Engagement of children and parents in developing outcome measures and determining minimal important difference: focus on probiotics and antibiotic-associated diarrhea

by

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Abstract

Introduction

Patient engagement as a major component of patient-oriented research (POR) emphasizes that patients should be engaged not only as participants, but also as research partners.

Having patient perspectives to inform the content and relevance of patient-reported outcome measures (PROMs) is now a requirement in many regulatory body guidelines. Increasing use of PROMs in pediatric populations has been documented frequently. As such, child and adolescent involvement to establish content validity of pediatric instruments has been recommended.

Minimal important difference (MID) is defined as the smallest difference/change which patients perceive as important. Historically, healthcare providers have had the sole role in MID estimation. However, over time, calls to incorporate patient perspectives have emerged.

Recent calls to determine MID from the patient's perspective are especially relevant for therapies that are accessed by consumers without a prescription (e.g., probiotics). According to the latest Cochrane systematic review, probiotics have moderate protective effects in preventing antibiotic-associated diarrhea (AAD) in children. However, no studies reported seeking the perspective of children or parents about the MID of probiotics in preventing AAD and there is no specific validated instrument available to measure the incidence and severity of pediatric AAD.

The objective of this thesis was to investigate whether and how children and/or parents have been engaged in developing PROMs and determining MID, and to use patient-centered approaches to 1) inform the MID of probiotics in prevention of pediatric AAD and 2) to validate an instrument for the measurement of incidence and severity of AAD in children.

Methods

Two review studies were conducted. In chapter 2, the method, stage, and level of engagement of the studies developing a new PROM in the pediatric population which engaged children and/or their parents in the process of development were described. In chapter 3, characteristics and findings of the studies reporting patient involvement in determining MID of any intervention were described.

In the survey study described in chapter 4, parents of children presenting to the emergency department of a children's hospital and pediatricians were approached to develop parent and pediatrician-derived MID.

In chapter 5, with the help of a patient advisory group, an instrument was developed to measure the incidence and severity of pediatric AAD. The internal consistency and convergent validity of the instrument were examined in a prospective observational study in children (birth to 17 years old) newly prescribed antibiotics or on antibiotics for ≤ 7 days.

Results

Both review studies showed scarcity of evidence in engagement of children/parents either in developing pediatric PROMs or determining MID.

The survey study showed good agreement between parents and clinicians regarding MID of probiotics in preventing pediatric AAD. Half of the participants in both groups reported they would use probiotics if it reduced the risk of AAD by 39%. The most important outcomes to parents and clinicians in measurement of pediatric AAD were identified.

In the PAAD instrument development study, we found a broad range of incidence risk of AAD (27%-83%) by applying four different definitions of diarrhea. Cronbach's α for the severity scale was less than 0.7. A high correlation was found between the PAAD severity score and numerical rating score of diarrhea severity reported by parents ($r>0.5$).

Conclusion

This doctoral dissertation showed that existing evidence regarding child/family engagement in PROM development and MID determination is sparse and at a preliminary stage. The estimated MID of probiotics in preventing pediatric AAD will help in sample size calculation and interpretation of results of future randomized clinical trials. Lastly, the PAAD instrument developed, and validity tested in this thesis will enable accurate measurement of pediatric AAD in future studies.

Preface

This thesis is an original work by Samaneh Khanpour Ardestani.

Ethical approval was obtained from the University of Alberta Health Research Ethics Board for Projects Named "Determination of minimal important difference perceived by parents/guardians and clinicians regarding probiotic therapy in prevention of pediatric antibiotic-associated diarrhea", No. Pro00058517, December 23, 2015, and "Development and validation of a patient/proxy-reported measure for pediatric antibiotic-associated diarrhea", No. Pro00072474, February 22, 2019. Recruitment of patients were conducted by me under the supervision of my PhD supervisor, Dr. Sunita Vohra, and guidance of my PhD supervisory committee, Drs. Joan Robinson, Hien H. Huynh, Hsing Jou and Levinus A. Dieleman.

Chapter 2 and 3 of this thesis are review studies which did not require ethics approval. I was responsible for the study design, literature search, data screening and extraction, analysis/ interpretation and writing the manuscript drafts to be submitted to the related publishing journals. Three second reviewers, Xin Mei Chen, Drs. Kiran J Pohar Manhas and Ammar Hassanzadeh Keshteli, participated in the review studies of this thesis.

