Graham:** Conceptualization (supporting); formal analysis (supporting); writing – reviewing & editing (equal); supervision (supporting). **Pranesh Chakraborty:** Conceptualization (supporting); writing – reviewing & editing (equal); supervision (supporting). **Kumanan Wilson:** Conceptualization (supporting); writing – reviewing & editing (equal); supervision (supporting). **Beth K. Potter:** Conceptualization (equal); methodology (equal); investigation (supporting); formal analysis (supporting); writing – original draft (supporting); writing – reviewing & editing (equal); supervision (co-lead).

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4.9 List of supplemental files

The following can be found in the supplemental information for Chapter 3:

- Supplemental File 4-1: PRISMA flow diagram outlining results from search and screening process (Adapted from: Liberati et al. 2009).
- Supplemental File 4-2: List of included studies for targeted literature review (n=25).
- Ethics approval letters (see Supplemental File 2-3)

4.10 Citations

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5 Integrated Discussion

While some broadly define rare diseases as having a prevalence of 150 cases per 100,000 births, this definition is controversial and definitions of 'rare' vary substantially across jurisdictions [1]. Several authors and organizations specifically define ultra rare diseases as those with a prevalence < 1 case per 100,000 births in order to distinguish those diseases for whom achieving conventional evidence standards may not be possible [1,2]. The majority of these rare diseases are genetic in origin and approximately 70% present during childhood [3]. Many rare diseases manifest as serious chronic, progressive, life-shortening conditions for which transformative, disease-modifying therapies do not exist [4]. Consequently, there are significant unmet health care needs in these populations. Over the last 30 years, legislation in many jurisdictions (e.g., Orphan Drug Act in the United States) has provided incentives for industry to develop novel therapies for rare disease patients [5,6]. These incentives, coupled with prioritization of rare disease research at an international level [7], have resulted in the rapid emergence of numerous therapies for rare diseases, all of which are expected to have rigorous evaluation and review prior to implementation [8].

Gold standard methods used to evaluate the effectiveness of interventions in order to inform decision making regarding their use primarily include randomized controlled trials (RCTs) as well as systematic reviews and meta-analyses of RCTs [9,10]. In the context of rare diseases, and particularly for ultra rare diseases, conventional RCTs are often challenging to implement while maintaining adequate internal validity and minimizing bias [11,12]. These challenges have been well described in the literature and largely relate to the typically small, clinically heterogeneous, and geographically dispersed patient populations that are characteristic of many rare diseases [13]. As a result, there is often substantial uncertainty in the clinical evidence for many rare

disease therapies regarding potential harms or adverse effects, impact on quality of life, long term impact on health outcomes, and/or cost-effectiveness [14]. This imperfect evidence contributes to uncertainty and disagreement among stakeholders when making complex decisions about using, recommending, prescribing, and/or reimbursing new and existing rare disease therapies.

As is the case for much of health care policy, decision making regarding rare disease therapies is a complex process that involves many factors. As described by Lomas, there is an 'institutional structure for decision making' that involves a variety of formal (those who directly participate in decision making processes) and informal (those who influence decision making processes in other ways) actors [15]. In our context, health system decision makers, such as government officials, are considered formal actors, while stakeholders like patients and families, clinicians, and policy advisors are considered informal actors. Within the institutional structure for decision making, both *information* (i.e., knowledge derived from evidence, anecdote, experience, media) and *values* (i.e., one's beliefs, ideologies, interests) are important influencing factors [15]. This dissertation is primarily focused on the *information* piece because decision making in this context is often dominated by the quality of information, particularly the clinical evidence, upon which a decision is justified.

That said, there are several other factors beyond the availability and quality of evidence that may shape decision making among various stakeholders. The first is *cost*. From a public payer perspective, the high price associated with rare disease therapies coupled with the typically modest clinical benefit, make it difficult for rare disease therapies to meet standard cost-effectiveness thresholds, thus impacting decision making regarding use and reimbursement [16]. Related to cost, decisions may also be influenced by *feasibility* issues associated with integrating

a new therapy into the existing system of care if adequate resources are not available to administer a therapy. Additionally, *ideologies* held among stakeholders and the political climate may also conflict with what the clinical evidence says and have an influence on decision making [15,17]. Value judgements, including unmet need, innovation of the candidate therapy, disease severity, rarity, treatment alternatives (or lack thereof), among others, have been identified as important influencing factors in different decision making contexts [18,19].

The difficulty of decision making when there is imprecise, sometimes conflicting, clinical evidence concerning rare disease therapies has long been recognized but has not been sufficiently dealt with. Currently, little guidance is available that addresses different stakeholder needs for managing uncertainty in context of decision making about rare disease therapies. As such, the goal of this dissertation was to integrate stakeholder perspectives and evidence related to how rare disease therapies are evaluated to better understand key drivers of uncertainty in decision making and make suggestions to guide future evidence generation, synthesis, and knowledge translation to help manage uncertainty in this context.

5.1 Summary of Research Findings

Using the taxonomy of uncertainty in health care put forth by Han and colleagues [20], Chapter 2 of this dissertation focused on identifying challenges and potential solutions for mitigating *scientific uncertainty*, which is data-centred and related to clinical evidence. Chapter 2 outlined the design of a meta-narrative literature review and a set of focus group interviews to enhance our understanding of the perceived challenges and proposed methodological solutions for generating strong clinical research concerning rare disease therapies [13]. The main findings from this work revealed three fundamental challenges for generating robust clinical effectiveness

evidence including: limitations in recruiting a sufficient number of study participants for adequate statistical power, inability to address heterogeneity in treatment effects across the clinical spectrum, and reliance on short-term outcomes whose clinical relevance is often not validated [13]. When these challenges cannot be overcome or adequately addressed, scientific uncertainty may be amplified, and evidence-informed decision-making processes about rare disease therapies become more challenging. This study showed that numerous methodological approaches have been suggested in order to reduce scientific uncertainty concerning rare disease therapies, and there has been increased recognition over time that pragmatic and patient-oriented methodological approaches (e.g., patient registries that incorporate patient-centred outcomes) are important towards addressing current gaps in knowledge about these therapies [13]. Comparing these approaches to conventional explanatory study designs (e.g., RCTs), there are important tradeoffs with respect to internal and external validity that may be exacerbated in the rare disease context and that warrant further exploration towards increasing their value in mitigating scientific uncertainty. In addition, there is a need for inclusive discussions among all stakeholders to identify approaches to evidence generation that address the decisional needs within each group.

Chapter 3 of this dissertation sought to gain a deeper understanding of why and how different stakeholders choose whether to participate in trials or other types of research, and how they value research findings in their decision-making processes. We conducted three separate focus group interviews with patients with rare metabolic diseases or their family members, specialist metabolic physicians, and policy advisors to elicit their perspectives on participation in research activities and how research findings are used to support decision-making at both individual- and population-levels. Data from the focus group interviews did not support conventional

perspectives that patients and families choose to participate in research studies mainly because of therapeutic misconception (gaining access to treatment). Rather patients and family members expressed more nuanced views that included advancing science and having the opportunity to share their experiences as motivation for participation in clinical research. That said, patients/family members and physicians both described the difficulties in weighing harms versus benefits of accepting treatments not well-supported by evidence. Physicians also reported feeling conflicted in their dual role as patient advisor/advocate and evaluator of the evidence. These findings highlight key matters of *personal uncertainty*, which is patient-centred and comprises both psychosocial and existential elements (e.g., how a therapy may impact one's quality of life or personal relationships) [20], and considerations of the role that evidence plays in health-related decision making processes. Thus, identifying and implementing ways of easing issues of personal uncertainty cannot be overlooked among potential solutions for managing overall uncertainty in health related decision-making.

Not surprisingly, the results from Chapter 3 demonstrated that policy advisors were primarily focused on critically appraising the evidence to inform recommendations for the health system and population level decision-making. In this population level context, *practical uncertainty*, as it relates to structures and processes of health care (e.g., whether implementation of a therapy is feasible within the current system of care) [20], as well as scientific uncertainty are salient issues among stakeholders. Chapter 4 of this dissertation explored, in more detail, the challenges experienced by physicians and policy advisors when evaluating rare disease therapies from a health system perspective and determining their value for money. We integrated the findings from focus group interviews with a targeted literature review to identify characteristics of rare diseases and their candidate therapies that may warrant special consideration in health

technology assessment (HTA) and health policy decision making. Characteristics raised by study participants to consider in order to reduce both scientific and practical uncertainties in HTA included bringing together evidence that adequately describes and accounts for the nature and severity of the disease, the anticipated effect of the therapy, and the long-term effectiveness of the therapy. These findings were corroborated in the literature, which described specific frameworks for conducting HTAs for rare diseases that have been implemented in some jurisdictions. There remains an opportunity to further optimize HTA for rare disease therapies to address practical uncertainties and improve rare disease health policy decision making by developing a harmonized HTA strategy that can be operationalized and implemented across jurisdictions according to their specific circumstances.

We have summarized the findings from this dissertation according to the different decision problems that are faced by patients with rare diseases and their family members, health care providers, and policy advisors, highlighting the various areas that are influenced by scientific, practical, and personal uncertainties (Table 5-1). The objective of this chapter is to present an evaluation framework for rare disease therapies that advocates for a collaborative approach that operates across the lifecycle of a rare disease therapy and addresses these key areas of uncertainty.

Table 5-1. Describing decisions and dilemmas across stakeholder groups based on a synthesis of findings from this dissertation.

Stakeholder group	Decision	Dilemma	Issues of uncertainty
Patients and families	Should I participate in a trial of treatment X?	Recognition that evidence development is important and that there is an altruistic aspect of participating in research, but also wanting to make the best decision to maximize personal benefit. Potential therapeutic misconception	*Personal uncertainty* • Will the personal benefit be "worth it" (e.g., will there be compromises on quality of life, activities of daily living, etc.)?
Patients and families	Should I accept treatment X?	Limited evidence available regarding the benefits and/or harms for a treatment. Willingness to "try anything" in the absence of existing effective therapies, but also not wanting to compromise quality of life.	*Scientific uncertainty* • Is/are the outcome(s) relevant and meaningful to me? • Are the results applicable to my situation? *Personal uncertainty* • Will the personal benefit be "worth it" (e.g., will there be compromises on quality of life, activities of daily living, etc.)?
Physicians and care providers	Should I prescribe or recommend treatment X?	Limited evidence available regarding the benefits and/or harms for a treatment. Recognition that we have scarce resources within the health system but wanting to advocate for patients regardless of cost to the system.	*Scientific uncertainty* • What is the natural history of the disease? • Are research results applicable to my patient (external validity)? • Is/are the outcome(s) clinically meaningful and/or patient-centred? • Is the duration of the study sufficient? How certain are we of the long term implications of treatment? • Is the study internally valid? *Practical & personal uncertainty* • How do I best advocate for my patient? • Can the health-system support this treatment (i.e., high price, resource availability)?

Health policy advisors	Should I recommend that treatment X be used and/or reimbursed?	Limited evidence available regarding the benefits and/or harms for a treatment. Need to balance opportunity costs across the whole health system	*Scientific uncertainty* • What is the natural history of the disease? • Is/are the outcome(s) clinically meaningful and/or patient-centred? • Is the duration of the study sufficient? How certain are we of the long term implications of treatment? • Is the study internally valid? *Practical uncertainty* • Can the health system support this treatment (e.g., high price)? • What are the opportunity costs associated with this treatment?

5.2 Evaluation framework and research ecosystem

Based on the findings from this dissertation, we have developed an evaluation framework with the goals of: i) addressing and mitigating important aspects of uncertainty from the perspective of the knowledge user stakeholders as described in Table 5-1; ii) promoting evidence-informed decision making at the individual and population level about rare disease therapies; and iii) improving the efficiency of the generation, synthesis, and use of evidence in making decisions about rare disease therapies. Towards this end, we have developed a set of eight principles within these three broad areas: evidence generation, evidence synthesis, and decision support (Figure 5-1).

The three components of the evaluation framework are interrelated (Figure 5-1). While we see these components as operating within a cycle of evidence generation, evidence synthesis and decision support, the relationships can be bidirectional. The principles highlighted within each component follow from the findings of the three studies in this dissertation and address key areas of uncertainty for stakeholders who are knowledge users in the research ecosystem (patients and families, clinical providers, and policy advisors). Ideally, the framework would be adopted using a coordinated, lifecycle approach with respect to the principles across all three components, but it is also possible to act on the principles within a single component of the framework. Critical to the successful implementation of this approach and based on the findings from Chapters 2-4, we strongly advocate that an inclusive research ecosystem be enhanced or developed in order to adopt these principles. This broad collaboration across all relevant stakeholder groups should integrate and respond to the needs of knowledge users (patients and families, clinical providers, and policy decision-makers and advisory) and partner users with knowledge producers (academic researchers, industry-based researchers, and HTA producers). This ecosystem

approach is aligned with integrated knowledge translation, by including multi-stakeholder engagement throughout the entire lifecycle of a rare disease therapy, from conceptualization through to implementation.

Figure 5-1. Evaluation framework overview.

Integrated knowledge translation is an approach that brings together researchers and knowledge users (patients and family members, health care providers, policy advisors, health system decision makers, industry) to co-produce and apply knowledge that is most relevant and impactful for knowledge users [21]. Knowledge users bring unique expertise to a research project via lived experience and can provide context for implementation that, coupled with researchers' methodological and scientific expertise, may improve efficiency and reduce

research waste [22]. Embracing an IKT approach means engaging knowledge users throughout the entire research process, including determination of the research questions and which methodological approach to use, selection of outcome measures and development of data collection tools, as well as interpretation and implementation of study findings [21,22]. Partnering with knowledge users from the beginning and actively engaging them in all aspects of the research process ensures that the information needs among knowledge users are identified and adequately addressed such that the evidence generated can be used to inform their decision making [22]. Towards the goal of generating the most relevant and actionable evidence, we suggest that researchers collaborate and engage meaningfully with patients, families, health care providers, policy makers, and other knowledge users when evaluating rare disease therapies, beginning with conceptualization of research questions through to implementation of study findings.

Several strategies have been discussed or implemented with respect to adopting an IKT approach to research [23]. These include: involving knowledge users as part of the leadership team for a research project, hosting meetings/workshops with knowledge users (e.g., routine research team meetings, steering committee meetings etc.), providing regular updates (i.e., newsletters) regarding research progress, deliberative dialogue approaches, In the context of rare diseases, stakeholders interested in co-creating an evaluation-focused research ecosystem within a specific disease area or jurisdiction could leverage foundational work and build on existing networks - e.g., the Rare Disease Clinical Research Network in the US requires active collaboration with patient advocacy organizations as research partners [24] and there are other examples of existing or new rare disease research networks that have a multi-stakeholder and patient-partnered focus (e.g, Treat-NMD neuromuscular network (https://treat-nmd.org/), CAREforRARE

(http://care4rare.ca/), and INFORM RARE (https://www.informrare.ca/)). While the IKT approach is broadly accepted, formal methods to evaluate the impact of knowledge user engagement in this context are lacking. Thus, we also propose that tools to evaluate the effectiveness of IKT approaches in the context of rare diseases be developed or adapted.

5.2 Evidence generation

Considering the collective findings from the studies included in this dissertation, some common issues emerged that warrant attention. Evidence generation activities mainly focus on reducing scientific uncertainty about the efficacy and effectiveness of a particular intervention but may also incorporate elements to reduce practical and/or personal uncertainty depending on the scope of the research question. The findings from Chapter 2 of this dissertation demonstrated that there are well-known challenges with respect to robust study design and outcomes measurement when using conventional evidence generation methods for rare diseases, particularly for ultra-rare diseases such as the mucopolysaccharidoses (estimated birth prevalence for all mucopolysaccharidoses combined is ~1.5 cases per 100,000 live births [25]) [13]. Inadequately addressing these challenges may contribute to decisional uncertainty among stakeholders (Table 5-1); thus, we suggest the following improvements to primary evidence generation that focus on reducing important aspects of uncertainty identified in this dissertation.

Principle #1: Use innovative methodological approaches to evaluate rare disease therapies, if necessary and relevant

As our initial study (Chapter 2) demonstrated, numerous methodological solutions have been proposed in the literature with respect to overcoming challenges associated with conducting rigorous evaluative studies in small patient populations while maintaining adequate internal validity and minimizing bias [13]. These alternative methodologies include, but are not limited to, crossover trials including n-of-1 trials, adaptive randomization strategies, incorporation of Bayesian analytical techniques, as well as methods that incorporate evaluative studies within observational cohorts or registries (e.g., registry-based randomized trials) [13,26,27]. All of these designs seek to create statistical or practical efficiencies in order to make the best use of limited numbers of patients available for participation in research studies and further reduce the uncertainty in evidence surrounding a specific therapy by maintaining internal validity [13]. We suggest that less conventional designs are appropriate when significant compromises to the internal validity of a standard RCT would be inevitable in accordance with the International Rare Disease Research Consortium's Small Population Clinical Trial Task Force [28]. For example, in instances where very low disease prevalence (e.g., for many ultra-rare diseases) would prohibit sufficient recruitment of study sample to reach statistical efficiency.

If application of these designs has been well justified, **we propose acceptance of alternative designs as best evidence when formally evaluating rare disease therapies in order to inform health policy decision making and reduce scientific uncertainty,** with recognition of associated limitations (see below, principle #4). Continuing to encourage the development and application of study designs for primary evidence generation that create efficiencies in the number of patients required will help reduce scientific uncertainty (Table 5-1). While these study designs seek to preserve internal validity and minimize bias and confounding, we recognize there are tradeoffs with respect to external validity and estimating true relative effects of a therapy that

also must be addressed and that these tradeoffs are of major concern to decision makers (see principle #2 below).

Principle #2: Emphasize robust pragmatic or real world effectiveness evidence as a complement to explanatory evidence when evaluating existing and new rare disease therapies

The results described in Chapter 2 of this dissertation highlighted stakeholder concerns about the applicability of study findings from available evaluative studies to real world settings [13]. In order to maintain strong internal validity, RCTs typically include very homogenous study populations and study protocols often do not accurately reflect actual clinical practice [29]. Much of the debate and/or uncertainty that arises around the effectiveness of rare disease therapies comes from unclear evidence concerning the real world use of the therapy. The findings from our work suggest that uncertainty about: external validity of results derived from highly controlled studies; comparative effectiveness against existing interventions/standard of care; and impacts on longer term health outcomes, are often cited as major concerns among stakeholders when reviewing clinical evidence to inform decision-making (Table 5-1). As a way to address these uncertainties, we suggest that evidence generation activities should not only focus on safety and efficacy, but also prioritize development of robust methods to capture pragmatic or real world data and to then incorporate these data into evaluations of treatment effectiveness. **An increase in strong real world clinical evidence on rare disease therapies is likely to address elements of scientific uncertainty experienced across all stakeholder groups, as well as address the practical uncertainty related to integrating new interventions into an existing system of care (Table 5-1)**.

Proposed approaches from the literature for generating real world evidence include development of disease and technology specific registries, integrating research with data capture in electronic medical records, and reviewing health administrative databases [30,31]. In an effort to improve the availability and quality of real world effectiveness data for some treatments for rare diseases, the National Institute for Health and Care Excellence (NICE) in the United Kingdom develops managed access agreements with drug companies seeking reimbursement for their products [32]. Managed access programmes provide interim approval regarding the availability and reimbursement of a therapy with the understanding that a specific set of universally agreed upon criteria for further evidence development will be met by the manufacturer within a given time period [32]. Recently, NICE conducted an evaluation of an expensive enzyme replacement therapy for neuronal ceroid lipofuscinosis type 2, a rare nervous system disorder (estimated birth prevalence <1 case per 100,000 live births in many jurisdictions [33], and recommended the therapy be funded based on the short-term clinical evidence that is available [34]. However, the evaluation committee made this recommendation contingent on adherence to a managed access agreement, which includes collection of real world data (i.e., long-term clinical outcomes, quality of life, and neurodevelopmental outcomes) to demonstrate that the extrapolation of clinical benefit based on short-term clinical data is reasonable [34]. Using this approach, NICE has encouraged further evidence generation that specifically targets reduction in uncertainty around the real world clinical benefit of this rare disease therapy. Similar policies could be adopted in other jurisdictions.

Principle #3: Integrate clear patient-centred outcomes in the design of clinical evaluative studies for rare disease therapies

An important finding from Chapter 2 of this dissertation was the shift in focus from explanatory evidence generation to more patient-oriented evidence generation. This was mainly born out of the criticism that many of the outcomes relied upon in past explanatory studies of rare disease therapies have been surrogate endpoints, presumably chosen by researchers at least in part in an effort to reduce sample size requirements and/or trial duration [35,36]. Without rigorous validation [36,37], surrogate endpoints often have unclear clinical relevance and do not accurately reflect the values of rare disease patients and families [38]. As a result, stakeholders often struggle to interpret study results based on these outcomes and express concern about the applicability of the information to their situation (Table 5-1) [13]. **Towards reducing scientific and personal uncertainty (Table 5-1), we suggest that researchers work with rare disease patients, their families, and other stakeholders to select clear patient- and family- centred outcomes and use them as important primary outcomes in clinical evaluative studies of rare disease therapies.**

Ideally, identifying relevant patient-centred outcomes (how a patient feels, functions, or survives) should be accomplished using multi-stakeholder consensus methods to ensure that chosen outcomes are meaningful across stakeholder groups [39–41]. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative has established specific methodology with respect to the development of core outcome sets (COS), an agreed upon, standardized set of outcomes that should be measured and reported across studies in a given disease area [40,41]. Stakeholder involvement, particularly patient and public involvement, is emphasized within the COMET Initiative's COS development process to ensure that final COSs include outcomes that are most relevant to patients, families, and their caregivers [41]. Measuring patient-centred outcomes may require adapting and/or validating existing tools in rare disease populations. In

addition, we suggest that defining an appropriate minimal patient and clinically important difference also be prioritized by researchers when choosing relevant outcome measures and that this be determined in collaboration with key knowledge users (i.e., patients, families, clinicians, policy advisors). Generating evidence based on clearly meaningful, patient-centred outcomes may reduce scientific uncertainty across all stakeholder groups and lead to improved decision making (Table 5-1).

