Patient Involvement in the Regulatory Process and Rare Disease Patient Perceptions of Treatment Benefits and Harms

by

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Abstract

Patient involvement in healthcare decision-making is becoming an essential part of healthcare policy in today's patient centred environment. It supports responsive and transparent healthcare programs and policies that are informed by patients for patients. While regulatory agencies, the bodies responsible for the approval of new medicines, involve patients in the regulatory process, little is known about the involvement context or the type of patients engaged. The purpose of this thesis was to explore patient involvement within the regulatory process and gain insights into rare disease patient perceptions of treatment benefits and harms. It contains three papers. The first comprises a review of proposed and current regulatory patient involvement using the International Association for Public Participation Spectrum. The second paper presents findings from three fora and surveys conducted in three different Canadian cities. The fora were used to elicit treatment harm and benefit attributes and treatment benefit priorities from rare disease patients and caregivers. Surveys were used to gather patients' and caregivers' levels of expectations of treatment benefit. Their input highlighted the need for survey questions to be relevant and meaningful to health contexts of the target population. The third paper, informed by the second paper, provides an understanding of harm acceptance while considering increasing levels of treatment benefit in a specific rare disease. It was found that mucopolysaccharidosis patients accept lower levels of harm than caregivers, where caregivers consistently selected the maximum level of harm for maximum treatment benefit. The findings of all three papers demonstrate that patient input around the acceptability of different benefit-harm trade-offs is needed in order to make regulatory decisions more patient-centred.

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Introduction

In October 2012, Health Canada (HC), Canada's regulatory agency, announced the development of an orphan drug framework to stimulate research and innovation for new rare disease medicines[1]. Regulatory agencies are the governmental bodies responsible for evaluating new medicines for quality, safety and efficacy and for authorizing them for marketing and sale in a country. The definition of rare diseases varies by jurisdiction and is dependent on national or regional legislation and policy[2]. Rare diseases have been referred to as a complex mosaic of progressive and chronically debilitating conditions[3] or life threatening illnesses that affects no more than 5 in 10000 people[2]. Medicines used to treat rare diseases are called orphan drugs. The process to evaluate an orphan drug is complex due to small patient populations and limited knowledge and understanding[3] of the disease for which it is indicated. This creates challenges for regulatory agencies which have limited access to information about orphan drugs[4].

One way to increase understanding of rare diseases and the perceptions of the benefits and harms of medicine is to involve rare disease patients. Patient involvement informs how healthcare systems are designed and delivered by providing insights on patient needs and preferences[5]. Rare disease patient involvement can build awareness of real life health experiences that otherwise would be missing from the medicine review process.

HC's orphan drug framework states that an orphan drug regulatory medicine review will be informed by patients[1,6]. In order to inform medicine authorization decisions, HC launched two patient involvement pilot projects[1] in August, 2014. These two pilot projects asked rare disease patients for insights on four questions:

- How their rare disease affects their daily life function;
- What treatments are currently available to treat their rare disease;
- What treatment benefits are important to them; and

- What levels of treatment harm they would tolerate[1].

Although, HC stated that it intends to use the pilot project patient feedback to review and revise its approach for collecting patient insights, it is unclear what approach HC intends to use for future elicitation of patient insights.

The purpose of this thesis was to explore the approaches that regulatory agencies use to involve patients and to identify ways to elicit input around benefit and harm acceptance from rare disease patients.

The thesis is comprised of three papers, each building upon the previous one. Together the papers examine:

1. Which approaches regulatory agencies have used to elicit patient and caregiver perspectives;
2. What treatment benefits rare disease patients and caregivers feel are most important;
3. How much benefit rare disease patients and caregivers expect to gain from new treatments; and
4. How much harm rare disease patients and caregivers are willing to accept for varying levels of treatment benefit across different treatment attributes.

The first paper explores proposed and existing opportunities for patient involvement in the regulatory context. Insight on involvement approaches (the involvement level and method) and the impact of patient involvement are presented using the International Association of Public Participation spectrum of participation. This paper also describes patient involvement across multiple jurisdictions and regions for both common and rare diseases and highlights the approaches used to ascertain patient perceptions of treatment benefits and harms.

Building on the first paper, the second paper presents rare disease patient perceptions of treatment benefits and harms using two different approaches. Treatment benefits most important to patients were elicited using focus groups. The amount of benefit patients expect to gain from treatment was determined using a survey. Benefit and harm insights from the second paper were gathered to inform the creation of a generic tool, the objective of the third paper.

Paper three describes the development of a generic online survey and how it was used to determine the amount of harm rare disease patients were willing to accept for varying levels of benefit across different treatment attributes. Based on the findings from paper two, a specific group of rare disease patients was selected to test the generic online survey.

Collectively, the papers within this thesis can help to inform HC's approach to gathering rare disease patient treatment perspectives in a relevant and meaningful way within the regulatory context.

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Chapter 1. Patient Involvement in the Healthcare Regulatory Process: A Review of the Literature

Introduction

The involvement of patients in health care decision-making, while not new, is a policy imperative in today's politicized and patient-centred health care climate[1]. Although no universal definition of patient involvement has been adopted[2], the term may be described as "any form of participation in the making of decisions, at whatever stage or level, from consultation at the end of the decision making process to joining working throughout the entire decision making process"[3(pvii)]. Recognized as a means of enhancing health care practice, patient involvement facilitates responsive and transparent programs and policies that constitute a health care system informed by patients for patients.

There are different ways of involving patients and there is little awareness and use of involvement levels and associated methods for patients with common or rare diseases. This is particularly true of patient involvement within the regulatory process of new medicines, including the evaluation of benefits and harms. Therefore, insights into past and current patient involvement opportunities may serve as an important guide for regulatory bodies to inform future involvement efforts and increase decision-making relevancy and meaningfulness.

More recently, regulatory bodies have begun to involve patients in their processes[4]. However, the level and method of involvement varies across them. In the United Kingdom (UK), the Medicines and Healthcare products Regulatory Agency (MHRA) involves patient representatives on a Patient Information Expert Advisory Group to improve benefit and harm communications to elicit advice from patients on continued stakeholder involvement. Across Europe, the European Medicines Agency (EMA) involves patients as members of Scientific Advisory Committees and seeks patient perspectives for ad hoc requests. The USA Food and Drug Administration (FDA) Patient Representative Program seeks consumer

representatives to participate on advisory committees, meetings, and workshops. Medsafe, New Zealand's regulatory authority, uses its website to involve the public in therapeutic product consultation.

Within the regulatory process, bodies such as EMA, the FDA, and the Australian Therapeutic Goods Administration (TGA) are tasked with reviewing the quality, safety, and efficacy of medicines. The evaluations of therapies involve scientific and stakeholder analysis of multiple factors including details of the medical condition, available treatments, and the assessment of benefits and harms[5]. EMA describes the evaluation process as balancing the desired effects or 'benefits' of a medicine against its undesired effects or 'risks'[6]. The agency recommends medicines in which the benefits outweigh the harms. However, "weighing up the benefits and risks of a medicine is a complex process, since it involves the evaluation of a large amount of data. In addition, there is always some uncertainty around the actual benefits and risks of a medicine, because they can only be determined by looking at the information that is available at a given point in time"[6(p8)]. Issues of jurisdictional dependency, variability and unique patient populations, such as patients with rare diseases, further complicate patient involvement in the evaluation of benefits and harms.

Objective

The purpose of this study was to identify proposed or existing involvement opportunities for patients within regulatory processes, describing what is known about their involvement context, level, method, and effect or impact.

Background

Over the last few decades, there has been increasing acknowledgement of the value of patient involvement in healthcare decision-making. The International Alliance of Patients' Organizations (IAPO) states "that the healthcare system is designed and delivered to address the healthcare needs and preferences of patients so that healthcare is appropriate

and cost-effective"[7(p1)]. Similarly, the National Health Service in the United Kingdom (UK) mandates patient and public involvement within its constitution, supporting patient participation in direct health decision-making and in the planning of services[8]. Within North America, the Canadian Foundation for Health Care Improvement supports Canadian health organizations to integrate "initiatives that engage patients and families in designing, delivering and evaluating health services with the goal of improving the quality of care"[9(p1)]. Comparably, the Institute for Healthcare Improvement in the United States of America (USA) and the Institute for Patient and Family Centered Care (USA) endorse the facilitation "of an action plan to ensure that sustained, meaningful partnerships with patients and families are in place in hospitals and health systems"[10(p3)].

Though a standardized definition does not exist within Canada, this paper identifies a rare disease as life threatening or serious chronic condition that affects a very small percentage of the population[11,12]. Due to the small patient population, limited evidence is available to assist regulatory bodies in the process of weighing treatment benefits and risks for 'orphan drugs', which are used to treat patients with rare diseases. This reduces the likelihood that such drugs, which are often costly, will be recommended for authorization[13,14]. Given the costs of treatment, the complexity of the diseases and, in some cases, the lack of knowledge around disease progression, Health Canada (the Canadian regulatory authority) is developing an Orphan Drug Framework to support the classification, approval and oversight of drugs for rare disease patients in Canada[11].

Identifying the level and method of patient involvement can lessen barriers by providing an infrastructure to guide the patient involvement activities to achieve the involvement goals. Forbat et al., postulate that "one of the greatest barriers to truly integrating patient involvement into health services, policy and research is the conceptual muddle with which involvement is articulated, understood and actioned"[15(p2547)].

Methods

A review of the published and grey literature for patient involvement was performed following published methods for conducting scoping reviews in health services research[16].

Study Eligibility Criteria

Inclusion criteria were description of proposed or current approaches to involving patients in benefits and harms evaluation or regulatory processes, in general. For comparability, only countries with similar economies, social demographics and demand for healthcare to Canada, (i.e. member countries of the Organization for Economic Co-Operation and Development (OECD)) were included. These countries were Australia, New Zealand, Canada, Italy, UK, and USA. Regulatory bodies representing the European Union were also included. Study selection was completed by two reviewers, who independently scanned the titles and abstracts of citations that were identified through the search for inclusion in the review. All studies exploring patient involvement within the regulatory process were included. Studies limited to clinical research or applications within the health care system (direct patient and clinician interaction) and those that pertained to medical devices or other therapeutic products were excluded. Only English language articles were included.

Search Strategy

Articles published from 2000 to February 2015 were identified using PubMed (MEDLINE and non-MEDLINE) and grey literature sources. Since patient involvement in regulatory processes is a recent phenomenon, the starting year for the search was set at 2000. Search terms included Medical Subject Headings (MeSH) terms, 'patient preference' and 'patient participation', as well as text words 'patient value', 'patient perspective', 'patient engagement', 'patient involvement' and 'consumer involvement'. These were combined with MeSH and text words to capture the concepts for regulatory approval and rare diseases. Searches for grey literature included the websites of rare disease organizations and regulatory agencies of the specific OECD countries. Search terms included 'rare

diseases', 'rare disorders', 'orphan drug'. 'patient involvement', 'patient engagement', 'regulatory', 'regulation', 'licensing', 'approval'. The full published and grey literature search is shown in Appendix A.

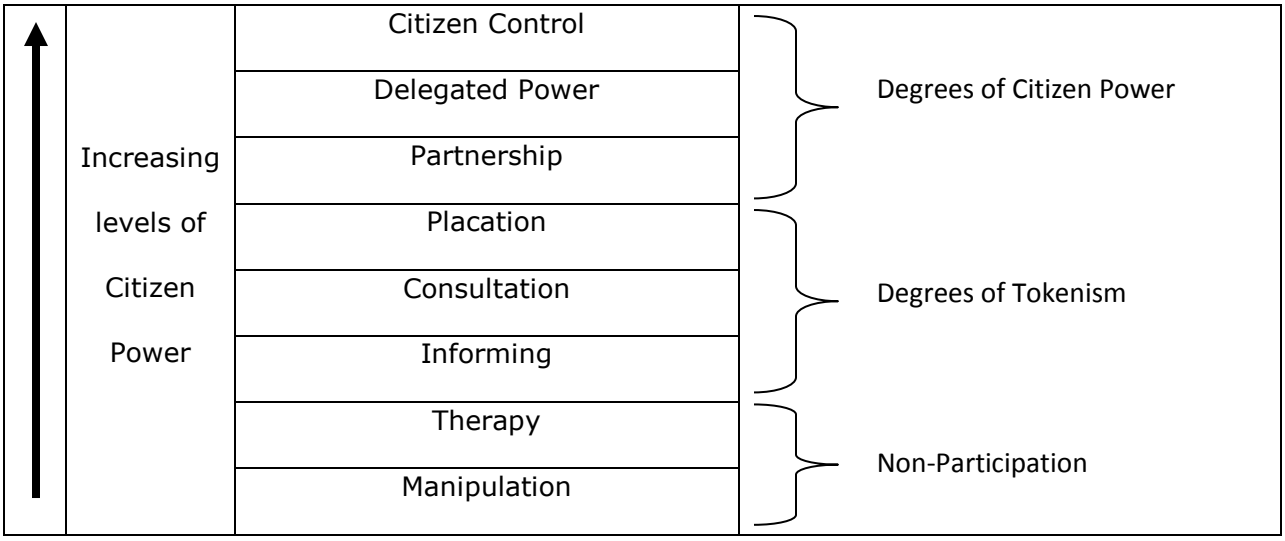
Data Collection and Analysis

A standard data abstraction form was created and pre-tested (see Appendix B). Extracted data items included patient involvement (proposed and existing), involvement setting (regulatory process and alternate), involvement level and applied method of involvement, and the inclusion of benefits and harms evaluation (proposed and existing).

One reviewer extracted the data, entering the information into tables separated into peer reviewed literature and grey literature. The data were analyzed using thematic analysis. This involved the identification of recurring themes using deductive coding based on predetermined criteria and literature review objectives. Identification and selection of codes were based on the literature of the IAP2 involvement model. An involvement model acts as foundation or framework and provides information and guidance in support of stakeholder involvement. The codes for involvement context and benefits/harms were reviewed by the study team then applied by theme. Findings from the published and grey literature were coded based on identified themes and counted. The results were then summarized through narrative review. Tables were created to represent themes found within the literature, including document characteristics (Author, Title, Publication Year, Jurisdiction), involvement characteristics (involvement level [inform to empower], and involvement method [as defined and demonstrated by the International Association for Public Participation (IAP2)[17]], and benefit and harms characteristics (objective/action set and result/conclusion achieved).

Although lacking a published critical appraisal, the IAP2 Spectrum of Public Participation is an internationally known involvement model that is transferable across multiple populations[18]. The IAP2 model is used to guide patient engagement activities within healthcare systems and focuses on aspects of involvement not addressed by Arnstein's Ladder of Citizen Participation (depicted in Figure 1)[19]. Tritter and McCallum report that Arnstein's model has several deficits, including limited attention to involvement processes, outcomes and those who participate[19]. Arnstein's model is also thought to lack evolution, inclusion and collaboration[19].

Figure 1. Arnstein's Ladder of Citizen Participation

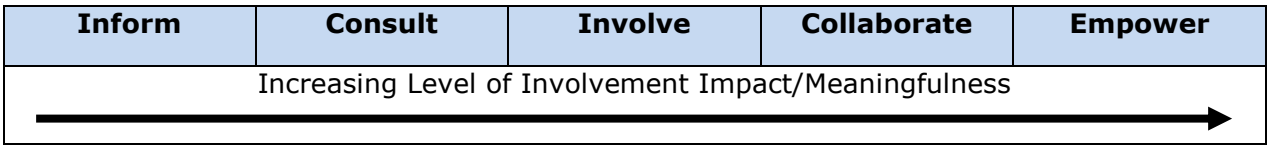


The IAP2 model was used in this review because a modified version of it was included in Health Canada's Health Policy Toolkit for Public Participation[20]. Health Canada is currently in the process of developing an Orphan Drug Framework and may utilize the pre-existing toolkit. The IAP2 defines its public participation spectrum as (depicted in Figure 2):

- **Inform:** to provide the [patient/public] with balanced and objective information to assist them in understanding the problem, alternatives, opportunities and/or solutions;
- **Consult:** to obtain [patient/public] feedback on analysis, alternatives, and/or decisions;

- **Involve:** to work directly with the [patient/public] throughout the process to ensure that [patient/public] concerns and aspirations are consistently understood and considered;
- **Collaborate:** to partner with the [patient/public] in each aspect of the decision including the development of alternatives and the identification of the preferred solution; and
- **Empower:** to place final decision-making in the hands of the [patient/public][17].

Figure 2. The IAP2 Spectrum of Public Participation



Results

The peer reviewed literature search identified 126 published documents. After reviewing titles and abstracts, 66 were selected for full text review. Of these, 48 were excluded, since they pertained to research and clinical trials or did not involve patients. The data extraction form was applied to the remaining 18 pieces of literature, 13 of which were further excluded since they did not specifically address the regulatory process or describe patient involvement activities. Although not all grey literature search results were relevant, website hits ranged from zero to 246. The grey literature search identified 118 documents. Of these, 71 were excluded as they did not describe patient involvement or were relevant to the regulatory process. In total, 52 documents met the inclusion criteria, five published documents and 47 pieces of grey literature.

Overall characteristics of included documents

Document type

None of the five included peer reviewed documents were empirical studies. One was an editorial, one a news item, one an essay, and two summary overviews. Table 1 summarizes the characteristics of these reports. Grey literature, containing a variety of types of

documents (organizational reports, webpages and conference proceedings), was organized, labelled, and placed into one of four categories: consultative (1); guidance (8); information (22); and activity overview (13). The following provides a brief categorical description of specific documents used for this paper. A *consultative* document represents a document that reported on actively involved stakeholders; documents of this category include workshops or proceedings of public hearings. *Guidance* documents produced by regulatory agencies or patient organizations provide direction in efforts of planning and supporting future involvement activities, such as frameworks, proposals, and procedures. Documents categorized as *information* share knowledge from both regulatory agencies and patient organizations, and include one press release on a lecture and multiple websites. *Activity overviews* are documents that describe involvement proceedings that have taken place, and include outcome reports, annual reports, and summaries. Three of the 47 documents were not classifiable by a single category and required designation into a combined category of activity overview and guidance (2) and guidance and information (1). Documents labelled 'activity overview and guidance' described involvement activities that have taken place and offer suggestions for future involvement. The document classified as 'guidance and information' described the regulatory process and organization characteristics. Table 2 summarizes the grey literature characteristics and document types into the categories mentioned above.

Jurisdiction

Of the five pieces of published literature, two described the USA regulatory process. The rest covered perspectives from the international community (USA and Europe) (1), Canada (1), and Europe (1). Of the 47 pieces of grey literature, the majority were European based (20) with the remaining from the UK (12), the USA (6), Australia (2), New Zealand (3), Italy (2), and Canada (2).

Publication Date

The published and grey literature covered a date range from 2006 to 2014. Specifically for the grey literature, many of the documents from 2006-2011 explored the planning of patient involvement in future regulatory endeavours.

Involvement Characteristics

Within the literature, patient involvement contexts were categorized using the IAP2 levels of involvement: *Inform, Consult, Involve, Collaborate and Empower*. The documents represented either a single level of involvement or combinations of involvement levels. Table 3 presents an overview of the document involvement levels and methods.

Inform

Eleven documents were categorized as *inform* since they explicitly related to the provision of information to assist patients in understanding alternatives, opportunities and/or solutions[17]. The IAP2 goal or promise associated with this level of involvement is 'we will keep you informed'. Some examples of *inform* methods include fact sheets, information packages and websites[17].

Several jurisdictions, including Europe, UK, US, Canada, Italy, New Zealand and Australia reported regulatory related information through their associated regulatory agencies or patient organizations websites. Table 4 provides an overview of the application and frequency of each involvement level.

The EMA[21,22], European Organization for Rare Diseases (EURORDIS)[23], MHRA[24], Genetic Alliance UK[25], FDA[26], Health Canada[27], Agenzia Italiana del Farmaco (AIFA)[28], Medsafe[29], and TGA[30] use their respective websites to communicate regulatory information, opportunities for involvement and health and safety topics to patients and other audiences. Information on adverse event reporting is also available and includes an overview on what

an adverse event is, how to report an adverse event, and why reporting adverse events are beneficial. Patient organization websites (Patients Network for Medical Research and Health (EGAN), EURORDIS and Genetic Alliance UK) provide adverse event information in different forms including links to regulatory agency adverse event reporting applications[23], reports and documents[31] and the organization's internal programs[22].

As another *inform* level method, MHRA used a lecture to communicate the importance of patient involvement in the regulatory process. Cayton, UK's Department of Health National Director for Patients and the Public participated in the second MHRA annual lecture and asserted that society "must recognize that regulatory decisions cannot be simply "right" or "wrong". Such decisions are not just scientific. They are complex social judgements that involve weighing benefits against risks. Perceptions of benefit and risk vary between people and across time, and therefore regulatory decisions are expected to provide "the best answers for the moment"[4(p1)].

Consult

As the most frequently applied level of involvement, *consult* was reported in 22 documents representing patient organizations (3), regulatory agencies (16) and other literature (3). Used to obtain feedback on decisions, this level of involvement includes acknowledgement of stakeholder perspectives. The IAP2 promise is to keep stakeholders informed of how their input influenced decision-making[17]. Authors, regulatory bodies and patient organizations reported *consult* level involvement in multiple documents, employing 16 different *consult* level methods. Table 5 represents the five involvement levels and their associated involvement methods found in the 52 documents. The table also indicates the document and number of times a specific method was applied to elicit patient insights. Of the *consult* level involvement methods, the most common methods applied were surveys and review of documentation or information.

Across regulatory bodies, surveys comprised qualitative and quantitative questions. To assess the involvement of patient organizations[32,33] and patients[34,35] in regulatory activities, EMA utilized surveys in four instances. In 2008 and 2011, EMA reported the results of an annual satisfaction questionnaire containing Likert-scale and open-ended questions to assess patient and consumer organization interaction with EMA. This showed that participants were either 'very satisfied' or 'satisfied' with the process and outcomes of EMA involvement activities[32,35]. To elicit stakeholder insights on how to improve the communication of medicine benefit and harms, EMA used a six question multiple-choice survey, concluding similar participant responses between patient, consumer, and health professionals[33,36]. Survey participants stated that regulatory bodies should be the source of accurate information and communicate benefit-harm information that includes the medicine's characteristics, the factors that influence benefits and harms and the affected population[36]. The EMA's Scientific Advisory Groups (SAG) provide expert advice on medicines and include patient members in their activities[5]. To evaluate the involvement of SAG patient representatives, EMA requested the insights of patients, the SAG Chair and Rapporteur(the person appointed to report on meeting proceedings)[34]. The Chair and Rapporteur responses were distributed equally across the Likert style questions (ranging from agree to disagree) when asked if patient representatives' involvement contributed to SAG process and outcomes. In contrast, patient participants responded more positively to the same questions about their contributions and involvement benefit[34]. Although the FDA uses online dockets and surveys to elicit patient preferences and perceptions if unable to participate in person in FDA meetings, the "challenge becomes turning anecdotal reports into structured and meaningfully data that can be incorporated in to an assessment framework" for benefits and harms[37(p652)].

Regulatory bodies provided patients with opportunities to review documents and information. EMA patient representatives actively participate in document and information review as part of their role on SAGs or on ad hoc requests. Since 2007, patients have

participated in reviews of information on medicines[5,38], products and safety communications[35,36,39,40], package leaflets[32,35,36,40,41], European public assessment reports (EPAR)[32,35,40] and other documents[32,35]. In 2009, patients' and consumers' organizations (PCO) were invited to review EMA's guidelines on the process of leaflet and EPAR review[35]. Defined by EMA, a leaflet is information provided in a package or medicine describing how the medicine should be administered[40]. An EPAR, available on EMA's website, is a summary that contains information on a medicine and the context of its approval[40]. In 2010, EMA produced a safety and communications document explaining why feedback is sought, the activity scope, and the specific procedural principles including an overview of involved stakeholders and the consultation process[40]. In addition, all EMA patient representatives must undergo training to review EMA documents[35]. Patient advocates involved in regulatory processes through EURORDIS also play a role in clarifying information for patients[42]. Although the effects of the patient involvement activities were not discussed, the 2011 report on the progress of interaction between EMA and PCOs included results of surveyed patients on their perceptions of the document and information review process. Respondents were generally satisfied or very satisfied with the feedback review process, the amount of document review training and the level of patient recommendations included in the final product[35]. Similarly, in 2006, the MHRA created the Expert Advisory Group to determine and expand the role of patient advisors, which resulted in improved patient information leaflets through consultation with patient organizations[41].

Involve

In eight sources of information within the documents pertaining to EMA and the FDA, the level reported was *involve*, in the form of conferences or meetings. Patient and consumer representatives regularly took part in EMA conferences, workshops and ad hoc meetings between 2007 and 2010[5,32,35,39]. Moulon summarized the interactions of the Patient and Consumers Working Party and reported on a workshop involving multiple European PCOs

that was held to reinforce relationships, improve communication and network[36]. The creation of EMA's Committee for Medicinal Products for Human Use (CHMP) was an outcome of that workshop[36].

Similarly, the FDA Patient Representative Program often selects patient members to present at "FDA meetings and workshops on disease specific or regulatory and health policy issues"[43(p1)]. As part of the FDA Patient-Focused Drug Development Program, disease specific meetings were utilized as the means to hear patient perspectives on what treatment benefit is the most meaningful and the context surrounding treatments for the illnesses[37,44]. The first three meetings focused on myalgic encephalomyelitis and chronic fatigue syndrome, lung cancer and HIV and enabled the participants to "discuss their disease symptoms, treatment options and the side effects they endure", and inform the creation of FDA's Benefit-Risk Framework[37(p651)]. The Framework will "lay out which benefits and risks were considered during a drug review, how available evidence was interpreted and what the implications of the evidence are for the benefit-risk assessment"[37(p651)].