Chapter 4 of this thesis has been published as:

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I was responsible for the concept development, study design, development of the surveys, recruitment of parents and clinicians, data analysis/interpretation, and manuscript writing. All other authors provided advice and guidance in study development and conduct, as well as critical review of the final paper. Staff of the Women and Children's Health Research Institute, University of Alberta, helped with the development of surveys in REDCap website.

Chapter 5 of this thesis is under peer-review.

Dr. Vohra and I conceptualized the overall project. I designed the study and data collection forms with the help of a patient advisory group and my PhD supervisory committee members, recruited and followed-up with the participants, analyzed the data, and wrote the draft manuscript. All my committee members provided advice and guidance in study development and conduct, as well as critical review of the final paper. Staff of the pediatric emergency department of Stollery Children's Hospital helped with the recruitment of the participants.

Dedication

To my husband Ammar, for his endless love, constant support and always believing in me, even in the most challenging times of my PhD journey.

To my parents, AliAkbar and Zahra, whom their love has been my motivation to keep going, and

To my sister, Narges, and brother, Mohammad Mahdi, inspirations of my dreams.

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Table of Contents

List of tables

List of figures

Chapter 1: Introduction

1.1 Patient Oriented Research

The Canadian Institutes of Health Research (CIHR) defines patient-oriented research (POR) as "a continuum of research that engages patients as partners, focuses on patient-identified priorities, and improves patient outcomes. This research, conducted by multidisciplinary teams in partnership with relevant stakeholders, aims to apply the knowledge generated to improve healthcare systems and practices" (1). Accordingly, patient engagement includes approaches to actively involve patients in “governance, priority setting, conducting research, and knowledge translation” (1).

Engaging patients in research has several potential benefits for both researchers and patients. Improving the quality of research design and relevance and applicability of research, increasing enrolment of participants, decreasing attrition, and stronger rapport with patients represent potential advantages for researchers. Patient engagement in research also enables patients to build confidence, feel empowered and valued, to build trust and understanding with researchers, and to have influence in research and receive improved quality of care (2, 3).

Patients can be engaged at all stages of a research cycle from developing the research question, to designing research methods, collecting data, analysis and interpretation of results, and dissemination of findings (1-5).

According to the Canada’s Strategy for Patient-Oriented Research (SPOR) (1), engaging patients in research represents a spectrum. The nature of the study and capacity of the patient partners affect the level of engagement. There are six “levels of patient and researcher

engagement in health research" adapted by Dr. Vandall-Walker from the International Association for Public Participation (IAP2) spectrum (6). These levels include *inform/learn*, *participate, consult, involve, collaborate,* and *lead/support*. The levels *consult, involve, collaborate,* and *lead/support* are considered to be active patient engagement. At the *consult* level, patients only provide feedback when needed; at the *involve* level, patients are members of research advisory committees and work with researchers throughout the project; at the *collaborate* level, patients are equal partners with the researchers and are co-investigators and members of research steering committees; in the final level, *lead/support*, patients lead the research and make decisions for the research team (6).

Different initiatives across the globe have been established to improve these approaches. Initially, in UK (1996) an advisory group called INVOLVE was established by National Institute for Health Research "to support active public involvement in NHS, public health, and social care research," (7). In the US, Patient-Centered Outcomes Research Institute (PCORI) (2010) was founded by the support of the US government to promote high quality research by collaboration with patients, caregivers, and all beneficiary stakeholders (8). In Canada, Strategy for Patient-Oriented Research (SPOR) (2011) was formed by the CIHR to transform the patient role from care receiver to active partner by involving them in all aspects of research (1).

As a major component of POR, improving patient outcomes is a priority, including developing and using patient-reported outcome measures (PROMs).

1.2 Patient-reported outcome measures (PROMs)

PROMs are instruments or standardized questionnaires that measure patient perspectives about their own functional or health status/wellbeing (9, 10). They measure outcomes that are

important to patients other than the usually measured outcomes (e.g., biomarkers, measures of morbidity and mortality) (11). While researchers may choose outcomes to assess physiological effects of treatment, these may not be the same as the outcomes deemed important by individuals with lived experience of the condition. For example, a medication may show beneficial effects on survival in a clinical study, but patients may not adhere to the treatment because of its adverse effects on aspects of quality of life (12). Rheumatologists, as pioneers in seeking patient perspectives in research outcomes, found that outcomes of fatigue, disturbed sleep and sense of wellbeing were not among the outcomes usually measured in clinical trials of rheumatoid arthritis, yet were identified as important by individuals with lived experience (13). As patients are the ultimate decision-makers regarding treatment adherence, outcomes they prioritize should be assessed. Patient-reported outcomes are particularly useful in conditions where objective measurements are not easily accessible, such as fatigue, nausea, pain, and functional syndromes (11).