5. 3 Evidence synthesis

Standard evidence synthesis methods that form the evidence base for health care decision making (e.g., systematic reviews and HTA) seek to appraise and combine evidence from multiple sources pertaining to a particular intervention [42]. Similar to primary evidence generation, evidence synthesis efforts aim to reduce scientific uncertainty by providing a clearer estimate of the potential benefits and harms of a given therapy; this is accomplished by combining clinical evidence of treatment effectiveness across sources. The findings from Chapter 4 of this dissertation revealed that, in practice, different approaches to synthesizing and interpreting evidence for rare disease therapies are frequently adopted out of necessity and that there are several areas for improvement in how such evidence syntheses, particularly HTAs, are conducted. Based on these findings, we make the following suggestions.

Principle #4: In evidence syntheses, incorporate a broad range of efficacy and effectiveness evidence, including evidence from non-randomized sources depending on specific contextual factors

Evidence synthesis studies that seek to determine the efficacy or effectiveness of therapeutic interventions typically focus on evaluating evidence from RCTs, assigning lower weighting to studies that do not randomize participants to receipt of the active or comparison intervention and thus are at a higher risk of bias and confounding [42,43]. With a paucity of highly internally valid RCTs available for many rare disease therapies [44,45], such systematic reviews may end up "empty" or with very few studies despite the availability of evidence from studies that do not satisfy inclusion criteria for the review. The results from Chapters 3 and 4 of this dissertation corroborated that health care providers and policy advisors were concerned about the limited availability and quality of evidence and offered additional considerations that may be incorporated into a more tailored framework for conducting HTAs for rare disease therapies. **Based on these findings and towards reduction of scientific uncertainty (Table 5-1), we propose that evidence synthesis producers consider inclusion of evidence from sources other than standard RCTs, in the context of rare diseases where conducting RCTs may be especially challenging with such small patient populations.**

That said, to maintain high quality and draw appropriate inferences, it remains important for evidence synthesis producers to continue to evaluate risk of bias within the reviewed studies and identify limitations that may preclude strong conclusions about the effectiveness of the therapy. There are a number of risk of bias assessment tools available for observational studies (e.g., Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) [46], Research Triangle Institute (RTI) Observational Studies Risk of Bias and Precision Item Bank [47]). In particular, Cochrane has developed the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [48] and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group has developed guidance around interpreting tools like the

ROBINS-I to assign a degree of certainty to non-randomized studies [49]. Incorporating the use of such tools to describe the quality of non-randomized studies is critical to ensure that appropriate conclusions are drawn with respect to the effectiveness of the intervention(s) under study and that evidence gaps are identified.

Principle #5: In evidence syntheses, incorporate evidence regarding natural history of the disease and/or intended causal mechanism of the candidate therapy, when relevant

When the clinical efficacy and effectiveness evidence is weak, evidence syntheses may need to be expanded further to incorporate evidence related to the natural history of a rare disease and the proposed causal pathway linking an intervention to potential altered natural history. While this is unconventional in a systematic review of the effectiveness of an intervention, as described in Chapter 4, it is a strategy that has been recommended and in some jurisdictions adopted within HTA for rare disease interventions, to improve the utility of evidence syntheses used to support policy decision-making. **Adopting this principle will thus serve to reduce scientific uncertainty for all stakeholders, particularly for policy advisors and health care providers for whom incomplete understanding natural history was an important source of uncertainty (Table 5-1)**. This approach would highlight evidence gaps and in turn identify needs for additional primary research regarding natural history.

Principle #6: Routinely review and update evidence syntheses supporting health care decision-making for rare disease therapies to ensure decisions are made using best currently available evidence

At the time of an initial evidence review for regulatory or reimbursement approval, rare disease therapies typically have less mature data supporting them [44,50,51]. Given that the rare disease landscape is rapidly changing [52], new clinical evidence may quickly emerge that markedly changes previous conclusions about treatment effectiveness. Based on this, we suggest regular review and revision of evidence syntheses to incorporate new evidence regarding rare disease therapies to ensure that the best available evidence informs decision making. For example, living systematic reviews are high quality, up-to-date online summaries of health research that are updated rapidly and frequently as new information becomes available [53]. This type of review is differs from a conventional systematic review in its publication format, adaptation of workflow, research team management, and statistical methods [53]. Another approach that has been adopted by some HTA organizations is routine review and/or reassessment of health technologies after the initial HTA is complete. In context of policy decision making, particularly health economic evaluation, value of information analyses could have a role in understanding the impact new information may have on current understanding.

While this suggestion could easily apply to all evidence syntheses regardless of disease prevalence, the sparsity of evidence available for many rare diseases, especially those considered ultra rare, makes this suggestion particularly important. Efforts are still needed to encourage researchers conducting primary studies to engage with patients and knowledge users as partners, to adopt patient centred outcome measures in their studies (principle #3). Adopting such strategies that include meaningful stakeholder engagement and using patient-centred outcomes and core outcome sets, will facilitate evidence syntheses as studies will be comparable and also more combinable through meta-analysis.

5.4 Decision support

Ultimately the purpose of an evaluation framework and research ecosystem is to promote evidence informed decision making both at an individual and population level. At a population level, knowledge users involved in making policy recommendations are primarily policy advisors although we learned from the studies reported in Chapters 3 and 4 that health care providers also perceive that they have a role in population-level decisions. The needs of population-level decision-makers with respective to evaluative evidence are frequently addressed through HTA. At an individual level, decisions about recommending and using rare disease therapies are made by health care providers and by patients and families respectively. These stakeholders identified both scientific and personal uncertainty in making decisions about individual patient care.

Principle #7: Develop a harmonized HTA strategy for rare disease therapies to support policy decisions (at the population level), with guidance that can be tailored to the needs of specific jurisdictions

From Chapter 4, HTA for rare disease therapies is made challenging by uncertainties in clinical and economic evidence, which leads to inconsistent policy decision-making. Several rare disease-specific HTA strategies and processes have been used or recommended, either in isolation or as part of a specific framework, to address these challenges. These strategies include consideration of a broader range of evidence as well as specific characteristics of the disease or therapy (per principle #4 and #5), specifically eliciting and considering perspectives from disease experts, providing funding approval on condition of systematic long-term evidence generation, and revising HTA processes for considering cost-effectiveness. Some HTA or policy organizations have rare disease therapy-specific HTA strategies (e.g., Highly Specialized

Technologies Programme at NICE [54], the Ontario Evaluation Framework for Funding Drugs for Rare Diseases [55]). However, these strategies are not consistently and transparently applied across jurisdictions. To accomplish a broader inclusion of evidence, we suggest that HTA for rare disease therapies be further optimized by formally evaluating and comparing these various HTA strategies, leading to a standard HTA rare disease framework that can be tailored to the needs of individual organizations or jurisdictions. **This framework should address key aspects of scientific and practical uncertainty highlighted by health care providers and policy advisors (Table 5-1**).

Principle #8: Develop shared decision making tools (e.g., decision aids, lay evidence summaries) to promote the use of evidence in decision making by patients, families, and health care providers (at the individual level)

Patients, family members, and health care providers often experience issues of personal uncertainty when making decisions about whether to accept or recommend a rare disease therapy (Table 1). This uncertainty stems from individual preferences and values related to a patient's treatment goals, the impact that the therapy may have on their everyday life, as well as their personal relationships. Exacerbation of these personal uncertainties is possible in the absence of clear evidence of clinical benefit (scientific uncertainty). Successfully managing or coping with uncertainties in this context could be accomplished using shared decision-making strategies that involve active participation by patients and providers when making health care decisions [56,57]. Shared decision making explicitly integrates evidence-based practice principles with patient preferences and values such that choices concerning treatment are inherently patient-centred and well informed. At a minimum, and aligned with the findings of Chapter 3, this should include

accessible lay summaries for patients and families that identify potential harms and benefits for them; and summaries for providers that clearly identify clinical practice implications. In support of this approach, we recommend the development and application of shared decision making tools for rare disease therapies as a way to manage personal uncertainties experienced by rare disease stakeholders, particularly patients and their families.

One way to employ shared decision making and cope with uncertainty is to develop patient decision aids concerning health care options. Decision aids include balanced information about the decision at hand, the available options, and absolute risk, and they encourage patients to think about their values and attitudes towards potential trade-offs associated with the therapy [58]. Few reports regarding the use of decision aids for patients affected by rare diseases are available in the literature [59], however, Vandemheen et al. demonstrated the effective use of a decision aid for adult patients with cystic fibrosis, a rare genetic lung disease, concerning lung transplantation [60]. The authors showed that using an evidence-informed decision aid significantly reduced decisional conflict compared to usual processes for clinical decision making, and participants in the decision aid group also had increased knowledge and more realistic expectations about the potential harms of lung transplantation [60]. This example highlights the potential benefit of decision aids and other shared decision making tools in the rare disease context; however, this area remains largely untapped with respect to rare diseases and presents an excellent opportunity to conduct further research that will potentially directly benefit patients and their families [61]. **Targeted efforts to distill evidence into lay summaries, provider-oriented clinical summaries, and decision aids could serve to reduce personal uncertainty as identified by patients and families as well as health care providers (Table 5-1).**

5.5 Conclusion: A Call to Action

Successfully mitigating uncertainty in the decision making context for rare disease therapies will require the uptake and rigorous evaluation of the above evaluation framework and its accompanying principles. Much of what we have discussed involves developing or adapting innovative methods for evidence generation and synthesis. Broadening the scope of clinical evaluative research for rare diseases will place strain on an already resource-limited research ecosystem, so we must work to put mechanisms in place that will catalyze research beyond that of efficacy trials for rare diseases, while making it manageable to implement the framework. In addition, future research should seek to determine how best to implement the framework, including eliciting stakeholder perspectives on barriers and facilitators related to adopting the framework's principles.

Towards adoption of our evaluation framework, rare disease stakeholders must first create *strategic alliances* to bring together key knowledge users and producers, making use of existing research networks such as European Reference Networks and the Rare Disease Clinical Research Network in the United States, among others, to promote efficiencies by building on existing strengths and sharing research infrastructure that fosters innovation and reduces duplication of effort. Once such alliances are in place, stakeholders should collectively prioritize their goals and develop an action plan that includes key performance indicators and defines responsibilities of each participating stakeholder. Following the development of a shared action plan, collaborators may need to seek additional resources for implementation and to monitor success over time.

Implementing the principles in this evaluation framework represents a paradigm shift towards collaborative research (full engagement of knowledge users throughout the research process) and will enable greater evidence-informed decision making about rare disease therapies at the

individual and population levels. We challenge the rare disease community to embrace the framework and come together to operationalize a plan of action.

5.6 Citations

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Supplemental Information for Chapter 2

Supplemental File 2-1: Search strategies for meta-narrative review.

MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to June 21, 2017)

1. exp Epidemiologic Study Characteristics as Topic/
2. Research Design/
3. Patient Outcome Assessment/
4. Treatment Outcome/
5. Rare Diseases/
6. Orphan Drug Production/
7. 1 or 2 or 3 or 4
8. 5 or 6
9. 7 and 8
10. limit 9 to English language

EMBASE (Embase Classic + Embase 1947 to June 21, 2017)

1. *epidemiology/
2. *controlled study/
3. *clinical trial/
4. *randomized controlled trial/
5. *observational study/
6. *methodology/
7. *outcome assessment/
8. *treatment outcome/
9. rare disease/
10. orphan drug/
11. rare disease*.tw.
12. orphan disease*.tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
14. 9 or 10 or 11 or 12
15. 13 and 14

Pubmed

1. (((epidemiologic study characteristics as topic[MeSH Terms]) OR research design[MeSH Terms]) OR patient outcomes assessment[MeSH Terms]) OR treatment outcome[MeSH Terms]
2. (rare diseases[MeSH Terms]) OR orphan drug production[MeSH Terms]
3. 1 and 2

Supplemental File 2-2: List of articles included in the meta-narrative review (n=60).

Authors	Year	Title	Journal
P. B. Shieh	2015	Duchenne muscular dystrophy: clinical trials and emerging tribulations	Current Opinion in Neurology
B. C. Stunnenberg, W. Woertman, J. Raaphorst, J. M. Statland, R. C. Griggs, J. Timmermans, C. G. Saris, B. J. Schouwenberg, H. M. Groenewoud, D. F. Stegeman, B. G. van Engelen, G. Drost and G. J. van der Wilt	2015	Combined N-of-1 trials to investigate mexiletine in non-dystrophic myotonia using a Bayesian approach; study rationale and protocol	BMC Neurology
L. V. Hampson, J. Whitehead, D. Eleftheriou, C. Tudur-Smith, R. Jones, D. Jayne, H. Hickey, M. W. Beresford, C. Bracaglia, A. Caldas, R. Cimaz, J. Dehoorne, P. Dolezalova, M. Friswell, M. Jelusic, S. D. Marks, N. Martin, A. M. McMahon, J. Peitz, A. van Royen-Kerkhof, O. Soylemezoglu and P. A. Brogan	2015	Elicitation of expert prior opinion: application to the MYPAN trial in childhood polyarteritis nodosa	PLoS ONE
P. Nony, P. Kurbatova, A. Bajard, S. Malik, C. Castellan, S. Chabaud, V. Volpert, N. Eymard, B. Kassai, C. Cornu, Cresim and C. Epi	2014	A methodological framework for drug development in rare diseases	Orphanet J Rare Dis
K. Facey, A. Granados, G. Guyatt, A. Kent, N. Shah, G. J. van der Wilt and D. Wong-Rieger	2014	Generating health technology assessment evidence for rare diseases	International Journal of Technology Assessment in Health Care
J. J. Gagne, L. Thompson, K. O'Keefe and A. S. Kesselheim	2014	Innovative research methods for studying treatments for rare diseases: methodological review	BMJ
L. V. Hampson, J. Whitehead, D. Eleftheriou and P. Brogan	2014	Bayesian methods for the design and interpretation of clinical trials in very rare diseases	Statistics in Medicine
W. Hu, J. Cai and D. Zeng	2014	Sample size/power calculation for stratified case-cohort design	Statistics in Medicine
D. Bolignano, E. V. Nagler, W. Van Biesen and C. Zoccali	2014	Providing guidance in the dark: rare renal diseases and the challenge to improve the quality of evidence	Nephrology Dialysis Transplantation

J. P. Krischer, R. Gopal-Srivastava, S. C. Groft, D. J. Eckstein and N. Rare Diseases Clinical Research	2014	The Rare Diseases Clinical Research Network's organization and approach to observational research and health outcomes research	Journal of General Internal Medicine
E. Basch and A. V. Bennett	2014	Patient-reported outcomes in clinical trials of rare diseases	Journal of General Internal Medicine
B. Huang, E. H. Giannini, D. J. Lovell, L. Ding, Y. Liu and P. J. Hashkes	2014	Enhancing crossover trial design for rare diseases: limiting ineffective exposure and increasing study power by enabling patient choice to escape early	Contemporary Clinical Trials
C. Tudur Smith, P. R. Williamson and M. W. Beresford	2014	Methodology of clinical trials for rare diseases	Best Practice & Research in Clinical Rheumatology
K. Fischer, R. Ljung, H. Platokouki, R. Liesner, S. Claeyssens, E. Smink and H. M. van den Berg	2014	Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry	Haemophilia
L. Abrahamyan, I. R. Diamond, S. R. Johnson and B. M. Feldman	2014	A new toolkit for conducting clinical trials in rare disorders	Journal of Population Therapeutics & Clinical Pharmacology
A. S. Kesselheim and J. J. Gagne	2014	Strategies for postmarketing surveillance of drugs for rare diseases	Clinical Pharmacology & Therapeutics
E. Picavet, D. Cassiman, W. Pinxten and S. Simoens	2013	Ethical, legal and social implications of rare diseases and orphan drugs in Europe: meeting report of a Brocher symposium	Expert Review of Pharmacoeconomics & Outcomes Research
E. F. Augustine, H. R. Adams and J. W. Mink	2013	Clinical trials in rare disease: challenges and opportunities	Journal of Child Neurology
J. P. Bai, J. S. Barrett, G. J. Burckart, B. Meibohm, H. C. Sachs and L. Yao	2013	Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants	AAPS Journal
M. Luisetti, I. M. Balfour-Lynn, S. R. Johnson, M. Miravitlles, C. Strange, B. C. Trapnell, H. van Bronswijk and C. Vogelmeier	2012	Perspectives for improving the evaluation and access of therapies for rare lung diseases in Europe	Respiratory Medicine
J. Armstrong-Wells and N. A. Goldenberg	2011	Institution-based prospective inception cohort studies in neonatal rare disease research	Seminars in Fetal & Neonatal Medicine
J. A. Cole, J. S. Taylor, T. N. Hangartner, N. J. Weinreb, P. K. Mistry and A. Khan	2011	Reducing selection bias in case-control studies from rare disease registries	Orphanet J Rare Dis
S. Gupta, M. E. Faughnan, G. A. Tomlinson and A. M. Bayoumi	2011	A framework for applying unfamiliar trial designs in studies of rare diseases	Journal of Clinical Epidemiology
B. E. Miyamoto and E. D. Kakkis	2011	The potential investment impact of improved access to accelerated	Orphanet J Rare Dis

		approval on the development of treatments for low prevalence rare diseases	
M. Puopolo and M. Pocchiari	2011	Need to improve clinical trials in rare neurodegenerative disorders	Annali Dell'Istituto Superiore di Sanita
P. I. Dickson, A. R. Pariser, S. C. Groft, R. W. Ishihara, D. E. McNeil, D. Tagle, D. J. Griebel, S. G. Kaler, J. W. Mink, E. G. Shapiro, K. J. Bjoraker, L. Krivitzky, J. M. Provenzale, A. Gropman, P. Orchard, G. Raymond, B. H. Cohen, R. D. Steiner, S. F. Goldkind, R. M. Nelson, E. Kakkis and M. C. Patterson	2011	Research challenges in central nervous system manifestations of inborn errors of metabolism	Molecular Genetics & Metabolism
L. Abrahamyan, C. S. Li, J. Beyene, A. R. Willan and B. M. Feldman	2011	Survival distributions impact the power of randomized placebo-phase design and parallel groups randomized clinical trials	Journal of Clinical Epidemiology
J. W. Gerss and W. Kopcke	2010	Clinical trials and rare diseases	Advances in Experimental Medicine & Biology
J. C. Carey	2010	The importance of case reports in advancing scientific knowledge of rare diseases	Advances in Experimental Medicine & Biology
M. Luisetti, I. Campo, R. Scabini, M. Zorzetto, Z. Kadija, F. Mariani and I. Ferrarotti	2010	The problems of clinical trials and registries in rare diseases	Respiratory Medicine
B. Kinder and F. X. McCormack	2010	Clinical trials for rare lung diseases: lessons from lymphangioleiomyomatosis	Lymphatic Research & Biology
J. H. van der Lee, J. Wesseling, M. W. Tanck and M. Offringa	2010	Sequential design with boundaries approach in pediatric intervention research reduces sample size	Journal of Clinical Epidemiology
A. J. Vickers and P. T. Scardino	2009	The clinically-integrated randomized trial: proposed novel method for conducting large trials at low cost	Trials
S. R. Johnson, B. M. Feldman, J. E. Pope and G. A. Tomlinson	2009	Shifting our thinking about uncommon disease trials: the case of methotrexate in scleroderma	Journal of Rheumatology
R. C. Griggs, M. Batshaw, M. Dunkle, R. Gopal-Srivastava, E. Kaye, J. Krischer, T. Nguyen, K. Paulus, P. A. Merkel and N. Rare Diseases Clinical Research	2009	Clinical research for rare disease: opportunities, challenges, and solutions	Molecular Genetics & Metabolism
B. M. Buckley	2008	Clinical trials of orphan medicines	Lancet

S. C. Chow and M. Chang	2008	Adaptive design methods in clinical trials - a review	Orphanet J Rare Dis
J. H. van der Lee, J. Wesseling, M. W. Tanck and M. Offringa	2008	Efficient ways exist to obtain the optimal sample size in clinical trials in rare diseases	Journal of Clinical Epidemiology
M. Behera, A. Kumar, H. P. Soares, L. Sokol and B. Djulbegovic	2007	Evidence-based medicine for rare diseases: implications for data interpretation and clinical trial design	Cancer Control
M. E. Haffner and J. V. Kelsey	1992	Evaluation of orphan products by the U.S. Food and Drug Administration	International Journal of Technology Assessment in Health Care
A. Bajard, S. Chabaud, C. Cornu, A. C. Castellan, S. Malik, P. Kurbatova, V. Volpert, N. Eymard, B. Kassai and P. Nony	2016	An in silico approach helped to identify the best experimental design, population, and outcome for future randomized clinical trials	Journal of Clinical Epidemiology
E. De Blieck, H. Adams, E. Augustine, J. Cialone, L. Dure, J. Kwon, F. Marshall, N. Newhouse, K. Rose, P. Rothberg, A. Vierhile and J. Mink	2013	Methodology of clinical research in rare diseases: Development of a research program in juvenile neuronal ceroid lipofuscinosis (JNCL) via creation of a patient registry and collaboration with patient advocates	Molecular Genetics and Metabolism
M. Vray, D. Girault, N. Hoog-Labouret, R. Porcher and J. C. Thalabard	2004	Methodology for small clinical trials.	Thérapie
B. Wilcken	2001	Rare diseases and the assessment of intervention: What sorts of clinical trials can we use?	Journal of Inherited Metabolic Disease
B. Feldman, E. Wang, A. Willan and J. P. Szalai	2001	The randomized placebo-phase design for clinical trials	Journal of Clinical Epidemiology
M. E. Haffner	1998	Designing clinical trials to study rare disease treatment	Drug Information Journal
R. J. Lilford, J. G. Thornton and D. Braunholtz	1995	Clinical trials and rare diseases: A way out of a conundrum	British Medical Journal
J. C. Maro, J. S. Brown, G. J. Dal Pan and L. Li	2014	Orphan therapies: making best use of postmarket data	J Gen Intern Med
R. N. Tamura, J. P. Krischer, C. Pagnoux, R. Micheletti, P. C. Grayson, Y. F. Chen and P. A. Merkel	2016	A small n sequential multiple assignment randomized trial design for use in rare disease research	Contemporary Clinical Trials
C. Y. Ponsioen, R. W. Chapman, O. Chazouilleres, G. M. Hirschfield, T. H. Karlsen, A. W. Lohse, M. Pinzani, E. Schrumpf, M. Trauner and G. J. Gores	2016	Surrogate endpoints for clinical trials in primary sclerosing cholangitis: Review and results from an International PSC Study Group consensus process	Hepatology
B. K. Potter, S. D. Khangura, K. Tingley, P. Chakraborty and J. Little	2016	Translating rare-disease therapies into improved care for patients and families: what are the right outcomes,	Genetics in Medicine

		designs, and engagement approaches in health-systems research?	
Hollak, C E, Aerts, J M, Ayme, S, Manuel, J	2011	Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders	Orphanet J Rare Dis
Kwakkenbos L, Jewett LR, Baron M, et al.	2013	The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: protocol for a cohort multiple randomised controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context	BMJ Open
Lachmann R, Schoser B	2013	The clinical relevance of outcomes used in late-onset Pompe disease: can we do better?	Orphanet J Rare Dis
Richesson R, Vehik K.	2010	Patient registries: Utility, Validity, and Inference	Advances in Experimental Medicine & Biology
Jones S, James E, Prasad S.	2011	Disease registries and outcomes research in children: Focus on lysosomal storage disorders.	Pediatr Drugs
Richesson R, Shereff D, Andrews J.	2010	[RD] PRISM Library: Patient Registry Item Specifications and Metadata for Rare Diseases	J Libr Metadata
Unkel S, Rover C, Stallard N, Benda N, Posch M, Zohar S, et al.	2016	Systematic reviews in paediatric multiple sclerosis and Creutzfeldt-Jakob disease exemplify shortcomings in methods used to evaluate therapies in rare conditions.	Orphanet J Rare Dis
Cornu C, Kassai B, Fisch R, Chiron C, Alberti C, Guerrini R, et al.	2013	Experimental designs for small randomised clinical trials: an algorithm for choice.	Orphanet J Rare Dis
Korn EL, McShane LM, Freidlin B.	2013	Statistical Challenges in the Evaluation of Treatments for Small Patient Populations.	Sci Transl Med

Supplemental File 2-3: Research Ethics approval letters

File Number: H06-17-26 **Date (mm/dd/yyyy):** 07/06/2017

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Beth	Potter	Medicine / Medicine	Supervisor
Doug	Coyle	Medicine / Medicine	Co-Supervisor
Kylie	Tingley	Medicine / Medicine	Student Researcher
Ian D	Graham	Medicine / Medicine	Other Collaborator

File Number: H06-17-26

Type of Project: PhD Thesis

Title: Understanding patient and caregivers' perspectives related to evidence about treatments for rare diseases: A focus group study

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
07/06/2017	07/05/2018	Approval

Special Conditions / Comments:
N/A

550, rue Cumberland, pièce 154 550 Cumberland Street, room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5387 • Téléc./Fax (613) 562-5338
www.recherche.uottawa.ca/deontologie/ www.research.uottawa.ca/ethics/

File Number: H06-17-26 **Date (mm/dd/yyyy):** 07/06/2017

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement (2010) and other applicable laws and regulations in Ontario, has examined and approved the ethics application for the above named research project. Ethics approval is valid for the period indicated above and subject to the conditions listed in the section entitled "Special Conditions / Comments".