Collaborate

The level of *collaborate* was identified in 19 documents reporting the involvement of regulatory and patient organizations in Europe, UK, USA, Italy and Australia. The IAP2 includes citizens' advisory committees, consensus building and participatory decision-making as collaborate methods[17]. Within the literature, the most frequent method involved variations of advisory committees. Patients and consumer representatives included members of advisory committees[22,32,43,45,46,47], scientific advisory groups / committees[22,32,34,35,36,5,39,42,48,49,50,51], advisory councils[30,52,53], decision making panel[45], agency management boards[35,5,39] and working groups / party[32,35,42,48,54].

Although the effects of the patient involvement pilot were not reported, EMA involved patient and consumer organization representatives as members of the Pharmacovigilance Working Party and found that patient collaboration at this level improved medicine safety communications through incorporating patient recommendations regarding transparency and trust in the regulatory process[54]. In 2011, EMA aimed to define the role of committee patient representatives and reported on committee challenges including meeting preparation (materials and knowledge) and documents (time and monetary)[49]. During a committee evaluation, patients responded similarly to the challenges of participating in committee meetings, stating "the information which was generally good, was received very late and therefore difficult to prepare sufficiently for the meeting"[34(p9)]. They also indicated that "more background information on EMA procedures and acronyms would be welcome" and that they "would have appreciated the paperwork earlier to study it"[34(p9)]. In the US, the FDA's Patient Representatives participate as members of advisory committees to provide the "patient perspective, ask questions, and give comments to assist the committee in making recommendations"[43(p1)]. The Milken Institute, an independent think tank, seeks to improve access to research and treatments through the *FasterCures* center[55]. The *FasterCures* Advisory Council membership includes patient advisors who work to "expand opportunities for the patient perspective to shape product development and influence regulatory decisions so that products patients value advance more rapidly from bench to the bedside"[52(p1)]. Italy's regulatory agency AIFA participates in EMA's Committees (specifically the Committee for Orphan Medicinal Products (COMP)) which seek involvement from PCOs through patient representative membership[47]. In 2012, the Australian government announced a strategy to improve relationships with TGA and their stakeholders[30]. The Australian Therapeutic Goods Advisory Council, which includes health consumer advocates, was established to provide advice on therapeutic quality measures, safe product usage and the engagement of stakeholders[53].

Empower

Only one instance of *empower* was amongst the 52 documents. Empower methods described by the IAP2 include citizen's juries, ballots and delegated decision. The Genetic Alliance UK utilized a citizen's jury to inform recommendations to regulators on benefits and harms insights. A citizens' jury is a group of 12 to 16 people selected to represent a particular community who are brought together to consider important topics and achieve consensus on issues[56]. Jury participants concluded that regulators "should include psychosocial factors in their decision making"(p12), "be more permissive for those treatments for people with rare and /or serious conditions"(p21), and that patients should be supported in their personal decision making[57].

Combinations

Several documents (12) included multiple involvement levels spanning from *inform* to *collaborate*. The documents were produced by regulatory agencies in Europe, USA and Australia (10) and patients' and consumer organizations in Europe(2) and took the form of *information*(5)*, activity overview*(3)*, guidance& information*(1)*, news*(1)*, overview*(1) *and editorial*(1).

Advice or Proposed Future Involvement

The development of a patient involvement infrastructure has been evolutionary within the EMA, MHRA, FDA and TGA. Awareness and uptake of patient inclusion in regulatory activities related to orphan drugs were first evidenced in 2000 when EMA was legislated to involve patient representatives in scientific committee work concerning the specialized medicines[36]. In 2002, EMA involved patient and consumer organizations in a workshop to improve patient representative communication and overall medicine safety. The workshop resulted in the creation of the scientific committee for human medicinal products (CHMP) in 2003[36]. Within the Canadian context, Health Canada is currently developing an Orphan Drug Framework to guide the development, evaluation, and approval of orphan drugs in

Canada[11]. Lee and Wong state that patients will inform the regulatory process in Canada as the patient perspective will be 'mandated'[58]. To inform the creation of the orphan drug framework, two pilot projects are underway to "simulate how input from patients will be gathered and incorporated into the drug submission review process"[59(p1)].

Effect of Patient Involvement

Although 52 documents reported on patient involvement within the regulatory process, there was limited assessment of the effects of such involvement. In three instances, EMA described its interactions with patient and consumer organizations and evaluated perceptions of stakeholders on advisory committees. Outcomes of a patient involvement satisfaction survey suggested improving the rationale and communication around the purpose of the involvement activity to ensure patient expectations are met[32]. Some patients expressed dissatisfaction as they felt unsure if their involvement contributed to change, recommending that PCOs receive feedback regarding their involvement[35]. When surveyed, the majority of EMA pilot committee chair persons and rapporteurs felt patient contributions had little to no impact on the decision, stating the "comments on the value of [the] therapy for patients was well received, but did not materially affect the outcome"[34(p5)]. Roth stated that the FDA has involved patients as members of 'product' review committees since the 1990s; however, "patient members typically occupy less than 10 percent of the slots on those committees, and they continually struggle to exert real influence on product decisions"[46(p29)]. Additionally, the precise rationale for the involvement or for the choice of involvement level, method and measurement approach are not explicit, making it difficult to critically appraise the effect of patient involvement within regulatory activity. Satisfying legal requirements[54] and closely monitoring patient involvement activities[36], EMA analyzed the benefits of involving patients and concluded that patients provide real life context of the effects of regulatory decisions and support increased process transparency[38].

Benefit and Harm

Benefits and harms were discussed in documents produced by regulatory agencies and PCOs. In total, 21 documents from 2006 to 2014 proposed the involvement of patients in benefit-harm assessment or reported existing involvement activities, which set an objective or described an action that produced a result or conclusion. Fifteen documents proposed future patient involvement and six documents described existing examples of patient involvement in benefits and harms evaluation. Within the documents, four reasons for involvement were identified and include insights on perceptions of benefits and harms (8), suggestions for future involvement (16), improvements to medicine information (2) and the effect of different diseases on benefits and harms (1). Detailed descriptions of existing instances of patient involvement are discussed below. Table 6 summarizes the key findings in the documents concerning benefit-harm and the involvement of patients.

Six documents reported existing patient involvement activities concerning benefits-harms, and four of these documented the objective or action and result or conclusion. A variety of stakeholders were described as providing their perspectives including: patients[36], rare disease patients[57], consumers[36], patients' and consumers' organizations[33,36], healthcare and professional organizations[33], regulatory authorities[33], the public[60] and healthcare professionals[60]. Four of the documents reported the use of surveys to identify participant insights on perceptions of benefits-harms[33,36,60] and on the improvement of benefit-harm information[36]. Looking to understand stakeholder perceptions of medicinal benefit-harms and their expectation of benefit-harm information and communication[33], EMA found:

- "Patients and healthcare professionals' expectations are similar
- Information on benefit and risk should always be communicated together
- Distinction between benefit and risk at the individual population levels should be clear

- Qualitative and quantitative information are necessary when describing benefit and risk
- Factors influencing benefit or risk should be clearly described
- Regulatory authorities should increase their role as a reliable source of information"[36(p193)].

The Genetic Alliance UK utilized a citizens' jury of rare disease patients to facilitate discussions and deliberations on understanding the perceptions of new medicine benefits and risks, the acceptable range of regulatory leniency and how patients want to be involved in regulatory benefit and harm assessment[57]. The jury produced four recommendations for regulatory decision makers, which suggested increased permissiveness of regulators in their decision-making (a lower safety threshold) and inclusion of "psychosocial factors" in treatment evaluation deliberations. Specifically, two recommendations highlighted the need to ensure active patient roles in the regulatory process and patient supports to make personal health related decisions.

While the documents used different approaches to gather patient and public insights regarding benefits and harms, outcomes of the involvement activities were not explicit, making it difficult to critically appraise the effect of patient involvement concerning benefits and harms.

Discussion

Systematic collation, synthesis, and critical appraisal of evidence exposed key gaps in the literature of patient involvement within the regulatory process. These gaps pertained to a limited explanation of rationale for selecting involvement levels and methods to achieve the desired objectives and goals, and minimal involvement of unique health populations (e.g., patients with rare diseases)

Although patient involvement appeared to be vital to relationship building and regulatory accountability, little is known about its actual effect on regulatory decision-making. In the review of the literature key themes emerged, including the value of patients' unique perspectives and the potential for increased transparency. The former was recognised by EMA through patient involvement on their advisory committees, which enabled EMA's access to patients' contextual knowledge and awareness of how regulatory decisions affect a person's life[38,38,50,51]. This reminded EMA regulators of their role and accountability to patients and the public[51]. Patient involvement also enabled a more transparent regulatory process. Through analysis of patient involvement experiences, EMA concluded that the inclusion of patients and consumers increases transparency[38]. Van Til and IJzerman state that the involvement of patients supports quality decision making and the moral accountability regulatory bodies have to healthcare recipients[45].

Another key theme in the findings was the need for patient feedback loops, although this theme was not discussed explicitly in the literature. For example, while patient ideas and suggestions were elicited, they were not necessarily incorporated into the subsequent decision. The EMA found that some patient representatives were dissatisfied when their recommendations were not fully incorporated[32,35]. Other regulatory stakeholders were uncertain of the contributory value of patient involvement in regulatory activities. EMA regulators also questioned the verbal contributions of patient committee representatives and the perceived lack of patient impact on activity outcomes, leading to the suggestion for ad hoc patient advisor presence[34]. The FDA observed that transforming patient perspectives into implementable feedback is a challenge[37]. Further regulatory involvement practices do not confirm the uptake of relevant meaningful patient insights. Similarly, the FDA encountered difficulty with patients' ability to impact committee decisions[46]. In review

of the findings, there is no evidence to suggest that patient involvement has had a direct impact on the benefit-harm assessment process.

While documents pertaining to the involvement of patients used multiple methods, representing all five IAP2 levels of involvement, they did not specify why a particular involvement level or method was chosen. Orphan medicines legislation has supported the inclusion of patient representatives on an EMA scientific committee[36]. However, there is no further information as to why the decision was made or what EMA hoped to achieve by involving patients in this way. EMA's procedural guide for patient review of regulatory communications included an overview of the interaction scope, the procedural steps, implementation guide (information, EPAR and safety communications) and why patients are involved[40]. It does not describe a specific involvement level or method.

The IAP2 model guides users through planning, implementing and evaluating patient involvement endeavours. However, this review identified a gap in the IAP2 model and its application. The gap involves the inability to determine whether the chosen IAP2 involvement method corresponds to the intended IAP2 involvement level and whether the stakeholders are aware of the goals and expectations associated with the involvement method and level. For example, regulatory bodies and patient representative organizations included patients as members on committees. Committees (and similar activities such as working groups, advisory groups, etc) are considered *collaborate* level involvement methods, where the objective is to work together to achieve a common goal. Although IAP2 categorizes committees as *collaborate*, without an involvement activity evaluation there is little way of knowing if the involvement of patients on committees is truly collaborative and influences decision-making. Patients involved on EMA committees were dissatisfied as they were unsure their involvement contributed to change[32]. Some EMA committee chairs and rapporteurs reinforced this sentiment [34]. Based on the IAP2 model, there may be an

assumption that patients involved at the collaborate level are genuine partners in every aspect of decision-making and involved in a collaborative way.

This review identified instances where the patient representative role could be considered tokenistic. For example, some EMA Committee patient representatives reported negatively on their experience, as they felt they had little influence over the decisions being made[32]. The FDA observed similar challenges in incorporating patient advisor perceptions. The FDA reported that the inclusion of patient insights in regulatory decision-making is not guaranteed[46]. Meaningful patient involvement is authentic and genuine. Tokenism occurs when the patient representative perceives them self to be a 'rubber stamp' on a decision that has already been made[61]. The National Institute for Health and Clinical Excellence (NICE) believes involving patients is an important endeavor and that to avoid tokenism, the involvement experience requires listening to the patient advisor and acknowledging their contribution[62].

The documents reviewed describe a variety of stakeholders participating in activities of regulatory agencies or PCOs. Patients involved in regulatory activities represent a variety of illnesses and perspectives. After fulfilling EMA criteria, PCOs may participate in involvement activities which require perspectives of general and unique patient populations, ensuring inclusion of the right patient groups for the regulatory activity and decision[32]. Unique populations, such as patients with rare diseases, are involved in regulatory agency involvement activities to advise on orphan drugs and associated information and communications. Rare disease patients are also called upon as experts, such as representatives from EURORDIS and EGAN, who provide the rare disease patient perspective[5]. Although it is unclear as to whether the EURORDIS and EGAN rare disease patient representatives are patients or individuals who represent the organizations, they serve on COMP so as to improve the lives of rare disease patients by advocating for their

health needs[22,23]. Similarly, the Genetic Alliance UK involved patients with rare illnesses to inform the regulatory process and build benefits-harms understanding for the complex context surrounding small populations[57].

To be responsive to rare disease populations, regulatory agencies have developed rare disease orphan drug frameworks. Franco asserts that orphan drug regulation is needed to stimulate orphan drug research and development and enable rare disease patients with the same access to medicines as other patients[12]. Lee and Wong report that due to the lack of regulation specific to medicines for rare disease patients in Canada, the rare disease patient population does not have access to beneficial medicines[58]. To mitigate this, Health Canada is in the process of developing an orphan drug framework to facilitate innovation, information sharing and collaboration in this area[11]. Rare disease patients are a unique subset of the population who exhibit different characteristics from general patients. The FDA regulations describe the distinct patient group and suggest that patients with rare conditions or diseases are more likely to accept increased harm for less benefit when weighing treatment options[63].

Conclusion

Findings from this review suggest that patient involvement within the regulatory process is complex, heterogeneous and continually undergoing development and improvement. Patient involvement includes all levels of participation described in the IAP2 framework, namely *Inform, Consult, Involve, Collaborate,* and *Empower.* The majority of regulatory patient involvement has been at the low end of the IAP2 spectrum where patients receive information from regulatory bodies, consult on benefit-harm preferences, make safety information suggestions or evaluate their involvement satisfaction. An essential step in developing strategies to promote regulatory patient involvement is the theoretical awareness and operational ability to apply involvement model principles and methodologies.

Given the limited evaluation of regulatory involvement activities, the evidence base to underpin methodological rigour around patient involvement levels and methods is poor. To respond to unique patient populations' health and treatment needs, patient involvement can be utilized to inform regulatory agencies of rare disease treatment gaps, disease impacts and benefit-harm preferences. These findings confirm that patient involvement facilitates regulatory decision-making transparency and provides an alternative real-life perspective. However, there is little evidence in the literature about the degree to which patient involvement affects benefits-harms evaluation and the regulatory process, overall.

Appendix A - Literature search strategy

Topic: Patient/consumer involvement/participation in the regulatory and pre-regulatory process for orphan drugs.

☒ English language only

☐ Human studies only n/a

☐ Study type filters: no

☒ Date range 2000 to date

1. PubMed (www.pubmed.gov; searched 17 Jul 2014, revised 4 Nov 2014)

#96	Search #60 AND #75 Filters: Publication date from 2000/01/01	294
#97	Search #60 AND #75	705
#95	Search #60 AND #93 AND #85	3
#94	Search #60 AND #93 AND #85 Filters: Publication date from 2000/01/01	2
#93	Search #75 OR #91	250526
#92	Search #75 OR #91 Filters: Publication date from 2000/01/01	133690
#91	Search legislation, drugs	15587
#90	Search legislation, drugs Filters: Publication date from 2000/01/01	9756
#86	Search #60 AND #75 AND #85	3
#85	Search #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84	32743
#84	Search "rare disease*"	11230
#83	Search "humanitarian drug exemption"	29
#82	Search "humanitarian device exemption"	38
#81	Search "rare condition*"	10666
#80	Search "rare disorder*"	5275
#79	Search "orphan disease*"	434
#78	Search "orphan drug*"	1136
#77	Search orphan drug production[mh]	803
#76	Search rare diseases[mh]	5071
#75	Search #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74	243288
#74	Search medical device legislation[mh]	70
#72	Search "device licensing"[ti]	0

#71	Search "drug licensing"[ti]	20
#70	Search legislation[ti]	7177
#69	Search "device approval*"[ti]	16
#68	Search "drug approval*"[ti]	259
#67	Search regulation[ti]	179329
#66	Search "regulatory process*"[ti]	99
#65	Search Government regulation[mh]	17778
#64	Search Legislation, Drug[mh]	25426
#63	Search United States Food and Drug Administration[mh]	23780
#62	Search drug approval[mh]	10915
#61	Search device approval[mh]	2246
#60	Search #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	37708
#59	Search "patient perspective*"	1073
#58	Search "patient value*"	74
#57	Search "patient participation"	18811
#56	Search "patient engagement"	482
#55	Search "patient involvement"	1129
#54	Search consumer*[ti] AND (participat*[ti] OR involve*[ti] OR engage*[ti])	329
#53	Search consumer participation[mh]	31945
#52	Search patient preference[mh]	3100
#51	Search patient participation[mh]	18015

Source	URL	Date	Search terms	Results
1. EURORDIS	http://www.eurordis.org/	21 Jul 2014	scanned rare disease policy section	-
2. Grey Literature Collection (New York Academy of Medicine)	http://www.nyam.org/library/	29 Jul 2014	Kw: rare diseases and kw patient, limited to GREYLIT, 2000-2014	149 refs (1 potentially relevant)
3. KU-UC (Reseau de recherché en santé des population du Quebec)	http://www.santepop.qc.ca/en/rechercheMotscles.html?2	29 Jul 2014	"rare diseases" / "orphan drug"	4 refs (0 relevant)
4. UK NHS	https://www.evidenc	29 Jul 2014	("patient involvement"	43 refs

Evidence	e.nhs.uk/		OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval)	(0 relevant)
5. Orphanet	http://www.orpha.net/consor/cgi-bin/index.php	29 Jul 2014	Scanned sections of web site	-
6. US Food & Drug Administration (FDA)	www.fda.gov	11 Aug 2014	("patient involvement" OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval)	23 refs
7. European Medicines Agency (EMA)	www.ema.europa.eu/ema/	11 Aug 2014 *EGAN=Patients Network for Medical Research and Health	("patient involvement" OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval) / + scanned sections on patient involvement	42 refs
8. EGAN: Patients Network for Medical Research and Health	www.egan.eu	20 Aug 2014	*scanned web page	3 refs
9. EURORDIS	www.eurordis.org	12 Aug 2014	("patient involvement" OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval)	16 refs
10. Health Canada	http://www.hc-sc.gc.ca/index-eng.php	12 Aug 2014	("patient involvement" OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval)	2 refs
11. Canadian Institutes of Health Research (CIHR)	http://www.cihr.ca/e/193.html	12 Aug 2014	("patient involvement" OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval)	5 refs

12. Canadian Foundation for Healthcare Improvement (CFHI)	http://www.cfhi-fcass.ca/	12 Aug 2014	"rare diseases" / "patient involvement"	26 refs
13. Australia. Therapeutic Goods Agency (TGA)	http://www.tga.gov.au/	20 Aug 2014	"rare disease*" / "patient involvement" / "patient engagement"/ "orphan drug*"	17 refs
14. New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE)	http://www.medsafe.govt.nz/other/about.asp	20 Aug 2014	"rare disease*" / "patient involvement" / "patient engagement"/ "orphan drug*"	11 refs
15. New Zealand. Pharmaceutical Management Agency (PHARMAC)	http://www.pharmac.health.nz/	20 Aug 2014	"rare disease*" / "rare disorders" / "patient involvement" / "patient engagement"/ "orphan drug*"	71 refs
16. Italian Medicines Agency	http://www.agenziafarmaco.com/en	21 Aug 2014	"rare disease" / "rare disorder" "patient involvement" / "patient engagement"/ "orphan drug"	10 refs
17. UK - Medicines & Healthcare Products Regulatory Agency (MHRA)	http://www.mhra.gov.uk/#page=DynamicListMedicines	21 Aug 2014	"rare disease*" OR "rare disorders" OR "patient involvement" OR "patient engagement" OR "orphan drug*"	246 refs
18. Google.ca	www.google.ca	11 Aug 2014	(("patient involvement" OR "patient engagement") AND ("rare diseases" OR "orphan drug") AND (regulatory OR regulation OR licensing OR approval)) AND FDA	Appx 18,400 hits (only scanned the first 10 pages only)

Appendix B: Data extraction form

Mandy Bellows
Patient Involvement and Trading off Risks and Benefits

Data Extraction Tool
Include: YES NO

Publication Title:			
Publication Date:		Author(s):	
Country:			

Study Characteristics

Research Question	
Research Purpose	
Research Design	Data collection Method
Research Setting	◻ Home ◻ Hospital ◻ Research Center ◻ Other, describe:_____
Involvement Setting	◻ Design of Clinical Trial ◻ Enrolled in Clinical Trial ◻ Clinical Trial Review ◻ Regulatory Process
Level of Participation	◻ Inform ◻ Consult ◻ Involve ◻ Collaborate ◻ Empower

Participant Characteristics

Perspective	◻ Carer ◻ Family Member ◻ Patient ◻ Child ◻ Adult ◻ Other, describe:_____
Treatment Context	◻ Prior to Treatment ◻ During Treatment ◻ After Treatment
Stage of Illness	◻ Preventative ◻ Screening ◻ Active Treatment ◻ Stable ◻ Slowing ◻ Cure ◻ Other, describe: _____
Type of Illness	◻ General, describe:_____ ◻ Rare Disease :_____ ◻ Other, describe: _____
Research Participants	Age: _____ Gender: _____ Ethnicity:_____ Education:_____ Social:_____ Economic:_____ Other, describe:_____

Key Factors Considered

◻ Experiences ◻ Behaviours ◻ Knowledge ◻ Preferences ◻ Values ◻ Attitude ◻ View ◻ Choice ◻ Other:_____	◻ Benefit ◻ Harm ◻ Other:_____ _____	◻ Risk Assessment ◻ Uncertainty ◻ Probability ◻ Gamble ◻ Trade Off ◻ Other:_____	Participation Method: ◻ Patient Reported Outcomes _____ ◻ Advisory Committee ◻ Survey ◻ Interview ◻ Focus Group ◻ Other: _____ _____

Notes

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Appendix C. Tables

Table 1. Characteristics of published documents

Primary Author	Publication Year	Jurisdiction[a]	Document Type (Self-Described)[b]
Lee[58]	2014	Canada	Overview
Moulon[36]	2010	Europe	Overview
Mullard[37]	2013	USA	News
Roth[46]	2011	USA	Essay
Van Til[64]	2014	International	Editorial

a Jurisdiction reports the location of document context

b Document type reports the type of document as described by the author or publication

Table 2. Characteristics of grey documents

Primary Author	Publication Year	Jurisdiction[a]	Document Type Self-Described[b]	Source[c]	Document Description[d]
EMA[48]	2006	Europe	Framework	Regulatory Agency	Guidance
EMA[32]	2008	Europe	Report	Regulatory Agency	Activity Overview
EMA[33]	2009	Europe	Information	Regulatory Agency	Activity Overview
EMA[65]	2009	Europe	Proposal	Regulatory Agency	Guidance
EMA[38]	2009	Europe	Reflection Paper	Regulatory Agency	Activity Overview & Guidance
EMA[54]	2009	Europe	Report and Proposal	Regulatory Agency	Activity Overview & Guidance
EMA[40]	2010	Europe	Procedure	Regulatory Agency	Guidance
EMA[35]	2011	Europe	Report and Analysis	Regulatory Agency	Activity Overview
EMA[49]	2011	Europe	Guidance Paper	Regulatory Agency	Guidance
EMA[34]	2011	Europe	Outcome Report	Regulatory Agency	Activity Overview
EMA[66]	2011	Europe	Road Map	Regulatory Agency	Guidance
EMA[39]	2013	Europe	Information	Regulatory Agency	Information
EMA[50]	2013	Europe	PowerPoint Presentation	Regulatory Agency	Activity Overview
EMA[51]	2013	Europe	Information	Regulatory Agency	Activity Overview
EMA[5]	Accessed 2014	Europe	Webpage	Regulatory Agency	Information
EMA[21]	Accessed 2014	Europe	Website	Regulatory Agency	Information
EGAN [67]	2013	Europe	Consultation Paper	Patient Organization	Information
EGAN [22]	Accessed 2014	Europe	Website	Patient Organization	Information
EURORDIS [23]	Accessed 2014	Europe	Website	Patient Organization	Information
EURORDIS [42]	Accessed 2014	Europe	Webpage	Patient Organization	Information
MHRA[4]	2006	United Kingdom	Press Release	Regulatory Agency	Information
MHRA[68]	2006	United Kingdom	Summary	Regulatory Agency	Activity Overview
MHRA[60]	2006	United Kingdom	Strategy	Regulatory Agency	Guidance
MHRA[41]	2007	United Kingdom	Annual Report	Regulatory Agency	Activity Overview
MHRA[69]	2008	United Kingdom	Summary	Regulatory Agency	Activity Overview
MHRA[70]	2011	United Kingdom	Website	Regulatory Agency	Information
MHRA[71]	2012	United Kingdom	Information	Regulatory Agency	Guidance
MHRA[72]	2012	United Kingdom	Summary	Regulatory Agency	Activity Overview
MHRA[24]	Accessed 2014	United Kingdom	Website	Regulatory Agency	Information
Genetic Alliance UK[57]	2012	United Kingdom	Report	Patient Organization	Activity Overview
Genetic Alliance UK[13]	2014	United Kingdom	Patient Charter	Patient Organization	Guidance
Genetic Alliance UK [25]	Accessed 2014	United Kingdom	Website	Patient Organization	Information
FDA[63]	2010	USA	Public Hearing	Regulatory Agency	Consultative
FDA[73]	2014	USA	Meeting/Network Notice	Regulatory Agency	Information
FDA[43]	2014	USA	Network News	Regulatory Agency	Information
FDA[26]	Accessed 2014	USA	Website	Regulatory Agency	Information
Woodcock, J., & Shuren, J.[44]	2013	USA	Website/Network News	Regulatory Agency	Activity Overview
Faster Cures[52]	Accessed 2014	USA	Website	Patient Organization	Information