PROMs are increasingly used either to evaluate effectiveness of treatments or to assess care outcomes in randomized clinical trials (RCTs) and the healthcare system, respectively (14-17). They can be generic and evaluate general aspects of health such as Short Form 36-item (SF-36) or be specific to a disease, function, or symptom such as Problem Areas in Diabetes scale (PAID)-5 (12).

Despite their popularity, there have been PROMs with poor or unknown quality, jeopardizing their use. Thus, the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) initiative was established to develop the tools which help researchers and healthcare providers select the optimal instrument with sound measurement properties (i.e.,

reliability, validity, and responsiveness) for their condition of interest. These guidelines are also applicable when developing PROMs (18).

COSMIN defines three main domains for evaluating the quality of a PROM (18, 19). Each domain constitutes of several measurement properties. The domain reliability measures the consistency of the scores over repeated measurements while there has been no change in the construct being measured. It includes consistency of the scores over time in the same responders (test-retest reliability), or across different raters on the same occasion (inter-rater reliability), or by the same raters across different occasions (intra-rater reliability) or by using different items of the same PROM (internal consistency). Validity is the ability of an instrument to measure the construct it is supposed to measure; it includes content, construct, and criterion validity. In content validity, relevance, comprehensiveness, and comprehensibility of the items of a PROM are being evaluated. Construct validity assesses if there is consistency between the scores of a PROM with hypotheses in terms of internal relationships (structural validity), relationships to other measures/constructs (convergent and discriminant validity), or differences between relevant groups (known groups validity). Criterion validity shows the performance of an instrument against a gold standard. Lastly, responsiveness evaluates the ability of an instrument to detect change over time if change has truly happened (18, 19).

COSMIN and regulatory bodies such as the US, Food and Drug Administration (FDA) are explicit in their guidance regarding patient input in developing PROMs. Having patient perspectives to inform the content and relevance of the instrument is now a requirement in these guidelines (17, 18).

Increasing use of PROMs in pediatric populations have been documented frequently. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has a task force

that specifically provides recommendations on good research practices for the design and use of pediatric PROMs (16). These recommendations emphasize child and adolescent involvement to establish content validity of pediatric instruments (16). Detailed methodological guidance to promote successful implementation of their recommendations, however, needs to be explored.

1.3 Minimal important difference (MID)

As important as inclusion of patients in the design stage of research, it is critical to have their input when interpreting the findings and determining meaningful thresholds regarding treatment response.

MID is defined as the smallest difference/change which patients perceive as important (18) and consider worthwhile despite risks, costs, and inconvenience of the intervention (20-22). This concept was first introduced by Jaeschke et al. (219) in 1989 and called "minimal clinically important difference" (MCID), to distinguish between statistically significant and clinically important results. MCID not only helped interpret study findings, but also facilitated calculation of RCT sample sizes. Initially, healthcare providers had the sole role in MID estimation (hence it was called MCID). However, over time, calls to incorporate patient perspectives have emerged (23, 24). Accordingly, investigators have employed different terminology based on their impression of the concept and the methods they implemented to determine this concept. Minimal important change/effect, clinically meaningful change/difference/effect, sufficiently meaningful/important change/difference/improvement/effect, smallest worthwhile effect, etc. are examples of this heterogeneous terminology. In this dissertation, we use the term MID.

To date, there is no gold standard method to determine MID. There are multiple approaches in the current literature: anchor-based, distribution-based, standardized effect sizes, health