During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: http://research.uottawa.ca/ethics/submissions-and-reviews.

Please submit an annual report to the Ethics Office four weeks before the above-referenced expiry date to request a renewal of this ethics approval. To close the file, a final report must be submitted. These documents can be found at: http://research.uottawa.ca/ethics/submissions-and-reviews.

If you have any questions, please do not hesitate to contact the Ethics Office at extension 5387 or by e-mail at: ethics@uOttawa.ca.

Riana Marcotte
Protocol Officer for Ethics in Research
For Daniel Lagarec, Chair of the Health Sciences and Sciences REB

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uOttawa

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa
Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
http://www.ohri.ca/ohsn-reb

July 25, 2016

Dr. Elizabeth Potter
University of Ottawa
Department of Epidemiology and Community Medicine
Roger Guindon Hall, Room 3230F
451 Smyth Road
Ottawa, ON K1H 8M5

Dear Dr. Potter:

Re: Protocol # 20160175-01H **Investigating the value of a tailored knowledge synthesis approach for rare diseases - Focus groups with stakeholders.**

Protocol approval valid until - July 24, 2017

I am pleased to inform you that this protocol underwent delegated review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved for the recruitment of English speaking participants only. No changes, amendments or addenda may be made to the protocol or the consent form without the OHSN-REB's review and approval.

Approval is for the following:
- Protocol dated July 4, 2016
- English Initial Recruitment Email- Metabolic Physicians dated July 12, 2016
- English First Follow-Up Recruitment Email- Metabolic Physicians dated July 12, 2016
- English Second Follow-Up Recruitment Email- Metabolic Physicians dated July 12, 2016
- English Recruitment Message- Garrod Association Newsletter dated July 12, 2016
- English Initial Recruitment Email- Policy Advisors dated July 12, 2016
- English First Follow-Up Recruitment Email- Policy Advisors dated July 12, 2016
- English Second Follow-Up Recruitment Email- Policy Advisors dated July 12, 2016
- English Focus Group: Demographic Details Questionnaire dated February 29, 2016
- English Focus Group Interview Guide dated March 15, 2016
- English Participant Informed Consent Form dated May 9, 2016

Your request for a French exemption is approved; the study may proceed in English only.

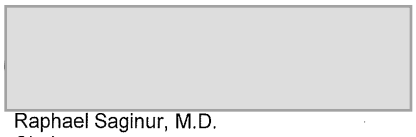
The REB no longer requires a 'valid until' date at the bottom of all approved informed consent forms. The consent forms currently approved for use by the REB are listed above.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

.../2

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.



Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

RS/kd

From: vbourada@cheo.on.ca
Subject: REB Protocol No 16/65X Final Approval - Delegated Review
Date: July 15, 2016 at 9:40 AM
To: Dr. Pranesh Chakraborty (Principal Investigator) pchakraborty@cheo.on.ca
Cc: Ms. Kylie Tingley (Research Coordinator) kting022@uottawa.ca, Ms. Monica Lamoureux (Research Coordinator) molamoureux@cheo.on.ca, Ms. Laure Tessier (Research Coordinator) LTessier@cheo.on.ca, vbourada@cheo.on.ca

RESEARCH INSTITUTE
INSTITUT DE RECHERCHE

CHEO Research Ethics Board
Approval - Delegated Review

Principal Investigator: Dr. Pranesh Chakraborty
REB Protocol No: 16/65X
Romeo File No: 20160257
Project Title: CHEOREB#16/65X - Investigating the value of a tailored knowledge synthesis approach for rare diseases – Focus groups with stakeholders
Primary Affiliation: Biomedicine\Newborn Screening
Protocol Status: Active
Approval Date*: July 15, 2016
Valid Until:** May 15, 2017
Annual Renewal Submission Deadline: 15 April 2017

Documents Reviewed & Approved:

Document Name	Comments	Version Date
Protocol	Protocol July 4 2016	2016/07/04
Consent Form	Consent form	2016/05/09
Recruitment Materials	Recruitment July 12 2016	2016/07/12
Questionnaire/Survey	Focus group demographic questionnaire	2016/02/29
Other Document	Focus group interview guide	2016/03/15

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed under the delegated review stream, which is reserved for projects that involve no more than minimal risk to human subjects.

In respect to this study, my signature below certifies, that as a representative of this Research Ethics Board:

1. The membership of this Research Ethics Board complies to the Tri-Council Policy Statement on Ethical Conduct for Research involving Humans;
2. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part C Division 5 of the *Food and Drug Regulations* **and** Part 4 of the *Natural Health Products Regulations;*
3. This Research Ethics Board carries out its functions in a manner consistent with ICH Good Clinical Practices: consolidated guidelines and applicable laws and regulations of Ontario and Canada; and
4. This Research Ethics Board has reviewed and approved the protocol and informed consent form for this study; which is to be conducted by the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing.

Final approval is granted for the above noted study, with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. Investigators must submit an annual renewal report to the REB 30 days prior to the expiration date stated above.
3. The investigator must not implement any deviation from, or changes to, the protocol, consents or assents without the approval of the REB.
4. The investigator must, prior to use, submit to the Board changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
5. Investigators must provide the Board with French versions of the consent form, unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
6. The investigator must promptly report to the REB all unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
7. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
8. Investigators must submit a final report at the conclusion of the study.

Should you have any questions or concerns, please do not hesitate to contact the Research Ethics Board Office at 613-737-7600 ext. 3350 or 2128.

Regards,

Dr. Carole Gentile
Chair, Research Ethics Board
Présidente, Comité d'éthique de la recherche
401 Smyth Road, Ottawa, ON K1H 8L1
Tel: (613) 737-7600 ext. 3624 | Fax/Téléc: (613) 738-4202 | gentile@cheo.on.ca

*The final approval date for initial delegated study applications approved with or without modifications will be the date the REB has determined that the conditions of approval have been satisfied.

**The expiry date of REB approval for initial study application that required no modifications will be as follows:

- If the date of review and approval was **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date of review and approval by the Chair and/or delegate *in the following year*;
- If the date of review and approval was **after** the 15th the expiry date will be the 15th of the month in which the date of review and approval by the REB *in the following year*.

The expiry date of REB approval for initial study applications that **require modifications** will be as follows:

- If the initial feedback was sent **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date the letter of REB feedback is issued to the investigator(s) *in the following year*;
- If the initial feedback was sent **after** the 15th the expiry date will be the 15th of the month in which the feedback was sent *in the following year*.

Supplemental File 2-4: Reprint of published article from *Orphanet Journal of Rare Diseases*.

Tingley *et al. Orphanet Journal of Rare Diseases* (2018) 13:104
https://doi.org/10.1186/s13023-018-0851-1

Orphanet Journal of Rare Diseases

REVIEW Open Access

Using a meta-narrative literature review and focus groups with key stakeholders to identify perceived challenges and solutions for generating robust evidence on the effectiveness of treatments for rare diseases

Kylie Tingley[1], Doug Coyle[1], Ian D. Graham[1,2], Lindsey Sikora[3], Pranesh Chakraborty[4,5,6], Kumanan Wilson[1,2], John J. Mitchell[7], Sylvia Stockler-Ipsiroglu[8,9], Beth K. Potter[1*] and in collaboration with the Canadian Inherited Metabolic Diseases Research Network

Abstract

Introduction: For many rare diseases, strong analytic study designs for evaluating the efficacy and effectiveness of interventions are challenging to implement because of small, geographically dispersed patient populations and underlying clinical heterogeneity. The objective of this study was to integrate perspectives from published literature and key rare disease stakeholders to better understand the perceived challenges and proposed methodological approaches to research on clinical interventions for rare diseases.

Methods: We used a meta-narrative literature review and focus group interviews with key rare disease stakeholders to better understand the perceived challenges in generating and synthesizing treatment effectiveness evidence, and to describe various research methods for mitigating these identified challenges. Data from both components of this study were synthesized narratively according to research paradigms that emerged from our data.

Results: Results from our meta-narrative literature review and focus group interviews revealed three fundamental challenges in generating robust treatment effectiveness evidence for rare diseases: i) limitations in recruiting a sufficient sample size to achieve planned statistical power; ii) inability to account for clinical heterogeneity and assess treatment effects across a clinical spectrum; and iii) reliance on short-term, surrogate outcomes whose clinical relevance is often unclear. We mapped these challenges and associated solutions to three interrelated research paradigms: i) explanatory evidence generation; ii) comparative effectiveness/pragmatic evidence generation; and iii) patient-oriented evidence generation. Within each research paradigm, numerous criticisms and potential solutions have been described with respect to overcoming these challenges from a research study design perspective.

(Continued on next page)

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Full list of author information is available at the end of the article

(Continued from previous page)
Conclusions: Over time, discussions about clinical research for interventions for rare diseases have moved beyond methodological approaches to overcome challenges related to explanatory evidence generation, with increased recognition of the importance of pragmatic and patient-oriented evidence. Future directions for our work include developing a framework to expand current evidence synthesis practices to take into consideration many of the concepts discussed in this paper.

Keywords: Rare diseases, Evidence generation, Comparative effectiveness, Patient-oriented outcomes, Evidence synthesis, Research methods,

Background

For many rare diseases, strong analytic study designs for evaluating the *efficacy* (does intervention X work under *ideal conditions*?) and *effectiveness* (does intervention X work in *real-world practice*?) [1] of interventions are challenging to implement because of small, geographically dispersed patient populations and characteristically high clinical heterogeneity [2]. A poor understanding of natural history for many rare diseases, scarcity of validated measures of disease progression, and various financial constraints (e.g., limited availability of research funding, high costs of trials for rare diseases) also add to the complexity of evaluating treatments for rare diseases [2–4]. As a result of these limitations, it is often not feasible to conduct conventional randomized controlled trials (RCTs), the gold standard for determining treatment efficacy [5]. Thus, rare disease researchers must often rely on other study designs that are more prone to bias when evaluating interventions, such as open label or uncontrolled trials, observational studies, and case reports. [6, 7]

The evidence that exists for clinical interventions for rare diseases therefore typically falls in the bottom half of the traditional evidence hierarchy [7, 8] and is methodologically flawed [6, 9]. For example, a recent systematic review of available evidence for 11 orphan medicines found that case studies represented the largest proportion (140/338; 41%) of study designs used to determine clinical effectiveness, while only 7% (14/338) of studies were double-blind, placebo-controlled RCTs [6]. Studies that have reviewed the evidence for clinical interventions for rare diseases that is submitted to regulatory and health technology assessment agencies in support of marketing authorization and reimbursement approval have also found limited RCT evidence for some rare diseases, particularly those considered 'ultra-rare' [10–13]. Newer processes for both regulatory approval and reimbursement approval may be shifting the standards in terms of evidence requirements in this rapidly evolving area [14–16]. A recent analysis of ClinicalTrials.gov comparing characteristics of completed or on-going trials for rare and non-rare disease treatments demonstrated that trials for rare disease therapies are likely to enroll fewer participants, be single arm, non-randomized, and open label [17], all of which can compromise the internal validity of a study.

The lack of high quality evidence and the typically high cost of clinical interventions for rare diseases commonly result in debates about the efficacy and effectiveness of these interventions among stakeholders [18, 19]. Disagreements about the evidence arise from differing views about the methodological rigour of the study design; what constitutes a meaningful outcome; and the minimal clinically important difference for a relevant outcome [20]. Disputes among stakeholders are further fueled by differing values and the institutional/political landscape surrounding decision-making processes about interventions for rare diseases [20, 21]. As a result, health policy recommendations, such as those concerning reimbursement for some clinical interventions for rare diseases, are variable across jurisdictions [22, 23].

The objective of this study was to integrate perspectives from published literature and key rare disease stakeholders to better understand the challenges and approaches to research for clinical interventions for rare diseases. More specifically, we sought to:

(1) identify perceived challenges in generating robust evidence for establishing treatment efficacy and effectiveness in the context of rare diseases; and
(2) describe various clinical evaluative research methods that have been suggested for mitigating the identified challenges in generating robust evidence, focusing on the perceived strengths and limitations specific to each.

Methods

Meta-narrative literature review

Meta-narrative approach

An initial scoping of the literature regarding our research topic revealed diverse perspectives on generating evidence for efficacy and effectiveness of treatments for rare diseases. We therefore chose to use an adaptation of the meta-narrative approach developed by Greenhalgh and colleagues specifically for systematically reviewing the literature on complex topics that have been conceptualized and studied differently among researchers [24].

Meta-narrative reviews encompass six main principles: (1) *pragmatism*, the included information should be driven by usefulness to the intended audience; (2) *pluralism*, the topic should be considered from multiple perspectives; (3) *historicity*, the included information should be presented according to its development over time; (4) *contestation*, any conflicting information should be used to generate higher-order insights; (5) *reflexivity*, there should be continual reflection on the review findings; and (6) *peer review*, the review findings should be presented to an external audience for feedback [24, 25]. Below we describe the methods for each phase of our review separately and sequentially, while recognizing that the phases overlap with each other [24].

Planning and search phases

Our interdisciplinary study team has expertise in epidemiology, health services research, health economics, and information science. We held a series of meetings to discuss the emerging findings from the literature and provide direction as the project progressed. We also agreed that the outputs from this review would include a summary of current knowledge across research paradigms on the topic of establishing efficacy or effectiveness for clinical interventions for rare diseases, and a framework to guide future evidence syntheses in this field (*currently under development*).

We used an initial exploratory search (snowball sampling and citation-searching) to identify important sources of information relevant to our study objectives, and in turn, developed a formal search strategy comprised of Medical Subject Heading (MeSH) terms and keywords. Our search strategy was developed iteratively (by LS and KT) and was not meant to be exhaustive, but was designed to identify *key* sources of scholarly information. Three electronic databases were searched: MEDLINE (Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to June 21, 2017), EMBASE (Embase Classic + Embase 1947 to June 21, 2017), and PubMed. Search strategies for each database can be found in Additional file 1. We also scanned reference lists from included studies for any additional citations.

All citations returned from the searches were reviewed using a two-stage approach. During the first stage, one member of the study team (KT) scanned titles and abstracts of all citations to identify potentially relevant records. For the second stage, full-text articles were retrieved for all citations identified during stage one, and one member of the study team (KT) reviewed the articles to determine final inclusion/exclusion. Given that the purpose of the search and screening phases was to identify *key* sources of information rather than to be exhaustive, and that the meta-narrative approach is reflexive by design, having only one member of the team screen citations and papers for eligibility was deemed appropriate. To help mitigate bias, we established the following inclusion criteria: (i) relevant to rare diseases or orphan medicines; and (ii) describes methods used to overcome challenges for establishing efficacy or effectiveness of clinical interventions for rare diseases. We did not limit inclusion to primary studies (i.e., review articles were included), but did exclude letters to the editor, conference abstracts, and commentaries. We also did not limit according to specific diseases or disease groups. Finally, given language constraints within the team, we excluded all articles not written in English.

Mapping, appraisal and synthesis phases

A fundamental aspect of the meta-narrative approach is constructing a story about how research on a given topic has unfolded over time [24, 25]. To this end, we extracted information from each report to identify key people, events, research questions, conceptual and theoretical issues, research findings, and areas of debate or disagreement. Data extracted from each study included (if applicable): bibliographic characteristics (publication date, author(s), geographical location), sponsorship/declared conflicts of interest, and report characteristics (type of study, disease(s) of interest, study objectives, main findings/conclusions, etc.). Additionally, we used the following guiding questions to extract further information to describe the different perspectives:

1. What study designs have been described for studying the efficacy or effectiveness of treatments for rare diseases?
2. What strengths, weaknesses, and risks of bias are reported as important for each study design?
3. What are the described tradeoffs in risk of bias among the study designs?
4. Is the choice of outcome(s) reported as an influence on the quality of evidence?

Data were extracted from each report by a single reviewer (KT) and findings were reviewed and discussed at team meetings. Bibliographic and report characteristics were synthesized descriptively, and all other study findings were synthesized narratively.

Focus group interviews with stakeholders

Design, sampling, recruitment, and participants

In parallel with the meta-narrative review, we conducted focus group interviews with three stakeholder groups to better understand their perspectives on generating evidence for clinical interventions for rare diseases. We recruited a convenience sample from three groups who could speak knowledgeably (based on formal knowledge

or experience) about evidence for interventions for rare diseases, including: physicians, policy advisors, and rare disease patients or caregivers. More specifically, we chose to include rare disease patients and caregivers as stakeholders because they are directly impacted by clinical research and could provide unique perspectives based on their lived experiences, especially in regards to outcomes that reflect quality of life and in considering how the selection of outcomes affects the relevance of the evidence produced. To facilitate the focus group discussions with physicians and patients/caregivers, we chose rare inherited metabolic diseases as a case study. For the patients/caregivers, we further narrowed the selection to mucopolysaccharidoses (MPS), a group of rare metabolic conditions, because this group of diseases typifies the characteristics of many rare diseases that present challenges for conducting strong analytic studies, including low prevalence (i.e., very small population), significant clinical heterogeneity, and, for some MPS types, the existence of expensive orphan drug treatments that require evaluation. In addition, this restriction supported an in-person discussion with patients/caregivers as we could meet with that group as part of an annual event (described below). We sought between five and eight participants per focus group, based on standard focus group interview methodology [26]. Individuals were eligible to participate if they had experience with the care of those diagnosed with a rare inherited metabolic disease (metabolic physicians), if they had experience in evidence review activities that result in recommendations being made about the development, use, and/or reimbursement of interventions for rare diseases (policy advisors) or if they were adults diagnosed with MPS or a related disease, or were the caregiver (i.e., parent/guardian) of someone diagnosed with MPS or a related disease.

Recruitment invitations were distributed by email to physician members of the Garrod Association (a professional association whose members are involved in caring for patients with inherited metabolic diseases), to policy advisors by a member of their professional network (using publicly available contact information), and to patients/caregivers attending the Canadian MPS Society's 2017 Annual Family Meeting. Individuals interested in participating were instructed to contact a member of the research team (KT), and eligible respondents were asked to provide signed, informed consent to participate in the study. Focus group interviews were conducted by telephone with the physicians and policy advisors, and in-person with the patients/caregivers in conjunction with the Canadian MPS Society's 2017 Annual Family Meeting held in Montreal, QC, Canada. The study protocol was approved by the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario Research Ethics Board (physicians and policy advisors), and the University of Ottawa Health Sciences and Sciences Research Ethics Board (patients/caregivers).

Data collection

Focus group interviews were conducted by a single member of the study team (KT) using a semi-structured interview guide and were attended by a second member of the team as an observer (BKP or JJM). The interview guide was tailored to the specific stakeholder group. The interview guide addressed general perspectives on the challenges of rare disease research, and more specific topics including generation and synthesis of evidence to establish treatment efficacy or effectiveness, and outcomes used in clinical evaluative studies. All interviews were audio-recorded with participants' consent and subsequently transcribed.

Data analysis

Each focus group transcript was analyzed using a qualitative descriptive approach that is aimed at *"obtaining straight and largely unadorned (i.e., minimally theorized or otherwise transformed or spun) answers to questions of special relevance to practitioners and policy makers"* [27]. Four members of the study team (KT, BP, DC, IG) met to identify the key concepts and themes that were present in the focus group data. These concepts/themes were organized into a coding system that was applied by one study team member (KT) using NVivo 10 Software (QSR International Pty Ltd.) and reviewed by a second member (BP) for credibility and trustworthiness [28].