Health Canada[11]	Accessed 2014	Canada	Webpage	Regulatory Agency	Information
Health Canada [27]	Accessed 2014	Canada	Website	Regulatory Agency	Information
AIFA[47]	Accessed 2014	Italy	Webpage	Regulatory Agency	Information
AIFA[28]	Accessed 2014	Italy	Website	Regulatory Agency	Information
Medsafe [74]	Accessed 2014	New Zealand	Webpage	Regulatory Agency	Information
Medsafe [75]	Accessed 2014	New Zealand	Webpage	Regulatory Agency	Activity Overview
Medsafe [29]	Accessed 2014	New Zealand	Website	Regulatory Agency	Information
TGA[30]	2011	Australia	Blueprint	Regulatory Agency	Guidance & Information
TGA[53]	Accessed 2014	Australia	Website	Regulatory Agency	Information

a Jurisdiction reports the document context location

b Document type reports the type of resource as described by the author or government agency

c Document source describes the author of the resources

d Document description differentiates between type of information the resource contains (i.e. provides guidance, an overview of involvement activities, describes a consultation, and provides information about involvement)

Table 3. Document involvement characteristics

Author	Publication Year	Level(s) of Involvement[a]	Involvement Method(s)[b]
Lee[58]	2014	Advice for future involvement	NA
Moulon[36]	2010	Consult/Involve/Collaborate	Advisory Committee Membership (Scientific Committees) Benefit/Harm Survey Workshops Working Groups Documentation/Information Review Ad Hoc Patient Consultation
Mullard[37]	2013	Consult/Involve	Patient Advocacy Group Survey Meeting speaking opportunities Meeting Online Docket Submission
Roth[46]	2011	Collaborate	Advisory Committee Membership
Van Til[64]	2014	Consult/Collaborate	Patient Consultations Decision Making Panel Ranking/Rating Benefits and Harms Conjoint Analysis Discrete Choice Experiment Best Worst Scaling
EMA[48]	2006	Advice for future involvement	NA
EMA[32]	2008	Consult/Involve/Collaborate	Advisory Committee Membership Working Group Membership Documentation/Information Review Survey Meeting Attendance Workshops/Conferences Ad Hoc Requests
EMA[33]	2009	Consult	Survey
EMA[65]	2009	Advice for future involvement	NA
EMA[38]	2009	Advice for future involvement	NA
EMA[54]	2009	Collaborate	Advisory Committee Membership (pilot)
EMA[40]	2010	Consult	Documentation / Information Review
EMA[35]	2011	Consult/Involve/Collaborate	Advisory Committee Membership Working Group Membership Documentation/Information Review Survey Meeting Attendance Workshops/Conferences Ad Hoc Requests
EMA[49]	2011	Collaborate	Advisory Committee Membership
EMA[34]	2011	Consult/Collaborate	Advisory Committee Membership Survey
EMA[66]	2011	Advice for future involvement	NA
EMA[39]	2013	Consult/Involve/Collaborate	Agency Board Membership

			Documentation/Information Review Scientific Advisory Group Membership Network Membership Workshops/Conferences
EMA[50]	2013	Collaborate	Advisory Group Membership
EMA[51]	2013	Collaborate	Advisory Committee Membership
EMA[5]	Accessed 2014	Consult/Involve/Collaborate	Documentation/Information Review Agency Board Membership Scientific Advisory Group Membership Ad Hoc Requests Guideline Preparation Workshops/Conferences
EMA[21]	Accessed 2014	Inform	Website
EGAN[67]	2013	Advice for future involvement	NA
EGAN[22]	Accessed 2014	Inform/Consult/Collaborate	Website Patient Consultation Advisory Committee Membership
EURORDIS[23]	Accessed 2014	Inform	Website
EURORDIS[42]	Accessed 2014	Consult/Collaborate	Scientific Advisory Group Membership Working Group Membership Documentation/Information Review
MHRA[4]	2006	Inform	Lecture
MHRA[68]	2006	Advice for future involvement	NA
MHRA[60]	2006	Consult	Survey
MHRA[41]	2007	Consult	Documentation/Information Review
MHRA[69]	2008	Consult	Forum
MHRA[70]	2011	Advice for future involvement	NA
MHRA[71]	2012	Consult	Adverse Event Reporting
MHRA[72]	2012	Advice for future involvement	NA
MHRA[24]	Accessed 2014	Inform	Website
Genetic Alliance UK[57]	2012	Empower	Citizens' Jury
Genetic Alliance UK[13]	2014	Consult	Collaborative discussion
Genetic Alliance UK[25]	Accessed 2014	Inform	Website
FDA[63]	2010	Consult	Public Hearing
FDA[73]	2014	Consult	Network Meeting Patient Network
FDA[43]	2014	Consult/Involve/Collaborate	Advisory Committee Membership Consultation Workshop (Presenter) Network Meeting (Presenter)
FDA[26]	Accessed 2014	Inform	Website
Woodcock, J., & Shuren, J.[44]	2013	Involve	Public Workshop
Faster Cures[52]	Accessed 2014	Collaborate	Advisory Council Membership
Health Canada[11]	Accessed 2014	Advice for future involvement	NA
Health Canada[27]	Accessed 2014	Inform	Website
AIFA[47]	Accessed 2014	Collaborate	Working Group Membership
AIFA[28]	Accessed 2014	Inform	Website
Medsafe[74]	Accessed 2014	Consult	Website Consultation

Medsafe[75]	Accessed 2014	Consult	Website Consultation
Medsafe[29]	Accessed 2014	Inform	Website
TGA[30]	2011	Inform/Collaborate	Website Advisory Council Membership
TGA[53]	Accessed 2014	Collaborate	Advisory Council Membership

a Level(s) of involvement reports one or more IAP2 involvement levels identified within the document and include inform, consult, involve, collaborate and empower. Documents that included proposed patient involvement were labelled 'Advice for future involvement'

b Involvement method(s) report one or more involvement method or activity associated with the IAP2 involvement levels identified in the documents. Documents that proposed patient involvement were labelled 'NA' to represent no application of involvement method

Table 4. Involvement levels and their application frequency

Primary Author	Publication Year	Inform[a]	Consult[a]	Involve[a]	Collaborate[a]	Empower[a]	Proposed[a]
Lee[58]	2014						X
Moulon[36]	2010		X	X	X		
Mullard[37]	2013		X	X			
Roth[46]	2011				X		
Van Til[64]	2014		X		X		
EMA[48]	2006						X
EMA[32]	2008		X	X	X		
EMA[33]	2009		X				
EMA[65]	2009						X
EMA[38]	2009						X
EMA[54]	2009				X		
EMA[40]	2010		X				
EMA[35]	2011		X	X	X		
EMA[49]	2011				X		
EMA[34]	2011		X		X		
EMA[66]	2011						X
EMA[39]	2013		X	X	X		
EMA[50]	2013				X		
EMA[51]	2013				X		
EMA[5]	Accessed 2014		X	X	X		
EMA[21]	Accessed 2014	X					
EGAN[67]	2013						X
EGAN[22]	Accessed 2014	X	X		X		
EURORDIS[23]	Accessed 2014	X					
EURORDIS[42]	Accessed 2014		X		X		
MHRA[4]	2006	X					
MHRA[68]	2006						X
MHRA[60]	2006		X				
MHRA[41]	2007		X				
MHRA[69]	2008		X				
MHRA[70]	2011						X
MHRA[71]	2012		X				
MHRA[72]	2012						X
MHRA[24]	Accessed 2014	X					
Genetic Alliance UK[57]	2012					X	
Genetic Alliance UK[13]	2014		X				
Genetic Alliance UK[25]	Accessed 2014	X					
FDA[63]	2010		X				
FDA[73]	2014		X				
FDA[43]	2014		X	X	X		
FDA[26]	Accessed 2014	X					
Woodcock, J., & Shuren, J.[44]	2013			X			

Faster Cures[52]	Accessed 2014				X		
Health Canada[11]	Accessed 2014						X
Health Canada[27]	Accessed 2014	X					
AIFA[47]	Accessed 2014				X		
AIFA[28]	Accessed 2014	X					
Medsafe[74]	Accessed 2014		X				
Medsafe[75]	Accessed 2014		X				
Medsafe[29]	Accessed 2014	X					
TGA[30]	2011	X			X		
TGA[53]	Accessed 2014				X		

a Involvement level(s) reported in the documents based on IAP2 (inform, consult, inform, collaborate and empower). Documents that proposed patient involvement were not assigned an involvement level and were placed in the 'proposed' column

Table 5. Involvement methods identified in the documents

Involvement Level[a]	Involvement Methods[b]
Inform	Lecture[4] Website[21,22,23-30]
Consult	Collaborative Discussion[13] Meeting Attendance/Speaking Opportunities[32,35,37] Survey[32-37,60] Meeting Online Docket Submission[37] Ranking and Rating/Conjoint Analysis/Discrete Choice Experiment/Best Worst Scaling[64] Information / Documentation Review[5,32,35,36,39-42] Adverse Event Reporting[21,23,24,26-29,71,76] Public Hearing[63] Patient Consultation[22,36,64] Forum[69] Network Meeting[43,73] Website Consultation[74]
Involve	Workshop/Conference[5,32,35,36,39,43,44,77,78] Preparing Guidelines[5] Patient Network[39,73]
Collaborate	Advisory Committee[22,32,34,35,43,46,49,51,53,54] Scientific Advisory Group[5,36,39,42,50] Agency Board[5,39] Advisory Council[30,52,53] Decision Making Panel[64] Working Group/Party[32,35,36,42,47]
Empower	Citizens' Jury[57]

a Involvement levels reported in the documents based on IAP2 (inform, consult, inform, collaborate and empower)

b Involvement method(s) report one or more involvement method or activity associated with the IAP2 involvement levels identified in the documents. Reference numbers indicate the number of times a specific method was applied and within which document

Table 6. Patient involvement and insights about medicine benefits and harms

Author	Publication Year	Status[a]	Involved Participants[b]	Reason for Involvement[c]	Objective/Action[d]	Result/Conclusion[e]
Moulon[36]	2010	Existing	• Patients • Consumers • Patient and consumer organizations	Insights on perceptions and information improvement	"More recently, the agency organized a survey related to information on benefit and risks, involving patients, consumers and health care professionals, as well as regulators."[36(p193)]	Summary of Results of Information on Benefit and Harm Survey[36(p193)]: • Patients and health care professionals expectations are similar • Information on benefit and harm should always be communicated together • Distinction between benefit and harm at individual level should be clear • Qualitative and quantitative information is necessary when describing benefit and risk • Factors influencing benefit or harm should be clearly described • Regulatory authorities should increase their role as a reliable source of information
Mullard[37]	2013	Proposed	• Patients • Patient organizations	Insights on perceptions and future involvement	"A main thrust of these meetings will be to inform the FDA's new benefit-risk framework… This framework will lay out which benefits and risks were considered during a drug review, how available evidence was interpreted and what the implications of the evidence are for the benefit-risk assessment"[37(p651)] Suggestion to use a Patient Stratification tool, "to ensure that patient input is stratified and applied appropriately during benefit-risk decision making."[37(p651)]	NA
Roth[46]	2011	Proposed	• Patients	Insights on perceptions and future involvement	"If patient representatives participate in negotiations as mediators, they can serve to balance risks and benefits and determine the appropriateness of any approval plan"[46(p31)]	NA
Van Til[64]	2014	Proposed	• Patients	Insights on perceptions and future involvement	"This paper discusses the potential of patient-based preference assessment of benefits and risks in the approval process for new healthcare technologies."[64(p1)] "In the regulatory context, stated preference methods could be used to identify preferences over characteristics of a drug and the trade-off between benefits and harms in choosing treatment."[64(p2)] "Despite the apparent appeal of state patient preference assessment in regulatory decision making, several barriers need to be overcome to enable patient preference assessment in the practical context of benefit-risk assessment."[64(p3)]	NA
EMA[33]	2009	Existing	• Patient and consumer organizations • Healthcare professional organizations • Regulatory authorities	Insights on perceptions	Participants, including those from patient and consumer organizations, were asked to complete a survey to complete a questionnaire on their understanding and expectations when medicine benefits and harms are being communicated. Taking part in Spring 2008, participants answered the following questions: • "What is the benefit –harm of a medicine for you? • Which information do you expect in terms of benefit, risk, and benefit-harm balance of a medicine? • Do you communicate benefit-harm information? If yes, how? • What information on benefit-risk, do you think is missing? • What would you propose to improve information on benefit-harm of medicine? • What is the minimum time necessary to address benefit-harm during a patient-healthcare professional consultation?"[33(p5)]	Responses were summarized to highlight similarities and differences: • Rather than develop a definition, all participant groups, "stressed a common principle for communicating essential information about the medicine to ensure safe and appropriate care of a patient to optimize his or her well-being. • Context of Benefit-Harm is multifaceted and includes factors such as: the patient, the disease to be treated, the therapeutic alternatives, and existing knowledge about the medicine. • Participants agreed that there is no one single method for communicating medicine benefits and risks. But the communication should be a balanced description of benefits to risks and any known factors should also be shared. Suggestion to distinguish between population and individual benefits and risks"[33(p5)] Participants provide insights on benefit information preferences including a desire for more qualitative and quantitative data and both primary and secondary end point results.
EMA[38]	2009	Proposed	• Patient and Consumer organizations	Insights on future involvement	Described as matters for consideration: determining the role of patients/consumers should play in benefit/harm consideration and developing procedures in the areas of assessment of benefit/harm and preparation/provision of information to the public (especially on safety related aspects) is a proposal for action. To determine the advantage of patient involvement in the Benefit/Harm discussion the following question was asked: Which would be the added value of consulting patients during the scientific process of benefit/harm evaluation and how should this interaction be established in practice?[38(p1)]	NA
EMA[54]	2009	Proposed	• Patient and consumer organizations	Insights on future involvement	"PHVWP Representatives believe that given the fast increasing amount of safety information on pharmaceuticals, patient involvement in product safety related communication and on risk/benefit discussions is necessary"[54(p3)]	NA
EMA[66]	2010	Proposed	• Patients • Consumers	Insights on future involvement		The Road Map to the Future includes: • "Interaction with Agency Key Stakeholders – Recognizing the added value of patients and consumers in benefit/harm considerations, in that they enrich regulatory decisions by complementing them with the views of those directly affected by regulatory decisions, the debate currently focuses on how to achieve more structured involvement of patients in the Agency's work"[66(p8)]. • "New and Emerging Science – requiring further investigation is the appropriateness of the current /legal regulatory framework, in particular with respect to the benefit/harm evaluation and the development of tools for the anticipation of potential safety issues"[66(p9)] • "The Agency's Strategic Areas 2011-2015 – Extrapolating the positive benefit/harm balance identified in a clinical-trial setting for a medicine in a given therapeutic

						indication for a well-defined target population to the real-life use of the medicine should be further explored[66(p13)] • "Strategic area: Facilitating access to medicines – Reinforce the benefit/risk-balance assessment model"[66(p18)] • Benefit/harm Assessment and Communication – work on improving the benefit/risk-balance model concentrates on three major aspects: ensuring a consistent approach, providing a better rationale for the outcome of the benefit/harm review and improving the communication with the various stakeholders"[66(p20)].
EMA[39]	2013	Proposed	• Patient and consumer organizations	Insights on future involvement	Planning for the future, EMA will, "continue to strengthen and streamline its collaboration with patients by working towards more regular involvement of patient representatives in benefit-harm evaluations, including with the new Pharmacovigilance Risk Assessment Committee"[39(p2)]	NA
EMA[51]	2013	Proposed	• Patients • Healthcare professionals • Regulatory authorities	Insights on future involvement	Describes a research example (PROJECT) which is "looking at ways of representing benefit and harm and at how these different methods, both textual and graphical, affect the perception of benefit-risk, and the consequent decisions made by patients, healthcare professionals and regulators"[51(p4)]. Conclusion notes include a need to, "identify where quantitative versus qualitative input are needed, and develop and validate new tools for eliciting values and preferences and representing benefit and risk"[51(p6)]	NA
EGAN[22,79]	Accessed 2014	Proposed	• Patients	Insights on future involvement	Webpage acknowledges the launch of EUPATI (European Patients' Academy on Therapeutic Innovation) where topics like risk/benefit assessment will be addressed.	NA
MHRA[4]	2006	Proposed	• Patients	Insights on future involvement	Cayton (Lecturer) articulated that regulatory decisions are, "not just scientific, they are complex social judgments which involve weighing up benefits against risks. Perceptions of benefit and harm vary between people and across time, and we should therefore expect regulatory decisions to provide "the best answers for the moment"[4(p1)]	NA
MHRA[68]	2006	Existing	• Patient advocate	Insights on information improvement	The Patient Information Expert Advisory Group advises on "European initiatives in the area of patient information including the European Commission's commitment to report on patient information practice; to advise on communications with patients and the public about risk/benefit of medicines, in particular PILs and when risk/benefit changes; and to advise the MHRA on ways to facilitate and promoted patient reporting and secure further patient engagement in the patient reporting process"[68(p1)].	Results of the Committee were results not reported
MHRA[60]	2006	Proposed	• Patient • Public • Healthcare Professionals	Insights on future involvement	"Strategic Priorities of MHRA include improving the understanding of the benefit/harm balance of medicines and medical devices amongst the general public and/or healthcare professionals by, identifying priority groups where understanding is currently low and targeting these groups with information about benefits and/or risks"[60(p5)] Success measures include effective day to day interaction with patient groups on benefit/harm issues, as measure by the greater frequency of such interactions and patient group feedback. Phase 2 of the action plan include the development of an Agency document "on weighing up risks and benefits through round table discussions with stakeholder groups, leading to a revision of the document if necessary and further reflection/action in relation to agency processes"[60(p7)]	NA
MHRA[41]	2007	Existing	• Patients • Public • Healthcare professionals	Insights on perceptions	The MHRA, "commissioned research to find out what the public and healthcare professional think about the risks and benefits associated with medicines, medical devices and medical equipment"[41(p8)] They sought to views on how well these items are regulated and how risks and benefits are communicated. Determining how patients can be further involved in regulatory process from expert advisory groups, information review and adverse event reporting[41].	Public Findings Harm + Benefits: • Qualitative – assumption that medicines are safe if it can be purchased or prescribed. Participants recognize that people react to medicines differently • Quantitative – Half 'know' about risks and side effects of medicines. Half weigh the risks and benefits where as some say they never do this.
MHRA[69]	2008	Proposed	• Patient organization representatives	Insights on future involvement	Forum Mandate: "to examine the tools and techniques currently available to enable the pharmaceutical industry and regulators to undertake formalized assessments of the benefits and risks associated with medicines, their use during the lifecycle of the medicine, and what developments were needed to improve on current practice. The Forum attendees, including patient group representatives were asked to consider: • What do regulators and the pharmaceutical industry need to enable them to undertake a benefit/risk assessment, and should both parties be employing the same tools/techniques? • To what extent are the currently available tools and techniques mature enough and applicable to meet the need? Are there other tools/techniques that have not been explored?	Meeting Conclusions include: • A framework for Benefit/harm assessment is needed within which different models can be applied • A group (including EMEA and FDA) with appropriate expertise and enthusiasm should be established to develop a pilot in benefit/harm decision analysis, drawing on work already underway in the medicines field but also considering the value and relevance of methodologies and tools in use in other sectors • The importance of improving transparency of decision making and finding ways better to communicate benefit/harm decisions to patient must not be overlooked.

					•Next Steps – identify a practical way forward and identify research needs; •Tools and methodologies for communicating benefit/risk"[69(p1)] The forum meeting included the following activities Presentations to explain: •"How benefit/harm decisions are currently undertaken by UK and US regulators; •What patients expect to be taken into account in the risk/benefit decision; •Various models available to inform benefit/harm decisions; •Future research needs"[69(p2)] Discussions of how to respond to the specific questions put to the meeting.	
Genetic Alliance UK[57]	2012	Existing	• Patients with rare diseases	Insights on perceptions and future involvement	A Citizens Jury was formed to take a role in a study to identify, "how patients with serious and or rare conditions perceive risks and benefits, and how effectively current regulatory decision making reflects their preferences. The discussions of the Jury were focused on the following questions: •How do patients with rare and/or serious conditions perceive the risks and benefits of new medicines? •To what extent should regulators be more permissive in their marketing authorization decisions? •How should patients be involved in the assessment of risks and benefits, and regulatory decision making?"[57(p5)]	Summarized results include: •"Regulators should include psychosocial factors in their decision making. •Regulators should be more permissive for those treatments for people with rare and/or serious conditions •Patients should be more involved in all stages of the process, from setting the research agenda to post-marketing authorization decisions. •Patients should be better supported to make their own decisions."[57(p12)]
Genetic Alliance UK[13]	2014	Proposed	• Patient with rare diseases	Insights on perceptions and future involvement	Recommendation for reconsideration of benefit /harm by NICE should be explicitly justified, involve patient consultation and refer to patient testimonies collected by EMA.	NA
FDA[63]	2010	Proposed	• Patients with rare diseases	Insights in different diseases	FDA Regulations Quote - 314.105(c) – "These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life threatening and severely debilitating illnesses than they would accept from products that treat less serious illness. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated"[63(p7)] Question and Answer about weighing benefits and risks - Quote from the Advanced Medical Technology Association: "Again, one of the areas that I think could improve is having more accessibility of experts to the process, using the clinical community who is more familiar with these products into the process, both during development as well as approval, not just as a panel to evaluate a product at the end of its development, but really to provide good information to the regulatory environment about what the benefits and risks and issues are for these specific patient populations so that it's much clearer, and working between the clinical community, the inventor, the innovative community, and the agency could go a long way"[63(p68)]	NA
FDA[43]	2014	Existing	• Patient representatives	Insights on future involvement	Consumer Representatives Role Description includes the need to discuss benefits and risks among other items of products under review.	Specific involvement activities not reported
FasterCures[52]	Accessed 2014	Proposed	• Patient representatives	Insights on future involvement	*FasterCures* is working to expand opportunities for patient perspectives to shape product development and influence regulatory decisions so that products patients value advance more rapidly from bench to bedside.	NA

a Status indicates if stakeholders were involved and benefit and harm insights were elicited (existing) or if there was planned future involvement of stakeholders and for elicitation of their benefit and harm insights (proposed)

b Identifies the stakeholders involved (or their planned involvement) and ranges from patients, consumers, healthcare professional, representative organizations and the public

c Reports on the reasons stakeholders were involved (or their planned involvement) and the type of information gathered (insights on future involvement, information improvement, perceptions of benefits and harms and the effects benefits and harms have on different illnesses

d Documents reported the purpose (an objective/action) of the proposed or existing stakeholder involvement

e Presence and description of the document finding (result/conclusion) of stakeholder involvement and receipt of benefits-harms insights. In some cases, findings were not available in documents with existing examples of stakeholder involvement. Documents that proposed stakeholder involvement in the elicitation of benefit-harm insights were labelled 'NA' to represent no result or conclusion was identified.

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Chapter 2. Involving patients and caregivers in the development of a survey to assess benefit-harm trade-offs associated with therapies for rare diseases

Introduction

The relationship between rare diseases and health care systems is complex and challenged by high per patient costs, timely access to effective treatments, and the profound impact of the disease on patients and families[1-3]. Over the last decade, efforts of patient groups and regulatory bodies have advanced rare diseases as a health priority, helping to influence public policy and stimulate research and incentives for medicine development[3]. Collaborative endeavours between stakeholders have led to patient involvement in the regulatory process for approval of new rare disease therapies, including assessment of treatment benefits and harms.

While a positive step, multiple challenges remain for regulatory bodies and the regulatory process, particularly around the assessment of treatment benefits and harms of patients with rare diseases. Little is known about how patients are involved in the regulatory process and patient perceptions of treatment benefits and harms. Since individual rare diseases affect small numbers of patients, disease knowledge, clinical evidence and patient insights are limited; this complicates the regulatory process[4-6]. Given the critical role of evaluation in the regulatory approval of new medicines, there is benefit to understanding patient perceptions of treatment benefits and harms. These may serve as an important guide for regulatory bodies and the regulatory process in the approval of new rare disease therapies.

Objective

The purpose of this paper was to identify the perceptions of treatment benefits and harms among patients with rare diseases, including their associated treatment benefit priorities and expectations of benefit.

Background

The evaluation of treatments through the regulatory process requires scientific and stakeholder analysis of the medical condition, available treatments, and expected outcomes, which explicitly involves the assessment of benefits and harms[7]. Approval of any treatment means there is a favourable benefit to harm balance. Rare diseases are often "life threatening or chronically debilitating, progressive condition[s]" that affect less than five in 10,000 people[8(p1)]. These challenges include uncertainties surrounding treatment benefits and harms, which are inevitable, given that regulatory evaluations occur at a fixed point in time[9,10]. They also involve differing stakeholder perspectives on benefits and harms, which are often difficult to reconcile. "Stakeholders may use different sources to inform deliberations about benefit and [harms] trade-offs, may define and prioritize benefits and [harms] differently, and may differ on the strength of evidence required to make a decision"[11(p1)]. In addition, there is the need to develop different requirements for rare disease benefit and harm decision-making (compared to drugs for common diseases) given the limited literature on patient involvement with rare diseases[6,12].