economic methods, pilot studies, review of the existing evidence, and opinion-seeking (20). Each of these methods has their own strengths and limitations. Anchor-based methods adopt an external criterion (the "anchor") to identify if the change that occurred is important according to that anchor (usually patient or clinical judgment) (19). Most often this method relies on within-patient change rather than differences between patients. Distribution-based and standardized effect size methods compare the change of outcome of interest, whether continuous or ordinal, to some other statistical parameters of variability (e.g., standard error of measurement, standard deviation, effect size, and smallest detectable change) (25). A common criticism of this approach is that the measured change is not necessarily clinically important. As a result, these measures are recommended to be used as supportive information alongside other estimates (20, 26). Health economic methods are inclusive but complicated and resource-intensive approaches and are therefore not very popular among clinical trialists for sample size calculation (20). Pilot studies are more helpful to determine associated components of sample size formula (e.g., event rate in the control group, standard deviation). Because pilot studies are often small, they are not able to generate precise estimates of MID. As reviewing the existing evidence generates a MID based on observed differences in previously conducted studies, this MID reflects what is realistic, rather than what effect size is felt to be important (20). While it is helpful for study design to be informed by realistic estimates of effect size, this approach does not confirm what effect size is felt to be important enough to warrant a change in behavior, i.e., whether or not to adopt the intervention under study as part of routine care.

Opinion-seeking methods, such as surveys, Delphi methods, and interviews can be used to elicit patients or/and clinicians' opinions about the change or difference they perceive as important (25). Opinion-seeking methods are useful for any type of outcome (i.e., binary, continuous,

survival) and scenarios with various degrees of complexity can be designed, in terms of related effects or their influence on practice. Trade-off tools can be presented in order to inform the target population about the potential benefits and harms of the intervention. The estimate of MID can be influenced by how scenarios are presented, methods of elicitation, and individual preferences (25). As such, estimated MIDs by these methods are relative and not absolute as they are dependent to the context and determined by human values.

In 2011, Cook et al. (20) conducted a systematic review to identify different methods for specifying a MID. Among different methods, they found 60 studies that sought opinions of patients, health care providers, and multidisciplinary experts to determine MID. Only 10 studies elicited patients' or both patients' and clinicians' opinions, and none involved children (20). Considering that the emphasis on patient involvement in research has increased considerably since 2011 and that, historically, pediatric involvement in research has lagged behind adults, it seems necessary to update this work and investigate the involvement of patients, including children and parents, in defining MID over time. Recent calls to determine MID from the patient's perspective are especially relevant for therapies that are accessed by consumers without a prescription (e.g., probiotics).

1.4 Probiotics and antibiotic-associated diarrhea (AAD)

Probiotics are non-pathogenic microorganisms that can be beneficial to the host if administered in adequate amounts (27, 28). Probiotic use has increased significantly in clinical and research settings and among the public in the recent decades (29).

According to the latest Cochrane systematic review (30), probiotics have moderate protective effect in preventing AAD. AAD is a common complication of antibiotic administration (31-33) and can occur anytime up to eight weeks after initiation of antibiotic therapy. AAD incidence

varies (5-62%) depending on patient population, setting, antibiotic type and duration of antibiotic use (34-41). Although mild-moderate diarrhea is more common than severe diarrhea in AAD, serious complications such as dehydration, and *Clostridium difficile* infection may also occur, especially in children (40, 41). It has been hypothesized that antibiotics influence the gut microbial balance which eventually interferes with their metabolic functions and antipathogenic effects, leading to diarrhea (32). To date, more than 30 RCTs (30) have studied the effectiveness and safety of probiotics for prevention of pediatric AAD. None of these studies reported seeking the perspective of children or parents about the most relevant outcomes and associated MID.

1.5 Measurement of AAD

In a previous systematic review (42), Johnston et al. showed that there is marked heterogeneity in definitions and measurements of acute diarrhea in children. This was confirmed later by a review reporting specifically on the outcomes related to pediatric antibiotic-associated adverse events in probiotic trials, which found that diarrhea was only clearly defined in 21 out of 37 studies. Among these 21 studies, 16 different definitions of diarrhea were documented (43). Johnston et al. also found that, despite their wide use, there is a disturbing lack of evidence on evaluating the validity and reliability of most commonly used pediatric diarrhea severity scales. To reduce heterogeneity, a core outcome set (44) and a core outcome measurement set (45) were developed in 2016 for clinical trials on pediatric acute diarrhea and acute gastroenteritis. Despite this, no specific instrument is available to measure pediatric AAD.

1.6 Thesis Objective

To investigate whether and how children and/or parents have been engaged in developing patient-reported outcome measures (PROMs) and determining minimal important difference (MID), and to use patient-centered approaches to inform the design of future RCTs in prevention of pediatric AAD. To achieve thesis objective, we conducted two review studies, a survey study, and a validation study.

