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The Patient, 2018; 11(3):353-359

Engagement of Canadian patients with rare diseases and their caregivers in the lifecycle of the therapy: A qualitative study

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Acknowledgement: This study was supported by funding from the Canadian Institutes of Health Research Emerging Team Grant (TR3 119194)

1 Introduction

It is now recognized that for the benefits of new and effective therapies developed through basic and early translational science to be provided to patients with rare diseases, health systems will need to change. For example, Potter et al. state: "There is a need for research to understand and improve health systems for rare diseases in order to ensure that new, efficacious therapies developed through basic and early translational science lead to benefits for patients. Such research must (i) focus on appropriate patient-oriented outcomes, (ii) include robust study designs that can accommodate real-world decision priorities, and (iii) involve effective stakeholder engagement strategies" [1]. One key stakeholder group which needs to be involved throughout the full lifecycle of a therapy, from pre-clinical studies to routine use or replacement with a new therapy, is patients with rare diseases and their caregivers. A recent scoping review identified a variety of opportunities for patients with rare diseases and their caregivers, and patient organizations to be involved in the lifecycle [2]. However, stakeholder engagement approaches in general have been criticised as being merely tokenistic [3-5] and, due to significant weaknesses in reporting, this review could not distinguish meaningful opportunities from tokenism [2]. In the specific case of rare diseases, it is not known exactly how patients and their caregivers may wish to be meaningfully engaged in the lifecycle of a therapy. Consequently, this study was designed ***to explore how Canadian patients with rare diseases and their caregivers believe they should be involved in the orphan drug lifecycle and to elucidate their opinions on their priorities for involvement.***

2 Background

Patients with a specific disease have knowledge or information about their disease and the therapies that treat it, which may be helpful in decisions made along the lifecycle of a drug. For example, it has been suggested that patient/caregiver information or knowledge could help drive research and development decisions, decisions regarding clinical trials, risk-benefit considerations during regulatory review and decisions regarding funding or coverage of the drug [6-8]. This is particularly true for rare diseases. A rare disease has been defined as a life threatening, seriously debilitating, or serious and chronic condition affecting less than 1 in 2,000 people [9]. Many rare diseases are genetic and develop in childhood. They are often poorly understood and patients may spend years without an accurate diagnosis. Additionally, rare disease patients struggle with limited access to effective therapies due to the uncertainties that regulatory and coverage decision-makers face when assessing orphan drugs. While all decisions around new drugs are made under uncertainty, this uncertainty is magnified for orphan drugs [10]. This is a result of inadequate information on a product at the point of decision-making, which is itself a result of the

difficulties faced in conducting clinical trials [11] and the poorly understood natural history of rare diseases[12,13]. Published literature suggests that the involvement of patients and caregivers throughout the lifecycle of orphan drugs may help to reduce some of the uncertainties that decision-makers face and may improve patient access to new therapies [14]. In this study, three sessions involving rare disease patients and their caregivers were held to elicit information from them as to when and how they would like to be involved during the orphan drug lifecycle.

3 Methods

Taking a pragmatic qualitative research approach, the research team collaborated with the Canadian Organization for Rare Disorders (CORD) to facilitate data collection at two national CORD events [15]. CORD is comprised of over 80 patient organizations, providing access to patients and caregivers from a broad range of rare disease communities across Canada. Data were collected from a deliberative session hosted at each event. Subsequently, eight patients and caregivers, drawn from the deliberative sessions, participated in a webinar. The webinar allowed additional elucidation and validation of the findings. The deliberative sessions and webinar are described in detail below (Table 1). At both the sessions and the webinar, the orphan drug lifecycle was used to guide data collection, with patients and caregivers being asked how they felt they should be involved at each stage.

Table 1. Data sources.