The current processes for evaluating the benefits and harms of treatments of rare diseases are frequently based upon experiences with common diseases, which is problematic given the "limited knowledge of the disease, small patient populations, and for many a lack of alternative treatment options"[12(p4)]. Benefits are typically measured comparatively to other treatments, a standard that poses considerable issues given the lack of treatments available. Similarly, the measurement of harm has also proven difficult given that standard evaluation necessitates large clinical trials and extensive knowledge of the disease[12]. One way to inform treatment benefit and harm evaluation is through the involvement of patients with rare diseases.

Over the last decade, scholarly work on ways to include patient perspectives around treatment harms and benefits has focused on strategies to elicit feedback from patients on

benefits and harms and future involvement preferences[4,13], including suggestions for a revised review process supporting those with rare diseases[14]. A 2012 Genetic Alliance UK report describes a citizens' jury that was convened to identify "how patients with serious or rare conditions perceive risks and benefits, and how effectively current regulatory decision making reflects their preferences"[15(p5)]. A citizens' jury is a group of people who are brought together to represent a community or population on a specific topic or issue where recommendations or opinions are identified[16]. The citizens' jury recommended that regulators use "psychosocial factors" in their decision making, increase authorization of treatments for rare disease patients, enhance patient involvement in the drug and treatment life cycle, and strengthen patient support of personal decision making[15]. Closely related, the FDA and Centre for Devices developed the Patient Preference Initiative, which advances the incorporation of patient preference information into the medical device regulatory process. In 2013, the FDA hosted a public workshop on the Patient Preference Initiative, which explored ways to include patient preferences (including patients with rare diseases) on treatment benefits and harms trade-offs[17] and ways to advance the knowledge and practice of treatment preference measurement[18]. An FDA report concluded that the rare disease patient group is unique due to its willingness to accept more risk of harm for benefit when assessing treatment options[14].

While a recent literature review has demonstrated that the adoption of patient involvement in health-decisions is varied and not systematic, regulatory bodies are increasingly recognizing "how vital patient involvement is to the regulation of medicines and healthcare products in the 21st century"[10(p1)]. In an effort to collect feedback from rare disease patients, regulatory bodies are in the process of developing frameworks to assess orphan drugs. A shift towards increased patient involvement is due to the perceived lack of meaningful and relevant benefit-harm preferences to inform the evaluation of treatments during the regulatory process[12]. The collection of rare disease patient information is

important as it addresses the needs of a unique and marginalized health population, informs innovative research, and addresses a gap in academic literature.

Methods

Two methods were used to gain rare disease patient insights on treatment benefit-harm attributes and the amount of benefit gain one expects from treatment. Focus groups were used to generate ideas and thoughts produced by a similar group of individuals[19] around characteristics of treatment attributes. They took place during fora hosted by the Canadian Organization for Rare Diseases (CORD). These fora bring together many individuals affected by different rare diseases across Canada. Focus groups were chosen because they are a meaningful and productive way of encouraging participant interaction and generating relevant and applicable wording for surveys or questionnaires[19]. The focus groups were scheduled to occur after other sessions during each forum to increase participant comfort.

After the focus groups an in-person survey was used to understand the amount of expected benefit rare disease patients anticipate from treatment. The in-person surveys enabled participants to request questions or clarification if needed[20]. There were no costs associated with the method[21] since the surveys were preprinted and no postal charges were incurred. Survey completion time was scheduled which enabled participants to complete the surveys at the CORD Forum. The survey was developed using large font and contained grade seven language.

Ethics approval was received from the University of Alberta Health Research Ethics Board.

Setting

The CORD hosted three fora in three Canadian cities (Toronto, Montreal, and Vancouver) in May and June of 2014. CORD is a national advocacy group that represents rare disease groups in Canada. During each forum, activities were designed to elicit patient and family perceptions, priorities, and expectations on treatment benefits and harms. Locations were

selected to ensure diverse geographical representation and maximization of participatory opportunities for patients and families. Travel and accommodations for patients and caregivers were provided by CORD.

Participants

Inclusion and Exclusion Criteria

Any rare disease patients or caregivers attending one of the three CORD forums able to speak French or English were eligible to participate. Patients were those individuals who had been diagnosed with a rare disease by a physician. Caregivers were defined as unpaid family members or friends responsible for taking care of a person with a rare disease. Those who could not read at a grade seven level were excluded, as the survey required this level of literacy.

Sampling Strategy

Convenience sampling was used to select participants. As a sampling technique, convenience sampling uses non-probabilistic methods to access participants who are readily available[22]. This strategy offers significant insights and usefulness for pilot studies and hypotheses generation[23].

During the introductory plenary session of each forum, a presentation on the study and its objectives was made. Information letters and consent forms were distributed to attendees. All attendees were asked to review the forms and indicate whether they would like to participate in two one-hour activities (one focus group and one based on individual exercises) scheduled during time periods that would not conflict with other forum sessions. Therefore, participation was voluntary and those who wished to participate were self-selected.

Data Collection

Two sequential approaches were used to gain insights from participants on treatment benefits and harms: focus groups and individual exercises involving spectrum surveys.

Focus Groups

Focus groups were used to determine what participants viewed as a treatment 'benefit' and a treatment 'harm'. Focus groups are an approach that offer a collaborative space where interaction among participants will produce in-depth information on a topic[24]. In addition, it is viewed as a valid method for developing questions for surveys[19].

During each group, participants discussed the following questions:

1) When you think about potential harms of a treatment, what words, thoughts, or characteristics come to mind?
2) When you think about potential benefits of a treatment, what words, thoughts, or characteristics come to mind?

Specific benefit and harm attributes were sought. For example, if participants responded with a general term similar to "quality of life" (QoL), they were asked to describe specific aspects of QoL. Attributes identified through the focus group were recorded on flip charts. Since the purpose of the focus group was to collectively generate a list of benefit and harm attributes, the session was not recorded. Participants then reviewed the list, comparing attributes to identify any overlaps among them. Three focus groups were conducted to compare benefit and harm attributes across the groups in an attempt to reach saturation.

Sticker Dot Voting

After each focus group, sticker dot voting was used to reduce the benefit attributes on the list to a manageable number for a survey. Sticker dot voting (or multi-voting) is a common activity used to prioritize brainstorming results[25]. The number of sticker dots provided to

each participant is determined by dividing the number of ideas by six and enabled participants to choose multiple different benefit attributes[26]. The method generates representative preferences quickly[27] and produces results that are easy to interpret[28].

Each participant was given five sticker dots and provided with instructions. Participants were asked to reflect on discussions during the focus group and select five treatment benefit attributes that were most important to them by placing a sticker next to them on a flip chart. Participants were not required to allocate all five of their sticker dots. However, they were not permitted to place more than one dot next to a particular attribute. Additionally, participants were asked to select their top treatment benefit attributes which coincides with the number of sticker dots provided[29]. Once the sticker dot voting was complete, the stickers were tallied and the benefit attributes with the most stickers (or votes) were circled. The results of the sticker dot voting activity identified five top benefit attributes, which were confirmed by participants through discussion at the end of the exercise. Importantly, based on the findings from focus groups, sticker dot voting was limited to benefit attributes only (this will be discussed further in the Results section).

Spectrum Surveys

The five 'prioritized' benefit attributes from each sticker dot voting exercise were used to develop survey questions. Survey question content and range (or benefit attribute levels) were based on insights from the rare disease patients and caregivers and were informed by decision support literature[30-33]and health related quality of life (HRQoL) tools[34-37] and resources[38-47].

HRQoL is multidimensional, incorporating physical, mental and social domains[48]. Similar domains have been identified in QoL indicator projects in Canada[49] and Wales[45]. Several HRQoL and well-being assessment tools exist, and although they differ in length and specificity, the domains of HRQoL are consistent. For example, Potoglou, et al., compared

two decision support methods utilizing nine social care and QoL domains including, food and drink, personal cleanliness, accommodation, safety, social participation, occupation, control, dignity, and living in one's own home[31]. Among the findings, Potoglou, et al., suggested that pilot testing be conducted to assess if interactions exist between the attributes[31].

Decision support tools aid individuals in making treatment decisions that align with their personal attitudes, values and preferences[50]. Several decision support methodologies exist and include best worst scaling, discrete choice experiments and bidirectional leaning scales. Best-worst scaling is used to rank two items (the best and worst option) based on their perceived importance[51-53], whereas a discrete choice experiment (DCE) is applied when several preference trade-offs are made, enabling treatment attributes to be measured at one time[54]. A bi-directional leaning scale is used to differentiate between two (or in some cases more) treatment options or attributes at opposite ends of a linear scale[50].

The survey utilized an adapted bi-directional leaning scale approach to elicit perceptions on amounts of benefit gained from a hypothetical treatment. This approach was chosen because it enabled respondents to select from a range of benefit levels across multiple QoL domains. Respondents chose between five levels, ranging from 0% to 100%, increasing in 25% percent increments. For example, an ability to work spectrum would contain labels, such as "unable to work" representing 0%, and "always able to work" representing 100%. A range of health and ability levels was needed to determine the amount of benefit participants expected. To determine the appropriate range (or scale) for the survey questions, decision support literature was used to develop multiple levels of health or ability. Bridges et al, have suggested that a wide range of levels be used even if they are conceptual or do not represent current technology[33]. Three to four levels is recommended, however if eliciting data to support research providing a full range of levels is appropriate[33].

The survey addressed several benefit attributes identified by participants and contained questions pertaining to a patient's current state and a hypothetical future state. Specifically, one question asked about a patient's current ability or health status and the second asked about a patient's future ability or health status. Current status was described as a patient's current disease management (which may or may not include treatment). Future status was described as his or her expectation or goal with respect to health status when treated with a new hypothetical treatment. Respondents who were caregivers completed the questions on behalf of the patient for whom they were responsible. Figure 3 represents the treatment benefit attribute spectra.

Surveys were in paper form and self-administered. Once completed, the participants placed their spectrum surveys into a sealable envelope to be collected by the investigator.

Data Analysis

To explore participants' insights on treatment benefits and harms, the data were analyzed using two approaches, thematic analysis and descriptive statistics.

Focus Groups and Sticker Dot Voting

The results (attribute lists and benefit priorities) emerging from the three fora were compared qualitatively using thematic analyses. The benefits, harms and benefit priorities were placed into separate tables and were manually reviewed by two independent researchers for duplication and data accuracy. Treatment benefit and harm attributes identified by focus groups were then grouped according to theme[55,56]. Similar words and key phrases were grouped revealing themes. Names for themes were created based on the descriptive commonality of the associated attributes. For example, organ health contains attributes related to the function of the internal organs. Constant comparative methods were used to compare previously collected data to new data. Themes were assessed and refined as new themes emerged. Specifically, the first and second focus group data were

compared and then each of those were compared to the third focus group. An iterative approach was used, whereby data already analysed were revisited when a new theme emerged. Treatment benefit and harm attributes were themed (discussed further in the Results section). The treatment benefit and harm attributes and benefit priorities across the fora were compared for similarities and differences. Relationships and inconsistencies across the attributes were highlighted.

Spectrum Survey

Responses to each attribute question on each spectrum survey were analysed using SPSS® Version 22. The expected improvement in health status, or 'benefit expectation' (i.e., the difference between future health status (with a new and effective treatment) and current health status) was first computed for each participant. The median, mean and range of benefit expectation values were then calculated for each attribute across all participants. The median was calculated for each benefit attribute to ascertain the midpoint from a range of values representing the amount of expected treatment benefit. The mean was calculated for each attribute's level of change (from current status (baseline) to future state) to determine the average amount of benefit expected. The range was reported for each attribute to identify the minimum and maximum amount of benefit respondents expected from treatment.

The extent to which values varied by fora location and type of respondent (patient vs caregiver) was explored graphically, as sample sizes were too small to perform quantitative comparative analyses and tests of statistical significance of differences.

Results

Focus Groups

Forty-one participants participated across the three fora. Sixteen participants participated in the Toronto focus group (13 patients; 3 caregivers), 14 in Montreal (10 patients; 4

caregivers) and 10 (9 patients; 1 caregiver) in Vancouver. Toronto focus group participants identified 31 benefit attributes and 50 harm attributes. Participants in Montreal identified 18 benefit attributes and 24 harm attributes. Vancouver participants identified fewer results and reported 15 benefit attributes and 19 harm attributes. Results of the three focus groups are presented in Table 7.

A number of attributes were identified across all three focus groups. These included attaining the functional ability to actively participate in life. Participants aspired to engage in family and work related activities and identified the functional (mental, physical and cognitive) abilities required to do so. Employment related attributes included "return to work", "ability to work", and "able to work". Family focused attributes were "functional family member", "participate as family member", "ability to parent", and "ability to take care of family". Consistent acknowledgement of treatment related adverse event and associated complications were presented by all groups and included "adverse events", "drug interactions", and "adverse drug reactions". Knowledge and understanding of rare diseases or disorders and the availability of associated treatment information were present across the three fora. Participants stated that there is limited availability of disease and treatment information and reported "lack of medical knowledge", "lack of information (drug)", and "lack of outcome measures".

Differences in views across focus groups included the reported effects of treatment on a disease or disorder and treatment characteristics. Participants in Toronto focused on physical and physiological effects of treatment and identified attributes such as "sleep", "blood pressure issues", and "cardiac /stroke". In contrast, Montreal participants focused on treatment characteristics such as "treatment convenience", "route of treatment", "treatment complexity", "length of treatment", and "lack of self-treatment autonomy". Compared to the Toronto and Montreal focus group participants, Vancouver participants identified limited access to healthcare providers ("lack of resources for OT/PT/Speech

Pathologist") and described clinician characteristics they encountered. Reported attributes related to clinician interactions were "wasting clinician time", "[patient] not listened to", "changing clinician mindset", and "look too normal – invisibility of disease". In addition to those attribute differences, a Vancouver participant shifted the focus away from treatment to disease prevention and lifestyle modification ("treatment vs. prevention"; and "everyone looks to drugs vs a change in lifestyle").

Treatment Attribute Themes

In total ten themes were identified. The themes were:

- Independence & Feeling of Contributing
- Mental Health
- Physical Comfort/Exercise/Diet
- Organ Health
- Appearance
- Life & Death
- Disease & Disorder
- Treatment Characteristics
- Pain
- Health Practitioners

Independence & Feeling of Contributing are associated with self-reliance and contributing to the lives of others. Attributes that fit into this theme included "employability", "autonomy" and "participation in organized groups". The *Mental Health* theme described aspects of a person's psychological, emotional and social wellbeing[57] and can include "self-esteem", "reduced anxiety" and "state of worry". The *Physical Comfort/Exercise/Diet* theme described a person's physical health and wellbeing and includes attributes such as "appetite", "muscle strength and "balance". *Organ Health* is associated with the

physiological function of one's body and includes "vision", "balance of hormones", "infertility" and "kidney failure". *Appearance* represented one's external image and presence. Attributes under this theme included "moon-face", "hair growth", and "buffalo hump" which are associated with specific rare diseases. The *Life & Death* theme referred to one's length of life or approach to death and includes attributes like "increased life expectancy", and "exit with grace". *Disease & Disorder* is associated with characteristics of an illness or condition. *Disease & Disorder* attributes included "remission (have or attain)", and "improved health outcomes and conditions". *Treatment Characteristics* referred to the administration, accessibility, and nature of medication and include attributes such as treatment effectiveness, "adverse drug reactions" and access of medications regardless of geographical location. *Pain* represented physical chronic and acute pain or discomfort and can be described as "headaches" and "pain [in general]". The *Healthcare practitioner* theme represented clinician associated characteristics, experiences, or resources. Attributes that fit into this theme included access to allied health professionals and "lack of physician understanding".

Toronto benefit attributes were grouped into eight of the 10 attribute themes, whereas the harms were themed into nine attribute themes. Six themes were applied to Montreal's benefit attributes, while the harms were categorized into seven themes. Corresponding with a lower number of identified attributes, Vancouver's benefits were categorized into four themes and harms into five themes. Table 8 provides an overview of the treatment benefit themes and associated attributes. Table 9 provides an overview the treatment harm themes and related attributes.

The treatment attributes identified in Toronto fit into nine of ten themes. Montreal results fit into eight themes, whereas Vancouver attributes related to five of the themes. The themes *Independence & Feeling of Contributing* and *Mental Health* applied to both the treatment benefits and harms of all three fora. The *Treatment Characteristic* theme applied

to the benefit and harm attributes for Toronto and Montreal but not Vancouver. Differences related to treatment themes were also apparent. Toronto participants reported appearance attributes resulting in an *Appearance* theme which was not mirrored by participants in Montreal or Vancouver. In Montreal, *Pain* was a theme used to describe treatment benefit whereas the *Pain* theme was associated to treatment harm by Toronto participants. *Pain* was not identified as an attribute in Vancouver. *Treatment Characteristics* attributes reported in Toronto and Montreal pertained to receiving treatment, including (i.e. travel, cost), treatment administration (i.e. time, simplicity, route) and adverse events (i.e. drug interactions). Participants in Vancouver responded using broad *Treatment Characteristic* terms as associated harm attributes were research related "lack of outcome measures". Table 10 provides an overview of the treatment benefit and harm themes identified in each fora.

Sticker Dot Voting

Table 11 contains the top five benefit attributes identified during each forum and the number of votes each priority received. Consistencies were identified between two but not all fora. Toronto and Montreal participants prioritized being active family members. Employment was highlighted by Toronto and Vancouver participants and referenced by Montreal participants in "return to normal life (education, family, play, career, planning)".

Priorities identified by participants in Vancouver focused on current health capacity and health state objectives ("improved health conditions and outcomes" and "health state stays stable") while participating in enjoyable life activities ("participate in things that bring joy" and "able to work"). The Montreal participants emphasized that treatments be uncomplicated and easy to manage ("simplicity of treatment"). Montreal participants also prioritized a reduction of "acute and chronic" pain and discomfort ("pain relief").

Spectrum Surveys

In total, 22 completed spectrum surveys were returned and represent 14 patients (63%) and eight caregivers (37%). Twelve participants (55%) completed the survey in Toronto; six patients and six caregivers. Montreal participants completed eight surveys (36%), six patients and two caregivers. In Vancouver two surveys were completed (9%), both of them by patients. The participants reported their disease or disorder on the survey. Participants were affected by the following diseases and disorders:

- Thalassemia Major (1) – is a genetic blood disorder characterized by fewer hemoglobin and red blood cells than normal[58]
- Ectopic Cushings Syndrome (2) – occurs when the adrenocorticotropic hormone is release by tumors in the body and not by the pituitary gland[59]
- Acromegaly (2) – is an adult hormonal disorder that develops when pituitary gland produces too much growth hormone[58]
- Asperger's Syndrome (1) – is a term used to describe Autism spectrum disorder and is defined as a serious neurodevelopmental disorder that limits a child's ability to communicate and interact with others.[58]
- Panhypopituitarism (4) – is a disorder where the pituitary gland makes little or no hormones[58]
- Phenylketonuria (1) – an illness that causes an accumulation of amino acid in the body[58]
- Atypical Hemolytic Uremic Syndrome (1) – is an disease of the kidneys where blood clots form and restrict or block blood flow causing end stage renal disease[60]
- Atypical Amyotrophic Lateral Sclerosis (1) – is an illness that effects the motor neurons of the brain or spinal cord responsible for controlling muscle movement and strength[60]

- Aplastic Anemia (1) – an illness that can develop at any age it is a condition that occurs when the body stops producing enough blood cells[58]
- Hemophilia B (1) – is an illness affects the blood's ability to clot due to an insufficient amount of clotting factor IX[58]
- Chiari Malformation, Syringomyelia, Elhers-Danlo Syndrome (2) – A Chiari malformation is a condition where brain tissue extends into the spinal canal[58], Syringomyelia is an illness associated with Chiari and is characterized by the development of a fluid filled cyst is within the spinal cord[58], Elhers-Danlo syndrome is a group of inherited disorders that affects the body's connective tissues including the skin, joints and blood vessel walls[58]
- Haemophilia (1) – an inherited blood clotting disorder[58]
- Fabry (2) – an illness that begins in childhood, it is described as an inherited disorder that effects different parts of the body and results from the accumulation of a type of lipid[60]
- Duchenne Muscular Dystrophy (1) – is an illness that effects mostly males and causes progressive muscle weakness[58]
- Primary Myelofibrosis (1) – is an illness characterized by the formation of scar tissue in the bone marrow limiting the body's ability to produce blood cells[60].

Figures 4 through 12 graphically represent the results of the spectrum surveys (i.e. Activities, Life Years, Social Contact, Work & School, Independence, Emotional, Cognitive Ability, Mobility, Pain). The survey used in Toronto did not include mobility and pain attribute spectra since those attributes were not identified by participants as benefit priorities. This resulted in a lower number for those spectra.

The average amount of *Activity* benefit expected to gain was 27%, as most participants sought 25% gain from new treatment. For *Life Years*, 10 out of 18 participants selected the same response for current and future state. Of the 10 participants, eight of them selected

the maximum amount of life years as they expect to live an additional 60 years with or without the new hypothetical treatment. The average expected amount of life years gained was 10.6. A twenty-five percent gain was reported for the *Social Contact* mean and median values. Although *Work & School* elicited a median of 25% and mean of 38% gain, this attribute exhibited the widest range of results. Four participants selected 100% gain on the *Work & School* spectrum, representing a change from 0% for baseline (i.e. "unable to work or attend school") to 100% for future state (i.e. "to always work or attend school"). The *Independence* attribute displayed varied responses. Although the mean and median were similar, participant results were spread across the benefit gain scale. Participants primarily selected 75% as baseline and chose the same value for their future state or expected a 25% gain resulting in complete independence (100%). Participants selected an average of 33% gain and 25% median for the *Emotional* attribute. Although the *Emotional* spectrum produced one 100% expected gain. When comparing expected benefit gain ranges, the rest of the results were more homogenous compared to other attributes. Most participants selected a range of 25% (n=9) or 0% (n=10) for *Cognitive Ability.* Vancouver and Montreal forum participants chose between 0-25% *Mobility* gain, as five of the 10 participants identified maximum benefit at baseline. Participant pain levels varied as the heterogeneity of responses ranged from excruciating pain to no pain resulting in a median of 25% and mean of 28%.

Baseline values of 50%-75% were primarily reported by participants in five of nine attribute spectra (i.e. "Activities", "Social Contact", "Independence", "Emotional", and "Cognitive"). At baseline, participants stated that they could do some or most activities, occasionally experienced loneliness or not at all, were mostly independent, experienced disappointment, frustration or optimism and contentment, and were occasionally or rarely confused. Most of the participants selected future state values of 75%-100% in seven of 12 attribute spectra (i.e. "Activities", "Life Years", "Social Contact", "Work & School", "Independence",

"Emotional", "Cognitive Ability"). Participants indicated that they expected future treatment would enable them to participate in most or all activities; not experience loneliness and enable them to connect with others frequently, attend work and school often or always, be mostly or completely independent, feel hopeful, happy and enthusiastic, and would rarely experience confusion while applying critical and flexible thinking. Dependent on baseline age, the "Life Years" future state indicated 60 more years of life was sought by the majority of participants. In general, the differences between baseline and future state values indicated participants seek 25%-50% improvement or gain from new treatments. Of the 168 participant responses, the majority of survey results fell within a 0% to 75% range. Five of the 168 responses (3%) identified a 100% range from baseline to future state.

The "Life Years" and "Cognitive Ability" spectra indicated the highest number of same value results, as 44% of participants chose "60 more years of life" and 45% of participants selected "purposeful and appropriate, critical and flexible thinking" for baseline and future states. Participants reported the maximum baseline and future state values, indicating their current status is optimal and no further improvement is expected.

For the attributes related to mental health, *Emotional, Social Contact* and *Cognitive Ability* participants' responses were homogenous. Between the three mental health attributes, most respondents selected a 25% to 50% gain from treatment and 82% of participants selected the maximum level of benefit gain. An increased ability to take part in *Activities* compared to *Work & School* was reported by participants and identified by the variability in benefit gains associated with those attributes. Fifty-nine percent of participants selected 25-50% gain for *Activities* vs. 29% of participants in *Work & School*. *Work & School* elicited several 75% and 100% gain responses (33%), whereas participants selected 75% gain range 9% of the time for *Activities*. The *Mobility* and *Independence* attribute results were similar for Vancouver and Montreal participants, where the expected benefit ranges were "no change" for both attributes, 60% and 50% respectively. Participants indicated they

were mostly independent or completely independent, requiring no assistance to participate in daily events. These results correspond to the range of pain reported by participants. Vancouver and Montreal participants sought increased expected benefit gains for *Pain* as 67% percent of participants desired 25-75% benefit gain resulting in either no pain or minor pain not requiring treatment.

Overall, there were no large differences between the patient and caregiver responses based on the small number of participants and the variety of illness represented. However the *Work & School* caregiver responses indicated a higher range average compared to patients (44% vs. 35%).

Fifty-five percent of participants completed all of the questions. The expected benefit gain range is reported between 50% and 100% across the nine attributes. The most common amount of expected benefit gain is 25% (median) as represented in seven of the nine (78%) attributes. The average amount of expected benefit gain ranged between 12.5% *Mobility* level and 38.1% in ability to attend *Work & School*. The expected average amount of *Life Years* gained was 10.6. Table 12 provides an overview of the descriptive statistics associated with the spectrum survey.