Results

Search & screening results

Electronic database searches returned 2871 records after removal of duplicates, of which 161 records were identified as potentially relevant based on the title and abstract scan. An additional 14 titles were identified as potentially relevant from scanning reference lists of included studies. Full text articles were successfully obtained for 172/175 records. Of the 172 full-text articles reviewed, 60 articles were included in this review (Fig. 1 [29]).

Descriptive study characteristics

Of the 60 articles we reviewed, 57 (95%) were published after 2000 (Table 1; Fig. 2). Based on the location of the corresponding author address, 27/60 articles (45%) were written by authors from the United States, 8 (13%) from authors in Canada, 5 (8%) from authors in the United Kingdom, and the remaining articles were written by authors across Europe and Australia (Table 1). Sixteen (27%) articles explicitly reported that their study was sponsored by industry or had some affiliation with

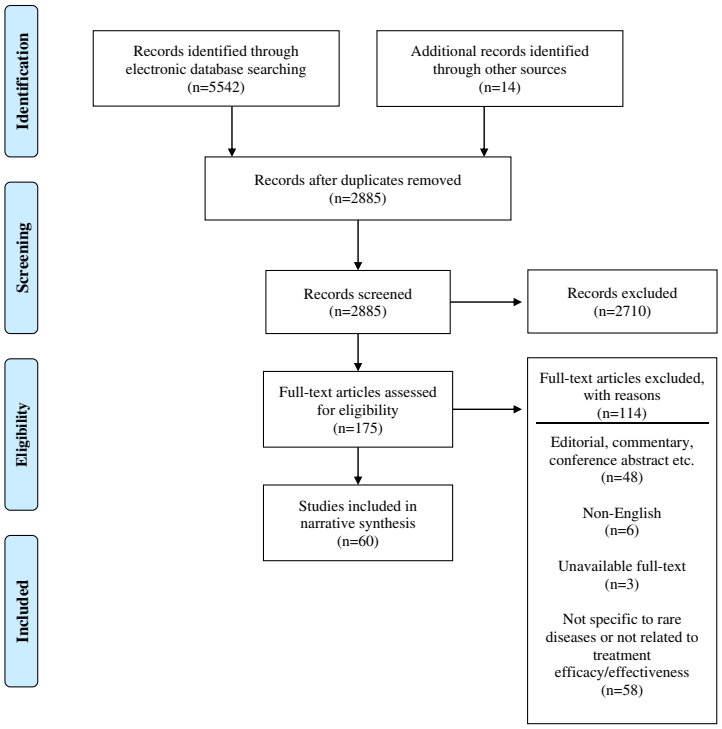

Fig. 1 PRISMA flow diagram outlining results from search and screening process. (Adapted from: Liberati et al. 2009) [29]

industry, while conflicts of interest/study sponsorship were not explicitly reported for a further 14 (23%). Over half of the included studies (33/60; 55%) reported on rare diseases in general, while the remaining articles focused on a specific disease or group of diseases. A majority of the articles included were review articles of research methods used to evaluate efficacy or effectiveness of interventions for rare diseases (39/60; 65%); however, 28% (17/60) described the application of a specific research method in the rare disease context (Table 1). While most of the articles reviewing methods were focused on rare diseases generally (26/39, 67%), many of the applied studies were specific to single diseases (13/17, 76%). A list of the included articles can be found in Additional file 2.

Description of focus group participants

We held three focus group interviews with 13 participants in total (physicians $n = 6$; policy advisors $n = 3$; patients/caregivers $n = 4$). Across the three groups there were 9 women and 4 men. Participants were from 5 provinces in Canada: British Columbia, Alberta, Ontario, Quebec, and Newfoundland and Labrador.

Research paradigms in establishing efficacy or effectiveness of clinical interventions for rare diseases

Three overlapping research paradigms through which stakeholders view the challenges and prioritize potential solutions for establishing efficacy or effectiveness of clinical interventions for rare diseases emerged from our data: (1) explanatory evidence generation, (2) comparative effectiveness/pragmatic evidence generation, and (3) patient-oriented evidence generation. The findings from our literature review and focus group interviews are discussed according to each of these paradigms. While each research paradigm is discussed separately, they are not mutually exclusive. A summary of perspectives across the three research paradigms is provided in Table 2.

Explanatory evidence generation

Much of the discussion in the literature and amongst focus group participants concerning evaluative clinical research in rare diseases centered on problems

Table 1 Descriptive characteristics of included studies ($n = 60$)

Study characteristic	Number of studies (%)
Year of publication	
1990–1994	1 (2)
1995–1999	2 (3)
2000–2004	3 (5)
2005–2009	7 (12)
2010–2014	39 (65)
2015-present (June 21, 2017)	8 (13)
Country (corresponding author address)	
United States	27 (45)
United Kingdom	5 (8)
Canada	8 (13)
France	4 (7)
The Netherlands	6 (10)
Germany	3 (5)
Italy	4 (7)
Belgium	1 (2)
Ireland	1 (2)
Australia	1 (2)
Sponsorship	
Industry affiliations	16 (27)
None (no conflicts of interest declared)	24 (40)
Other (e.g., government funding)	6 (10)
Not explicitly reported	14 (23)
Disease/disease group of focus	
Rare diseases in general	33 (55)
Disease groups:	
Inherited metabolic diseases[a]	2 (3)
Lysosomal storage disorders	3 (5)
Pediatric rheumatic diseases	1 (2)
Rare lung diseases	2 (3)
Rare neonatal diseases	1 (2)
Rare neurodegenerative diseases	1 (2)
Rare renal diseases	1 (2)
Individual disease(s):	
Alpha1-antitrypsin deficiency & pulmonary alveolar proteinosis	1 (2)
Batten Disease	1 (2)
Childhood polyarteritis nodosa	2 (3)
Duchenne muscular dystrophy	1 (2)
Familial hypercholesterolemia	1 (2)
Familial Mediterranean fever	1 (2)
Gaucher disease	1 (2)
Hemophilia A	1 (2)
Late-onset Pompe disease	1 (2)
Non-dystrophic mytonia	1 (2)
Pediatric multiple sclerosis & Creutzfeldt-Jakob disease	1 (2)
Primary sclerosing cholangitis	1 (2)
Scleroderma	2 (3)
Vasculitis (rare form)	1 (2)
Types of studies	
Review article of multiple research methods	28 (47)
Review article of a single research method	11 (18)
Application/case example of research method	17 (28)
Key article that operationalized steps for the research method	3 (5)
Other	1 (2)
Research paradigm discussed[a]	
Explanatory evidence generation	35 (58)
Comparative effectiveness/pragmatic evidence generation	30 (50)
Patient-oriented evidence generation	15 (25)

[a]not mutually exclusive as some studies discussed more than one research paradigm

associated with the inherent small numbers of patients available for study and adequate recruitment for conventional RCTs, long considered the gold standard explanatory design with a low risk of bias [5].

> *"I do find it quite difficult when the clinical trials are very short, very small numbers, and the endpoints are something like the six minute walk test in regards to really being confident that that is going to be an effective treatment for the patients that I'm seeing."* – Physician 4

> *"For common diseases, there's no reason for not doing a randomized controlled trial. I mean, that's one of the big points in the paper that we published a few years ago was that in order to be called rare, you should not have enough patients to confidently determine whether a treatment is efficacious or not."* – Policy Advisor 1

> *"Well the ex-[profession] in me looks at things like, you know, the size of the study, well MPS is [laughter around the table], okay that's not going to happen. You know, so you have to, it's hard when you're looking at MPS because the things that you would normally look for in a good study aren't going to be there because of the size of the sample…"* – Patient/caregiver 3

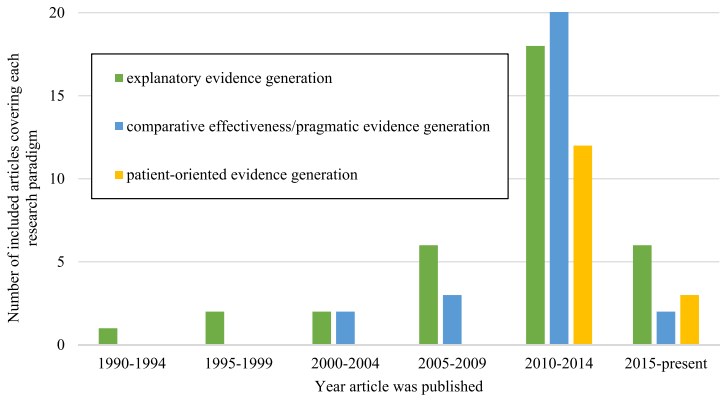

Fig. 2 Research paradigms discussed by year of publication (note: research paradigms are not mutually exclusive)

This paradigm was discussed by more than half (35/60, 58%) of the studies we reviewed, and was also the first that emerged in the literature in 1992 (Fig. 2). Most of the reports that discussed this paradigm were methodological review articles that focused on rare diseases in general or a group of rare diseases (24/35, 68%), rather than a single specific rare disease. The first author to highlight the challenges associated with fewer participants for clinical studies was Haffner, who took the perspective of a regulatory agency responsible for reviewing the safety and efficacy of orphan medicines [30, 31]. Haffner argued that orphan medicines should be as well-scrutinized as medicines for more common diseases but recognized that conventional RCTs are not always feasible due to small numbers [30, 31]. Some alternative research methods or design features for demonstrating safety and efficacy that may be acceptable to a regulatory agency were suggested, including the use of multicenter studies, crossover trials, randomized withdrawal trials, open label studies, open protocol studies, and incorporating historical controls or composite or surrogate endpoints [30, 31]. The discussion concerning explanatory evidence generation for clinical interventions for rare diseases continued from these early publications to the present day (Fig. 2). Others elaborated on the issues brought forth by Haffner and offered more suggestions to overcome the challenges related to small numbers and limited feasibility of conventional RCTs, while preserving internal validity and protecting against bias and confounding [2, 4, 18, 32–61].

While participants in our focus groups highlighted the limited feasibility of conventional RCTs because of small sample sizes, there was little emphasis in the focus group discussions on specific strategies that might be used to overcome this challenge. Thus, most of the results presented under the paradigm of explanatory evidence generation are derived from our meta-narrative literature review.

In general, the research methods or study design features that have been proposed in the literature to address small numbers while retaining internal validity and thus an explanatory focus have concentrated on three overarching strategies: (i) enhancing statistical efficiency at the design phase, so that fewer participants are required to conduct a robust evaluation; (ii) using Bayesian rather than frequentist analysis methods, also to reduce the number of participants required; and (iii) making participation more appealing to patients and families by maximizing time spent on the active treatment. Several methodological reviews were published on this topic in the last decade [36, 39, 40, 42, 45, 46, 61], some of which provided more detail about the methods described below; here we focus on the most commonly suggested research designs that focus on minimizing bias to maximize internal validity and explanatory power.

Strategies that have been proposed for enhancing statistical efficiency at the design phase for clinical evaluative studies of rare disease treatments include factorial trials and adaptive designs. Factorial trials are designed to test multiple treatments simultaneously using the same study population, thus reducing the overall number of participants needed [2, 33, 39, 40, 46, 49, 53, 57]. For example, in a 2×2 factorial design participants are randomized to either treatment A or control group A, and then randomized again to treatment B or control group B, which effectively reduces the sample size needed to test these two treatments by 50% because the same participants are being randomized [40]. However, authors have pointed out that this reduction in sample size only holds assuming there is no interaction between

Table 2 Summary of findings according to each research paradigm

Key research paradigms	Main perspectives from the literature	Main perspectives from focus group participants
Explanatory evidence generation	- internal validity for conventional RCTs in rare diseases is threatened because of the small and often heterogeneous patient population - with small numbers of participants, there is potential for unbalanced confounders across groups despite randomization, and poor statistical power to detect treatment effects- modifications to conventional RCTs have been proposed to help maximize internal validity (e.g., adaptive trials, application of Bayesian statistics) - lack of patient/family/clinician acceptance to the possibility of being randomized to a placebo group, study designs that make participation more appealing by maximizing time spent on- or guaranteeing provision of- the new treatment have been suggested (e.g., crossover trials, N-of-1 studies)	- challenging to evaluate evidence with small sample sizes and short duration of follow-up *"I do find it quite difficult when the clinical trials are very short, very small numbers, and the endpoints are something like the six minute walk test in regards to really being confident that that is going to be an effective treatment for the patients that I'm seeing." – Physician 4* *"Well the ex-[profession] in me looks at things like, you know, the size of the study, well MPS is [laughter around the table], okay that's not going to happen. You know, so you have to, it's hard when you're looking at MPS because the things that you would normally look for in a good study aren't going to be there because of the size of the sample…" – Patient/caregiver 3*
Comparative effectiveness/pragmatic evidence generation	- external validity is threatened in rare disease research by the desire to enroll homogenous groups of participants for explanatory trials (patient population is often inherently heterogeneous) - there are also substantial differences between trial protocols and real-world clinical practice, reducing the external validity of some studies (i.e., need to account for co-interventions, less frequent follow-up visits, etc.) - several study designs have been suggested that may compromise internal validity to some extent in order to address real-world effectiveness (e.g., pragmatic trials, registry studies, hybrid study designs)	- need to address heterogeneity in treatment effect across clinical spectrum *"…the way that the trials are designed, very sub, select populations with the actual disease of concern, which is already a narrow disease as it is. It makes it very difficult for us to know where and when these therapies are going to work. And so, when we're talking about rare diseases, it really has to be linked to not just research, but effectiveness research about natural history and epidemiology. And given the wide degree of heterogeneity with the diseases that we're dealing with, we're going into this with a huge degree of uncertainty about whether or not there really is any evidence to support that these therapies are going to work." – Policy advisor 2*
Patient-oriented evidence generation	- explanatory study designs tend to rely on short-term, surrogate outcomes that are not necessarily clinically meaningful or relevant to patients and/or families - important to engage with patients and/or families throughout the research process to define important outcomes and determine minimal clinically important difference- there has been a shift/push to improve use of more patient-oriented outcomes in clinical evaluative research for rare diseases (e.g., quality of life measures, activities of daily living)- more difficult to use patient-oriented outcomes because tools have not been standardized in rare disease populations	- very important to measure outcomes that are clinically relevant *"For me I think one of the big issues is the outcome measures that we're trying to document. For instance, with the lysosomal storage diseases, what is the relevance of a 6 min walk test? What is the clinical relevance of this type of test?" – Physician 5* *"…because yes, scientific research is important too, but it's this push-pull dichotomy between the happiness, the living life, just the simple moments, you know, going outside, sitting in the sun, that type of, going down to the beach, those things need to be equally measured…" – Patient/caregiver 4*

the treatments being administered concurrently; otherwise, statistical efficiency is lost [40]. Adaptive designs allow flexibility in trial procedures such that changes ("adaptations") based on interim analyses can be made after trial initiation without undermining the validity of the trial [59]. Two commonly discussed adaptive trial strategies are response-adaptive randomization and group sequential design [36, 40, 46, 53, 59, 61]. Response-adaptive randomization involves modifying treatment assignment probabilities with the accrual of data so that the number of participants randomized to the best-performing treatment arm ("play-the-winner") is increased and overall sample size is decreased [59]. Group sequential designs do not have a predetermined sample size, rather, small groups of participants are recruited over several phases and data are analyzed at the end of each phase to assess safety, futility, efficacy, or a combination of these until enough data have been accrued to justify study termination [59, 61]. Simulation studies have shown that sequential design approaches may, but do not always, reduce the eventual sample size compared to fixed sample size designs [35, 53, 62]. While adaptive trial strategies are often reported as a means to enhance statistical efficiency, some authors have questioned their usefulness based on the paucity of published practical application in the context of rare diseases [40, 59].

For conventional RCTs with small sample sizes, achieving sufficient statistical power to detect differences in treatment effects, especially when the treatment effect is expected to be modest, is challenging [52]. Several authors have argued (as early as 1995) that Bayesian techniques would be better suited in this context relative to standard frequentist approaches to analysis, because a Bayesian analysis is not as compromised by small numbers and offers more direct conclusions [32, 34, 41, 44, 45, 48, 50–52]. In such approaches, previously collected data or expert opinion is used to generate a prior probability (posterior) distribution for the unknown treatment effect, and Bayes theorem is applied as new data are accumulated to update the posterior distribution for the new treatment and inform clinical practice [48, 52]. As an example, Johnson and colleagues reanalyzed data from an RCT of methotrexate versus placebo in 73 patients with scleroderma, and demonstrated that methotrexate had more favorable odds of being beneficial for patients when a Bayesian approach was applied compared to the non-statistically significant findings obtained through a frequentist approach [32]. While several authors argued that Bayesian statistics offer an alternative approach to the analysis of small numbers of participants, some criticized the subjectivity in establishing prior distributions and were skeptical of the acceptance of results obtained using Bayesian statistics at the regulatory level [34, 36, 45, 48].

It was reported in the literature and in our focus group discussions that there can be a lack of patient/family/clinician acceptance of the possibility of being randomized to a control group, particularly for placebo-controlled studies of treatments for rare diseases where few treatment alternatives exist. Therefore, study designs that make participation more appealing by maximizing time spent on- or guaranteeing provision of- the active treatment have been suggested [4, 33, 36, 38–42, 44–47, 49, 51, 56, 57, 60].

> *"I agree with [name]'s comments that it's hard to have a placebo-controlled trial. I mean, certainly there has been trials to try to do that. …however, they're very short and really with these, like almost, like even to encounter, to have families agreeable to participate being a placebo for long-term, I think would be very difficult. I think for the short-term, for a few months or a year, families are agreeable, but after that I don't think they would be agreeable."* – Physician 2

The randomized placebo-phase design has the same design features of a conventional RCT, except that the time from enrollment in the study to the start of the experimental treatment is randomized for all participants [56]. All participants eventually receive the experimental treatment, and effectiveness is determined based on whether a response is observed sooner among those that received the treatment earlier [56]. Similarly, randomized withdrawal, early escape, and stepped wedge trials reduce time spent in a control arm or ensure that all participants eventually receive the intervention being studied, and have been proposed as alternative approaches to evaluate clinical interventions for rare diseases [40]. Crossover trials and n-of-1 trials also guarantee that participants receive the active treatment, but are different than conventional RCTs in that the treatment sequence is randomized with a washout period in between treatment regimens, such that each participant acts as his or her own control [2, 36, 41, 53, 57]. As some authors reported, n-of-1 trials are often embedded in clinical practice to help healthcare providers determine the best treatments for their patients [2, 36, 57]. While several authors have examined the advantages of crossover and n-of-1 trials, others have discussed the risk of carryover and period effects between phases, and have argued that these designs are generally not suitable for diseases that have an unstable disease course or for interventions that are not fast-acting with reversible effects [2, 18, 33, 36, 39, 44, 46, 53].

The three overarching strategies and associated research methods discussed above are not mutually exclusive, rather there is significant overlap among them in the literature. For example, in addition to being an attractive option for participants, crossover trials are also

considered statistically efficient and reduce the number of participants needed because each participant acts as his or her own control [2, 18, 33, 36, 39, 40, 44, 46]. Huang and colleagues have suggested that statistical efficiency could be further enhanced in crossover trials by allowing participants to "escape early" [41]. Similarly, authors have stated that trials using adaptive randomization can be attractive to participants because the likelihood of being randomized to the less effective treatment arm is reduced over time [36, 40, 46, 53, 59, 61]. Bayesian methods are also reported as a common design feature of adaptive trials as a means of improving statistical efficiency [34, 42, 59]. They have also been proposed as a means to combine results from multiple n-of-1 trials and enhance the usability of n-of-1 trial data in answering population-level questions about treatment efficacy and effectiveness [51].

A criticism of explanatory evidence generation reported both in the literature and in focus group discussions was that studies designed to evaluate the efficacy of an intervention typically limit enrolment to a very homogenous group of participants, which strengthens the robustness of the causal interpretation of the findings, but at the expense of a reduction in the external validity or generalizability of study results [4, 18, 44, 60]. Because rare diseases typically exhibit substantial clinical heterogeneity (discussed in the following section), some authors have questioned the suitability of the above-mentioned approaches for evaluating clinical interventions for rare diseases [4, 18, 44, 60]. Additionally, authors have argued that many conventional RCTs and other explanatory studies are short in duration, often due to resource constraints, and do not allow for adequate assessment of long term treatment effects, further compromising external validity [4, 18, 57]. Finally, some authors were concerned that unfamiliar approaches to research design, such as adaptive randomization or n-of-1 trials would not be accepted by regulatory agencies and other policy decision-making bodies [36]. Partly in response to some of these concerns, other research paradigms for evaluating clinical interventions for rare diseases have evolved.

Comparative effectiveness/pragmatic evidence generation

It is well established that there is a high degree of clinical heterogeneity among rare disease patients, such that patients with the same specific disease might have drastically different clinical manifestations based on patient characteristics such as age, disease characteristics such as residual enzyme activity levels, or for unknown reasons, and may respond differently to a given intervention [18, 42]. As several authors have discussed, this clinical heterogeneity is often not accounted for in conventional RCTs, and has raised concern among stakeholders about the applicability of study results to patients with clinical manifestations different from those included in RCTs [4, 18, 44, 60].

> *"And I find it frustrating in terms of research what I've found, and you guys know this, that each case is so unique and different, and so when you read a study or evidence-based research, I find that it, it's not a guarantee that it's going to directly correlate to your particular unique situation. So, you have to take that at face value and not think that 'oh because I read that study and that it is evidence based that this is exactly what's going to pertain to my situation."* – Patient/caregiver 4

> *"…there's a huge heterogeneity of this population. There's people with very severe diseases, people with very mild disease, and this is the nature of enzyme deficiencies. There's some people that have zero and some people will have, a lot, near normal enzyme activity, so we're going to get this heterogeneity. And this is one of the big problems, like [name] mentioned, how do we apply this clinically to a larger population of these patients? Are the results, for instance, with infantile-Pompe, how do we relate that to an adult Pompe patient?"* – Physician 5

> *"…the way that the trials are designed, very sub, select populations with the actual disease of concern, which is already a narrow disease as it is. It makes it very difficult for us to know where and when these therapies are going to work. And so, when we're talking about rare diseases, it really has to be linked to not just research, but effectiveness research about natural history and epidemiology. And given the wide degree of heterogeneity with the diseases that we're dealing with, we're going into this with a huge degree of uncertainty about whether or not there really is any evidence to support that these therapies are going to work."* – Policy advisor 2

In response to concerns about the external validity of study results, several authors and focus group participants have advocated for study designs that may compromise internal validity to some extent, by shifting away from the explanatory RCT, in order to address real-world effectiveness [2, 4, 7, 18, 42, 44–47, 55, 57, 58, 63–80].