With the increasing use of pediatric PROMs in clinical research and health care settings, the role of patient engagement in developing these measures have been highlighted. In the first study (chapter 2 of this thesis), we aimed to systematically review studies engaging children or their parents/guardians in developing PROMs for any disease and to assess the quality of their reporting.

Engaging patients in the interpretation of study findings is also an emerging issue in the patient-oriented research field. For example, more recently, patient input in determining minimal important difference is being thought. We, therefore, in chapter 3 of this thesis, aimed to review studies seeking patient opinions regarding MID for any disease.

To apply these patient-centered approaches in the clinical setting, we focused on probiotics and antibiotic-associated diarrhea in children. First, in a survey study described in chapter 4 of this thesis, we aimed to establish the MID that would prompt parents/guardians and clinicians to use probiotics for prevention of AAD and to obtain their opinions about the most important outcomes to be measured in clinical trials of AAD.

Then, considering that there is a huge heterogeneity in definitions and measurement of diarrhea and that no specific instrument to measure pediatric AAD, in chapter 5 of this

thesis, we aimed to design and validate a standardized instrument for the assessment of pediatric AAD incidence and severity. In this study, we used the most important outcomes identified in our survey study which parents and clinicians required to be measured and engaged parents and children in developing process of this measurement instrument.

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Chapter 2: Child and parent engagement in developing pediatric patient reported outcome measures: A systematic review

2.1 Abstract

Objectives: This review aimed to systematically review studies engaging children and/or their parents/guardians in developing pediatric patient reported outcome measures (PROMs) for any disease, and to assess the quality of patient engagement reporting.

Methods: Electronic databases including MEDLINE, EMBASE, PsychINFO, and CINAHL were searched from inception to September 2021. Studies described developing a new PROM in the pediatric population and engaged children and/or their parents in the process of development were included. Characteristics of the study, population, and PROM and the method, stage and level of engagement were extracted. The Guidance for Reporting Involvement of Patients and Public (GRIPP2-short form) checklist was used to assess the quality of patient and public reporting in the included studies.

Results: After removing duplicates, of 7450 remaining references, 131 studies were included. Different methods of interview (n=97, 74%) and focus groups (n=36, 27%) were the methods used most often by researchers to engage children and families. Concept elicitation, item generation and selection, relevance, and comprehensibility testing (content validity) were the stages for which patient/family input were mostly sought. The level of engagement was at *consult* level for most studies.

Conclusion: This review showed children and parents engagement in PROM development is at a basic level in the engagement continuum. Patients' views were usually obtained by focus group or qualitative interviews in concept elicitation, item generation and content validity testing

stages. Active engagement of children and parents/caregivers as co-researchers is recommended in all stages of pediatric PROM development from designing the study to dissemination of findings.

2.2 Background

Patient engagement has garnered increasing attention in the movement towards patient-oriented research (POR) in the recent decade (1-5). It emphasizes that patients should be engaged not only as participants but also as research partners (6). As patients are the ultimate decision-makers in their own health care, their active collaboration enhances the relevance and applicability of research to real-world users (2).

Patient-reported outcome measures (PROMs) are standardized questionnaires or series of questions that measure patient perspective about their own functional or health status/wellbeing (6, 7). There is growing use of PROMs in randomized controlled trials (RCTs) and in the healthcare system (8-11) to evaluate patient perception of health outcomes.

Although PROMs are used to reflect patient views about interventions/care, they are mainly developed by clinical experts and researchers rather than by patients (6). Whilst clinical experts are well informed, patients have experience of living with illness. Hence, their engagement in the process of development of PROMs is essential.

Patients can be engaged as active members of the research team at multiple stages to: review the quality and acceptability of existing PROMs, identify the need for new PROMs, design and conduct qualitative research, define and elaborate the theoretical/conceptual framework, select the method of measurement, select or formulate the items and response options, the structure and wording of the PROM, interpret the measurement properties and disseminate the research

findings (6, 12). A scoping review conducted in 2017 (13) revealed that 26% of the studies developing a new PROM did not engage patients at all.

As the importance of patient engagement has been recognized and promoted in the last decade in adults, the need for child engagement in decision making and research has also been highlighted (14). However, this may bring its own challenges, considering the varying neurodevelopmental abilities of children as well as the time and resources needed for training adults and children (14).

In this systematic review, we focused on the active engagement of children and their parents/guardians in the development of pediatric PROMs. We investigated whether they have been engaged in PROM development and elaborated on the methods of engagement.