Discussion

Overarching comments indicated a belief that treatment enables participants to live their lives and actively participate within their contexts. Respondents also identified physiological and psychosocial attributes, pertaining to the self, others, and society. Similar attributes were reported by rare disease patients in the study conducted by the Genetic Alliance UK[15] and benefit priorities identified by rare disease patients and caregivers, including HRQoL[31,42] and PRO[43] domains found in the literature.

Across all fora, participants identified 13 treatment benefit priorities, including the ability to participate in activities that bring joy, functional ability (cognitive and physical), life

expectancy, mental health, employment, functional family member, return to normal life, pain relief, improved health outcome and conditions, access to knowledge, treatment simplicity, and health state stability. This compares to the findings of Szende, Leidy and Revicki who explored how HRQoL and patient reported outcomes (PROs) have been utilized by EMA in decision-making and found the following domains were included in efficacy endpoint discussions: "patient reported symptoms, discomfort, pain, disability, physical functioning, general well-being and patient's global assessment of improvement"[42(p539)]. In the present study, important treatment factors identified by participants informed the development of attribute spectra. However, this is not always the case when developing PRO instruments. Exploring the creation of measurement instruments, McKenna found that PRO measurement literature pertaining to chronic diseases often describes how to measure a dimension, but there is little agreement on which dimensions assessments should be included[43]. In reference to the regulatory context, Bottomley, Jones and Claassens reported that the FDA plans to assess patient involvement in instrument development to determine the appropriateness and meaningfulness of the domains[61]. Decision makers are seeking treatment benefit outcomes that are relevant and important to rare disease patients[62], supporting the need for further investigation to determine if treatment nuances unique to rare disease patients are captured by current PRO and HRQoL measurement tools.

The survey results indicated significant variation for current and future status within each attribute, between the attribute spectra, and across participants. Such variation may be explained, in part, by heterogeneity in participants. There were many rare disease types represented by participants. The participants collectively experience illnesses and conditions that affect multiple body systems and structures, including endocrine, blood, pituitary, developmental, genetic, neurodegenerative, connective tissue, brain, lysosomal, muscle and bone marrow. Some participants suffered from the same illness. However, Wyrich and Vernon found that variation exists between rare diseases and among those

suffering from the same rare disease[62]. Participant illness complexity and symptom intensity may also contribute to the varied benefit ranges. Gagnier suggests that disease severity can cause variation in how treatment effects patients[63].

The benefit spectra were developed based on the insights of a diverse group of people representing a variety of illnesses. As such, there is a possibility that the spectra were not relevant to each rare disease. Bottomley, Jones and Claassens say "questionnaire development should match the characteristics of the target population"[61(p348)]. Chassany asserts that a tool must be selected based on its appropriateness for an illness and associated treatment[39]. McKenna agrees that disease specific tools be applied to elicit relevant and meaningful outcomes of particular patient groups ensuring their needs are focused on[43]. The inclusive approach to involve multiple rare disease types in determining benefit attribute priorities may have genericized the survey to the point that its relevance to individual rare diseases became limited. Patients and caregivers provided their perceptions of benefit priority and expectation inclusive of their personal values, preferences, treatment experiences and disease context. Further exploration is warranted to determine if patients recognize benefit attribute priorities different from caregivers and across diseases.

Although the hypothetical treatment future states elicited a benefit range between 0% and 100%, the most common range of benefit was 25% and 50%. Most future state responses represented the maximum amount of expected benefit as participants hope treatment will significantly affect their condition and QoL. Hoffman and Del Mar suggest that an overestimation of treatment benefit contributes to the psychological needs of an individual providing "hope, safety, a sense of control, action, and reassurance"[64(p283)]. Confidence in treatment benefit potential could result in increased treatment requests and prescription resulting in increased cost. Another cause of heightened benefit range could be due to a lack of disease knowledge, identified as a harm by participants. Weeks, et al. assert that an

overestimation of disease prognosis or lack of prognosis understanding affects one's treatment decision-making[65].

Limitations

There were several limitations, including a mixed respondent population. Although the majority of respondents were patients, caregivers who participated may have differing views based on their rare disease context. Conducting more homogenous focus groups (patients separate from caregivers) could help to inform perceptions of treatment benefit for each respondent group. Additionally, the focus groups did not achieve saturation and responses varied across the cities. The differences between the focus group responses were not explored in detail due to the inability to conduct additional focus groups in different cities or to reconvene the previous focus groups in Toronto, Montreal and Vancouver.

Conclusion

Over the last decade, patient involvement in health care has evolved to span multiple health contexts, including the regulatory approval of new therapies. This research identified multiple physiological and psychosocial treatment benefits and harms and benefit priorities of importance to rare disease patients and caregivers. Based on the findings, a single survey may not be appropriate for use with diverse groups of rare disease patients. Multidimensional tools are recommended to capture rare disease perceptions of treatment benefit and harm. The unique nature of rare diseases and their effect on individuals requires that future treatment benefit and harm research within specific rare disease types needs to be done. The present study contributes to the small body of literature on patient perceptions of treatment benefits and harms, which may help inform the regulatory process and treatment development.

Table 7. Treatment attributes brainstormed using focus groups in three Canadian cities

Treatment Uncertainty	Toronto	Montreal	Vancouver
	Brainstorming	Brainstorming	Brainstorming
Benefits	• Empowerment • Increased life expectancy • Participation in life • Productivity • Return to work • Functional family member • Self esteem • Functional (cognitive) • Tolerance for exercise • Hope • Skin tone/turgor • Employable • Mobility • Vision • Organized groups • Better/more sleep • Increased energy • 14 hours of function • Better memory • Remission (have or attain) • Less time needed for treatment • Weight stability • Possibility of transplant • Balance of Hormones • Control of Depression • Better Digestion • Well being • Appetite • Physiotherapy • Balance • Muscle Strength	• Pain decreases (pain relief) • Functional (physical) • Autonomy • Return to normal life • Longer life • Ability to plan life • Reduction of life uncertainty • Ability to work • Improves ability to cope • Mental Health • Decreased Financial burden • Participate as Family member • Physician understanding • Improving continuing of care (ability for transference across Canada) • Self-image • Simplicity of Treatment • Exit with Grace • Increasing certainty of treatment effectiveness	• Clinician Support • Ability to take care of family • Improved health outcome and conditions • Functional (physical and cognitive) • Happy • Able to work • Feeling of security • Participate in activities that bring joy • Health state stays stable • Disease advocacy • Ability to participate in research • Access to knowledge • Ability to Parent • Empowered to make a difference • Fit into Society
Harms	• Lack of Medical Knowledge • Lack of motivation • Buffalo Hump • Moon-face • Liver Toxicity • Reflux • Skin thinning • Strain on Relationships • Anxiety • Kidney Failure • Morbidity • Isolation • Sleep Apnea • Electrolyte Imbalance • Renal Insufficiency • Diabetes • Bruising • Self-worth • Stress • Blood Pressure Issues • Mobility • Disability • Loss of income • Tumor types • Impatience • Restless Leg Syndrome • Cardiac / Stroke • Stretch marks • Head aches • Migraines • Blindness • Frustrations • Confusion • Loss of Consciousness • Pain • Depression • Slurred speech • Infertility • Anti-social • Anger • Access to meds • Fatigue • Mood swings • Activities of daily living • Adverse Events • Hair Growth • Osteoporosis • Inability to work • Muscle Mass • Weight Fluctuations	• Pain (chronic and acute) • Lack of physician understanding • Fatigue • Weakness • Treatment complexity • Gastrointestinal bleeding • Route of Treatment • Functionality • Length of Treatment • Working (consistency and stability) • Kidney failure • Organ System Failure • Lack of self-treatment autonomy • Treatment convenience • Mental Health • Living moment to moment • Feeling of failure • Drug interactions • Labs (blood work, biomarkers, etc) • Appointments • Lack of follow up • State of worry • Sleep • Lack of information (drug)	• Drug Coverage • Cost • Lack of outcome measures • Diagnosis confusion • Awareness of illness • Lack of disease knowledge • Social Stigma • Isolation • Work time affected • Adverse drug reactions • Wasting clinician time • Changing mindset of clinicians • Treatment vs. Prevention • Patient not listened to • Look too normal (invisibility of disease) • Everyone looks to drugs vs a change in lifestyle • Lack of resources for OT/PT/ Speech Pathologist • Travel required • Burden of Illness

Table 8. Treatment Benefit attribute themes across the fora

	Toronto	Montreal	Vancouver
Treatment Benefits	• **Independence & Feeling of Contributing** o Participation in Life o Productivity o Functional family member o Employable o Return to work o Functional(cognitive) o Participate in organized groups • **Mental Health** o Empowerment o Self Esteem o Hope o Better Memory o Depression Control o Well being • **Physical Comfort/Exercise/Diet** o Weight Stability o Appetite o Balance o Mobility o Muscle Strength o Better/more sleep o Tolerance for Exercise o 14 hours of function o Increased Energy o Physiotherapy • **Organ health** o Vision o Balance of Hormones o Better Digestion • **Appearance** o Skin tone and turgor • **Life & Death** o Increased Life Expectancy • **Disease & Disorder** o Remission (have or attain) o Possibility of transplant • **Treatment Characteristics** o Less time needed for treatment	• **Independence & Feeling of Contributing** o Autonomy o Functional(physical) o Return to normal life o Decreased financial burden o Participate as family member o Ability to work o Ability to plan life • **Mental Health** o Improves ability to cope o Mental Health o Self-Image • **Life & Death** o Longer Life o Exit with Grace o Reduction of life uncertainty • **Health Practitioners** o Physician understanding of disease • **Pain** o Decreased Pain (Pain Relief) • **Treatment Characteristics** o Simplicity of Treatment o Increasing the certainty of treatment o Improving the continuity of care (transference of treatment across Canada)	• **Independence & Feeling of Contributing** o Ability to take care of family o Functional(cognitive and physical) o Able to work o Ability to parent o Disease advocacy o Empowered to make a difference • **Mental Health** o Happy o Feeling of security o Fit into society o Participate in activities that bring joy • **Disease & Disorder** o Improved health outcomes and conditions o Stable Health State o Ability to participate in research o Access to knowledge • **Health Practitioners** o Clinician support

Table 9. Treatment harm attributes themes across the fora

	Toronto	Montreal	Vancouver
Treatment Harms	• **Independence & Feeling of Contributing** o Loss of Income o Inability to work o Activities of Daily Living • **Mental Health** o Lack of Motivation o Anxiety o Isolation o Self-worth o Stress o Impatience o Frustrations o Depression o Antisocial o Anger o Fatigue o Mood swings o Confusion o Strain on Relationships • **Physical Comfort/Exercise/Diet** o Sleep Apnea o Restless Leg Syndrome o Loss of Consciousness o Weight Fluctuations o Mobility o Disability o Muscle Mass o Reflux • **Organ Health** o Liver toxicity o Kidney failure o Renal insufficiency o Electrolyte imbalance o Diabetes o Blood pressure issues o Cardiac / stroke o Blindness o Infertility o Osteoporosis • **Appearance** o Buffalo Hump o Moon-face o Skin Thinning o Bruising o Stretch Marks o Hair Growth • **Pain** o Headaches o Migraines o Pain (in general) • **Treatment Characteristic** o Access to Medications o Adverse Events • **Life & Death** o Morbidity • **Disease & Disorder** o Tumor types o Loss of Consciousness o Slurred Speech o Lack of Medical knowledge	• **Independence & Feeling of Contributing** o Inability to work consistently o Functionality • **Mental Health** o Fatigue o State of worry o Mental health o Feeling of failure o Living moment to moment • **Physical Comfort/Exercise/Diet** o Weakness o Sleep • **Organ Health** o Gastrointestinal bleeding o Kidney Failure o Organ System Failure • **Pain** o Chronic and Acute Pain • **Treatment Characteristics** o Time required o Treatment Route o Lack of Self Treatment Autonomy o Treatment convenience o Treatment complexity o Lab work o Drug interactions o Appointments o Lack of information (drug) • **Health Practitioners** o Lack of Physician understanding o Lack of follow up	• **Independence & Feeling of Contribution** o Work time affected • **Mental Health** o Social Stigma o Isolation • **Treatment Characteristics** o Lack of Outcome measures o Adverse Drug Reactions o Cost o Drug coverage o Treatment vs. Prevention o Everyone looks to drugs vs. change in lifestyle o Travel required • **Disease & Disorder** o Diagnosis Confusion o Awareness of illness o Lack of Information o Lack of disease knowledge o Burden of Illness • **Healthcare Practitioners** o Changing mindset of clinicians o Wasting Clinician Time o Patient not listened to o Look to normal (disease invisible) o Limited access to OT/PT/Speech Pathologist

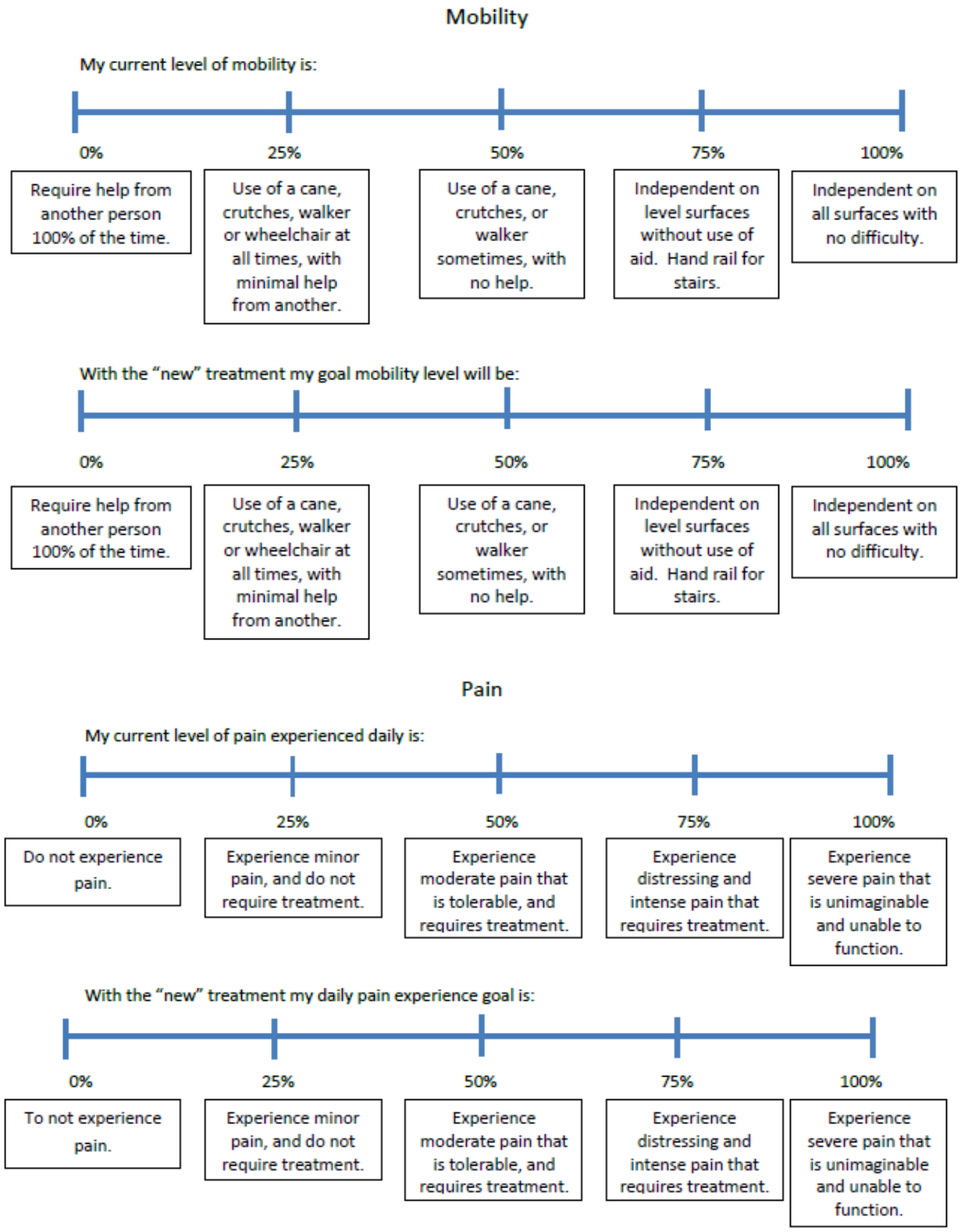
Table 10. Treatment benefit and harm attribute themes identified across the fora

Treatment Attributes Themes		Toronto	Montreal	Vancouver
Benefits	Independence & Feeling of Contributing	X	X	X
	Mental Health	X	X	X
	Physical Comfort/Exercise/Diet	X		
	Organ Health	X		
	Appearance	X		
	Life & Death	X	X	
	Disease & Disorder	X		X
	Treatment Characteristics	X	X	
	Pain		X	
	Health Practitioners		X	X
Harms	Independence & Feeling of Contributing	X	X	X
	Mental Health	X	X	X
	Physical Comfort/Exercise/Diet	X	X	
	Organ Health	X	X	
	Appearance	X		
	Life & Death	X		
	Disease & Disorder	X		X
	Treatment Characteristics	X	X	X
	Pain	X	X	
	Health Practitioners		X	X

Table 11. Prioritized treatment benefit attributes determined using sticker dot voting

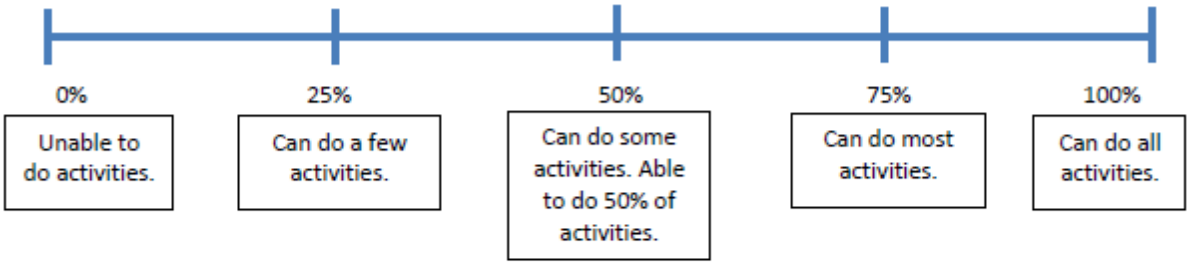
Treatment Uncertainty	Toronto		Montreal		Vancouver	
	Top 5 Priorities	Votes (N)	Top 5 Priorities	Votes (N)	Top 5 Priorities	Votes (N)
Benefit Attributes	Increased life expectancy	5	Return to normal Life (education, family, play, career planning)	7	Improved health outcome and conditions	7
	Functional (cognition)	4	Functional (Physical)	6	Able to work	5
	Control of depression	3	Pain decreases / relief	6	Health state stays stable	5
	Return to work	3	Simplicity of treatment	4	Participate in things that bring joy	4
	Functional family member	3	Participate as Family member	4	Access to Knowledge	4

Figure 3. Treatment benefit attribute spectra

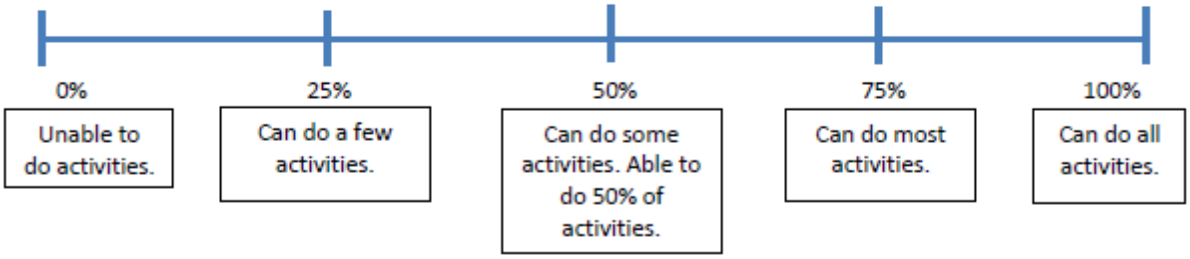


Activities

My current ability to do activities* is:



With the "new" treatment, my activities* level goal is:

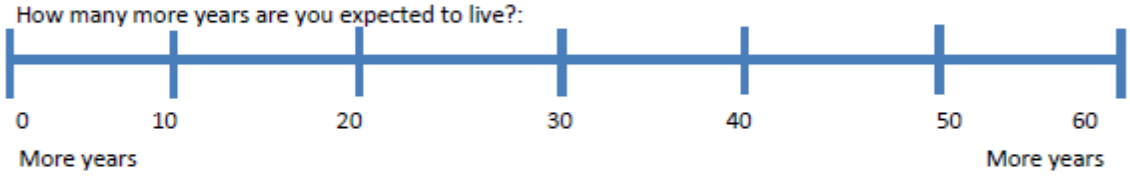


* Activities include, spending time with family and friends, doing leisure activities like sports, reading books, going for tea or coffee, etc.

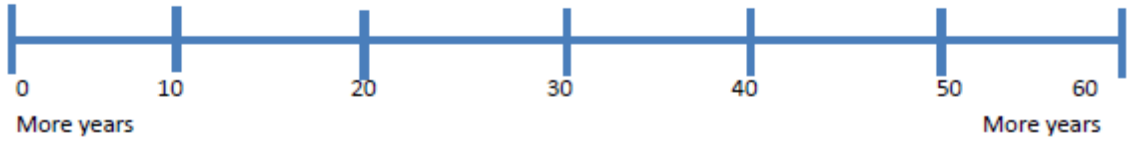
Life Expectancy

Do you have a disease/disorder that affects your life span?_____

How many more years are you expected to live?:

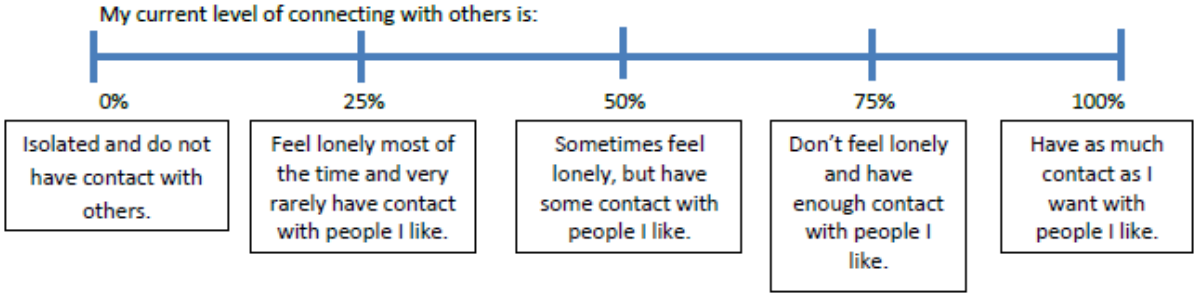


With the "new" treatment, how many more years of life would you expect to gain?:

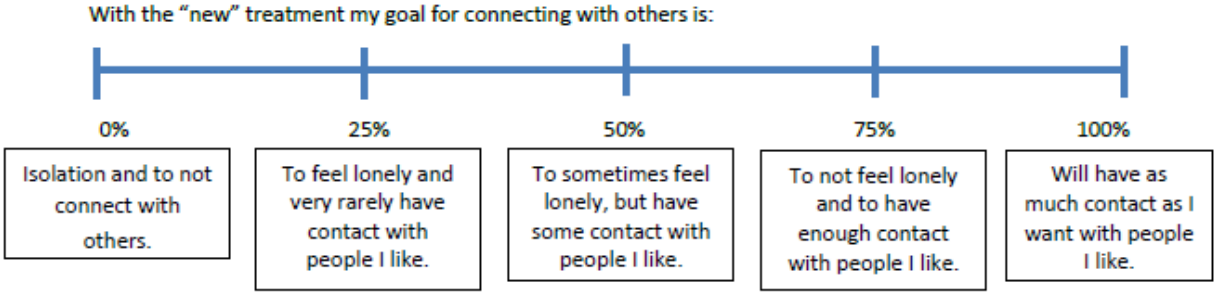


Social Contact

My current level of connecting with others is:

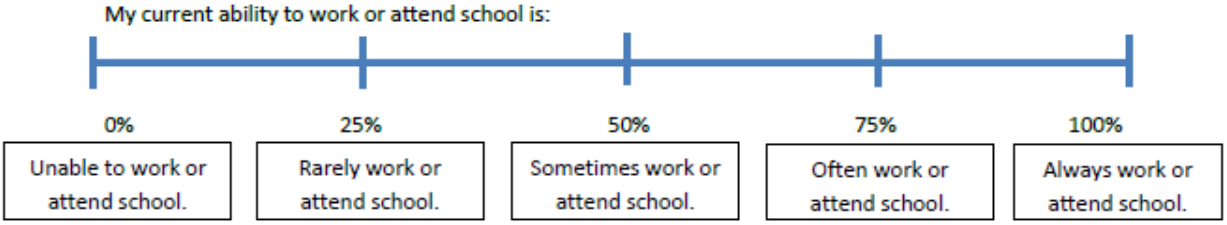


With the "new" treatment my goal for connecting with others is:

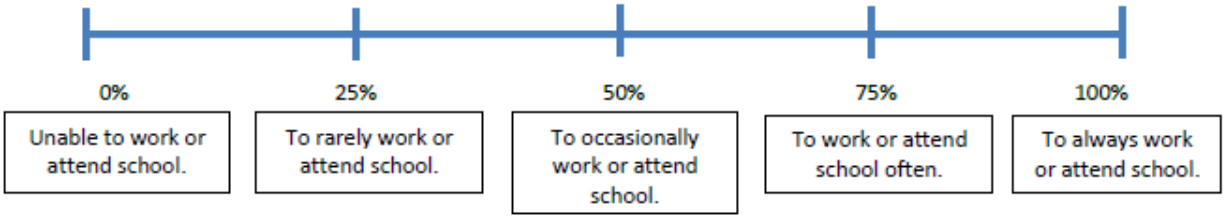


Work/School

My current ability to work or attend school is:

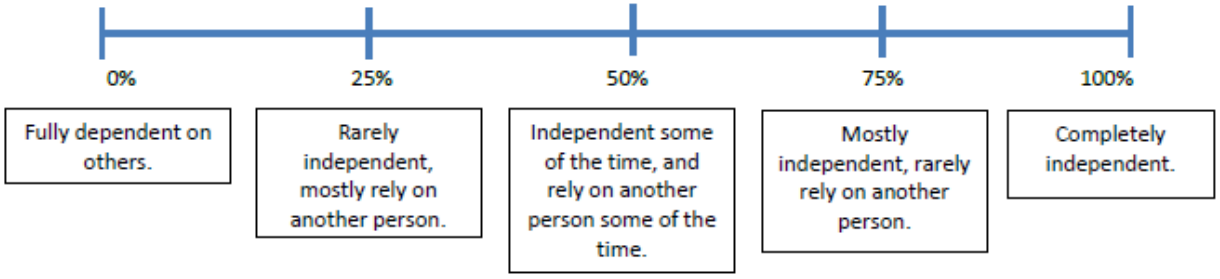


With the "new" treatment my goal for working or attending school is:

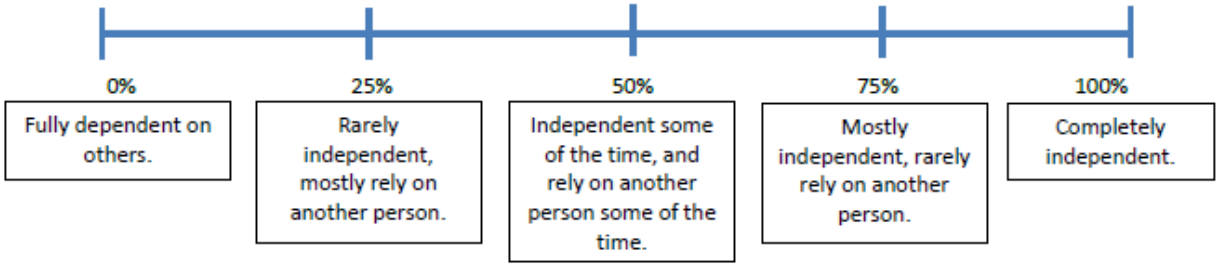


Independence

My current level of daily independence is:

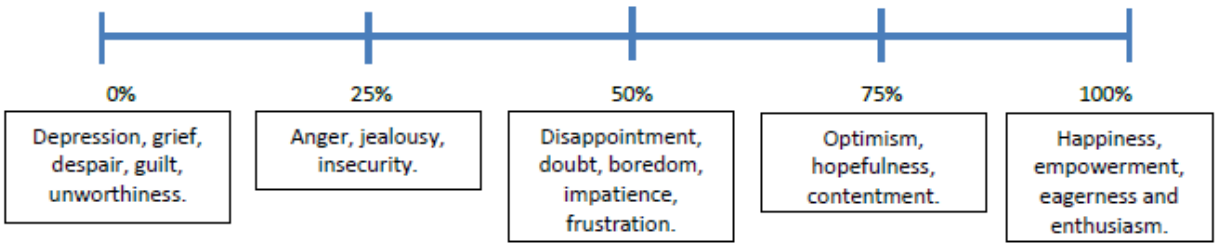


With the "new" treatment, my goal level of independence is:

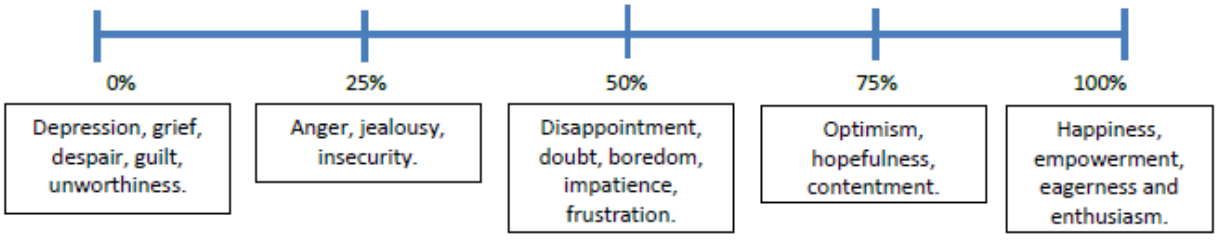


Emotional

My current emotional state is:

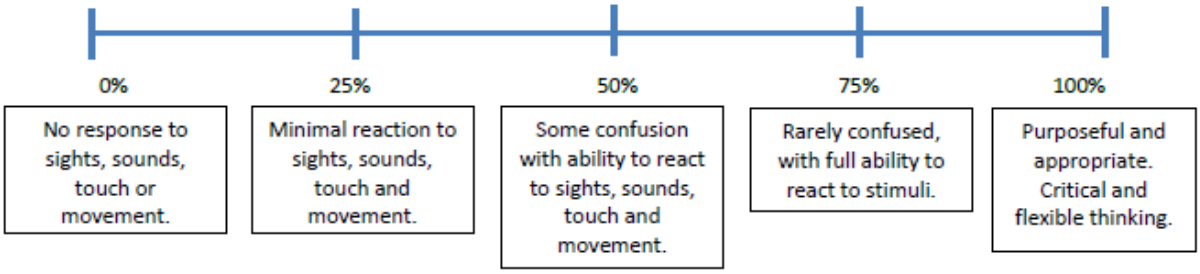


With the "new" treatment, my goal emotional state is:



Cognitive Ability

My current cognitive ability is:



With "new" treatment, my goal cognitive ability is:

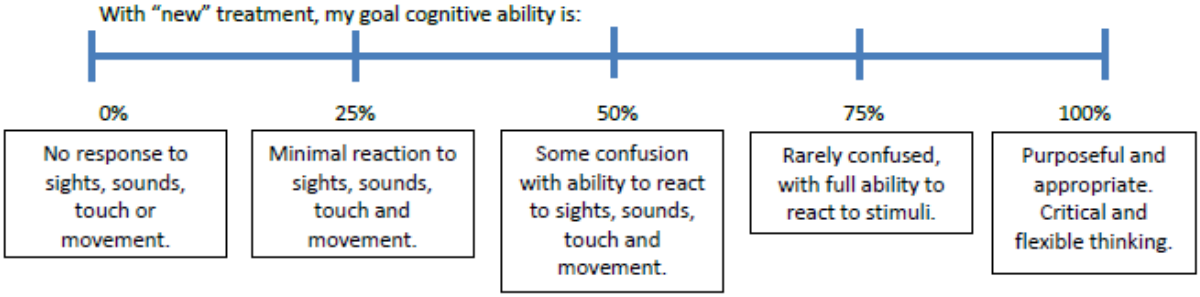


Figure 4. Treatment benefit attribute spectrum - activities

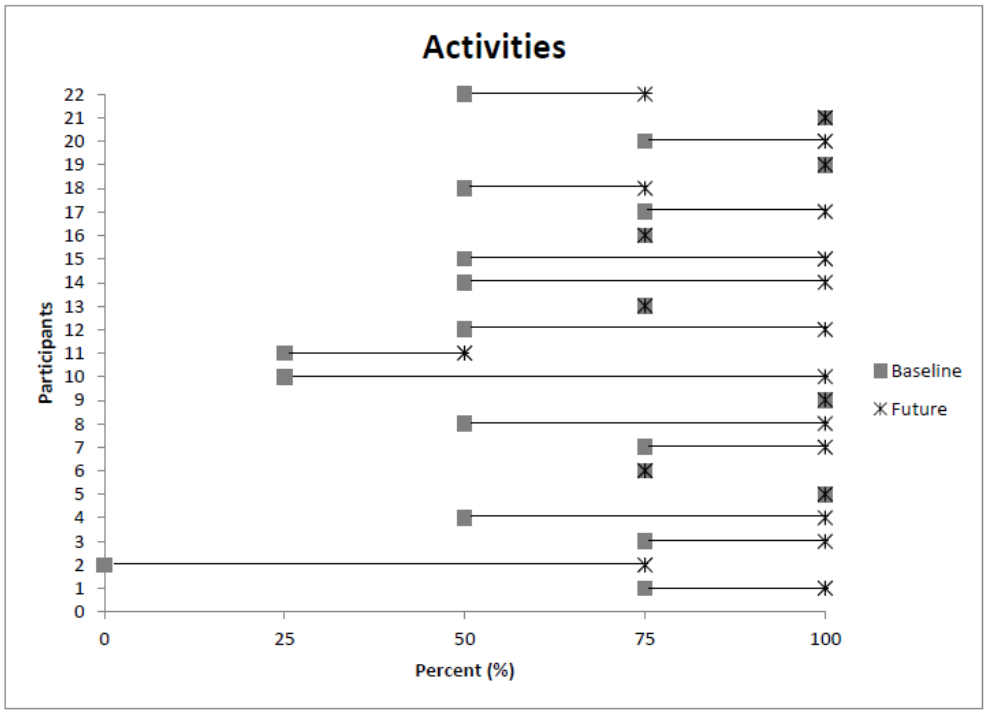


Figure 5. Treatment benefit attribute spectrum - life years

Figure 6. Treatment benefit attribute spectrum - social contact

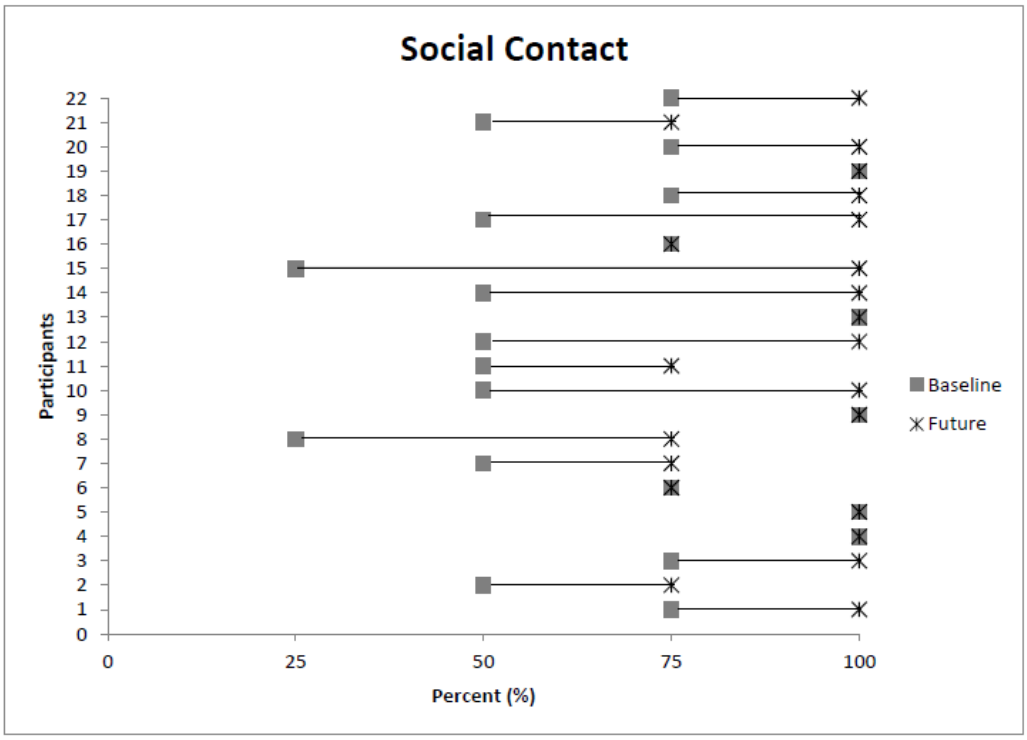


Figure 7. Treatment benefit attribute spectrum - work & school

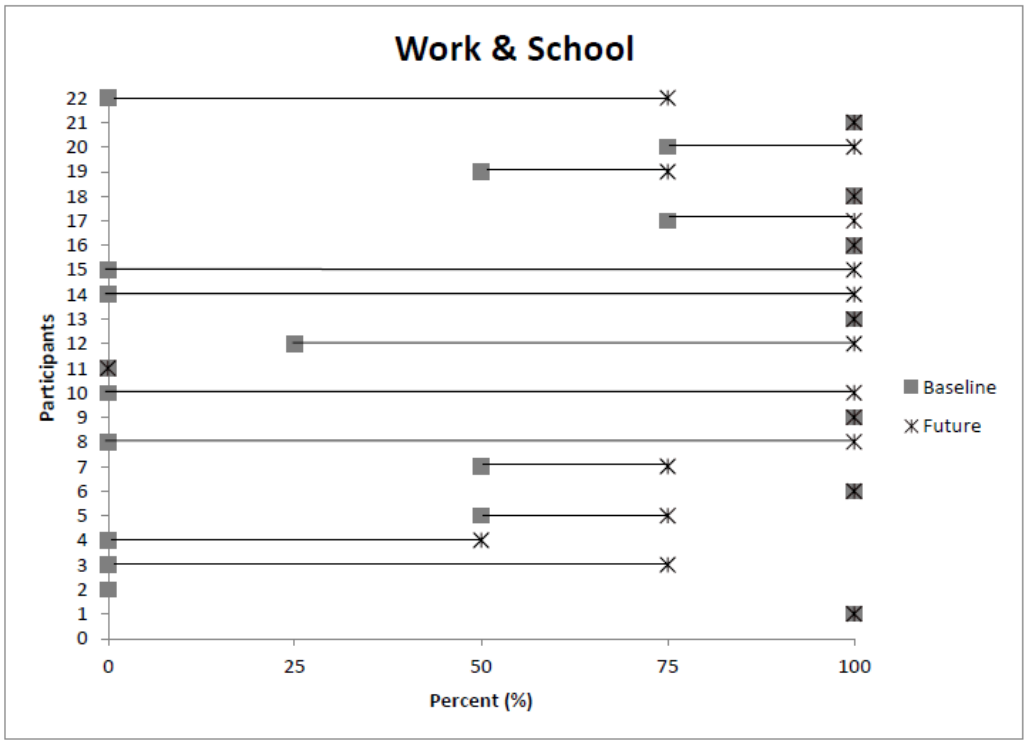


Figure 8. Treatment benefit attribute spectrum - independence

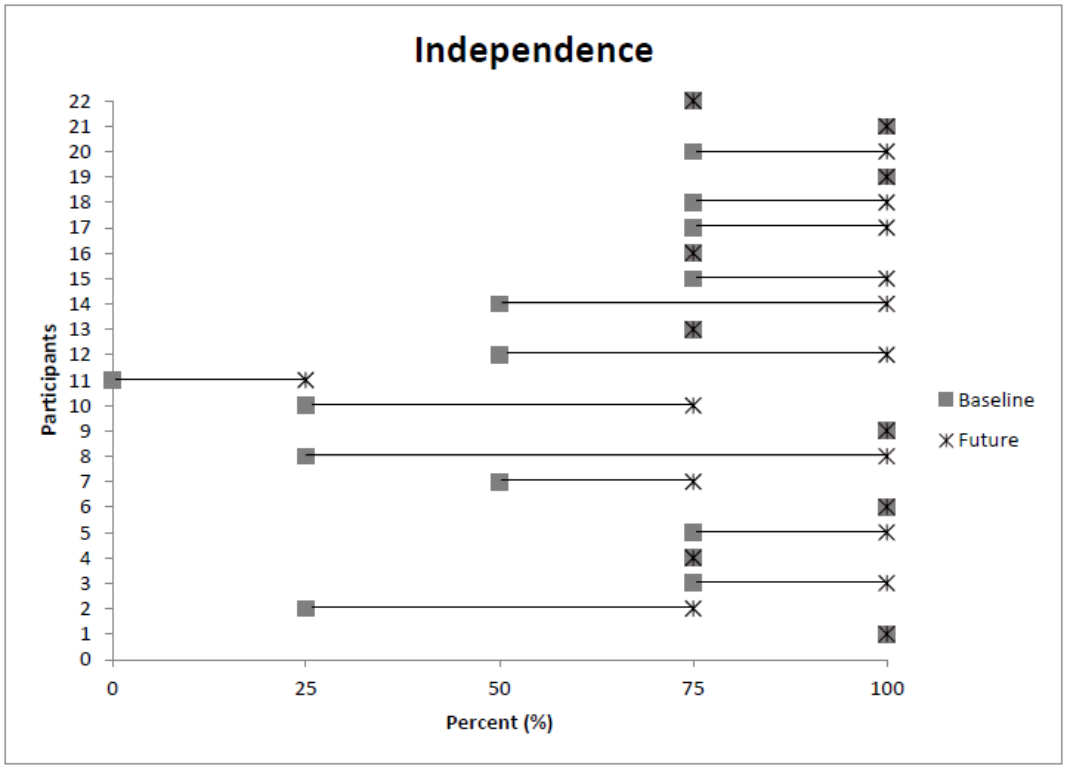


Figure 9. Treatment benefit attribute spectrum - emotional

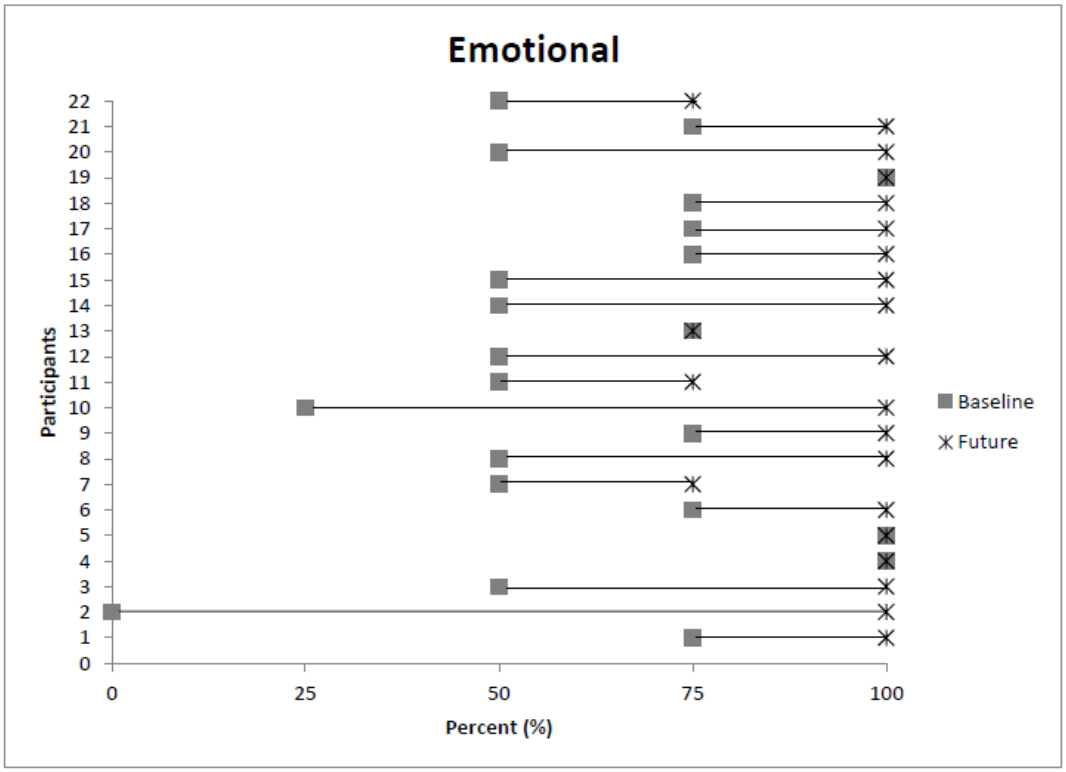


Figure 10. Treatment benefit attribute spectrum - cognitive ability

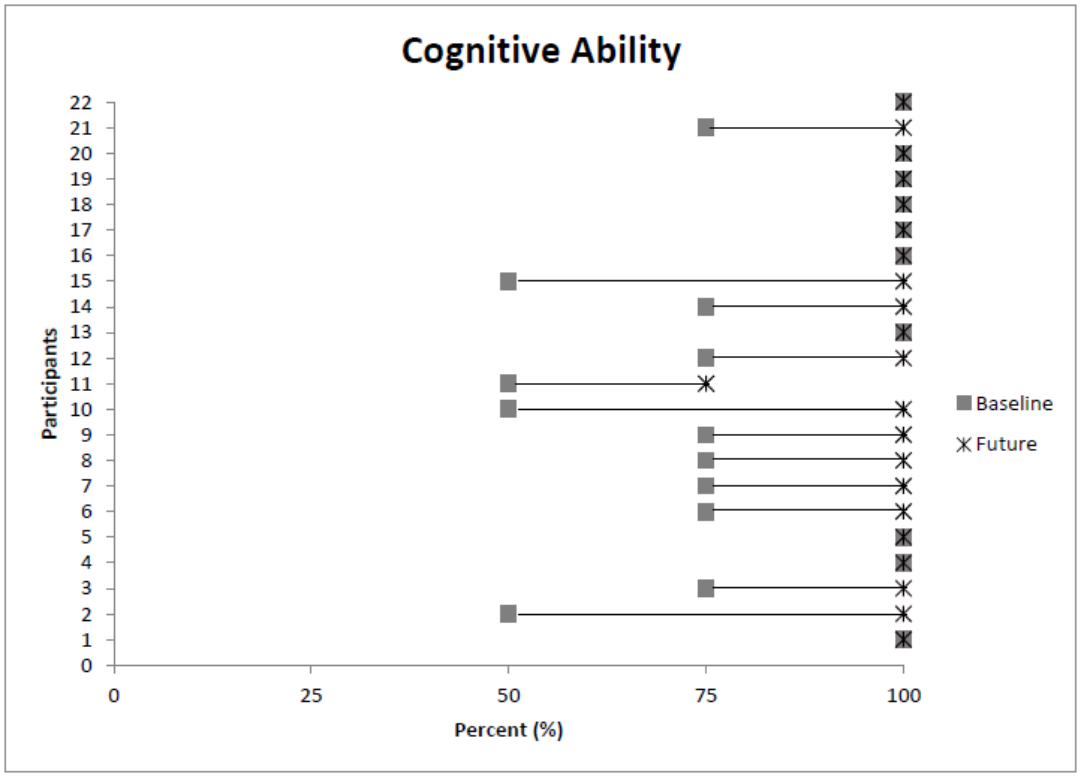


Figure 11. Treatment benefit attribute spectrum - mobility

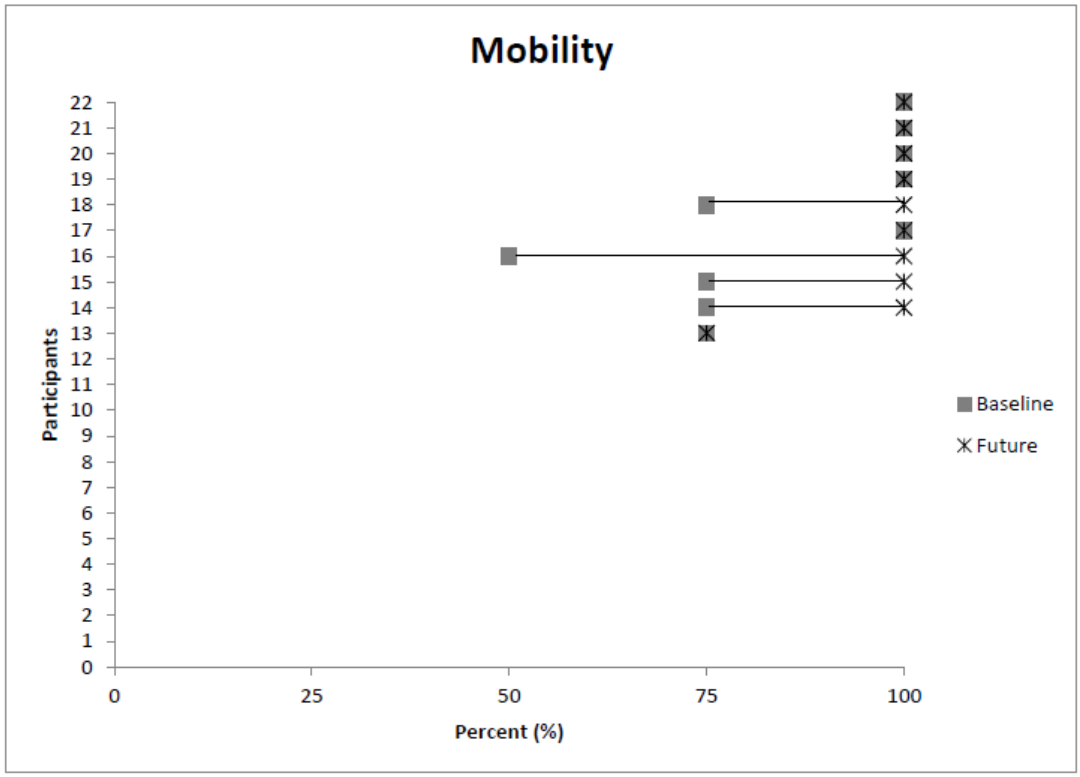


Figure 12. Treatment benefit attribute spectrum - pain

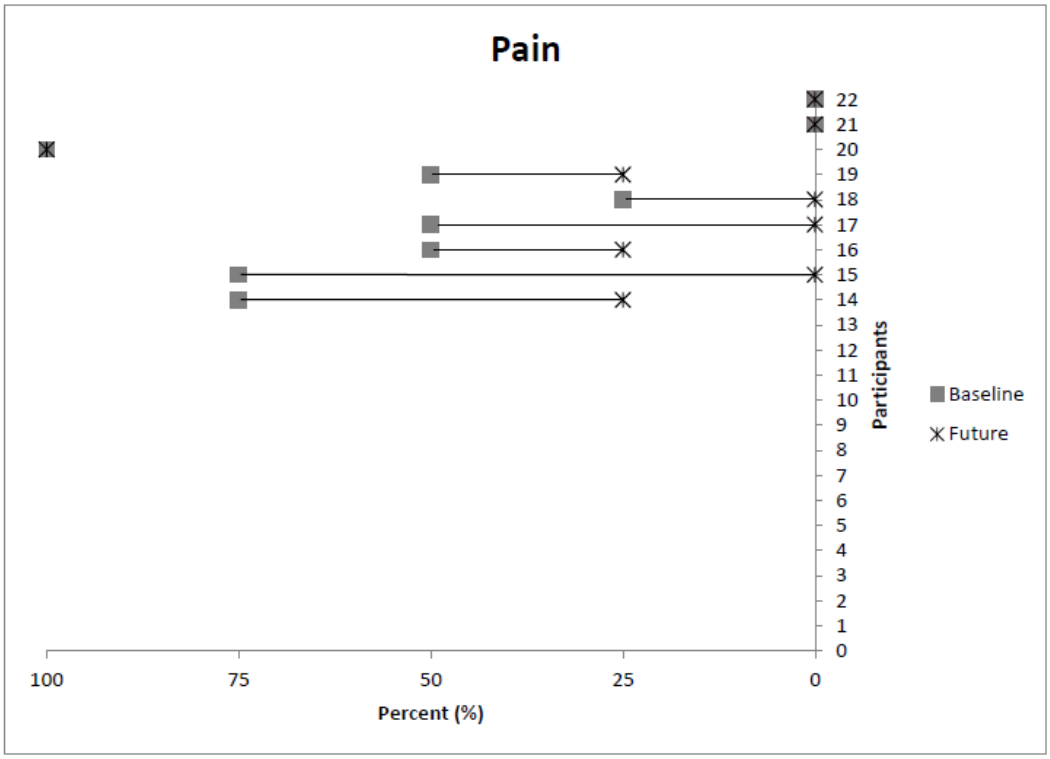


Table 12. Spectrum survey descriptive statistics

Attributes	N[a]	Range	Mean	Median
Activities	22	75	27.27	25
Life Years	18	50	10.56	0
Social Contact	22	75	25.00	25
Work & School	21	100	38.10	25
Independence	22	75	21.59	25
Emotional	22	100	32.95	25
Cognitive Ability	22	50	17.05	25
Mobility	10	50	12.50	0
Pain	9	75	27.78	25

a Number of respondents

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Chapter 3. Testing a survey in a rare disease population to assess harm tolerance while varying types and amounts of benefit

Introduction

Rare diseases include a complex mosaic of conditions[1] and are defined in Europe as illnesses that affect less than five in 10,000 people[2] and often represent a "life threatening or chronically debilitating, progressive condition"[3(p1)]. Recently, patient organizations and regulatory bodies have contributed to the advancement of rare disease research and therapy development. This advancement has occurred by involving patients in a variety of ways. Despite progress, challenges remain. Regulatory bodies are faced with limited knowledge of rare diseases, lack of treatment options and few assessments of patient perceptions on medical treatment benefit expectations and harm tolerances[1].