Characteristics	Deliberative session 1	Deliberative session 2	Webinar
Who were the participants?	• Patients • Caregivers • Physicians • Researchers • Patient organizations • Industry • Government	• Patients • Caregivers	• Patients • Caregivers
How many participants were there?	• 118 (46 patients, caregivers, and/or patient organization representatives)	• 14	• 8
Which disease communities were represented?	• Cancers • Non-cancerous tumor disorders • Blood disorders • Metabolic disorders • Connective tissue disease • Endocrine disorders • Lung disorders • Secretory gland disorder • Epileptic encephalopathies • Vision disorders	• Cancers • Non-cancerous tumor disorders • Blood disorders • Metabolic disorders • Connective tissue disease • Endocrine disorders • Lung disorders • Secretory gland disorder • Epileptic encephalopathies	• Cancers • Non-cancerous tumor disorders • Blood disorders • Metabolic disorders • Connective tissue disease • Endocrine disorders • Lung disorders • Secretory gland disorder • Epileptic encephalopathies
Where and when did the session take place?	• At CORD's Consultations Towards a Canadian Plan for Rare Diseases Conference (Toronto, November 2013)	• Following CORD's Rare Diseases Day Conference (Ottawa, March 2014)	• Online (August 2015)
What was the initial objective?	• To identify what can be done to address the different	• To identify how patients and families specifically can	• To identify how patients and families believe they

	uncertainties that exist throughout the orphan drug lifecycle	contribute to reducing uncertainties	should be involved throughout the orphan drug lifecycle, and • To validate the findings from the previous sessions
What materials were provided?	• Presentations on the orphan drug lifecycle, challenges of R&D and decision-making on orphan drugs, the 4 main uncertainties decision-makers face, and existing policy tools that aim to reduce these uncertainties	• A summary presentation on the orphan drug lifecycle, the 4 main uncertainties decision-makers face, and existing policy tools that aim to reduce these uncertainties	• A summary of existing and proposed opportunities for patients, caregivers, and patient organizations involvement identified in a scoping review and deliberative sessions 1 & 2
Who facilitated the session?	• One researcher	• One researcher	• One researcher
How did information flow between the participants and the facilitator?	• Two-way	• Two-way	• Two-way
Were the sessions recorded and transcribed?	• Yes	• No	• Yes
Were field notes taken?	• No	• Yes	• No
Did the participants have the opportunity to review and clarify their responses?	• No	• Yes*	• Yes

* Participants subsequently participated in the Webinar where given the opportunity to comment on a summary presentation that included their responses from deliberative session 2

3.1 Data analysis and interpretation

Audio recordings and field notes from the sessions were analysed thematically using **eclectic coding** [16].

Descriptive and **process coding** were used to identify the topic (e.g., reimbursement decision-making) and the activity (e.g., providing input) respectively. This yielded a list of activities that patients and caregivers felt they could be involved in. However, additional information on these activities was obtained using **values coding** (reflecting perspectives, values, attitudes or beliefs about the specific type of engagement), **evaluation coding** (assigning judgements about the merit, worth, or significance of programs or policy) and **emotion coding** (labeling the emotions recalled and/or experienced by the patients/caregivers, or inferred by the researcher about the patient/caregiver). Illustrative examples of the results of the coding are presented in Online Resource 1. The activities were further grouped into Goals that patients and caregivers hoped to achieve by participating in those activities they had identified.

Interpretation of the results was possibly influenced by the researcher's background. AD has past experience volunteering with youth who have life-threatening, and sometimes rare, conditions. To minimize bias and ensure the accuracy of the analysis, results were sent to patients and representatives from national rare disease organizations for member checking.

4 Results

Three overall goals for patient/caregiver engagement emerged from the sessions. These were goals that patients and caregivers hoped to achieve through their involvement in different activities and included: (1) improved coverage decision-making, (2) improved care for patients, and (3) greater awareness of rare diseases. A detailed description of the ways in which patients and caregivers indicated they should participate in the orphan drug lifecycle, including examples from the transcripts, can be found in Tables A-1, A-2, and A-3 in Online Resource 2. The patients, caregivers and patient organization representatives who reviewed the study results had no disagreement with them nor additional information to add.