> *"…I think the effort like the Canadian group CIMDRN to look at long-term outcomes, where there's natural selection of various treatment groups, I think will be very helpful over the long term because of the challenges we have in doing strict study designs, and lack*

of financial supports for long-term studies. This effect to observational studies and looking at outcome differences in naturally, sort of, selected difference maybe as helpful in rare diseases I think as the designed studies." – Physician 1

Almost 10 years after discussions about explanatory evidence generation for clinical interventions for rare diseases emerged in the literature, the research paradigm of comparative effectiveness/pragmatic evidence generation started to develop (first discussion published in 2001). This paradigm was discussed by half (30/60, 50%) of studies included in this review, and was first mentioned by Wilcken in 2001 [7]. Like the previous research paradigm, most of the reports that discussed this paradigm were methodological review articles that focused on rare diseases in general or a group of rare diseases (21/30, 70%), rather than a single rare disease. Wilcken suggested that for some rare diseases, conventional RCTs remained possible, but for others, observational studies with historical controls could be used to evaluate treatment effectiveness [7]. Since that initial publication, many authors have discussed research designs that take a more pragmatic approach to evaluating treatment effectiveness in rare diseases, and often explicitly attempt to include a broader patient population and longer-term observation in natural settings. These designs include: pragmatic clinical trials, observational studies (e.g., cohort studies and registries, case series, case reports), and hybrid designs that incorporate both randomization and systematic observation [2, 4, 18, 42, 44–47, 55, 57, 58, 63–80].

While participants in our focus groups questioned the suitability of explanatory RCTs for establishing effectiveness of clinical interventions for rare diseases, little of the discussion focused on specific solutions to overcome this challenge. Like the previous research paradigm, most of the results presented under the paradigm of comparative effectiveness/pragmatic evidence generation are derived from our meta-narrative literature review.

Incorporating more pragmatic features into RCTs has been suggested as a means to improve external validity while maintaining the element of randomization to help control for unmeasured confounding and maintaining other standard methodological features of explanatory RCTs, such as blinded outcome assessments [18, 45, 57]. These pragmatic RCTs feature design elements that better reflect actual clinical practice, including: enrolling participants with differing clinical presentations, taking into consideration the system of care in which the new treatment will be delivered (e.g., using standard-of-care as a comparator instead of placebo), following participants for a longer period of time, and incorporating outcomes that are meaningful from a patient/care provider standpoint (patient-oriented research will be discussed in the following section) [18, 45, 57]. Authors have criticized pragmatic RCTs because they do still estimate average treatment effects and thus are not necessarily better suited to investigating potential heterogeneity of treatment effects relative to explanatory RCTs [18].

Among the most common observational rare disease research designs discussed in the studies we reviewed are patient registries [4, 18, 42, 47, 58, 64, 65, 67, 72–74, 77, 80] and cohort studies [68, 78]. Because these observational studies do not typically have strict inclusion or exclusion criteria for participants, nor do investigators manipulate participants' treatment(s), some authors have argued these studies better reflect real-world clinical practice and the clinical heterogeneity that typifies many rare diseases [18, 42, 67, 72]. As reported in the literature, registries have multiple purposes including: evaluating clinical- and/or cost-effectiveness of therapies; monitoring safety of new or existing therapies; evaluating diagnostic tools; monitoring quality of care; and assessing natural history over time [67]. We identified several examples of registries being used to evaluate treatment effectiveness of interventions for rare diseases, for example, enzyme replacement therapy for lysosomal storage disorders [72]. The International Collaborative Gaucher Group Registry was established in 1991 and, at the time of the publication of a paper by Jones and colleagues (2011), had collected longitudinal clinical data for almost 6000 patients [72]. Several authors stated that an additional advantage of registries is that they can be used to identify potential participants for recruitment into future research studies, including clinical trials [18, 67, 73, 76, 77]. Some authors have also suggested that observational patient registries may play an important role in post-market evaluation of interventions for rare diseases by serving as a platform to collect longitudinal clinical and quality of life data [47]. While observational patient registries are an attractive method for the evaluation of longer term outcomes in real-world settings, some authors reported that results remain prone to residual confounding in the absence of randomization, especially confounding by indication (when patient characteristics influencing the choice of treatment also influence the outcome) [18, 44]. A few authors discussed variability in the quality of registry data, as observational patient registries tend to be heterogeneous in the depth of data collection and the definitions applied to included data elements, particularly in the context of the multi-center and sometimes multi-national nature of rare disease research [42, 65]. In addition, some authors described the potentially important influence of complete case ascertainment and data collection on the accuracy of study results, particularly given

that registry participation may be associated with receipt of particular treatments or lead to different investigations [67, 73, 81].

In recent years (since 2009), some authors have suggested that elements of both explanatory and observational studies can be combined into "hybrid" study designs that attempt to mitigate challenges faced by both approaches [18, 63, 75]. For example, Vickers and colleagues suggested that the "clinically-integrated randomized trial," which seeks to integrate randomization into standard clinical care, would be suitable for rare disease research, addressing the threat of confounding while maintaining an element of pragmatism and enhancing generalizability [63]. The key feature of the clinically-integrated randomized trial is that there is no difference between the care a patient routinely receives, follow-up, payment, or documentation (e.g., charting), other than the fact that treatment was assigned randomly with informed consent from participants [63]. In the context of rare diseases, the authors argued that the clinically-integrated randomized trial is attractive because there is often considerable uncertainty about the most effective course of treatment for patients and that trials could easily be conducted worldwide to maximize the number of participants [63]. Another design that incorporates elements of both explanatory and observational approaches and has been suggested in the context of rare diseases is the "cohort multiple randomized controlled trial (cmRCT)" [75]. The cmRCT seeks to enroll an observational cohort of patients, with participants routinely reporting on a minimum set of core outcomes [75, 82]. At the time of enrollment in the cohort, participants give their consent for 1) their longitudinal data to be used in aggregate; and 2) to be randomly selected to participate in potential RCTs of new or existing interventions with the understanding that only those who have been selected to be offered the intervention under study will be contacted [75, 82]. Those who are eligible for the RCT, but who were not randomly selected to be offered the intervention serve as the control group and are not contacted about the study [75, 82]. According to the literature, launching RCTs using this design increases the efficiency of research by accommodating multiple trials and comparison of multiple treatments, allows for longer follow-up of participants, provides pragmatic/real-world evidence, and accommodates clinical heterogeneity by enrolling participants across the clinical spectrum [18, 75, 82]. Concerns that have been raised with these "hybrid" study designs include: potential for confounding and bias in the observational component of the study, and the feasibility of implementing such a study design [18, 75, 82].

Finally, there is discussion in this literature about other observational designs such as case-control studies, small case series and case reports; however, these approaches are not commonly suggested as potential solutions for improving pragmatic evidence generation for establishing effectiveness of treatments for rare diseases. Some authors have suggested that case-control designs, where individuals who have experienced a certain outcome (cases) are matched to and compared with individuals who have not experienced the outcome of interest (controls), are well suited for studying rare diseases, particularly in instances where there could be a long lag time between the treatment and outcome of interest [2, 80]. However, there are concerns about the potential for introducing selection bias in choosing controls [2]. Other authors have argued the importance of case series and case reports in the context of establishing treatment effectiveness for rare diseases [47, 66]. Case series and case reports typically include in-depth information related to clinical manifestations of disease, treatment, and follow-up for a single patient or small group of patients [47, 66]. While authors have acknowledged there are clear limitations in terms of establishing treatment effectiveness, they have argued that this evidence can provide a better understanding of natural history for many rare diseases, and can identify unexpected harms or benefits of treatments, which could be of particular importance for diseases considered "ultra-rare" [47, 66]. Similar to the concept of using case reports as pragmatic evidence, several focus group participants reported relying on some anecdotal evidence to help inform medical-decision making:

> *"I think all of the different information is important, and including anecdotal, right? Because we deal with very rare disorders sometimes, and you often go to clinicians who have seen these conditions and have treated them, and may take their point of view about a certain treatment. So, you may say that's anecdotal, but it may be extremely valuable if there's only a handful of patients who have received that treatment. So, I think all of the studies and designs, including anecdotal evidence, I personally use that in determining whether I think about a treatment for a patient."* – Physician 1

> *"…sometimes it all depends on the experience of what other people lived. Sometimes people tell you not to go there because they've has a bad experience. So, I like to have the bad and the good ones too, and then make my mind and take better decisions."* – Patient 2

The main criticism in the literature for comparative effectiveness/pragmatic evidence generation is the inherent risk for bias and confounding because of the lack of randomization; however, there have been efforts made to mitigate this risk. As previously discussed, some authors

have suggested incorporating pragmatic elements into RCTs [18, 45, 57], while others have proposed methods to overcome challenges in non-randomized studies. For example, Cole and colleagues demonstrated the use of case-control matching using the risk-set method for participants enrolled in the International Collaborative Gaucher Group Registry [69]. The authors applied this method to balance "cases", i.e., Gaucher patients with skeletal avascular necrosis, and controls according to demographic and clinical factors [69]. Use of propensity scores to match participants has also been suggested as a means of reducing the risk of bias in observational studies of rare diseases [44].

Patient-oriented evidence generation

One of the main criticisms, both in the literature and by focus group participants, of highly internally valid, explanatory study designs is their tendency to rely on short-term, and often surrogate, outcomes that are not necessarily clinically meaningful [9].

> *"Most of the time study with rare diseases rely on surrogates and the surrogates are selected usually on the basis of biochemical indicators of some biological activity of the treatment. And so, for enzyme replacement therapy, the reduction in the concentration of a substrate in urine or blood is regarded as evidence of a biological pivot, a biological activity, but there's far too many examples where a surrogate, such as the one I've just described, are really, there's no relationship to what the clinical outcomes are."* – Policy Advisor 1

> *"…I have a concern that sometimes outcome measures are defined by what funding and drug approval [agencies] like FDA want to see, right? [chuckles]. Rather than what the clinician may feel for a particular rare disease is far more important. …it becomes challenging to design appropriate studies and pharma is at the end of the day interested in getting approval and funding approval, and may target outcome measures that are demanded by various bodies rather than perhaps going for the most clinically appropriate outcome measures."* – Physician 1

Only in the last decade (Fig. 2) has a discussion in the literature emerged regarding the importance of patient-oriented evidence generation in rare diseases (the first appearing in 2010). This discussion emphasizes the need for outcomes that are of direct importance to patients and caregivers. Fifteen of 60 reports (15/60, 25%) discussed issues related to the paradigm of patient-oriented evidence generation, making it the research paradigm with the smallest proportion of literature. The majority of reports that discussed this paradigm were again methodological review articles (13/15, 87%), and the remaining two articles described case examples specific to one rare disease.

Connected to the paradigm of explanatory evidence generation, some authors have suggested the use of surrogate outcomes as proxies for patient-oriented outcomes such as survival or quality of life because they can be measured relatively quickly and require fewer participants to reach statistical efficiency [33, 83–85]. For example, in 2010, Kinder and colleagues reported that functional outcomes such as exercise tolerance, survival, and quality of life were the most salient outcomes to consider for rare lung disease studies because they have undeniable meaning for patients; however, the authors also described the limited feasibility of conducting explanatory RCTs that include these outcomes and argued that surrogate outcomes could therefore be developed and used as proxies for patient-oriented outcomes [33]. Several authors and focus group participants expressed concern about the lack of validation of surrogate outcomes; a clear understanding of the natural history of disease and proposed causal mechanism of a treatment in relation to the disease is needed in order to establish, with reasonable certainty, the relationship between surrogate and patient-oriented outcomes [33, 70, 73, 85, 86].

> *"…in order to identify reasonable outcomes measures for any clinical trial, one has to know the what the natural history of the disease is. So, those are major challenges, and what we're faced with in the pharmaceutical industry, who are anxious to do as short a study as possible, for rare disease almost always use surrogate markers as evidence of effectiveness and the relationship between the surrogate marker and clinical outcome is often completely unknown."* – Policy Advisor 1

For example, the six-minute walk test (6MWT) is a common surrogate outcome measure used in clinical evaluative studies for many rare diseases [83, 84, 87]. The 6MWT was originally developed for patients with moderate to severe lung disease as a means of assessing overall functional status and as a predictor of morbidity and mortality [88] but has since been used in studies of many rare diseases, including late-onset Pompe disease and Duchenne muscular dystrophy, among others [84, 87]. An important criticism of this extension of its use is the lack of adequate validation to determine if observed changes in the 6MWT reflect meaningful changes for patients [83, 84, 87].

> *"For me I think one of the big issues is the outcome measures that we're trying to document. For instance,*

with the lysosomal storage diseases, what is the relevance of a 6 minute walk test? What is the clinical relevance of this type of test?" – Physician 5

Partly in response to concerns about the relevance and validity of surrogate outcomes being used in clinical research for interventions for rare diseases, there has been a shift towards incorporating patient-oriented outcomes in clinical research [4, 42, 45, 74, 89].

"…because yes, scientific research is important too, but it's this push-pull dichotomy between the happiness, the living life, just the simple moments, you know, going outside, sitting in the sun, that type of, going down to the beach, those things need to be equally measured…" – Patient/caregiver 4

"We need to know more what's going to happen in terms of lifespan, in terms of morbidity, in terms of the operations these patients are getting, in terms of growth as well. Is this something that we're seeing improvement?" – Physician 5

"I think that [name] made reference to this earlier about the importance of evaluating quality of life. And unfortunately, this is not really done. I don't know of a single study that has done this rigorously for the diseases that I happen to be involved with or have been. And so, for example, the fact that a child may require an intravenous infusion of some medication that takes six hours of infusion and needs it every week. They're missing a day of school every week. That's twenty percent of their schooling! This is never, in my experience, never evaluated. Now that's not a direct measure of quality of life, but you could easily imagine that it would have a significant indirect impact on quality of life." – Policy Advisor 1

In the literature and among our focus group participants, much of the discussion regarding patient-oriented outcomes has focused on developing outcomes that are meaningful based on the lived experiences of patients and their caregivers [18, 42, 74, 89]. Tudur Smith and colleagues used the example of juvenile idiopathic arthritis to demonstrate that clinical research initially focused on outcomes related to clinical disease activity and disease damage, but more recently has shifted to identifying and validating outcomes that are most important to patients and parents, such as health related quality of life, functional assessments, and pain assessments [45]. Basch and Bennett advocated for the use of patient-reported outcomes in clinical studies for interventions for rare disease as the best measurement tools for how a patient feels and functions [89]. Participants in our focus groups also expressed a desire for researchers to incorporate outcomes beyond those directly related to the patient, including parent- and family-related outcomes.

"One quick comment about the whole family because I know, obviously, a lot of this is directed towards the patient, the person with [disease], but it's, you know, so linked and so connected, that I find there's a direct, you know, effect on the child through the parents, so I'd like to see more supports, research for the parents that are also kind of surviving through this…" – Patient/caregiver 4

A common criticism is that many outcome measures, including patient-oriented outcome measures, have not been validated or standardized for the population of interest, leading to questions about the applicability of study results [4, 42, 70].

"… we know that some of these tests or some of the questionnaires have not been standardized for these particular populations, and we're faced with always the question is it clinically relevant for these patients? I think overall, there's agreement that they are, but we run into this problem all the time with, you know, Pompe or the different MPS' because there hasn't been long enough natural history studies, there has not been standardization of these tests, so we're choosing these measuring tools for these particular studies without really knowing if they're the best tools. And this is very relevant for the quality of life questionnaires, we sometimes use the SF36 or we use specific pain criteria, APPT or something like that, but we haven't actually standardized this for these populations, so we don't actually know if what we're measuring is clinically relevant." – Physician 5

In response to this criticism, some researchers have begun to identify/develop and validate standard sets of outcome measures that can be used in clinical research evaluating treatment effectiveness in their populations [4, 45, 76]. Another concern that has been raised with respect to outcomes is that it may not be possible to use the same outcome measure within the same disease if there is substantial clinical heterogeneity among patients [4, 42, 45, 84, 89]. Some authors and focus group participants also noted that clinical heterogeneity has implications for identifying the minimal clinically important difference [42].

"…the main trial showed an improvement of 22.5 meters after 6 months in the six-minute walk test, which there's quite a variability in outcomes depending

on which patients you're looking at, but that the average improvement. What does that really mean is a very difficult decision because for somebody that is walking perhaps 300 meters in six minutes and improves by 22.5 meters, that's probably not clinically significant, if we're just looking at a six-minute walk test. But, if someone is not very mobile at all and has that improvement, we might actually have a more clinically significant impact with that treatment." – Physician 5

Finally, some focus group participants expressed concern about balancing subjective outcomes (e.g., patient-reported quality of life) with more objective outcomes (e.g., biomarkers of disease progression) because of possible placebo effects with patient-reported outcomes.

"I think there needs to be a combination of objective and subjective outcome measures and quality of life measures because, certainly, quality of life is extremely important, but my sense is that it's a lot more vulnerable to placebo effect. As well, just in the sense that a lot of these families are extremely invested in being on their therapy because it is their only therapeutic option. And so by relying on quality of life measures very heavily, I think we can end up advocating for treatment for patients that aren't really clinically benefitting." – Physician 6

Discussion

Randomized controlled trials have long been considered the 'gold standard' in evidence-based medicine due to their superior ability to maximize internal validity [5]. However, our review and focus group findings describe criticisms of conventional explanatory RCTs to establish treatment effectiveness for rare disease therapies. There was agreement across the focus group interviews and with the literature we reviewed that the main challenges in generating robust treatment efficacy and effectiveness evidence for rare diseases includes: i) limitations in recruiting a sufficient sample size to achieve planned statistical power for many rare diseases, especially those with a low prevalence such as MPS; ii) difficulties in accounting for characteristic clinical heterogeneity of many rare diseases; and iii) frequent reliance on short-term, surrogate outcomes whose clinical relevance is often unclear. We mapped these three perceived challenges and associated methodological solutions to three interrelated research paradigms that emerged from our data: i) explanatory evidence generation, ii) comparative effectiveness/pragmatic evidence generation, and iii) patient-oriented evidence generation. Discussions related to explanatory evidence generation were the first to arise in the rare disease literature (in 1992) and have persisted through 2016, with 58% (35/60) of the reports we reviewed examining this research paradigm. The paradigm of comparative effectiveness/pragmatic evidence generation, which was discussed in 50% (30/60) of reports, emerged in the literature in the early 2000s and has also persisted through 2016, with a substantial increase in the number of reports in the literature over the last decade. The paradigm of patient-oriented evidence generation developed more recently in the literature (beginning in 2010) and has been discussed in 25% (15/60) of reports included in this review. Based on the year of publication for the included studies, there appears to be a shift in perspectives over time with increased criticism of conventional explanatory RCTs and associated recognition of the importance of pragmatic and patient-oriented evidence generation in the context of establishing treatment effectiveness for rare diseases.

Several methodological solutions have been suggested within each research paradigm to address the perceived challenges that were identified both in the literature and by our focus group participants. For explanatory evidence generation, the potential solutions include: study designs that incorporate elements to improve statistical efficiency and reduce the required sample size (e.g., factorial trials, adaptive designs, applying Bayesian statistical methods), and study designs that ensure receipt of or maximize time spent on active treatment to help boost participation (e.g., randomized placebo-phase designs, crossover/N-of-1 trials). For comparative effectiveness/pragmatic evidence generation, study designs or features that have been proposed to improve the external validity of study results include: incorporating pragmatic elements into conventional RCTs, registries/cohort studies, and hybrid designs such as cmRCTs. For patient-oriented evidence generation, authors and focus group participants suggested that incorporating outcomes that are considered important by patients and their caregivers (e.g., health-related quality of life) is critical to improve the applicability of study results.

Notably, though numerous non-conventional study designs were described in the literature we reviewed, few of the suggested approaches appear to have been applied successfully in the context of rare diseases. Only 28% (17/60) reports included in this review were considered applications or case examples of a specific research method. As suggested by Gupta and colleagues, the paucity of real-world application of these designs, particularly the non-conventional explanatory RCT designs, may be related to a lack of acceptance of unfamiliar study designs [36]. New therapies for many rare diseases are rapidly developing, so there is an increasing

opportunity to apply some of these non-conventional study design strategies to evaluate efficacy and effectiveness of emerging treatments for rare diseases [Stockler-Ipsiroglu et al. Innovations in therapies and evidence creation for inborn errors of metabolism, in progress].

Among the suggested methodological strategies, there are tradeoffs with respect to internal and external validity, some of which may be exacerbated in the context of rare diseases. For example, external validity is compromised in many explanatory RCTs in favour of maintaining strong internal validity to reduce potential bias and confounding. In addition, because of the small number of individuals available to participate in research, relying on randomization procedures to balance patient characteristics (both known and unknown) will not always be successful. By contrast, study designs that can better accommodate clinical heterogeneity and enhance external validity may introduce a risk of confounding and bias. And while external validity can be compromised if the outcomes(s) included in a study are not considered important by clinicians and patients, many patient-oriented outcome measures require additional validation and long-term follow-up. With these tradeoffs in mind, strategies for both comparative effectiveness/pragmatic and patient-oriented evidence generation are increasingly being recognized as important for investigating the effectiveness of treatments for rare diseases, with explanatory RCTs becoming less dominant in the literature in recent years.

The results of our meta-narrative review corroborate the conclusions of methodological reviews that have focused on approaches to generating evidence for interventions for rare diseases [36, 39, 40, 42, 45, 46]. To our knowledge, our study is the first to incorporate stakeholder perspectives in addition to data from the published literature and to include a description of how perspectives have evolved over time using a meta-narrative review. Many of the approaches described in previously published reviews are specific to explanatory evidence generation. For example, both Gupta and colleagues and Cornu and colleagues provide algorithms that could be used by researchers to facilitate decision-making about which explanatory trial design to apply for a particular rare disease research question [36, 40]. Previous reviews included limited discussion of pragmatic evidence generation, with the exception of observational methods such as registries or cohort studies [42, 46]. Gagne and colleagues were the only authors among our reviewed studies to include an in-depth discussion about strategies that could be used to mitigate bias and confounding in observational studies of interventions for rare diseases [46]. Previously published reviews rarely mentioned patient-oriented outcomes in the context of evidence generation related to rare diseases.