Assessing benefit and harm tolerances is not an exact science because evidence rarely demonstrates certainty about treatment effects[4]. Factors that influence treatment benefit and harm uncertainties involve evidence validity, treatment complexity, individual significance, future contexts and concepts not yet known or understood[5,6]. The uncertainties in treatment benefit and harm challenge decision makers. One way to address these limitations is to involve patients in the regulatory process. Patients can provide key insights into patient perceptions on benefit expectations and harm tolerances. Such insights are crucial, given that choices made by other stakeholders may not represent those of patients[7].

Objective

To determine how much harm a specific group of rare disease patients are willing to accept for different types and amounts of benefit utilizing an online survey.

Background

In order to gain insights on patient preferences around treatment benefits and harms, decision-makers (regulators) use multiple quantitative methods. These methods explore

how treatment outcomes, patient preferences, and related evidence should be examined and measured[8]. One such method is the benefit-harm assessment approach, which involves hypothetical medical interventions and attributes[9]. Six benefit-harm methodologies have been described in the literature. These include direct-elicitation, conjoint analysis[9], frameworks, metrics, estimation techniques, and survey techniques[10]. Direct-elicitation methods include the ranking of variables within a preferred level of benefit or harm, selecting a preferred medical treatment or choosing between two competing health outcomes that increase in severity (worse or better)[9]. Examples of direct-elicitation include rating-scales, threshold techniques and standard-gamble methods[9]. Conjoint analysis uses a unique question format, ranking options by most preferred to least preferred, indicating the strength of preference between two options and choosing the preferred option from a set of alternatives[9]. Example of conjoint analysis includes ranking, graded pairs and discrete-choice experiments[9]. Frameworks use qualitative or quantitative approaches that provide instructions or describe methods to balance benefit-harms[10]. Metrics are defined as measurement systems that indicate benefit-harm thresholds or weight preferences[10]. Estimation techniques integrate benefit-harm data from multiple sources applying other methodologies and deal with statistical uncertainty[10], while utility surveys support the function of other methodologies and increase decision transparency[10].

While regulatory agencies, the bodies responsible for authorization of new medicines, recognize the value of such approaches they are not using specific benefit-harm assessment methodologies or methods[11] nor do they have guidance on which approach to apply[8]. For example, the European Medicines Agency (EMA) does not specify a particular method[11]. The Food and Drug Administration (FDA) in the United States of America recognizes that there is an interpretive component to clinical information that can lead to patients valuing things differently than providers or other stakeholders from whom the FDA seeks advice[8,12]. Health Canada is currently developing an orphan drug framework to support the

authorization of medicines for patients with rare diseases. Although patient involvement will be mandated[13], it is not yet clear which methods will be used to elicit patient preferences around treatment benefits and harms in the evaluation process.

Methods

An online questionnaire was designed to determine attitudes of Mucopolysaccharidosis (MPS) patients and caregivers and test survey feasibility. Those affected by MPS are a good proxy for a rare disease patient group because the illness is metabolically based, affects children, is heterogeneous and lacks treatment options - all characteristics of many rare diseases. The survey elicited information on willingness to tolerate harm under varying types and amounts of benefit and to gain feedback on the appropriateness and meaningfulness of the survey questions. As rare disease patients are spread across the country, it is usually not possible to gather enough data from one small area. The online survey method was chosen because it facilitates collection of information over a large geographical area with few resources required (i.e. printing, paper and postal charges)[14]. Online surveys also facilitate increased completion rates[15,16] and internet based applications allow for patients to respond from home if limited by health reasons[16,17]. Paper based surveys have recently transitioned to the internet and are considered appropriate for research[15]. Although widespread internet usage is relatively new and dependent on geographical location[18], most individuals, especially those 50 and younger, experience daily interactions with the internet (i.e. internet banking, email, accessing Google©, social media, etc). The MPS population represents a similar age group since participants are either caregivers of young children or are young adults themselves (as most patients do not have a normal lifespan).

Ethics approval was received from the University of Alberta Health Research Ethics Board.

Setting

A national (Canada) sample of patients' and caregivers' perceptions was elicited through an online survey over two months in the fall (September – November) 2014.

Participants

Given the limited literature on the preferences of rare disease patients around benefits and harms[19], this study is built upon literature pertaining to preference elicitation of chronic disease patients, specifically that focus on muscular dystrophy, rheumatoid arthritis, cancer (breast, colorectal, lung and renal), osteoarthritis, asthma, Crohn's disease, Alzheimer's, and multiple sclerosis. Chronic diseases are illnesses that have a long duration and change minimally over a long period of time[20]. Based on the literature, patient benefit-harm insights have been predominantly collected by questionnaire or interview methods[9]. An internet based survey approach was used to explore harm tolerances with different types and amounts of benefit in patients and caregivers affected by MPS. MPS is a complex and multi system rare disease that affects the majority of the body's cells[21,22]. Although innovative research is identifying new symptomatic treatments, the treatments remain costly and in some cases are unavailable to MPS patients[22].

MPS affects approximately one in 25,000 people and belongs to a family of inherited metabolic disorders defined by a damaged or missing enzyme which causes permanent cell damage and affects multiple body organs and functions[23]. While there are eight different types of MPS characterized by different levels of onset, severity and symptoms[24], similarities exist between the syndromes[21], and general characteristics of MPS include pain, cardiac disease and a shortened lifespan[21,22,25]. Genetic testing can be done before birth[21]. MPS may not be detectable at birth as some symptoms manifest with age[21]. It is an illness that primarily affects infants and children. Depending on the variety of MPS types, individuals are affected differently.

Sampling Strategy

This research was conducted with rare disease patients belonging to the Canadian Society for Mucopolysaccharide and Related Diseases Inc. Patients were recruited between September and November 2014 using convenience sampling [26]. The Canadian MPS Society, a rare disease patient advocacy group was accessed through a national patient organization (Canadian Organization for Rare Diseases (CORD)). Approximately 300 Canadians are affected by MPS[27], of whom 96 belong to the Canadian MPS Society and, therefore, were included in the study[28].

Inclusion and Exclusion Criteria

Any patient or caregiver affected by MPS who could read the English language at a grade seven level was eligible. English language level was determined by Flesch-Kincaid Readability Statistics within the word processing software. Patients were defined as individuals who had been diagnosed with MPS by a physician. A caregiver was defined as an unpaid family member or friend responsible for taking care of a person with MPS. Those without computer access were excluded.

Data Collection

Canadian MPS Society members were sent an email containing an overview of the study, an information letter and link to the survey. Additionally, study information and survey details were included in two monthly e-newsletters and two paper based newsletters. Following the initial contact, reminders were sent every two weeks via email, Facebook and Twitter. All communication to participants was approved and disseminated by the Canadian MPS Society Executive Director. Appendix A contains a copy of the information letter sent to participants. Appendix B contains the survey questions used to assess whether harm tolerances varies by amount of benefit across eight different types of benefit (referred to as treatment attributes).

Although this was not an objective of the study, an open-ended question format was used to elicit qualitative information about the survey questions themselves. This enabled respondents to provide detailed answers not available using other question formats. Table 13 describes the questions in the survey.

The survey was developed and distributed using online software (Survey Monkey®). It did not mandate question completion and participants could skip questions they were not comfortable answering.

The first page of the survey contained an introduction outlining its purpose and an overview of the question intent. While demographic data was not captured, the survey gathered information on disease type (MPS type) and participant type (patient or caregiver). Due to the small MPS community in Canada, demographic information was not collected to maintain the anonymity of the respondents.

Tolerance of Harm with varying levels of Benefit across Treatment Attributes

A one page information overview described this section of the survey and informed participants of the terms and definitions used. Instructions on how to complete the survey were included. Participants were asked to consider six levels of treatment harm (increasing levels of negative effect or side effect) alongside three levels of increasing treatment benefit (amount of benefit). Treatment benefit levels presented a current state (baseline) and three future states. These four states are referred to as benefit levels. The future states represented increasing levels of benefit (25%, 50%, and 75%). Results of an earlier study were used to inform the development of the online survey[29]. The previous study informed the treatment attributes (described below) and the three benefits levels as the majority of participants indicated that they expected between 0% and 75% benefit gain from treatment[29].

Treatment attributes were created with insights from rare disease patients[29] and information on health related quality of life (HRQoL) resources[30]. Specifically, treatment attributes and priorities were sought from rare disease CORD forum attendees in Toronto, Montreal and Vancouver in May and June 2014[29]. The eight treatment attribute domains were: *Ability to function as a family member or friend- Physical Function, Mental Function and Emotional Function*, ability to *Participate in activities that bring joy*, *Ability to attend work or attend school*, effect on *Length of life*, level of *Pain control* and effect on *Health status*[29]. The A*bility to function as a family member or friend*, refers to ones' ability to actively parent or meet friends for coffee. The *Ability to function as a family member or friend- Physical Function* was described as the ability to take part in exercise or physical activities such as climb a flight of stairs, go for a walk, or play sports. The *Ability to function as a family member or friend- Mental Function* was defined as the ability to think clearly. The *Ability to function as a family member or friend- Emotional Function* referred to feeling secure and comfortable. The ability to take part in things that are satisfying described the *Participate in activities that bring joy* treatment attribute. The *Ability to attend work or attend school* was defined by the ability to work and/or attend school. *Length of life* was described as how many years of life one expects to live. *Pain Control* is the ability to manage physical and/or mental pain. *Health Status* referred to how stable one's life is.

Harms were described using two terms: negative effect and side effect. A negative effect is an accidental physical injury due to medical care that requires treatment or time in hospital or that results in permanent harm or death[31]. A side effect is defined as a secondary, typically undesirable effect of a drug or medical treatment[32]. Harm levels were informed by the Institute for Healthcare Improvement (IHI) Global Trigger Tool for Measuring Adverse Events[33]. The IHI developed the IHI Global Trigger Tool (IGTT) to "accurately [identify] adverse events (harm)";it has been applied in several established health facilities[33].

For the purposes of this study, an adapted version of the IGTT was created, representing six levels of harm progressing in severity from *No negative effect* or *side effect* to *Action required to sustain life*. The original version included ten categories relating to adverse events that did or did not reach or affect the patient. Additionally, the IGTT categories were reworded to fit the context of accepting a treatment vs. receiving a treatment in error. Therefore the validity of the survey tool is not confirmed. In the adapted version, *No negative effect* or *side effect* referred to the respondent's unwillingness to accept any negative effect or side effect of treatment. *Temporary negative effect* or *side effect* and *no action required* referred to the tolerance and acceptance of temporary negative effects or side effects where no additional medical treatment is required. *Temporary negative effect* or *side effect* and *action required* referred to the tolerance and acceptance of temporary negative effects or side effects requiring additional medical treatment such as requiring an Advil® or Tylenol®). *Temporary negative effect* or *side effect* and *requires hospital stay* refers to the tolerance and acceptance of temporary negative effects or side effects that require a hospital stay. *Permanent negative effect* or *side effect* refers to the tolerance and acceptance of permanent negative effects or side effects where one's body can no longer breathe on its own and requires the help of a breathing machine for the rest of one's life. *Action required to sustain life* referred to the tolerance and acceptance of emergent life-saving medical treatment such as cardiopulmonary resuscitation (CPR).

The survey questions were tested by members of a research group at the School of Public Health at the University of Alberta in Edmonton, Canada. The research group is knowledgeable about rare diseases, rare disease research and the treatment lifecycle and is part of a CIHR funded team grant on rare disease. The group provided insights on appropriate wording and whether enough information was provided to complete the survey. They also recommended examples be included to describe the harm levels and treatment

attributes. The examples were included to provide the respondents with a frame of reference.

Survey Question Feedback

The last section of the survey contained open-ended questions about the appropriateness and meaningfulness of the survey questions. To determine whether the survey questions could elicit the information they were intended to and their applicability, respondents were provided with a large free text space. Participants could skip questions they were not comfortable answering. Table 13 contains an overview of the survey feedback questions.

Data Analysis

Online responses were automatically uploaded into Excel and SPSS databases software (Excel Microsoft 2010 and IBM SPSS® Statistics 22) for analysis. Two researchers independently reviewed the exported data for accuracy. Missing data were excluded for the analysis. Data were included if harm tolerance levels were reported for the benefit levels for one treatment attribute.

Tolerance of Harm with varying levels of Benefit across Treatment Attributes

Responses by participant type (patient, caregiver, combined) were assessed using ranges and medians for each treatment attribute. The range represents the minimum and maximum harm tolerance level for the treatment attributes and benefit levels. The median represents the midpoint harm level from a range of values selected by respondents for each treatment attribute's benefit level. Harm tolerance changes were determined for treatment attributes and benefit levels. These were calculated medians and ranges and are referred to as change medians and change ranges. The change median and change ranges represent the amount of harm tolerance change from the current benefit level compared to the other levels of increasing benefit. Sample sizes were too small to perform quantitative tests of

statistical significance of differences. Table 14 contains the descriptions of different harms and benefits that respondents were asked to trade off.

Survey Question Feedback

Responses to open-ended questions were analyzed using content analysis. Content analysis is a qualitative health research method used to provide data for contextualizing clinical interventions, improving surveys, and analysis in small research projects[34]. It involved reviewing chunks of text, identifying themes within the text, and assigning codes to the themes. If a new theme was identified, the previously coded text was reviewed to see if the new theme/code applied. This process was done iteratively until all text was coded. Table 15 presents data elements for the qualitative responses.

Results

Tolerance of Harm with varying levels of Benefit across Treatment Attributes

Twenty five participants responded to the online survey. Four patients (16%) and 21 (84%) caregivers participated. Of the 25 respondents, six (25%) entered their MPS type but did not answer any of the survey questions. Another six respondents began to answer the treatment attribute harm tolerance and benefit level questions and then stopped. No explanation was provided and it was not possible to follow up with them because the surveys were anonymous. Respondents' contact details were not sought limiting the ability to connect with the participants afterwards. The survey was designed to be anonymous in hopes of improving the chances that respondents would answer candidly and comprehensively. Sixteen respondents (4 patients and 12 caregivers) completed the benefit levels of the first three treatment attributes (*Ability to function as a family member or friend- Physical, Mental and Emotional Function*). Fourteen respondents completed the benefit level questions for two treatment attributes (*Participate in activities that bring joy* and *Ability to attend school or wor*k). Three treatment attributes (*Length of life, Pain*

control and *Health status*) were completed fully by respondents. Overall, 13 complete data sets which represented three (23%) patients and 10 (77%) caregivers.

Respondents harm ranges were consistent across five treatment attributes (*Ability to function as a family member or friend- Physical, Mental and Emotional Function, Participate in activities that bring joy, and Length of life)*. Patient harm tolerance responses ranged from 1 to 3 across the benefit levels, and caregiver harm tolerance responses ranged from 1 to 6 across the benefit levels. Two treatment attributes (*Ability to attend work or attend school* and *Health Status*) reported a patient harm tolerance range of 1 to 3 across the benefit levels, whereas caregiver harm tolerance responses ranged from 1 to 5 across the benefit levels. The *Pain control* treatment attribute was the only attribute that produced a patient harm tolerance range of 1 to 4 across the benefit levels. Caregivers reported a harm tolerance range of 1 to 5 across the benefit levels for *Pain control*. Compared to caregivers, patients tolerated lower harm levels across the treatment attributes and benefit levels. Moreover, in the majority of cases (94%), patients selected the lowest harm levels. There were two cases (6%) where patients and caregivers responded similarly as the maximum harm tolerance level and median for *Pain control* were the same for two benefit levels (25% and 50%). Table 16 represents the harm tolerance level ranges and medians across the benefit levels and treatment attributes by participant type.

For all treatment attributes except *Pain control*, patients accepted harm tolerance levels of 1, 2 or 3 across all benefit levels, which corresponded to *No negative effect* or *side effect* (1), *Temporary negative effect* or *side effect* and *no action required* (2) and *Temporary negative effect* or *side effect* and *action required* (3). Patients selected the *Temporary negative effect* or *side effect* and *requires hospital stay* (4) harm level for *Pain control* across all benefit levels except the current one, suggesting patients have a higher tolerance of harm for *Pain control*. Patients accepted harm up to *Temporary negative effect* or *side*

effect and *action required* (3), 87.5% of the time regardless of the increasing benefit level. In only one instance (3.1%), patients accepted harm up to T*emporary negative effect* or *side effect* and *no action required* (2) for *Ability to Function as a Family member - Mental Function.*

Caregivers reported harm tolerance levels ranging from 1 to 5 for three treatment attributes *Ability to attend work or attend school*, *Pain control* and *Health status*) across the benefit levels. These harm tolerance levels corresponded to *No negative effect* or *side effect* (1), *Temporary negative effect* or *side effect* and *no action required* (2) and *Temporary negative effect* or *side effect* and *action required* (3), *Temporary negative effect* or *side effect* and *requires hospital stay* (4) and *Permanent negative effect* or *side effect* (5). Caregivers selected the maximum harm tolerance level, *Action required to sustain life* (6), across the benefit levels of five treatment attributes, *Ability to function as a family member or friend-Physical, Mental and Emotional Function, Participate in activities that bring joy, and Length of life*. Caregivers chose *Temporary negative effect* or *side effect* and *requires hospital stay* (4) for 16 of 32 (50%) responses and selected the maximum harm tolerance levels, *Permanent negative effect* or *side effect* (5) or *Action required to sustain life* (6), for the maximum benefit level (75%) across all treatment attributes.

Median results for all respondents ranged between 2 and 3.5 harm tolerance levels across the benefit levels and treatment attributes. The current benefit level medians ranged from 2 to 3, the 25% benefit level medians ranged from 2 to 3, the 50% benefit level median was 3 and the 75% benefit level medians ranged from 3 to 3.5. Increasing harm tolerance medians across the benefit levels indicate respondents' willingness to accept *Temporary negative effect* or *side effect* and *no action required* (2) or *Temporary negative effect* or *side effect* and *action required* (3) for each treatment attribute. Table 17 provides an overview

of harm tolerance level ranges and medians across benefit levels and treatment attributes for all respondents harm tolerance range.

Four treatment attributes, *Ability to function as a family member or friend – Mental Function, Ability to attend work or attend school, Length of life, and Health status*, indicated a zero change median for patients across the benefit levels. The *Ability to function as a family member or friend – Physical Function* treatment attribute indicated a change median of 0.5 across the benefit levels. One treatment attribute, *Ability to function as a family member or friend – Emotional Function*, change median ranged from 0 to 0.5, and another treatment attribute, *Pain control*, change median ranged from 0 to 1. For caregivers, five treatment attributes, *Ability to function as a family member or friend- Physical, Mental and Emotional Function*, *Participate in activities that bring joy and Length of life,* reported change medians that ranged from 0 to 1 across the benefit levels. Two treatment attributes, *Ability to attend work or attend school* and *Pain control*, reported change median ranges of 0 to 0.5 and one treatment attribute, *Health status*, reported a change median range of 0.5 to 1 across the benefit levels. Table 18 gives an overview of the patient and caregiver harm tolerance changes across the benefit levels by treatment attribute type.

The patient harm tolerance change range was -2 to 2. Results of -2 levels were reported across all benefit levels for the *Participate in activities that bring joy* treatment attribute only. The patients indicated a 0 to 2 harm tolerance level change range for five treatment attributes, *Ability to function as a family member or friend- Physical and Mental Function, Pain control Length of life* and *Health Status.* Two treatment attributes, *Ability to function as a family member or friend – Emotional Function* and *Ability to attend work or attend school*, reported a harm tolerance level change range of 0 to 1. The caregiver harm tolerance level change range was calculated between -1 to 3 for three of eight treatment attributes, *Ability to function as a family member or friend- Physical* and *Mental Function*

and *Length of life.* Two treatment attributes, *Ability to function as a family member or friend – Emotional Function* and *Pain control,* indicated a harm tolerance change range of 0-3 across the benefit levels. Two other treatment attributes, *Length of life* and *Health Status*, indicated a harm tolerance level change range of 0 to 2 across the benefit levels. The *Ability to attend work or attend school* treatment attribute indicated a harm tolerance level change range of -1 to 2. The data suggests the majority of patient respondents chose no increase in harm or an increase of 2 harm tolerance levels across the most treatment attributes and benefit levels. Caregivers were more likely to select higher harm tolerance levels across treatment attribute types and increasing benefit levels as evidenced by the variability in change medians and change ranges. The maximum amount of change was selected for the following four treatment attributes by both respondent groups: *Ability to function as a family member or friend – Physical*, *Mental Function*, *Length of life* and *Pain control*.

Survey Question Feedback

Twelve out of fourteen respondents completed the six open-ended survey questions in their entirety. Three respondents reported that the questions were easily understood. However, the majority of respondents replied with "no" or suggested that questions need improvement and clarity. One respondent reported having to read the questions twice and another respondent stated that the questions were "a bit confusing". Ten participants thought the survey was an appropriate length, while two respondents thought it was "almost" too long. Ten respondents (83%) felt the treatment attributes applied to their health and life contexts, however one respondent felt the questions were too 'ambiguous' and another respondent felt that 'some' of the treatment attributes applied. Seven of the 12 respondents (58%) reported that the benefit levels were meaningful, although five respondents found them repetitive and vague. Six respondents (50%) reported on the harm tolerance levels suggesting that they were meaningful, whereas six respondents

thought the harm tolerance levels were too general and not specific enough to their disease context. Two respondents thought there were too many harm tolerance levels to choose from. Overall, patients and caregivers responded similarly to the survey feedback questions and thought the questions were respectful of their experiences and health and disease contexts. Table 19 contains the survey question feedback.

Discussion

There was significant variability in the results of the tolerance of harm survey. Although demographic information was not collected so as to protect the anonymity of the participants, the responses reflect a diverse MPS population. Little is known about the culture, age, socioeconomic status or health care experience of those who participated in the survey. These factors can influence how much harm one is willing to accept when contemplating varying levels of treatment benefit. This finding is supported by McHorney, et al. whose work showed that ethnicity, age, socioeconomic and disease burden play a role in how survey questions are interpreted and completed[35]. The variability in survey results could also be due to the multiple types of MPS represented by the respondent group. Although similarities exist between MPS type[21], they are characterized by differing periods of onset, severity and symptoms[24] further influencing the result variability.