The major themes are briefly summarised below according to the 3 goals.

4.1 Improved coverage decision-making

All three groups of patients and caregivers identified ways in which they could be involved that would improve existing reimbursement coverage decision-making. First, participants felt that patients should have early engagement in the clinical trial process, providing input into clinical trial design, including identifying and selecting meaningful outcome measures.

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

In addition, participants saw value in patients enrolling in registries and submitting patient-reported outcome measures (PROMs) during clinical trials in order to collect important quality of life data not captured by the clinical outcomes. As one caregiver, reflecting on the types of information collected, said:

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

Patients and caregivers recognized that registries can be burdensome and that not all patients or caregivers want to participate in them. They felt that, if possible, patient organizations should establish registries (e.g., natural history; drug side-effects; etc.), but recognized that registries are expensive and most patient organizations have limited resources. In fact, patients and caregivers expressed significant frustrations around their previous experiences where,

having enrolled and participated, the registries were shut down due to a lack of funding. In addition to funding, participants noted additional issues associated with registries, such as ethical issues:

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

In spite of these barriers, there was general agreement that the benefits of improved data collection outweigh the associated burden.

"Rare disorders need another 10-15 years to come up with the evidence that [decision-makers] say we have to have and that's why [they] deny us. Let's give it to them." – Patient 1, session 1

Patients and caregivers also wanted to provide input into reimbursement decision-making. Some of the suggested areas of input were on the meaningfulness of the outcomes that are considered by decision-makers (*"to better qualify what is meant by a benefit"*); on treatment burden (*"they thought it was just a matter of convenience"*), including burden on the caregiver; on the benefit-harm ratio and their willingness to accept risk (*"what risk you're willing to take on should be taken into consideration"*); and to identify and provide information that is missing from a drug submission before a negative decision is made based on insufficient data (*"sometimes it could just be that a patient will write it out right, there's something missing"*).

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

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

Others felt that patients and patient organizations simply do not know how to use the submission form effectively. Regardless of these difficulties, participants felt that patients, caregivers, and patient organizations should still complete patient submissions.

Patients and caregivers identified ways in which they should be involved revolving around managed access programs (MAPs). MAPs are provisional coverage arrangements that aim to provide interim access while requiring

the generation of the information required to support a more definitive coverage decision within a set period of time [17]. Although none of the patients or caregivers had previous experience with MAPs, they were very interested in them as a way of providing patients with access to potentially beneficial orphan drugs while allowing for the collection of additional data on their effectiveness with real-world use. However, they felt that it is crucial to also have patient and caregiver input into the design of the programs to ensure that their needs and perspectives are considered. The arrangements need to be *"systematic and fair on both sides" (Caregiver 4, session 2).*

Other ways in which patients and caregivers felt that they should be involved within the goal of improving coverage decision making (and the following two goals) can be found in Tables A-1, A-2, and A-3 (Online Resource 2).

4.2 Improved care for patients

Patients and caregivers discussed the highly heterogeneous nature of rare diseases and the importance of considering individual differences when treating a patient with a new orphan drug. They spoke about the fear and confusion that many patients and their caregivers have experience when starting a new treatment.

Patients and caregivers suggested that patients should actively engage with their physician, choosing when to start and stop a new treatment. This approach would allow ongoing monitoring of their response to the treatment.

"So, instead of having specific stopping criteria that it's stated between the patient and their clinician, rather than a set rule within the drug plan criteria." – Caregiver 1, session 1

Some of the patients and caregivers felt that stopping criteria for a new drug based on a clinical measure (e.g., % increase in lung function) may be inappropriate as patients have very different experiences on drugs which are not captured by clinical outcomes (e.g., being able to walk up a set of stairs). They also supported the inclusion of a "buddy" system through which patients on a drug would provide support for new patients accessing the treatment.