Our work is not without limitations. The search strategy that was developed for the meta-narrative portion of this study was not exhaustive, so there is a possibility that some literature may have been missed. However, our intention was to identify key literature on this topic. In addition, we only had a single reviewer (KT) who determined study eligibility, which could have led to selection bias in the articles chosen; however, clear inclusion and exclusion criteria were used and the study team met several times to review selected literature and discuss emerging findings. We only conducted three focus group interviews with a relatively small, convenience sample of participants; consequently, we may have missed some perspectives. Our patient/caregiver focus group was particularly narrow in its focus on a single group of rare diseases. Because we were able to leverage an existing meeting of an otherwise geographically dispersed group of patients and families with MPS, an advantage of our approach was the ability to conduct an in-person focus group interview and thus ascertain the views of the participants more fully. However, some of the perspectives may have been specific to that disease group and future research could explore the perspectives of patients and families with other rare diseases, including those with a relatively higher prevalence for whom conventional explanatory studies might be more feasible (e.g., cystic fibrosis).

Conclusions and future directions

Through our meta-narrative literature review and focus group interviews we identified several perceived challenges and potential solutions for generating robust treatment effectiveness evidence for rare diseases according to three interrelated research paradigms: explanatory, comparative effectiveness/pragmatic, and patient-oriented evidence generation. Over time, there has been more recognition that observational studies, such as patient registries and cohort studies, are important approaches for clinical evaluative research in the context of rare diseases to address gaps in comparative effectiveness/pragmatic and patient-oriented evidence generation. Developing better methods to mitigate potential bias and confounding would increase the value of these approaches for establishing treatment effectiveness in the rare disease context. From a policy perspective, there is a need for inclusive discussions amongst patients and their families, clinicians, and policy advisors, including those involved in regulatory and reimbursement decision-making about interventions for rare diseases, in order to identify solutions that meet the needs of all stakeholder groups. Finally, little research has been done with respect to developing knowledge synthesis methods that consider the challenges faced in generating robust evidence for rare diseases. Future directions for our work include developing a framework to expand current evidence synthesis practices to take into consideration many of the concepts discussed in this paper.

Additional files

Additional file 1: Search strategies for electronic databases. (DOCX 64 kb)
Additional file 2: List of articles included in meta-narrative literature review. (XLSX 53 kb)

Abbreviations
6MWT: Six-minute walk test; cmRCT: Cohort multiple randomized controlled trial; RCT: Randomized controlled trial

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Availability of data and materials
The datasets generated during and/or analysed during the meta-narrative portion of this study are available from the corresponding author upon reasonable request. The datasets generated during and/or analysed during the focus group portion this study are not publicly available to protect the privacy of the participants.

Authors' contributions
KT contributed to the study design, developed the protocol for the meta-narrative review, developed the interview guide for the focus group interviews, conducted all focus group interviews, conducted all data analysis and interpretation of findings, and drafted the manuscript. DC and IDG contributed to the design and supervision of the study, interpretation and critical review of the findings, and revisions to the manuscript. LS contributed to the design of the meta-narrative review, critical review of the findings, and revisions to the manuscript. PC and KW contributed to the design and supervision of the study, critical review of the findings, and revisions to the manuscript. JJM and SS contributed to the critical review of the findings and revisions to the manuscript. BKP contributed to the design and supervision of the study, review of the protocol for the meta-narrative review, review of the focus group interview guide, data verification and analysis, interpretation and critical review of the findings, and revisions to the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval for this study was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board, the Ottawa Health Science Research Network Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

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

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Supplemental Information for Chapter 3

Supplemental File 3-1: Focus group interview guide.

A1. FOCUS GROUP INTERVIEW GUIDE – Patients/families

[Following the initial introduction of the research project, this specific study's purpose, their consent to participate in the focus group, and arrangements for a suitable meeting time – all prior to the focus group interview.

The focus group is essentially intended to be 'semi-structured' i.e., the script does not need to be followed verbatim and is dependent the flow of discussion among the participants].

Preamble items

- Hello and welcome to our session. Thank you for taking the time to join us to talk about evidence related to treatments for rare diseases. You participation is greatly appreciated. My name is [*researcher*] and assisting me is *[name of person assisting]*. We're both from the [*institution*].
- This project is part of my PhD research, which is focused on rethinking the way we summarize evidence when we are thinking about treatments for rare diseases.
- One of the components of my project is to speak with different stakeholders – including patients or caregivers of patients with rare diseases, health care providers, and policy decision-makers – to understand how people with different perspectives think about evidence and treatments. Today, I am interested in your views, based on your lived experience as patients or caregivers.
- I will be asking you what you think about evidence related to treatments for rare diseases. For example, I will ask you what evidence means to you, whether and why it's important to you when you think about decisions regarding treatments, and what kind of evidence is more or less meaningful from your perspective.
- We need your input and want you to share your honest and open thoughts with us.
- The information that you share with us today will be used to develop methods for evaluating evidence for rare diseases. This may help to improve the quality of decision-making regarding treatments for rare disease and may benefit future patients and families, clinicians, and policy advisors.

Ground rules

- Before we get started, I'd like to set a few ground rules for our discussion.
- Number 1. We want you to do the talking and would like for everyone to participate.
- Number 2. There are no right or wrong answers. Every person's experiences and opinions are important and we are looking to get a range of opinions. Please feel free to share your point of view even if it is different from someone else's. And keep in mind that we're just as interested in negative comments as positive comments.

- Number 3. Please remember that what is said in this room during our session stays here. Confidentiality is important in making sure everyone feels respected and comfortable sharing.
- Number 4. We are tape recording this session because we don't want to miss any of your comments. People often say very helpful things in these discussion and we can't write fast enough to get them all down. We will be on a first-name basis during this discussion, and we won't be using any names in our reports, so your identity will be kept confidential outside of this group.
- As mentioned previously, our discussion today is expected to take between 45 and 60 minutes to complete.
- Does anyone have any questions or points for clarification?

Icebreaker/opening round-robin question?

- Let's start with some introductions. Please tell us your first name, where you're from, and why you decided to join us today.
- Okay – great! Now that everyone is warmed up a bit, let's get into today's discussion.

Treatment effectiveness evidence for rare diseases

My first few questions focus on research in general.

- When I say 'evidence' or 'research', what comes to mind for you?
    - *[prompt]* What do you know about research surrounding therapies for MPS or other rare diseases?
- If you or someone close to you has participated in one or more research studies or if you were approached to participate in a research study related to treatment, what kinds of things would you consider before deciding to participate?
- Thinking about your experience as a patient and/or caregiver, when deciding whether to try a new or existing therapy, to what extent do you consider evidence, if at all?
    - Is research something that you talk with your doctor or other care providers about?
    - Are there other resources that you might consult to help you make a decision about the therapy?
    - How much would you rely on research versus other considerations, such as the experience of other patients?
- What do you think would make a high quality study or good evidence? What would you look for if you were trying to decide whether a study provides helpful information for making a decision about whether you or someone you care about uses a specific treatment?
    - *[prompt]* What aspects of a research study make the results more or less convincing to you (*[further prompts]:* for example, who is in the study [are they similar to you or to the person you care for, how many people studied], does everyone get the treatment [is there a comparison group], how long are people followed, how do they decide whether the treatment has benefits, do they need to look for adverse effects/safety –etc)
- We have talked about a number of different aspects of studies that would make them more or less helpful for making decisions about treatments, for example [list from

previous answers – e.g., people studied are similar to you or the person you care for, there is a comparison group, people were followed for a long time, a lot of people studied, etc..]. Of these, what do you think is the most important thing to look for in a study?
- Are you aware of any of the research concerning treatments that are available for MPS?
    - If so, what is your opinion about that evidence?

Outcomes

Thank you for all of your comments about research and evidence in general. Now we're going to switch the focus a bit to talk more specifically about outcomes [which was one of the study features we mentioned].

To look at the effects that treatments have on patients in a study, researchers measure outcomes. For example, for MPS, outcomes might include quality of life, results of a blood test, or adverse effects.

- Have you heard of any outcomes that are used in studies of treatments for MPS?
    - *[prompt]* For example, has anyone heard of the 6-minute walk test? Or biomarkers like urinary GAGs?
- Do you think it matters what outcomes are used in a study?
- What do you think would make a good outcome for a study evaluating a treatment for children with one of the MPS conditions?
    - Of these, which would you consider most/least relevant and why?
- Who should decide what outcomes are measured?
- How much does an outcome have to change in the participants in a study in order to conclude that a treatment is effective?
    - *[prompt]* If the patients in a study have better scores, on average, on the outcome after the treatment compared to before (or the patients who receive the treatment have better scores than those who don't), should we conclude that a treatment is effective? Does it matter how much better the scores are?

Different types of evidence to evaluate treatments

Thank you all for sharing your perspectives about outcomes. So far we have mainly been thinking about evidence when it comes to helping with decisions about whether to treat an individual patient. Now I want to talk specifically about the different kinds of evidence that policy decision-makers use. For example, policy decision-makers might use evidence along with other considerations to make decisions about whether a treatment will be covered by a public drug plan.

Usually policy decision-makers rely on what are called evidence syntheses or systematic reviews. Systematic reviews are projects that aim to summarize or bring together all of the individual studies that have been done to evaluate a treatment. A systematic review tells us about the overall state of the evidence about a treatment. So, my next few questions focus on the systematic reviews that are used to help with policy decisions about treatments for rare diseases.

- What kinds of studies do you think researchers should look at when they conduct a systematic review to summarize evidence about a treatment for MPS or another rare disease?
    - *[prompt]* Do you think that these reviews should only rely on studies that have some of the characteristics we talked about earlier –e.g., include people who are like the patients who the decision is being made about, have a comparison group, rely on important outcomes, etc? Or would you want them to summarize all of the evidence? If you think they should use all of the evidence, should they put more emphasis on the higher quality studies? Are there any risks with using all of the evidence?
        - *[further prompt]* e.g., safety/side effects; resources that could go into developing or funding better treatments.

- Do you think the kind of evidence that researchers summarize in a systematic review should be different depending on the disease or the treatment, or other aspects of the specific situation? In other words, should the standards for evidence be different for different kinds of decisions?
    - *[prompt]* For example, what if there are no studies that use high quality designs? What if there are no other treatments available? Are there risks or downsides to relying on lower quality evidence if that is all that is available or if there are no other treatment options?

Ending questions

- Of all the things that we discussed today, what to you is the most important?
- The purpose of today's discussion was to gain a better understanding of your perspectives on evidence related to treatments for rare diseases. Is there anything that you feel we may have missed or that you would like to add?

Concluding items

- We really appreciate you taking the time to meet with us today.
- If you have any questions or concerns, please do not hesitate to contact me at any time.

A2. FOCUS GROUP INTERVIEW GUIDE – Metabolic physicians

[Following the initial introduction of the research project, this specific study's purpose, their consent to participate in the focus group, and arrangements for a suitable meeting time – all prior to the focus group interview.

The focus group is essentially intended to be 'semi-structured' i.e., the script does not need to be followed verbatim and is dependent the flow of discussion among the participants].

Preamble items

- Hello and welcome to our session. Thank you for taking the time to join us to talk about evaluation of evidence regarding the effectiveness of treatments for rare diseases. You participation is greatly appreciated. My name is [*researcher*] and assisting me is *[name of person assisting]*. We're both from the [*institution*].
- This project is part of my PhD research, which is focused on rethinking the way we combine evidence from studies of treatment effectiveness for rare diseases.
- Specific to this session, I'm interested in your views concerning evidence about the effectiveness of treatments for rare diseases and the value a different approach to evidence synthesis might have.
- I will be asking you about your perspectives on evidence in general, evidence about rare disease treatments, in particular, evidence about enzyme replacement therapy for mucopolysaccharidosis type I (MPSI) and Pompe disease.
- You were invited to participate because you have had experience treating patients affected by a rare disease.
- We need your input and want you to share your honest and open thoughts with us.

Ground rules

- Before we get started, I'd like to set a few ground rules for our discussion.
- Number 1. We want you to do the talking and would like for everyone to participate.
- Number 2. There are no right or wrong answers. Every person's experiences and opinions are important and we are looking to get a range of opinions. Please feel free to share your point of view even if it is different from someone else's. And keep in mind that we're just as interested in negative comments as positive comments.
- Number 3. Please remember that what is said in this room during our session stays here. Confidentiality is important in making sure everyone feels respected and comfortable sharing.
- Number 4. We are tape recording this session because we don't want to miss any of your comments. People often say very helpful things in these discussion and we can't write fast enough to get them all down. We will be on a first-name basis during this discussion, and we won't be using any names in our reports, so your identity will be kept confidential outside of this group.
- As mentioned previously, our discussion today is expected to take between 45 and 90 minutes to complete.
- Does anyone have any questions or points for clarification?

Icebreaker/opening round-robin question?

- Let's start with some introductions. Please tell us your first name, where you're from, and why you decided to join us today.
- Okay – great! Now that everyone is warmed up a bit, let's get into today's discussion.

[Metabolic physicians]

Evaluation & synthesis of evidence
My first questions focus on evidence in general, and the ways that the strength of evidence is graded or evaluated.

- Thinking about your practice and the patients that you care for, when deciding whether or not to recommend a new or existing therapy, to what extent do you consider evidence, if at all?
- What kinds of evidence do you rely on in an ideal scenario?
    - *[prompt]* For example, are there certain research study designs that you look for (i.e., randomized controlled trials, systematic reviews, observational studies, etc.)? Evidence of biologic mechanism? Safety data? Anecdotal evidence from other physicians? Clinical practice guidelines?
- Are there particular study designs that you would never consider as part of the evidence base when deciding whether or not to recommend a new or existing therapy?
    - Why not consider those study designs?
- Given the challenges in the generation of evidence for treatment effectiveness for rare diseases, are there any differences in the types of evidence that you would consider for a rare disease versus a more common disease?
- Are there any differences in the extent to which you rely on evidence versus other considerations, such as anecdotes from other physicians?

- If you do read a particular study to inform a decision, how would you evaluate the quality of each piece of evidence that you've identified as part of the evidence base?
    - *[prompt]* What aspects of a piece of evidence make it more convincing than another? How do you identify the strengths and/or weaknesses of a piece of evidence?
- Are you familiar with any guidelines or established criteria for evaluating the quality of evidence, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process?
    - Do you use any of these guidelines in your quality assessments?
- Thinking specifically about the evaluation of evidence for treatments for rare diseases, are there any additional criteria you might look for or any that you feel are less important or applicable?

- Thinking about your experience with MPSI and/or Pompe disease, are you aware of the enzyme replacement therapies that are available?
    - If so, do you happen to know about any evidence regarding their effectiveness? What is your opinion about that evidence?
    - Would the nature of the evidence (e.g., study design, number of patients, etc.) make a difference in your opinion?

My next few questions focus on evidence synthesis.

- Traditionally, evidence synthesis practices (systematic reviews) that are designed to summarize the evidence around treatment effectiveness for an intervention, focus on combining evidence from randomized controlled trials or quasi-randomized controlled trials because of the methodological rigour associated with these study designs. Do you think that researchers who conduct systematic reviews should be considering other types of evidence?
- Thinking specifically about the synthesis of evidence for treatments for rare diseases, do you have any concerns about current practice?
    - *[prompt]* For example, do you think we are missing valuable evidence by only including randomized or quasi-randomized controlled studies in systematic reviews?
- Do you think that there would be added value in expanding current evidence synthesis approaches to include specific considerations for rare diseases?
    - For example, do you think there is value in adding guidance about inclusion of single case studies or case series to current evidence synthesis practices for rare diseases?
- Is there anything specific that you would like to see added to or changed about the way evidence is currently being evaluated and synthesized for rare diseases?
    - *[prompt]* Are there areas for improvement?

Outcomes

Thank you for all of your comments about the evaluation and synthesis of evidence. Now we're going to switch the focus a bit to talk specifically about the evaluation of outcomes in the context of rare diseases.

A key factor in the evaluation of a new or existing intervention is determining the relevance of a chosen outcome for the population of interest, and its associated minimal clinically important difference.

- Ideally, what kinds of outcomes do you feel are the most informative in the context of recommending/prescribing treatments for your patients?
    - *[prompt]* For instance, if you had to rank the following outcomes, patient-reported outcomes (e.g., number of headaches, pain, quality of life), clinical outcomes (e.g., survival), biomarkers (e.g., blood cholesterol) and other surrogate/intermediate endpoints on how informative they are, which would you consider the most informative? Least informative?
- In clinical research, there is often more than one outcome measure used across studies, thinking your practices for evaluation and synthesis of evidence used to inform clinical practice, how would you prioritize or determine which outcomes were most relevant to your patient?
    - *[prompt]* Are there any specific criteria that you might use to assess the strength of an outcome?
- Once you have chosen an outcome to focus on, how do you determine what constitutes a meaningful improvement?

    - *[prompt]* How much of an improvement over an existing treatment would you need to see in a new treatment before recommending its use?
- In the context of rare diseases, studies of treatment effectiveness evidence often rely on surrogate endpoints or biomarkers. For example, many of the studies that evaluate the effectiveness of enzyme replacement therapy for lysosomal storage disorders typically use forced vital capacity or the 6-minute walk test as outcomes. Given that lysosomal storage disorders are chronic, progressive diseases, do you think these outcomes are appropriate?
    - Based on your experience treating MPS I patients, what would be the ideal outcome to use in research for treatment effectiveness? And for those with Pompe disease?
    - In each of these cases, what would you consider a clinically meaningful improvement?

Ending questions

- Of all the things that we discussed today, what to you is the most important?
- The purpose of today's discussion was to gain a better understanding of your perspectives on evaluating and synthesizing the evidence base for treatments for rare diseases, and the value a more tailored synthesis approach might have. Is there anything that you feel we may have missed or that you would like to add?

Concluding items

- We really appreciate you taking the time to meet with us today.
- If you have any questions or concerns, please do not hesitate to contact me at any time.

A3. FOCUS GROUP INTERVIEW GUIDE – Policy advisors

[Following the initial introduction of the research project, this specific study's purpose, their consent to participate in the focus group, and arrangements for a suitable meeting time – all prior to the focus group interview.

The focus group is essentially intended to be 'semi-structured' i.e., the script does not need to be followed verbatim and is dependent the flow of discussion among the participants].

Preamble items

- Hello and welcome to our session. Thank you for taking the time to join us to talk about evaluation of evidence regarding the effectiveness of treatments for rare diseases. You participation is greatly appreciated. You participation is greatly appreciated. My name is [*researcher*] and assisting me is *[name of person assisting]*. We're both from the [*institution*].
- This project is part of my PhD research, which is focused on rethinking the way we combine evidence from studies of treatment effectiveness for rare diseases.
- Specific to this session, I'm interested in your views concerning evidence about the effectiveness of treatments for rare diseases and the value a different approach to evidence synthesis might have.
- I will be asking you about your perspectives on evidence in general, evidence about rare disease treatments, in particular, evidence about enzyme replacement therapy for mucopolysaccharidosis type I (MPSI) and Pompe disease.
- You were invited to participate because you have had experience in reviewing evidence in the context of health policy recommendations.
- We need your input and want you to share your honest and open thoughts with us.

Ground rules

- Before we get started, I'd like to set a few ground rules for our discussion.
- Number 1. We want you to do the talking and would like for everyone to participate.
- Number 2. There are no right or wrong answers. Every person's experiences and opinions are important and we are looking to get a range of opinions. Please feel free to share your point of view even if it is different from someone else's. And keep in mind that we're just as interested in negative comments as positive comments.
- Number 3. Please remember that what is said in this room during our session stays here. Confidentiality is important in making sure everyone feels respected and comfortable sharing.
- Number 4. We are tape recording this session because we don't want to miss any of your comments. People often say very helpful things in these discussion and we can't write fast enough to get them all down. We will be on a first-name basis during this discussion, and we won't be using any names in our reports, so your identity will be kept confidential outside of this group.
- As mentioned previously, our discussion today is expected to take between 45 and 90 minutes to complete.
- Does anyone have any questions or points for clarification?

Icebreaker/opening round-robin question?

- Let's start with some introductions. Please tell us your first name, where you're from, and why you decided to join us today.
- Okay – great! Now that everyone is warmed up a bit, let's get into today's discussion.

[Policy-advisors]

Evaluation & synthesis of evidence

My first questions focus on evidence in general, and the ways that the strength of evidence is graded or evaluated.

- Can you briefly describe what your overall process is for reviewing evidence ahead of making health policy recommendations about whether or not a new or existing treatment should be eligible for reimbursement?
- Thinking about your process for reviewing evidence, what kinds of evidence do you rely on in an ideal scenario?
    - *[prompt]* For example, are there certain research study designs that you look for (i.e., randomized controlled trials, systematic reviews, observational studies, etc.)? Evidence of biologic mechanism? Safety data?
- Are there particular study designs that you would never consider as part of the evidence base for making health policy recommendations about treatments/interventions?
    - Why not consider those study designs?
- Given the challenges in the generation of evidence for treatment effectiveness for rare diseases, are there any differences in the types of evidence that you would consider for a rare disease versus a more common disease?

- Have you heard of MPS I, Pompe disease, or other rare diseases where expensive enzyme replacement therapies (ERT) are already available or are being considered?
    - If so, do you know anything about the evidence regarding effectiveness? Have you had any specific experiences in considering that evidence?
    - Can you describe any challenges that you experienced in evaluating that evidence?

- In the context of recommendation questions that pertain to interventions, how would you evaluate the quality of each piece of evidence that you've identified as part of the evidence base?
    - *[prompt]* What aspects of a piece of evidence make it more convincing than another? How do you identify the strengths and/or weaknesses of a piece of evidence?
- Do you follow any established guidelines or criteria for evaluating the quality of the evidence for new or existing interventions?
    - *[prompt]* For example, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process?
- Thinking specifically about the evaluation of evidence for treatments for rare diseases, are there any additional criteria you might look for or any that you feel are less important or applicable?

My next few questions focus on evidence synthesis.