In reference to harm tolerance with varying benefit, patient respondents showed less willingness to accept harm than caregivers. In the majority of cases, patients tolerated harm to a distinct level regardless of the amount of treatment benefit. While harm requiring limited medical intervention was tolerable by patients, caregivers frequently chose higher levels of harm involving invasive procedures. Due to the differences amongst patients and caregivers, treatment benefits and harms decisions solely made by caregivers may not reflect the patients' interests or wishes. This finding is supported by that of Ready et al, whose work demonstrated that caregivers make decisions that do not necessarily align

with the patients' preferences[36]. In evaluating decision-making for life-altering treatments in those affected by severe illnesses, Hauke et al found that patient wishes did not resonate with those of their caregivers[37]. Hauke et al also observed decision disagreements amongst patients and their caregivers[37].

While the survey results regarding the treatment domains and benefit levels were mostly positive, this is not true of the harm tolerance levels. A majority of the respondents thought the harm levels were not specific to the disease context and included too many options. Paling reported on the complexities of communicating treatment harms and offered strategies for improving patient understanding of harm[38]. Paling suggests that patients prefer to have a general vs. detailed understanding of the facts and often use emotions to guide decision-making surrounding treatment risks and harms[38]. These findings contradict those of McKenna regarding tool development. McKenna found that well developed tools are designed for the population in question and contain relevant questions that are acceptable[39]. Additionally, McKenna reported that generic scales are inadequately receptive to determine whether a treatment is effective[39]. Next steps to improve the survey's meaningfulness and relevancy would include further involvement of MPS patients and caregivers, to gain insights into question refinement related to the levels of harm, benefit and treatment attributes. Testing the revised survey with a group of key informants within the MPS community would improve the surveys' validity and relevancy.

Limitations

There were several limitations, including a small patient response rate. A small response rate limits the ability to generalize the results and understand the true tolerance of harm while applying increasing levels of benefit in a rare disease population. There is a possibility of sampling bias since only an online version of the survey was used (versus using a paper survey too), but the bias is small. For this sample and organization, memberships are

issued to families and therefore the survey is completed by one family representing several family members[22]. Additionally, an online survey was deemed appropriate considering the demographics of the rare disease population because the illness affects a population that is young and therefore accustomed to the internet[22], and since the method is preferred form of communication used by the representative Canadian patient organization[28]. The survey gathered responses from patients and caregivers affected by six types of MPS. Although similarities exist across the MPS types, differences in symptom severity and complexities within each type could have contributed to the variation in results and level of meaningfulness of the survey questions. There were a large number of incomplete responses and little is known about why the respondents stopped answering the questions if they did. The incomplete survey responses could compromise the survey tool validity due to non-response bias and limited ability to generalize the results[35]. Although questions elicited responses about the appropriateness and meaningfulness of the survey questions, the survey did not seek insights on the effectiveness of using the online survey tool as a method of gathering rare disease patient and caregiver preferences. None of the respondents provided feedback suggesting that it was an inappropriate mechanism.

Conclusion

Patients with rare diseases are a unique subset of the population that can inform the regulatory process in several jurisdictions. Although multiple quantifiable methods for preference elicitation exist, regulatory agencies do not have a standardized approach to incorporate patient benefit-harm preferences. This research identified disparate patients and caregivers results when comparing the tolerance of harms across treatment attributes and levels of benefit. While the patient population was limited, findings show that patients are less tolerant of high levels of harm compared to caregivers. Although, the online survey was respectful and adequate in length, harm levels require revision to ensure that they are meaningful for all patients and caregivers and applicable for small populations.

Appendix A. Information Letter

Patient Preferences around Therapies for Rare Diseases

Principal Researcher:

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Research Supervisors / Co-Researchers:

Tania Stafinski, Director, Health Technology & Policy Unit, School of Public Health, University of Alberta Phone: 780-492-4791

Dev Menon, Professor, Health Technology & Policy Unit, School of Public Health, University of Alberta Phone: 780-492-9080

Dear Team Member:

You are being invited to take part in a research study. The project will help us learn about patient wants, values and choices when making health care decisions.

Background:

Patient involvement is an important factor in improving health quality and safety. It is important to know what patients and families want and value and how they make choices. This information will help to create health policies and improve healthcare delivery.

Purpose:

The purpose of this research project is to learn what patients and families want and value, and to learn how choices are made when choosing among unclear treatment options.

The Plan:

If you choose to join, you will be asked to complete a short survey. The survey will take up to 15-30 minutes.

Possible Benefits:

Those who take part will have the satisfaction of contributing to health policies and healthcare delivery.

Possible Risks:

No long-term risks are involved. All reasonable steps will be taken to protect your identity. Your privacy will be protected. Taking part in the study will not affect your present or future care. If any questions make you feel uncomfortable you do not have to answer them.

Privacy:

Your personal information is not being collected. Any data collected or report created will not identify you. Researchers will not know your name.

Data will be stored on computers that are password protected and that have current virus protection. The information will also be mixed up and will only be readable with a code.

Any paper data will be stored in a locked cabinet. Once the study is complete all computer files and paper data will be saved for 7 years. Computer files will then be removed from the Health Technology & Policy Unit network drive. All paper data will be shredded. Only the final report will remain.

By completing the survey, you allow the researchers to collect and use the information you provide.

Taking Part is Optional:

Taking part is entirely optional. You do not have to take part if you do not want to. You are free to drop out of the research project at any time. You can also request to withdraw your data from the study up until October 31, 2014 by contacting the Principal Researcher (Mandy Bellows) at 780-945-7951. Your health care or the care of a loved one will not be affected in any way.

Payment of Expenses:

Patients and Families –thank you for taking part. You should not have any expenses.

The plan for this study has been reviewed for its adherence to ethical guidelines by a Research Ethics Board at the University of Alberta. For questions regarding participant rights and ethical conduct of research, contact the Research Ethics Office at (780) 492-2615.

Please contact the Principal Researcher if you have any questions or concerns:

Mandy Bellows, Principal Researcher at Phone: 780-945-7951

Appendix B. Online Pilot Survey

Current and Future State (please place an (X) in the column that fits best)		Negative Effect or Side Effect Levels					
		No negative effects or side effect	Temporary negative effect or side effect and no action required	Temporary negative effect or side effect and action required (e.g. a treatment causes headaches and you take Advil or Tylenol)	Temporary negative effect or side effect and requires hospital stay (e.g. a treatment causes serious dehydration and you are admitted to hospital)	Permanent negative effect or side effect (e.g. your body can no long breathe on its own and you require the help of a breathing machine for the rest of your life)	Action required to sustain life (e.g. a treatment causes your heart to stop, and you require CPR)
Benefit Category	When thinking about your **current** ability to function as a family member and friend, what level of negative effect or side effect do you **currently** accept?						
	a. Ability to function physically						
	b. Ability to function mentally						
	c. Ability to function emotionally						
	What level of negative effect or side effect would you accept in the **future** for a **25% increased ability** to be a functional family member and friend?						
	a. Ability to function physically						
	b. Ability to function mentally						
	c. Ability to function emotionally						
	What level of negative effect or side effect would you accept in the **future** for a **50% increased ability** to be a functional family member and friend?						
	a. Ability to function physically						
	b. Ability to function mentally						
	c. Ability to function emotionally						
	What level of negative effect or side effect would you accept in the **future** for a **75% increased ability** to be a functional family member and friend?						
	a. Ability to function physically						
	b. Ability to function mentally						
	c. Ability to function emotionally						

Current and Future State (please place an (X) in the column that fits best)		Negative Effect or Side Effect Levels					
		No negative effects or side effect	Temporary negative effect or side effect and no action required	Temporary negative effect or side effect and action required (e.g. a treatment causes headaches and you take Advil or Tylenol)	Temporary negative effect or side effect and requires hospital stay (e.g. a treatment causes serious dehydration and you are admitted to hospital)	Permanent negative effect or side effect (e.g. your body can no long breathe on its own and you require the help of a breathing machine for the rest of your life)	Action required to sustain life (e.g. a treatment causes your heart to stop, and you require CPR)
Benefit Category	When thinking about your **current** ability to participate in activities that bring you joy, what level of negative effect or side effect do you **currently** accept?						
	What level of negative effect or side effect would you accept in the **future** for a **25% increased ability** to participate in activities that bring you joy?						
	What level of negative effect or side effect would you accept in the **future** for a **50% increased ability** to participate in activities that bring you joy?						
	What level of negative effect or side effect would you accept in the **future** for a **75% increased ability** to participate in activities that bring you joy?						
	When thinking about your **current** ability to work or attend school, what level of negative effect or side effect do you **currently** accept?						
	What level of negative effect or side effect would you accept in the **future** for a **25% increased ability** to work or attend school?						
	What level of negative effect or side effect would you accept in the **future** for a **50% increased ability** to work or attend school?						
	What level of negative effect or side effect would you accept in the **future** for a **75% increased ability** to work or attend school?						

Current and Future State (please place an (X) in the column that fits best)		Negative Effect or Side Effect Levels					
		No negative effects or side effect	Temporary negative effect or side effect and no action required	Temporary negative effect or side effect and action required (e.g. a treatment causes headaches and you take Advil or Tylenol)	Temporary negative effect or side effect and requires hospital stay (e.g. a treatment causes serious dehydration and you are admitted to hospital)	Permanent negative effect or side effect (e.g. your body can no long breathe on its own and you require the help of a breathing machine for the rest of your life)	Action required to sustain life (e.g. a treatment causes your heart to stop, and you require CPR)
Benefit Category	When thinking about your **current** length of life, what level of negative effect or side effect do you **currently** accept?						
	What level of negative effect or side effect would you accept in the **future** for a **25% increase** in length of life?						
	What level of negative effect or side effect would you accept in the **future** for a **50% increase** in length of life?						
	What level of negative effect or side effect would you accept in the **future** for a **75% increase** in length of life?						
	When thinking about pain control, what level of negative effect or side effect do you **currently** accept?						
	What level of negative effect or side effect would you accept in the **future** for a **25% improvement** in pain control?						
	What level of negative effect or side effect would you accept in the **future** for a **50% improvement** in pain control?						
	What level of negative effect or side effect would you accept in the **future** for a **75% improvement** in pain control?						

Current and Future State (please place an (X) in the column that fits best)		Negative Effect or Side Effect Levels					
		No negative effects or side effect	Temporary negative effect or side effect and no action required	Temporary negative effect or side effect and action required (e.g. a treatment causes headaches and you take Advil or Tylenol)	Temporary negative effect or side effect and requires hospital stay (e.g. a treatment causes serious dehydration and you are admitted to hospital)	Permanent negative effect or side effect (e.g. your body can no long breathe on its own and you require the help of a breathing machine for the rest of your life)	Action required to sustain life (e.g. a treatment causes your heart to stop, and you require CPR)
Benefit Category	When thinking about your health status, what level of negative effect or side effect do you **currently** accept?						
	What level of negative effect or side effect would you accept in the **future** for a **25% improvement** in health status?						
	What level of negative effect or side effect would you accept in the **future** for a **50% improvement** in health status?						
	What level of negative effect or side effect would you accept in the **future** for a **75% improvement** in health status?						

Table 13. Survey feedback questions

1. Are the survey questions easy to understand?
2. Are the survey questions sensitive and respectful?
3. Are the benefit attributes important to you
4. Are the percentages of benefit increase (i.e. 25%, 50%, 75%) meaningful?
5. Are the harm levels (i.e. negative effect and side effect levels meaningful?
6. Is the survey too long?

Table 14. Data elements - Tolerance of harm with varying levels of benefit across treatment attributes

Benefit Attribute	Harm Level[a,b,c,d,e,f]	Question Type	Analysis Type
A[g] - Current[o]	1-6	Likert	Descriptive Statistics
A – 25%	1-6	Likert	Descriptive Statistics
A – 50%	1-6	Likert	Descriptive Statistics
A – 75%	1-6	Likert	Descriptive Statistics
B[h] – Current[o]	1-6	Likert	Descriptive Statistics
B – 25%	1-6	Likert	Descriptive Statistics
B – 50%	1-6	Likert	Descriptive Statistics
B – 75%	1-6	Likert	Descriptive Statistics
C[i] – Current[o]	1-6	Likert	Descriptive Statistics
C – 25%	1-6	Likert	Descriptive Statistics
C – 50%	1-6	Likert	Descriptive Statistics
C – 75%	1-6	Likert	Descriptive Statistics
D[j] – Current[o]	1-6	Likert	Descriptive Statistics
D – 25%	1-6	Likert	Descriptive Statistics
D – 50%	1-6	Likert	Descriptive Statistics
D – 75%	1-6	Likert	Descriptive Statistics
E[k] – Current[o]	1-6	Likert	Descriptive Statistics
E – 25%	1-6	Likert	Descriptive Statistics
E – 50%	1-6	Likert	Descriptive Statistics
E – 75%	1-6	Likert	Descriptive Statistics
F[l] – Current[o]	1-6	Likert	Descriptive Statistics
F – 25%	1-6	Likert	Descriptive Statistics
F – 50%	1-6	Likert	Descriptive Statistics
F – 75%	1-6	Likert	Descriptive Statistics
G[m] – Current[o]	1-6	Likert	Descriptive Statistics
G – 25%	1-6	Likert	Descriptive Statistics
G – 50%	1-6	Likert	Descriptive Statistics
G – 75%	1-6	Likert	Descriptive Statistics
H[n] – Current[o]	1-6	Likert	Descriptive Statistics
H – 25%	1-6	Likert	Descriptive Statistics
H – 50%	1-6	Likert	Descriptive Statistics
H – 75%	1-6	Likert	Descriptive Statistics

a No negative effect or side effect

b Temporary negative effect or side effect and no action required

c Temporary negative effect or side effect and action required

d Temporary negative effect or side effect and requires hospital stay

e Permanent negative effect or side effect

f Action required to sustain life

g Ability to Function as a Family Member or Friend – Physical Function

h Ability to Function as a Family Member or Friend – Mental Function

i Ability to Function as a Family Member or Friend – Emotional Function

j Participate in Activities that bring Joy

k Ability to Attend Work or Attend School

l Length of Life

m Pain Control

n Health Status

o Current level of ability or health (with no or current treatment)

Table 15. Data elements - Survey feedback questions

Qualitative Survey Questions	Question Type	Analysis
1. Are the survey questions easy to understand?	Open-ended	Content Analysis / Qualitative Description
2. Are the survey questions sensitive and respectful?	Open-ended	Content Analysis / Qualitative Description
3. Are the benefit attributes important to you	Open-ended	Content Analysis / Qualitative Description
4. Are the percentages of benefit increase (i.e. 25%, 50%, 75%) meaningful?	Open-ended	Content Analysis / Qualitative Description
5. Are the harm levels (i.e. negative effect and side effect levels meaningful?	Open-ended	Content Analysis / Qualitative Description
6. Is the survey too long?	Open-ended	Content Analysis / Qualitative Description

Table 16. Harm [a,b,c,d,e,f] tolerance level ranges and medians across benefit levels and treatment attributes by participant type

Benefit Attributes	Participant Type (N[h])	Range (Median)			
		Current[i]	25%[g]	50%[g]	75%[g]
Ability to Function as a Family Member or Friend – Physical Function	Patient (4)	1-3 (2)	2-3 (2.5)	2-3 (2.5)	1-3 (3)
	Caregiver (12)	1-5 (2)	2-4 (2.5)	2-5 (3)	2-6 (4)
Ability to Function as a Family Member or Friend – Mental Function	Patient (4)	1-2 (1.5)	1-3 (1.5)	1-3 (1.5)	1-3 (1)
	Caregiver(12)	1-4 (2)	1-4 (2)	1-4 (3)	1-6 (3)
Ability to Function as a Family Member or Friend – Emotional Function	Patient (4)	1-3 (2)	2-3 (2)	2-3 (2.5)	1-3 (2.5)
	Caregiver (12)	1-4 (2)	1-4 (2.5)	2-4 (3)	2-6 (3)
Participate in Activities that bring Joy	Patient (4)	1-3 (2.5)	1-3 (1.5)	1-3 (2)	1-3 (2.5)
	Caregiver(10)	1-4 (2.5)	1-4 (3.5)	1-4 (3.5)	1-6 (4)
Ability to Attend Work or Attend School	Patient (4)	1-3 (1)	1-3 (1)	1-3 (1)	1-3 (1.5)
	Caregiver (10)	1-5 (3)	2-4 (2.5)	2-4 (3)	2-5 (3.5)
Length of Life	Patient (3)	1-3 (2)	1-3 (2)	2-3 (2)	2-3 (3)
	Caregiver (10)	1-6 (3)	1-5 (3.5)	2-6 (4)	2-6 (4.5)
Pain Control	Patient (3)	1-3 (2)	1-4 (2)	2-4 (2)	2-4 (3)
	Caregiver (10)	1-4 (2.5)	2-4 (3)	2-4 (3)	2-5 (3)
Health Status	Patient (3)	1-3 (2)	1-3 (2)	2-3 (2)	2-3 (3)
	Caregiver (10)	1-4 (2.5)	2-4 (3)	1-4 (3.5)	1-5 (3.5)

a No negative effect or side effect

b Temporary negative effect or side effect and no action required

c Temporary negative effect or side effect and action required

d Temporary negative effect or side effect and requires hospital stay

e Permanent negative effect or side effect

f Action required to sustain life

g Increasing levels of treatment benefit

h Number of respondents

i Current level of ability or health (with no or current treatment)

Table 17. Harm [a,b,c,d,e,f] tolerance level ranges and medians across benefit levels and treatment attributes for all respondents

Benefit Attributes	Range (Median)							
	N[g]	Current[h]	N[g]	25%[i]	N[g]	50%[i]	N[g]	75%[i]
Ability to Function as a Family Member or Friend – Physical Function	16	1-5(2)	16	2-4(2.5)	16	2-5(3)	16	1-6(3)
Ability to Function as a Family Member or Friend – Mental Function	16	1-5(2)	16	1-4(2)	16	1-4(3)	16	1-5(3)
Ability to Function as a Family Member of Friend – Emotional Function	16	1-4(2)	16	2-4(2.5)	16	2-3(3)	16	1-6(3)
Participate in Activities that bring Joy	14	1-4(2.5)	14	1-4(2.5)	14	1-4(3)	14	1-6(3.5)
Ability to Attend Work or Attend School	14	1-5(2.5)	14	1-4(2)	14	1-4(3)	14	1-5(3)
Length of Life	13	1-4(3)	13	1-5(3)	13	2-6(3)	13	2-6(3)
Pain Control	13	1-4(2)	13	1-4(3)	13	2-4(3)	13	2-5(3)
Health Status	13	1-4(2)	13	1-4(3)	13	1-4(3)	13	1-5(3)

a No negative effect or side effect

b Temporary negative effect or side effect and no action required

c Temporary negative effect or side effect and action required

d Temporary negative effect or side effect and requires hospital stay

e Permanent negative effect or side effect

f Action required to sustain life

g Number of respondents

h Current level of ability or health (with no or current treatment)

I Increasing levels of treatment benefit

Table 18. Patient and caregiver harm tolerance changes across the benefit levels by treatment attribute

Patient or Caregiver		Harm tolerance change from baseline across the levels of benefit		
		25[a]	50[a]	75[a]
Ability to function as a family member or friend – Physical Function				
Patient	Change Median	0.5	0.5	0.5
	Change Range	0-1	0-2	-1-2
Caregiver	Change Median	0	0.5	1
	Change Range	-1-3	-1-3	1-3
Ability to function as a family member or friend – Mental Function				
Patient	Change Median	0	0	0
	Change Range	0-2	0-2	-1-2
Caregiver	Change Median	0	0	1
	Change Range	-1-3	-1-3	-1-3
Ability to function as a family member or friend – Emotional Function				
Patient	Change Median	0	0.5	0.5
	Change Range	0-1	0-1	-1-1
Caregiver	Change Median	0	0	1
	Change Range	0-3	1-3	0-3
Participate in Activities that bring joy				
Patient	Change Median	-0.5	0	1
	Change Range	-2-1	-2-1	-2-1
Caregiver	Change Median	0	0.5	1
	Change Range	0-1	0-1	0-2
Ability to attend work or attend school				
Patient	Change Median	0	0	0
	Change Range	0	0	0-1
Caregiver	Change Median	0	0	0.5
	Change Range	-1-1	-1-2	-1-2
Length of life				
Patient	Change Median	0	0	0
	Change Range	0	0-1	0-2
Caregiver	Change Median	0	1	1
	Change Range	-1-2	0-2	-1-3
Pain control				
Patient	Change Median	0	1	1
	Change Range	0-1	0-1	0-2
Caregiver	Change Median	0	0.5	0.5
	Change Range	0-3	0-3	0-3
Health status				
Patient	Change Median	0	0	0
	Change Range	0	0-1	0-2
Caregiver	Change Median	0.5	0.5	1
	Change Range	0-2	-1-2	-1-2

a Levels of increased benefit (25%, 50%, 75%)

Table 19. Survey feedback question responses

Are the survey questions easy to understand?	Are the survey questions sensitive and respectful?	Are the Benefit Categories important to you?	Are the percentages of benefit increase (i.e. 25%, 50%, 75%) meaningful to you?	Are the negative effect and side effect levels meaningful to you?	Is the Pilot Survey too long?
Not really	Yes	Yes	Yes	Yes	No
Fairly, but need to be clearer for caregiver speaking on behalf of patient.	Yes	Yes, but still too ambiguous	Somewhat	No, not really...would need to know more details pertaining to our specific situation	Almost but doable. I wouldn't want it any longer.
Somewhat, but very broad.	Yes, but far too general	Yes	No, too general and too often	No, too general and too often	No, but it is too general, not specific enough for individual patient/caregiver
No.	Yes	No	No	No	No
They were a bit confusing, but I got through them.	Yes				
No					
Yes	Yes	Yes	Yes	Yes	No
Yes	Yes	Yes	Yes	No	Not really
Yes	Yes	Yes	Yes	Not always appropriate considering the context of the question	No
Got to read them twice	Yes	Yes	Somewhat	Yes	No
With one exception, it is not clear whether, as a Grandmother, I should be attempting to answer all of the questions. Many seem to be addressed to patients or parents and not other family members...yet you seem to invite everyone who is a member of the patient's family?	Yes	Yes	Yes	Yes...because I have seen them.	No
Not all of them	Yes	Some	Yes partly	Yes partly	Not really
Yes, although I am a parent/caregiver submitting the responses and it wasn't always clear that I was answering the questions on behalf my child (I did respond with respect to my child's health condition, not my own).	Yes	Yes	Yes, because I would be willing to accept more negative effects for increased benefits.	Yes	No
Not really.	Yes	Yes	Almost too repetitive	No. too many options/words	Almost.

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Conclusion

This thesis comprised three, sequential papers, which began with the exploration of patient involvement in the healthcare regulatory benefit-harm evaluation process and concluded with attempts to discern perceptions of treatment benefit priorities and harm tolerances.

Through a review of published, peer-reviewed and 'grey' literature, 52 resources identified regulatory patient involvement in Europe (21), United Kingdom (12), United States (8), Australia (2), New Zealand (3), Canada (3), Italy (2), and the international community (1). While regulatory agencies involved patients utilizing all five levels of the International Association for Public Participation model, there is little understanding of why or how the involvement levels or methods were selected. There is also little known about whether the goals and expectations of all stakeholders were met. Similarly, little is known about the effect of patient involvement on regulatory decision-making in the evaluation of treatment benefits and harms and generally on the involvement of patients with rare diseases.

Based on the gaps in the literature, there was a need to understand rare disease perceptions of treatment benefit and harm. Individuals with rare diseases identified 13 benefit attribute priorities. These included: the ability to participate in activities that bring joy, functional ability (cognitive and physical), life expectancy, mental health, employment, being a functional family member, return to normal life, pain relief, improved health outcomes and conditions, access to knowledge, treatment simplicity, and health state stability. Those with rare diseases expect between a 0% to 75% increase in treatment benefit from their normal state. Several rare diseases were represented with the intent to develop a generic tool to gather perceptions of treatment benefits and harms. However, multidimensional specific tools are recommended to capture insights that are relevant and meaningful to the target population.

Treatment attribute priorities and benefit level expectations were used to inform the development of a survey to determine the tolerance of harm in a specific rare disease population. Mucopolysaccharidosis patients and caregivers reported different levels of harm tolerance across increasing levels of benefit. Caregivers were willing to accept more harm for increased benefit compared to patients across all treatment attributes. However, patients were willing to accept only minimal health care intervention, regardless of the level of treatment benefit. While survey respondents reported that the questions were respectful, they preferred questions that were clearly relevant to their specific disease context.

Lastly, from the findings of this thesis, multiple topics were identified which could evolve into future research. They include:

- **Identification of why and how patient involvement levels and methods are selected for use in the regulatory process:** "Do regulatory agencies utilize a framework or model to guide their patient involvement practices?" Although patients are involved little is known why they are being involved at the level they are, especially due to the lack of evidence surrounding the inclusion of their insights to effect benefit-harms evaluation.
- **Assessment of the degree to which patient involvement effects the evaluation of medicines within the regulatory process:** "Does patient involvement (elicited patient views) make an impact on regulatory decision-making?" Despite reports of being satisfied with regulatory involvement activities little is known about how the involvement contributes to the final decision to authorize a treatment or not.
- **Identification of a multidimensional tool that effectively and efficiently captures relevant and meaningful rare disease benefit and harm insights:** "How do rare disease patients prefer to provide their benefit-harms insights?" and "What treatment attributes, levels of benefit and levels of harm are relevant and

meaningful to their specific disease context?" Despite positive feedback regarding the tolerance of harm survey, further work is needed that involves rare disease patients in survey development (questions and format) for gaining insights for informing future treatment evaluation decisions.