"I mean when we're personally looking at options of treatment, one of them was really scary and I was really frightened." – Patient 2, session 1

Patients and caregivers also encouraged engagement with researchers to support development of new projects on potentially beneficial treatments.

"That's how stem cell transplant therapy started…where the doctors were and the researchers were really encouraged by the parents…" – Caregiver 2, session 1

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

It was also suggested that patients and patient organizations should provide guidance to newly diagnosed patients. Patients described their own experiences of struggling to receive a diagnosis and, upon diagnosis, failing to receive proper care for a disease that is poorly understood. *"This is what a patient organization helps you with" (Patient 3, session 2)* stated one patient, who experienced negative health outcomes due to inappropriate prescribed treatment.

Having a patient organization or, when no organization exists, a single patient to help guide individuals through the process was seen as helpful. As one patient suggested:

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

Patients and caregivers also felt that, as experts on their disease, they should provide input into the development of clinical practice guidelines (CPGs). Some had been involved in patient organizations that had made a request to a pharmaceutical company to be involved in the development of CPGs, only for the request to be denied. One caregiver, reflecting on the stage at which patients might give input, suggested:

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

4.3 Greater awareness of rare diseases

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

"And the patient organizations can help with that. When we increase our knowledge of where the patients are and let them know that, because a lot of the patient organizations don't know who all of the people are who have that disease, that's big" – Caregiver 2, webinar

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

One way identified to accomplish this was through building relationships with all relevant stakeholders (e.g., funders, donors, physicians, etc.).

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

The study participants felt that patient organizations should engage their members to increase their involvement, e.g., by following new research results and sharing them with their members, and should actively work to convince others to join in the advocacy efforts of patient organizations.

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

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

Most of the patients and caregivers had participated in these opportunities and felt that it was important they continue to do so.

4.4 Goals and the Orphan Drug Lifecycle

After mapping each identified opportunity onto the orphan drug lifecycle, it became apparent that the goals of involvement identified by patients and caregivers transcend the individual stages, spanning the entire lifecycle (see Tables A-1, A-2, and A-3, Online Resource 2).

5 Discussion

This study demonstrated that patients with rare diseases and their caregivers are involved in various stages of the lifecycle of a drug for rare diseases. They are also prepared to be engaged in additional activity that would inform various aspects of rare disease management. This is an important addition to the literature on patient engagement which is limited, regardless of the disease. Studies have been published on patient involvement during individual clinical decision-making [18,19]; however, these are outside the scope of this study, which was a macro-level

analysis focused on large-scale processes (e.g. coverage decision-making). Some work has been published on the goals of patient involvement in health technology assessments and reimbursement decision-making, but these do not describe goals identified by the patients themselves [8,20].

Several of the opportunities that patients and caregivers identified were ways in which they have already been involved (e.g., registries; patient submissions). These findings are consistent with the results of the scoping review [2]. The patients and caregivers also emphasized two opportunities for involvement that were not identified in the review: an increased level of input into reimbursement decision-making (e.g., benefit-harm ratio acceptability) and participation in managed access programs. Some of the barriers to involvement that patients and caregivers identified in this study are also reflective of the scoping review findings, which found a significant gap in reporting on existing opportunities in Canada and limited reporting around the details of involvement. This gap prevents assessment of potential tokenism or the impact of involvement. Other research has also documented this lack of reporting [8]. Patients and caregivers in this study were concerned about tokenism and ensuring their input has an impact. Addressing these barriers is important for improving existing opportunities for involvement and for introducing new ways to involve patients and caregivers.

5.1 Strengths and weakness of the study

Both deliberative sessions were conducted at national events hosted by CORD. It is possible that individuals who choose to participate in these events are different from those who do not and are not representative of the rare disease population in Canada. However, CORD is comprised of over 80 different rare disease patient organizations and encourages patients and caregivers to attend their events by covering travel costs, increasing the likelihood that the sample was unbiased. Another limitation of the study is that only one researcher (AD) coded the transcripts. However, the results of the analysis were reviewed by two additional researchers (DM; TS) who also attended the sessions and webinar.