- Traditionally, evidence synthesis practices focus on combining evidence from randomized controlled trials or quasi-randomized controlled trials because of the methodological rigour associated with these study designs. Are there any other types of evidence that you would consider as part of an evidence synthesis for the purposes of health policy recommendations about treatments/interventions?
- Thinking specifically about the synthesis of evidence for treatments for rare diseases, do you have any concerns about current practice?
    - *[prompt]* For example, do you think we are missing valuable evidence by only including randomized or quasi-randomized controlled studies in systematic reviews?
- Do you think that there would be added value in expanding current evidence synthesis approaches to include specific considerations for rare diseases?
    - For example, do you think there is value in adding guidance about inclusion of single case studies or case series to current evidence synthesis practices for rare diseases?
- Is there anything specific that you would like to see added to or changed about the way evidence is currently being evaluated and synthesized for rare diseases?
    - *[prompt]* Are there areas for improvement?

Outcomes

Thank you for all of your comments about the evaluation and synthesis of evidence. Now we're going to switch the focus a bit to talk specifically about the evaluation of outcomes in the context of rare diseases.

A key factor in the evaluation of a new or existing intervention is determining the relevance of a chosen outcome for the population of interest, and its associated minimal clinically important difference.

- Ideally, what kinds of outcomes do you feel are the most informative in the context of making health policy recommendations about interventions?
    - *[prompt]* For instance, if you had to rank the following outcomes, patient-reported outcomes (e.g., number of headaches, pain, quality of life), clinical outcomes (e.g., survival), biomarkers (e.g., blood cholesterol) and other surrogate/intermediate endpoints on how informative they are, which would you consider the most informative? Least informative?
- In clinical research, there is often more than one outcome measure used across studies, thinking your practices for evaluation and synthesis of evidence used to inform health policy recommendations, how would you prioritize or determine which outcomes were most relevant to your question?
    - *[prompt]* Are there any specific criteria that you might use to assess the strength of an outcome?
- Once you have chosen an outcome to focus on, how do you determine what constitutes a meaningful improvement?
    - *[prompt]* How much of an improvement over an existing treatment would you need to see in a new treatment before recommending its use?

- In the context of rare diseases, studies of treatment effectiveness evidence often rely on surrogate endpoints or biomarkers. For example, many of the studies that evaluate the effectiveness of enzyme replacement therapy for lysosomal storage disorders typically use forced vital capacity or the 6-minute walk test as outcomes. Given that lysosomal storage disorders are chronic, progressive diseases, do you think these outcomes are appropriate?
- Thinking specifically about your experience in evaluating the evidence for ERT for MPS I and/or Pompe disease, did you face any challenges related to outcomes?
    - If so, can you briefly describe your concerns?

Ending questions

- Of all the things that we discussed today, what to you is the most important?
- The purpose of today's discussion was to gain a better understanding of your perspectives on evaluating and synthesizing the evidence base for treatments for rare diseases, and the value a more tailored synthesis approach might have. Is there anything that you feel we may have missed or that you would like to add?

Concluding items

- We really appreciate you taking the time to meet with us today.
- If you have any questions or concerns, please do not hesitate to contact me at any time.

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Stakeholder perspectives on clinical research related to therapies for rare diseases: therapeutic misconception and the value of research

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Abstract

Background: For many rare diseases, few treatments are supported by strong evidence. Patients, family members, health care providers, and policy-makers thus have to consider whether to accept, recommend, or fund treatments with uncertain clinical effectiveness. They must also consider whether and how to contribute to clinical research that may involve receiving or providing the therapy being evaluated.

Objective: To understand why and how patients and families with rare metabolic diseases, specialist metabolic physicians, and health policy advisors choose whether to participate in studies and how they use and value research.

Methods: We conducted separate focus group interviews with each stakeholder group (three groups in total); two groups were conducted by telephone and the third was held in-person. Participants were recruited using purposive sampling. We analyzed each interview transcript sequentially using a qualitative description approach to inductively identify key themes. Several strategies to ensure credibility and trustworthiness were used including debriefing sessions after each focus group and having multiple team members review transcripts.

Results: Four patients/caregivers, six physicians, and three policy advisors participated. Our findings did not support conventional perspectives that therapeutic misconception (gaining access to treatment) is the main motivating factor for patients/caregivers to participate in clinical research. Rather, patients'/caregivers' expressed reasons for participating in research included advancing science for the next generation and having an opportunity to share their experiences. Patients/caregivers and physicians described the difficulties in weighing risks versus benefits of accepting treatments not well-supported by evidence. Physicians also reported feeling conflicted in their dual role as patient advisor/advocate and evaluator of the evidence. Policy advisors were primarily focused on critically appraising the evidence to make recommendations for the health system.

Conclusions: Stakeholders differ in their perspectives on rare disease research but share concerns about the risks versus benefits of therapies when making individual- and population-level decisions.

Keywords: Rare diseases, Qualitative research, Research participation, Evidence-based medicine, Therapeutic misconception

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Background

For many rare diseases, there are few or no established treatments supported by strong evidence that the intervention alters the natural history of illness [1, 2]. This paucity of proven effective treatment options requires patients, caregivers, health care providers, and policy advisors to consider whether to accept, recommend, or fund emerging or controversial treatments where there is substantial uncertainty about potential benefits and harms, decisions which may be particularly difficult for diseases which are progressive and life-shortening [3–5]. Several authors have reported that patients and care providers demonstrate a willingness to try treatments without existing evidence because of a hoped-for or even expected clinical benefit over supportive care or no treatment [3, 4, 6–8]. This expectation of benefit conflicts with one of the central tenets of conducting research to establish the effectiveness of a new or existing intervention, which is the concept of *clinical equipoise* [9].

Clinical equipoise, the presence of uncertainty or disagreement in the expert medical community about the comparative benefits or harms for a given intervention [10], provides the ethical basis for assigning study participants to different treatment groups in a clinical research study [9, 11]. Pai et al. reported that one of the barriers to conducting clinical research for rare diseases is the perceived lack of clinical equipoise among patients, caregivers, and health care providers [4]. If patients and/or care providers choose to participate in a trial to gain access to an intervention they already believe to be effective, then there is no clinical equipoise from their perspective [12]. This phenomenon is known as *therapeutic misconception,* which exists when clinical trial participants believe that the purpose of research is to benefit the individual rather than to generate generalizable knowledge to advance science [13, 14]. Therapeutic misconception leads to a reluctance among some patients and caregivers to participate in studies where there is a chance they will be assigned to a placebo or control group rather than the new treatment group [12, 15]. Coupled with small, geographically dispersed patient populations and characteristic clinical heterogeneity for many rare diseases [12, 16], this reluctance among patients and caregivers to participate may exacerbate challenges faced by researchers to recruit adequate sample sizes for rare disease clinical studies and thus limit the conclusions that can be drawn [17].

Recognizing that it is challenging to recruit a sufficient number of participants for clinical trials related to rare diseases, several alternative study designs have been proposed to make participation more attractive to patients and families by maximizing the time spent on- or guaranteeing the provision of- the experimental treatment [18, 19]. For example, in crossover and n-of-1 trials each participant receives both the control and experimental treatments, but the order in which each treatment is delivered is randomized [20, 21]. Using adaptive randomization procedures to reduce the likelihood of being assigned to the less effective treatment group over time may also make participation in clinical research studies more appealing [20, 22]. While these alternative designs may improve participant recruitment, there remains a need to consider how to reconcile the scientific and ethical concept of clinical equipoise with the potential therapeutic misconception experienced by patients or families when choosing to participate in clinical research.

As part of a larger project that seeks to develop specific guidance for the evaluation and synthesis of evidence for treatments for rare diseases, the objective of this paper is to describe different stakeholder perspectives on the role of research related to the development and evaluation of treatments for rare diseases. Specifically, we were interested in developing a deeper understanding of why and how patients and families, health care providers, and health policy advisors choose whether to participate in trials or other types of research, and how they use research findings to support decision-making at both an individual- and population- level.

Methods

This study is described according to the Standards for Reporting Qualitative Research reporting guidelines [23].

Qualitative approach

Recognizing that there were likely to be differing perspectives among stakeholders on the generation and evaluation of evidence for clinical interventions for rare diseases, we chose to conduct a series of focus group interviews to better understand the factors that stakeholders take into consideration when making decisions about research related to clinical interventions. Our study was conducted from an interpretivist point of view using a qualitative description approach, designed to allow researchers to develop a deep understanding of and describe a particular phenomenon based on participants' experiential knowledge [24, 25].

Sampling and recruitment strategy

We recruited participants using purposive sampling, a deliberate, non-probability sampling method used to select participants who can provide rich data related to the research topic [26, 27] comprising three groups of stakeholders: rare disease patients or caregivers, physicians, and policy advisors. Each group was chosen because they had formal knowledge and/or lived experience related to the research topic. To facilitate the focus group interviews, we chose rare inherited metabolic

diseases (IMD) as a case study. For the patients and caregivers, we further narrowed the selection to those diagnosed with mucopolysaccharidoses (MPS), a group of IMD with several characteristics that typify many rare diseases (e.g., significant clinical heterogeneity; see Box 1 for description of MPS). Individuals were eligible to participate if they were adults diagnosed with MPS or were the adult caregiver (i.e., parent/guardian) of someone diagnosed with MPS, if they were a physician providing health care to those diagnosed with rare IMD, or if they had experience in evidence review activities that resulted in recommendations for the development, use, or reimbursement of interventions for rare diseases (policy advisors). Between five and eight individuals were sought for each focus group according to established focus group methodology in order to facilitate discussion while allowing each participant to be heard [26].

We distributed recruitment invitations by email to physician members of the Garrod Association (a professional organization whose members are involved in caring for children with IMD), to policy advisors by a member of their professional network using publicly available contact information, and to patients/caregivers attending the Canadian MPS's Society's 2017 annual Family Meeting. Individuals interested in participating in the focus groups contacted the lead author (KT) for more information and to confirm eligibility. Eligible respondents were asked to provide signed informed consent to participate in the study.

Data collection

Focus group were held separately for each stakeholder group; the patient and family focus group was conducted in person in conjunction with the Canadian MPS Society's 2017 Annual Family Meeting, while focus groups with physicians and health policy advisors were conducted via teleconference. We conducted two focus groups by telephone in order to reach a geographically dispersed group of people across Canada who would otherwise be unable to gather in-person [28]. We reasoned physicians and policy advisors would likely have greater familiarity with the topic, thus may be comfortable convening via teleconference, whereas an in-person focus group may be important for patients and families.

We developed a semi-structured interview guide for each focus group that included questions related to the generation and evaluation of evidence for clinical interventions for rare diseases. Topics included: general perspectives on rare disease research, reasons for participating in research activities, outcomes used in clinical studies, and challenges in establishing treatment efficacy and effectiveness. The interview guide was reviewed by all members of the research team and by a representative from the Canadian MPS Society. One team member (KT) conducted all three focus group interviews, with at least one additional team member attending as an observer.

Data processing and analysis

Each interview was audio-recorded with participants' consent and transcribed for data analysis. The transcripts were analyzed sequentially using thematic analysis [29], which involved generating a set of initial codes based on interesting features of the data and then organizing those codes into key themes related to the research topic. To do this, a series of research team meetings were held to review the transcripts and inductively identify emerging concepts from each interview. Key concepts that were identified in the focus group data were organized into a coding system that was applied by one member of the study team (KT) using NVivo 10 software (QSR International Pty Ltd.) across the entire data set. Coded transcripts were reviewed and verified by a second team member (BP) to confirm all codes had been applied appropriately and that no themes had been overlooked. We used several strategies to ensure credibility and trustworthiness of our data [30], including: debriefing sessions after each focus group to identify key perspectives, multiple

Box 1 Brief description of mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a group of seven heritable conditions that have an autosomal recessive inheritance pattern, except for MPS II which is X-linked [43]. Overall birth prevalence estimates for MPS vary by country/region and range from 1.04 to 4.8 per 100,000 live births [44]. These disorders are characterized by specific enzyme deficiencies that cause an accumulation of glycosaminoglycans (GAG) in the lysosomes of most cells [43, 45]. This buildup of GAG results in a wide spectrum of cell, tissue, and organ damage. The clinical manifestations of MPS begin early in life and are chronic, progressive, and typically involve multiple organ systems. Common clinical symptoms include: vision, hearing, cardiovascular, airway, and joint problems, organomegaly, musculoskeletal and facial abnormalities, among others [43, 45]. Similar to many other rare diseases, there is substantial clinical heterogeneity both between different MPS and within the same MPS [43, 45]. The spectrum ranges from mildly affected to severely affected. In addition to other symptoms, severely affected individuals may also experience neurocognitive deficits that are not present in more attenuated forms of the diseases [43, 45]. Currently, transformative treatments are limited for MPS, so care is generally supportive to help manage various symptoms [45]. For those with severe MPS I, early hematopoietic stem cell transplantation is recommended as standard of care to slow the progression of symptoms, particularly neurocognitive impairments [46, 47]. In addition, enzyme replacement therapy, an expensive orphan drug, is available for MPS I, II, and VI32,33; however, the extent of its efficacy is debated in the literature.

research team members reviewing transcripts, multiple team discussions to identify themes, and transcript coding verification by a second team member.

Results

Focus group characteristics

We completed three focus group interviews with a total of 13 participants (physicians n = 6; policy advisors n = 3; patients/caregivers n = 4). Each focus group interview lasted between 45 and 75 min. Across the three groups there were nine women and four men. Participants were from five provinces in Canada: British Columbia, Alberta, Ontario, Quebec, and Newfoundland and Labrador. Regardless of group size, all participants were engaged throughout the discussion with very little prompting from the moderator. Data from our focus group interviews revealed several key themes related to therapeutic misconception, reasons for participation in research activities, and how stakeholders value research.

Making choices about participation in research

Given their role in the health system, policy advisors are typically not directly involved in clinical research, so results related to participation in research are derived from focus groups with patients, caregivers, and physicians. Both patients/caregivers and physicians identified several reasons for participating in studies that seek to evaluate therapies for rare diseases. Some of their perspectives overlapped and others were unique to a single group (Fig. 1).

For example, some members of the physician group described their perception that patients and families often participate in clinical research, and even believe they are benefitting, out of a sense of desperation or willingness to try anything, especially when treatment options are limited.

> *"...you have patients or families that are experiencing a devastating condition and they want to try anything." – Physician 4.*
> *"... a lot of these families are extremely invested in*

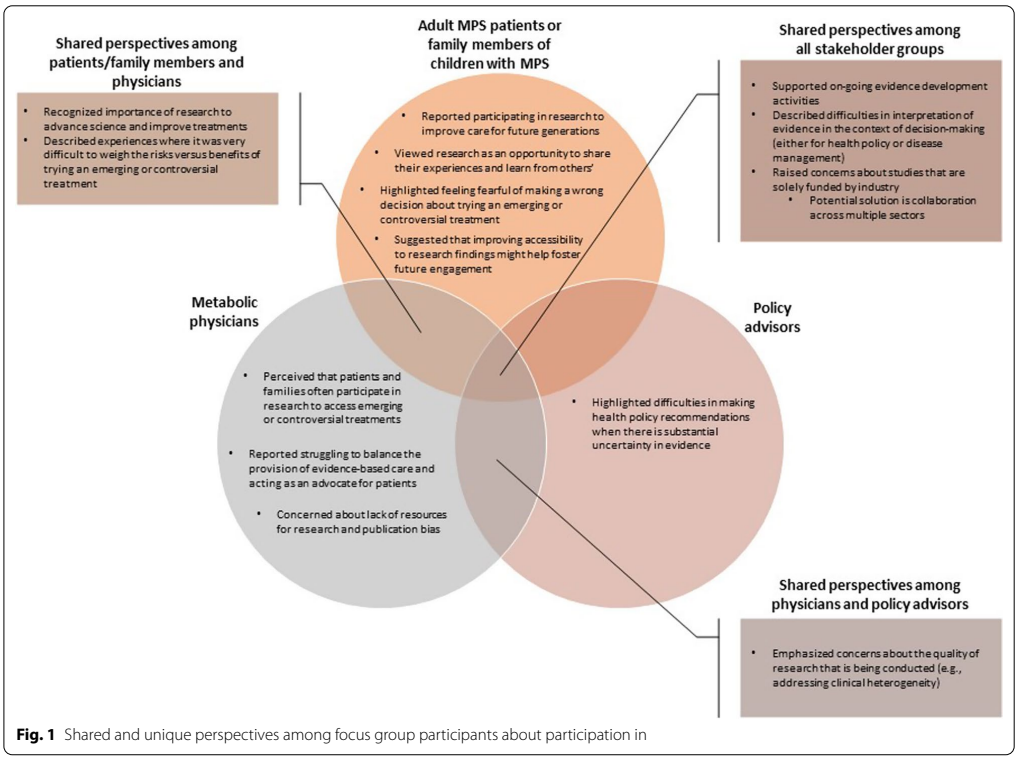

Fig. 1 Shared and unique perspectives among focus group participants about participation in

being on this therapy because it's their only therapeutic option." – Physician 6.

Contrary to this view, patients and caregivers more frequently reported other reasons for choosing to participate in research activities and did not explicitly mention choosing to participate based on gaining access to treatment. For example, participants viewed involvement in research activities as a form of advancing science and an act of altruism of potential benefit to the next generation of individuals affected by the disease, understanding that they or their family members may be unlikely to personally benefit.

"…I think research of any kind is always useful for progressing science, and I've been involved in a number of different kinds of research studies over the years." – Patient/caregiver 3.

"I find it's hard because research takes so long [murmurs of agreement from the group]. It's like, when you start off with this and talk about research and all this stuff, you have a lot of hope, as in wow it's going to be done in no time, but then living with it, you think, you know what, maybe in somebody else's lifetime, but it won't be in our child's lifetime. But you have to keep researching because if you stop, well it will be in nobody's lifetime." – Patient/caregiver 1.

"…participating in research is really important, especially with such a complex and ever-changing environment with rare diseases and particularly MPS. Yeah, so just for the learning and for sharing information." – Patient/caregiver 4.

Patients and/or caregivers also described approaching research as an opportunity to share their own experiences and in turn to benefit from research findings that describe a broad range of experiences of other patients and families, to help inform decision-making.

"I think it's important to have a lot of information because nobody has the same thoughts. I know from experience, your thoughts change from early diagnosis from like 13 years ago to now. I have a totally different way of thinking about the medication, the outcome, the whole thing." – Patient/caregiver 1.

"I think it's important because sometimes it all depends on the experience of what other people lived sometimes people tell you not to go there because they've had a bad experience. So, I like having the bad and the good ones too and then make up my mind and take better decisions." – Patient/caregiver 2.

Some physician participants had similar views on the importance of research for furthering the development and improvement of rare disease therapies.

"…you're advocating for your patient and if these treatments don't ever happen, then they'll never evolve, so that we won't then get on to a better treatment. So, I think it's extremely important that these treatments do develop, but it's just tricky, sort of, coming up with the new treatments." – Physician 4.

It was clear that not all patients and caregivers found it easy to make the decision to participate in a research study or to try a new therapy. Participants described being fearful of making the wrong decision in choosing whether to participate.

"For parents, it's scary because if you say, okay we'll try this, but what if you made the wrong decision [agreement from others]. That's what always goes around in my head, what if I did it wrong? And usually we talk about it, my husband and I, but it seems to be like okay, mom you make the decision, but I don't want to make it all by myself. What if I'm wrong?" – Patient/caregiver 1.

Patients and their caregivers also reported difficulty with weighing the risks versus benefits of trying a new therapy and spoke about uncertainty about whether it would be "worth it".

"P1: But it's scary to try other things. After one thing fails, it's like okay, we could do this, but it sounds a little drastic. P4: I know, but what do we have to lose? P1: So what if it harms your child more than… P4: I know. P1: Sometimes you're so afraid that you just don't want to do anything. P4: Yup." – Patient/caregiver 1 & 4.

"I think it depends too on what you have to do to get that little bit of change. Is it going to cost a lot of pain and anxiety and for just a little bit? It's not really worth it because all that time spent could have been quality time spent doing, oh let's go out and just sit in the sun…" – Patient/caregiver 1.

Similarly, one of the participants from the physician group described an experience of having to weigh risks versus benefits and wondering whether trying an experimental treatment was the right decision for their patients.

"I was involved with two babies with [severe inherited metabolic disease] quite early when [treatment] was just first available… and in retrospect, now that we have more knowledge about who is going to respond to [treatment], you know, I think it may

have been that there was some harm done for those families, they could have had better quality of life. Both babies died, but you know, I think we were very optimistic at the time based on the publication of the studies, and you do wonder at the end of the day did I, was it more harmful for those families in regard to taking away quality time they could have spent with the baby and the family versus being back and forth in the hospital?" – Physician 4.

Despite the difficulties and uncertainty in making decisions to participate in clinical research or to try an experimental treatment, one caregiver highlighted the importance of being persistent and continuing to ask questions and do research.

"You always have to push. You can't sit back and just accept things sometimes. It's like, I know [name]'s situation came to a halt, but still kind of want to know why? And yeah, keep pushing and find out why does something happen? Why does it stop? And it's always, you got to keep push, push, push, push. No matter who and how, you just have to keep asking questions." – Patient/caregiver 1.

Lastly related to participation in research activities, patients or caregivers expressed a desire for research to be more accessible and noted that sharing findings from research in which they've directly participated may help encourage further research engagement.

"I find that when I read studies, I like the introduction and the conclusion, because the middle stuff is so scientific that even the ex-[profession] in me can't understand it." – Patient/caregiver 3.
"…user-friendly for the non-scientist parent. If it's too overwhelming then you don't really grasp. It could be sort of coded in a way that is easy for a tired parent." – Patient/caregiver 4.
"…I think that's a really important piece to keep people motivated to participate in these things is to at least have some sort of follow through that allows us to see if what we shared made any kind of a difference. So that would be one thing that I'd like to see…" – Patient/caregiver 4.

Perspectives on the value of research

There was general agreement among participants in all three groups about the importance of supporting evidence development for new or existing therapies for rare diseases (Fig. 1). However, given their diverse backgrounds, there were differences across groups in how participants reported using research findings, the specific concerns they had with respect to the quality of clinical research, and the value of research to them in their roles as providers, evaluators, and users of care (Fig. 1).

For example, participants in both the physician and policy advisor groups were largely critical of the quality of research that is conducted for many rare disease therapies. They described difficulties in interpreting the available clinical evidence with respect to its value for informing decisions about real-world patient care, particularly for rare diseases characterized by important clinical heterogeneity.

"…this is a huge problem in terms of trying to interpret information from clinical studies, from treatment outcomes. How do we look at clinical trials versus actual clinical work that we do, which is much longer term than that of short clinical trials? How do we deal with some of the heterogeneity of the lysosomal storage diseases?" – Physician 5.
"And given the wide degree of heterogeneity with the drugs that we're dealing with or the diseases that we're dealing with, we know we're going into this with a huge degree of uncertainty about whether or not there really is any evidence to support these therapies are going to work". – Policy advisor 2.

Physician participants also reported that when considering how to use research findings, they struggled between providing care that is evidence-based, which requires a critical evaluation of research, and wanting to be an advocate for their patients, especially when their patients have limited treatment options.

"…most of the clinical trials are with few patients and are relatively short-term, so there's always this conflict I think for clinicians between the short-term outcome measures and also our role as advocates for patients and families that may be very interested in pursuing these treatments, these very expensive treatments… you want to be an advocate but you [are] also a scientist and, you know, you may not be impressed by the outcomes or sometimes even study designs…." – Physician 4.

In considering how to best use evidence to inform routine patient care, one physician expressed concern about interpreting findings that show improved outcomes because of frequent interactions with the healthcare system as a result of being involved in a research study.

"One of the issues that's been brought up by some of these studies as well is that when these patients are getting [treatment], they're generally seeing the physician more frequently as well, and this is always a complicating factor in terms of treatment benefit. When they're seeing the physician

more frequently, they're more likely to get interventions that are unrelated to the [treatment] because they're there at that time and they're complaining about X and Y, and they're more likely to get treated earlier on, as opposed to patients who have had no therapy, and might only see the doctor one a year." – Physician 1.

Another concern included potential publication bias in the context of rare diseases in that study designs that are conventionally considered low quality are more difficult to get published.

"The problem is that it's often very difficult to get [observational] studies published, right? Even in journals dealing with rare disorders…" –Physician 1.

Finally, one concern that was raised in all three groups with respect to the quality of research was the difficulty of conducting high quality rare disease studies due to limited resources. In addition, participants across groups were concerned about potential bias in studies that are solely funded by pharmaceutical companies.

"And I think the conspiracy theorist in me wonders about who funds the research? Where is the funding coming from and what are their interests?" – Patient/caregiver 4.

"I have to say that there are concerns about the [name of research study] as well because, I mean, difficulties in obtaining funds continuously for a long period of time because it's not pharma funded and also just because of the resources. …there's still problems with that study because we just don't have the manpower to properly run a study and design it properly etcetera." – Physician 1.

"I think in a sense we are stuck with nobody having large enough pockets to fund a study looking at whether it's [treatment] or whether it's [treatment], we just don't have the funding to do that without pharma. So, you're between a rock and a hard place." – Physician 5.

Some participants suggested that one way to overcome this would be to approach research in a more collaborative way that involves individuals from across sectors (e.g., health technology assessment agencies, health policy decision makers, and academic researchers as well as industry).

"…perhaps having partnerships between pharmaceutical companies, governments, and clinicians to ensure that we do get appropriate long-term follow-up is going to help us get that data and again, improve treatments." – Physician 6.

Discussion

We identified several themes from our focus group data related to why individuals choose to participate in research activities and how different stakeholders value and use research in their roles as evaluators, care providers, and recipients of care. Patients, caregivers, and physicians that participated in our focus group interviews shared the understanding that research is important for the development and improvement of treatments; however, physicians discussed concerns that rare disease patients and families often participate in clinical research studies because of potential therapeutic misconception and, as a result, patients may be unwilling to accept assignment to a placebo or comparator group. Previous discussions in the literature have also posited that patients and families choose to participate in clinical research studies because of desperation and that the expectation of personal benefit can threaten clinical equipoise [3, 4, 6, 7]. In contrast, patients and caregivers who contributed to our study had more nuanced views about participating in clinical research which extended beyond gaining access to a potential therapy, raising questions about the influence of therapeutic misconception in their decision-making about participating. Individuals in our study reported participating in clinical research studies to advance knowledge for future generations affected by the disease, to share personal experiences, and as an opportunity to learn from experiences of others. A survey of more than 3000 people affected by a rare disease conducted by the European Organization for Rare Disorders similarly found that the main motivation for respondents to participate in research was to help the community and make scientific advancements rather than gaining access to new treatment options [31]. These findings suggest patients and caregivers understand that participating in research has implications beyond accessing potential treatments and that those implications play a role in decisions about taking part.

Patients, caregivers and some physicians did speak extensively about the difficulty of weighing the personal benefits and risks, including opportunity costs to patients, of participating in a clinical study or accepting a treatment that is not well-supported by evidence. This finding indicates that these stakeholder groups do consider the individual implications of participating in research but, again in contrast to the therapeutic misconception, it suggests that they recognize that experimental therapies may carry personal risk or may not be effective. This perspective demonstrates that clinical equipoise may not be significantly compromised among this stakeholder group. While our work demonstrated that patients, caregivers, and health care providers valued research, it remains important to manage expectations

of personal benefit and possible harms when strong evidence regarding an emerging intervention is unclear or not yet available.

Given their different roles in the health system as evaluators, care providers, and recipients of care, the ways in which participants from each group used and valued research findings differed. As described, patients, caregivers and physicians described potential personal benefits and risks of using treatments in the absence of strong evidence. Physicians also reported being conflicted in their role as both advocate/advisor for their patients and as an evaluator of the evidence base, suggesting that their priorities relate to whether there is sufficient evidence to support recommending a particular treatment and how to balance that evidence with patient and caregiver preferences. Policy advisor participants were primarily concerned about the quality of research that is being conducted. Policy advisors did not share the perspectives of patients or caregivers beyond the broad theme that uncertainty makes decision-making more difficult. This is perhaps not surprising given that the role of policy advisors is to critically appraise research and recommend if a treatment should be made available and/or reimbursed in the health system. Together, these findings suggest it is important to consider different roles and evidence needs among stakeholders when developing clinical research studies, approaching potential study participants, defining and prioritizing outcomes, and/or conducting evidence syntheses to ensure that scientific research is relevant and meaningful.

To our knowledge, there are few published studies discussing how different stakeholders value and engage with research in the context of rare diseases. Kesselheim and colleagues conducted a focus group interview study with patients, caregivers, and patient advocates; some similar themes emerged from their data including that participants reported experiencing difficulties in weighing the potential risks and benefits of accepting a controversial therapy. Some findings conflicted with the results from our study, namely our patient and caregiver participants did not report feeling desperate to try anything and did not discuss feeling uncomfortable in participating in a study with the potential to be randomized to a control group [32]. A focus group study with parents and clinicians of individuals with Duchenne muscular dystrophy regarding participation in research touched on similar themes of parents and clinicians finding it difficult to make decisions to participate in research when there is such a limited evidence base [33]. Regarding the themes we identified concerning the quality of research, it is established in the literature that the small, geographically-dispersed, and clinically heterogeneous patient populations that typify many rare diseases present challenges for meeting conventional evidence standards for establishing treatment effectiveness (e.g., there are few or no randomized controlled trials for many rare disease therapies) [18, 34].

While there is little published empirical research regarding stakeholder attitudes toward participation in rare disease clinical research, there is a rich literature discussing motivations for participating in research in other disease areas. For example, Dupont and colleagues discuss ethical aspects of the participation of pediatric cancer patients in clinical trials [35]. Similar to our findings, the authors highlight that there is a complex risk–benefit judgment entailed in families' decision-making about whether to participate in clinical research and that patient and family preferences should be carefully considered [35]. While there are key differences between pediatric cancers and rare genetic diseases (e.g., cancers are defined by incidence whereas rare genetic diseases are defined by prevalence, disease course may be very different), the challenges for clinical research are similar in many ways, especially given the relatively low incidence of pediatric cancer and the uncertainties surrounding potential therapeutic options [36, 37].

Though it was not discussed extensively by the participants in our study, some literature has shown therapeutic misconception as a strong motivating factor when choosing to participate in research [13, 14, 38, 39]. For example, Hendersen et al. demonstrated in their study of early phase gene therapy that while some participants may understand they are in a research study to generate generalizable knowledge, they may still have unrealistic expectations about the direct benefit of the therapy under study [38]. A recent survey of health care professionals working in pediatric cancer centres also demonstrated similar results to ours in that the majority of health care professionals surveyed believed perception of medical benefit for the child was a primary motivating factor for parents' consent for participation in early-phase clinical trials [40]. Therapeutic misconception is a complex concept that warrants further investigation in the field of rare diseases.

An important strength of our study is the in-depth insights generated about participating in clinical research studies and the perceived value of research in supporting health care decision-making. Using focus group methodology allowed participants to compare and contrast their perspectives with those described by others in the group and to build on others' ideas. Another strength of our study is the use of multiple methods to ensure credibility and trustworthiness of our data [30]. While the preferred sample size for focus group interviews is between five and eight individuals, we only recruited three and four participants to the policy advisor and patient/caregiver

focus groups, respectively. In addition, conducting two focus group interviews via teleconference may have reduced the interactions between participants and in turn, limited the richness of our data set [28]. Despite the small number of participants in these groups and the inclusion of telephone focus group interviews, there was still a lively discussion in each group. The small number of people in each group also allowed each participant ample time to speak and fostered a very in-depth discussion of the research topic. Thus, we do not feel that these factors substantially reduced the richness of the data collected. In future focus group studies, adding a webinar option could provide a good alternative to in-person focus groups [41]. We did not formally assess data saturation, so it is possible that we have not identified an exhaustive set of themes; however, the literature suggests that three focus group interviews is enough to identify the most prevalent themes in a dataset and approximately 80% of all possible themes [42]. Transferability of the results to the broader rare disease community may be limited given that we recruited a purposive sample of metabolic physicians and MPS patients and caregivers. In addition, patients and caregivers were recruited from a list of attendees at a national meeting for MPS patients and families which may have restricted the variation in perspectives. However, inherited metabolic diseases and specifically MPS, do exemplify some of the typical characteristics of rare diseases, including small patient populations, significant clinical heterogeneity, and few available treatment options; thus, it is likely that many of the themes identified in this work could be transferable to other rare diseases. Future work could explore perspectives among different rare disease groups to understand if their views align with our study. Additional work among other rare disease groups would also enable a more in-depth investigation of how disease progression/severity, timing, and other factors affect decision making regarding participation in research (e.g., is there less willingness to participate in clinical research studies among patients/families if the manifestations of the disease are less severe?).

Conclusion

In the context of rare diseases, health care decision-making (individual- and population- level) and clinical research are often intertwined, and the lines between individual care and participation in clinical studies are sometimes blurred. Our study identified different perspectives on how diverse stakeholders choose to participate in and use research in their roles as health care users, care providers, and policy advisors. Notably, the conventional wisdom that patients and family members participate in clinical research studies because of therapeutic misconception was not supported. We believe there is an opportunity to further investigate this finding in other rare disease populations and assess whether there is heterogeneity in opinions held among rare disease stakeholders from other jurisdictions as well. Overall, we found that stakeholders differ in their perspectives on rare disease research but share concerns about the risks versus benefits of therapies when making individual- and population-level decisions. This shared perspective provides opportunities for engaging all stakeholders toward collaborative approaches to the design, conduct, and use of research to evaluate care. Developing a deeper understanding of why stakeholders choose to participate in research activities and how they value research will inform the design of future clinical research studies and ensure that results are meaningful.

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Authors' contributions
Kylie Tingley: Conceptualization (equal); methodology (equal); investigation (lead); formal analysis (lead); writing – original draft preparation (lead); writing – reviewing & editing (equal). Doug Coyle: Conceptualization (equal) methodology (equal); formal analysis (supporting); writing – reviewing & editing (equal); supervision (co-lead). Ian D. Graham: Conceptualization (supporting); formal analysis (supporting); writing – reviewing & editing (equal); supervision (supporting). Pranesh Chakraborty: Conceptualization (supporting); writing – reviewing & editing (equal); supervision (supporting). Kumanan Wilson: Conceptualization (supporting); writing – reviewing & editing (equal); supervision (supporting). Beth K. Potter: Conceptualization (equal); methodology (equal); investigation (supporting); formal analysis (supporting); writing – original draft (supporting); writing – reviewing & editing (equal); supervision (co-lead). All authors read and approved the final manusript.

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Availability of data and materials
In order to protect the privacy of our study participants, research data are not publicly available.

Ethics approval and consent to participate
The study protocol was approved by the Ottawa Health Science Network Research Ethics Board, the Children's Hospital of Eastern Ontario Research Ethics Board, and the University of Ottawa Health Sciences and Sciences Research Ethics Board. Informed consent was received from all participants in this study.

Consent for publication
Not applicable.

Competing interests
None to declare.

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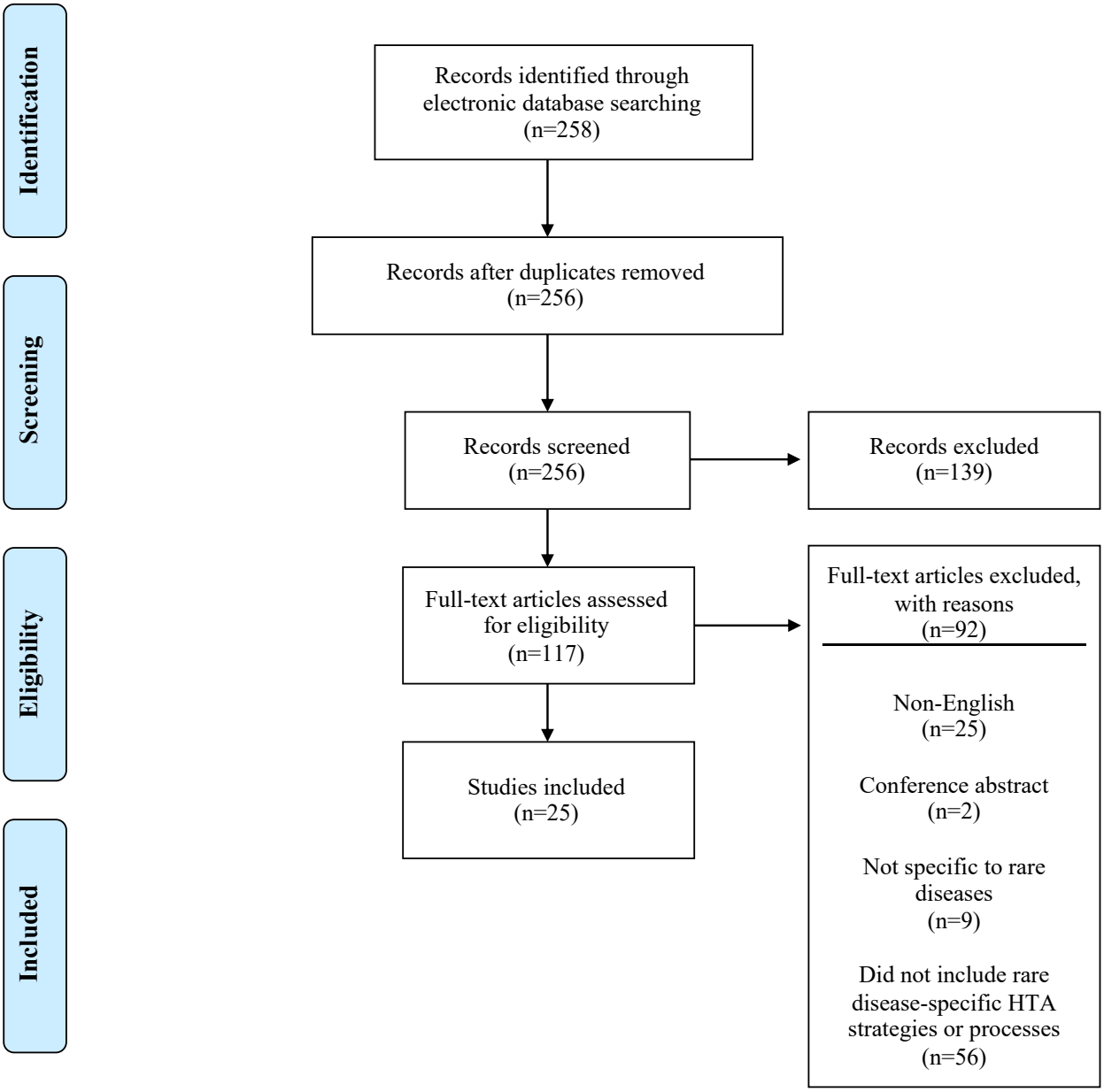
Publisher's Note

Supplemental Information for Chapter 4

Supplemental File 4-1: PRISMA flow diagram outlining results from search and screening process (Adapted from: Liberati et al. 2009).



Supplemental File 4-2: List of included studies for targeted literature review (n=25).

Author(s)	Year	Title	Source
Garrison LP, Jackson T, Paul D, Kenston M	2019	Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold.	Journal of Managed Care & Specialty Pharmacy. 25(7):793-799, 2019 Jul.
Loblova O, Csanadi M, Ozieranski P, Kalo Z, King L, McKee M	2019	Alternative access schemes for pharmaceuticals in Europe: Towards an emerging typology.	Health Policy. 123(7):630-634, 2019 Jul.
Loblova O, Csanadi M, Ozieranski P, Kalo Z, King L, McKee M	2019	Patterns of alternative access: Unpacking the Slovak extraordinary drug reimbursement regime 2012-2016.	Health Policy. 123(8):713-720, 2019 Aug.
Ollendorf DA, Chapman RH, Pearson SD	2018	Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers.	Value in Health. 21(5):547-552, 2018 05.
Pearson I, Rothwell B, Olaye A, Knight C	2018	Economic Modeling Considerations for Rare Diseases.	Value in Health. 21(5):515-524, 2018 05.
Richter T, Janoudi G, Amegatse W, Nester-Parr S	2018	Characteristics of drugs for ultra-rare diseases versus drugs for other rare diseases in HTA submissions made to the CADTH CDR.	Orphanet Journal Of Rare Diseases. 13(1):15, 2018 02 01.
Annemans L, Ayme S, Le Cam Y, Facey K, Gunther P, Nicod E, Reni M, Roux JL, Schlander M, Taylor D, Tomino C, Torrent-Farnell J, Upadhyaya S, Hutchings A, Le Dez L	2017	Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL).	Orphanet Journal Of Rare Diseases. 12(1):50, 2017 03 10.
Degtiar I	2017	A review of international coverage and pricing strategies for personalized medicine and orphan drugs.	Health Policy. 121(12):1240-1248, 2017 Dec.
Nicod E	2017	Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods	European Journal of Health Economics. 18(6):715-730, 2017 Jul.

		framework to systematically compare orphan drug decisions in four European countries.	
Nicod E, Berg Brigham K, Durand-Zaleski I, Kanavos P	2017	Dealing with Uncertainty and Accounting for Social Value Judgments in Assessments of Orphan Drugs: Evidence from Four European Countries.	Value in Health. 20(7):919-926, 2017 Jul - Aug.
Nicod E, Kanavos P	2016	SCIENTIFIC AND SOCIAL VALUE JUDGMENTS FOR ORPHAN DRUGS IN HEALTH TECHNOLOGY ASSESSMENT.	International Journal of Technology Assessment in Health Care. 32(4):218-232, 2016 Jan.
Schlander M, Garattini S, Kolominsky-Rabas P, Nord E, Persson U, Postma M, Richardson J, Simoens S, de Sola-Morales O, Tolley K, Toumi M	2016	Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement.	Journal of Market Access & Health Policy. 4, 2016.
Douglas CM, Wilcox E, Burgess M, Lynd LD	2015	Why orphan drug coverage reimbursement decision-making needs patient and public involvement.	Health Policy. 119(5):588-96, 2015 May.
Gutierrez L, Patris J, Hutchings A, Cowell W	2015	Principles for consistent value assessment and sustainable funding of orphan drugs in Europe.	Orphanet Journal Of Rare Diseases. 10:53, 2015 May 03.
Menon D, Clark D, Stafinski T	2015	Reimbursement of Drugs for Rare Diseases through the Public Healthcare System in Canada: Where Are We Now?	Healthcare Policy = Politiques de sante. 11(1):15-32, 2015 Aug.
Paulden M, Stafinski T, Menon D, McCabe C	2015	Value-based reimbursement decisions for orphan drugs: a scoping review and decision framework.	Pharmacoeconomics. 33(3):255-69, 2015 Mar.
Short H, Stafinski T, Menon D	2015	A National Approach to Reimbursement Decision-Making on Drugs for Rare Diseases in Canada? Insights from Across the Ponds.	Healthcare Policy = Politiques de sante. 10(4):24-46, 2015 May.
Facey K, Granados A, Guyatt G, Kent A, Shah N, van der Wilt GJ, Wong-Rieger D	2014	Generating health technology assessment evidence for rare diseases.	International Journal of Technology Assessment in Health Care. 30(4):416-22, 2014 Oct.

Schlander M, Garattini S, Holm S, Kolominsky-Rabas P, Nord E, Persson U, Postma M, Richardson J, Simoens S, de Sola Morales O, Tolley K, Toumi M	2014	Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders.	Journal of Comparative Effectiveness Research. 3(4):399-422, 2014 Jul.
Winquist E, Coyle D, Clarke JT, Evans GA, Seager C, Chan W, Martin J	2014	Application of a policy framework for the public funding of drugs for rare diseases.	Journal of General Internal Medicine. 29 Suppl 3:S774-9, 2014 Aug.
Iskrov GG, Raycheva RD, Stefanov RS	2013	Insight into reimbursement decision-making criteria in Bulgaria: implications for orphan drugs.	Folia Medica (Plovdiv). 55(3-4):80-6, 2013 Jul-Dec.
Winquist E, Bell CM, Clarke JT, Evans G, Martin J, Sabharwal M, Gadhok A, Stevenson H, Coyle D	2012	An evaluation framework for funding drugs for rare diseases.	Value in Health. 15(6):982-6, 2012 Sep-Oct.
Rosenberg-Yunger ZR, Daar AS, Thorsteinsdottir H, Martin DK	2011	Priority setting for orphan drugs: an international comparison.	Health Policy. 100(1):25-34, 2011 Apr.
Hughes DA, Tunnage B, Yeo ST	2005	Drugs for exceptionally rare diseases: do they deserve special status for funding?	Qjm. 98(11):829-36, 2005 Nov.
NICE Citizens Council	2004	NICE Citizens Council Report: Ultra Orphan Drugs	National Institute for Health and Care Excellence (NICE). NICE Citizens Council Reports, Citizens Council Reports No. 4. 2004 11 19