6 Conclusion

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

Reference List

1. Potter BK, Khangura SD, Tingley K, Chakraborty P, Little J: **Translating rare-disease therapies into improved care for patients and families: what are the right outcomes, designs, and engagement approaches in health-systems research?** *Genetics in Medicine* 2016, **18:** 117-123.

2. Dunn A, Menon D, Stafinski T: **A scoping review of patient and caregiver involvement in the orphan drug lifecycle.** *Submitted to Orphanet Journal of Rare Diseases* 2017.

3. Arnstein SR: **A Ladder of Citizen Participation.** *Journal of the American Institute of Planners* 1969, **35:** 216-224.

4. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N *et al*.: **Patient engagement in research: a systematic review.** *BMC Health Serv Res* 2014, **14:** 89.

5. Tritter J, McCallum A: **The snakes and ladders of user involvement: moving beyond Arnstein.** *Health Policy* 2006, **76:** 156-168.

6. Mavris M, Le CY: **Involvement of patient organisations in research and development of orphan drugs for rare diseases in Europe.** *Mol Syndromol* 2012, **3:** 237-243.

7. oude Egbrink M, IJzerman, M.: **The Value of Quantitative Patient Preferences in Regulatory Benefit-Risk Assessment.** *Market Access & Health Policy* 2014, **2:** 22761.

8. Douglas C, Wilcox E, Burgess M, Lynd L: **Why orphan drug coverage reimbursement decision-making needs patient and public involvement.** *Health Policy* 2015, **119:** 588-596.

9. Lee D, Wong B: **An orphan drug framework (ODF) for Canada.** *J Popul Ther Clin Pharmacol* 2014, **21:** e42-e46.

10. Morel T, Arickx F, Befrits G, Siviero P, Van Der Meijden C, Xoxi E *et al*.: **Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: A comparative study of managed entry agreements across seven European countries.** *Orphanet J Rare Dis* 2013, **8:** 198.

11. Meekings KN, Williams CS, Arrowsmith JE: **Orphan drug development: an economically viable strategy for biopharma R&D.** *Drug Discov Today* 2012, **17:** 660-664.

12. Dunoyer M: **Accelerating access to treatments for rare diseases.** *Nature Reviews Drug Discovery* 2011, **10:** 475-476.

13. IOM (Institute of Medicine): *Rare Diseases and Orphan Products: Accelerating Research and Development.* Washington, DC: The National Academies Press; 2010.

14. Menon D, Stafinski T, Dunn A, Short H: **Involving Patients in Reducing Decision Uncertainties Around Orphan and Ultra-Orphan Drugs: A Rare Opportunity?** *Patient* 2014, **8:** 29-39.

15. Savin-Baden M, Howell Major C: *Qualitative Research: The Essential Guide to Theory and Practice*, First edn. Routledge; 2012.

16. Saldana J: *The Coding Manual for Qualitative Researchers*, Second edn. Sage; 2012.

17. Stafinski T, McCabe CJ, Menon D: **Funding the unfundable: mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems.** *Pharmacoeconomics* 2010, **28:** 113-142.

18. Say R, Murtagh M, Thomson R: **Patients' prefernce for involvement in medical decision making: a narrative review.** *Patient Educ Couns* 2006, **60:** 102-114.

19. Levinson W, Kao A, Kuby A, Thisted R: **Not all patients want to participate in decision making.** *J Gen Intern Med* 2005, **20:** 531-535.

20. Abelson J, Giacomini M, Lehoux P, Gauvin FP: **Bringing 'the public' into health technology assessment and coverage policy decisions: from principles to practice.** *Health Policy* 2007, **82:** 37-50.