To prevent inconsistent and partial reporting, a checklist called Guidance for Reporting Involvement of Patients and Public (GRIPP) was first developed in 2011 (15) and updated in 2017 (GRIPP2 checklist) (16). The aim of the checklist is to facilitate the appraisal and interpretation of the findings of studies engaging patients and public, to learn from previous studies with patient and public involvement (PPI), and to recognize the impact of PPI. As a result, in this study, we also assessed the quality of PPI reporting of the included studies according to GRIPP2-short form checklist.

Objective: To systematically review studies engaging children and/or their parents/guardians in developing pediatric PROMs for any disease, and to assess the quality of PPI reporting.

2.3 Methods

The PRISMA guidelines for developing and reporting systematic reviews (SRs) were followed (17). The PROSPERO registration number is CRD42018106444.

2.3.1. Search strategy: Electronic databases including MEDLINE, EMBASE, PsychINFO, and CINAHL were searched from inception to September 2021, with the help of a health research librarian experienced in systematic review searches. Reference list of included studies and Patient-Reported Outcomes Measurement Information System (PROMIS) website (http://www.healthmeasures.net/explore-measurement-systems/promis) were searched for more relevant studies. No restrictions were applied in terms of publication type and language. Search terms related to PROMs were combined with search terms related to patient engagement in the pediatric population (Appendix A. for search strategy in MEDLINE).

2.3.2. Study selection and data extraction:

Two independent reviewers screened the references according to the following criteria.

Inclusion criteria:

1) Study design: Studies were considered to be developing a new PROM if they described any stage of instrument development and validation from selection of outcomes and item generation to psychometric testing. Studies focusing on the construction of conceptual framework/model of the condition without further development of the instrument were not included. Studies describing different phases of development of one instrument were included and are reported per instrument.

2) Population: The instrument must have been developed for use in the pediatric population. Since the pediatric age range differs across jurisdictions/organizations, we included all individuals less than 21 years of age (18). Studies with mixed adult and pediatric population were included if the instrument was designed for use in children.

3) Studies were included only if they engaged children or their parents in the process of development; participating in studies for psychometric assessments was not considered engagement.

4) Any condition and any settings were eligible for inclusion.

5) Non-English studies were eligible for inclusion.

Exclusion criteria: 1) Studies developing short version, translation, or alteration of a pre-existing PROM (these studies may not go through all development phases); if a study was adapted from/modified a previous PROM but went through all the development phases, it was considered for inclusion.

2) Studies developing patient-reported experience measures (PREMs).

3) Studies developing core outcome sets (COS) without development of PROM.

4) Review studies, narratives, opinion pieces, letters or editorials

5) Non-peer reviewed publications including conference abstracts, dissertations.

Two reviewers (SKA, KPM) screened titles and abstracts for relevant studies and then reviewed full texts of potentially relevant articles independently. Studies fulfilling the inclusion criteria were selected and any disagreements were resolved through discussion with a senior reviewer (SV). Data extraction took place using an *a priori* data extraction form by the primary reviewer (SKA).

The following information was extracted from the included studies: characteristics of the study including publication year, title, first author, country, characteristics of the population (age group/range, gender, sample size), PROM characteristics (name, generic (i.e., evaluates general aspects of health) or specific to a condition, condition of interest, patient or parent/proxy reported, health outcome measured), method of engagement (survey, interview, focus group,

etc.), the stage of engagement (concept elicitation, item generation, content validity testing, etc.), and the level of engagement (consult, involve, collaborate, lead/support).

According to the Canada's Strategy for Patient-Oriented Research (SPOR) (19), engaging patients in research represents a spectrum. The nature of the study and capacity of the patient partners affect the level of engagement. We used the "Levels of patient and researcher engagement in health research" adapted by Dr. Vandall-Walker from the International Association for Public Participation (IAP2) spectrum. This spectrum (Figure 2.1) constitutes 6 levels starting with *inform/learn* and *participate* levels up to *lead/support* level. Accordingly, we considered *consult*, *involve*, *collaborate*, and *lead/support* to be active levels of patient engagement. At the *consult* level, patients only provide feedback when needed; at the *involve* level, patients are members of research advisory committees and work with researchers throughout the project; at the *collaborate* level, patients are equal partners with the researchers as co-investigators and members of research steering committees; at the final level *lead/support*, patients lead the research and make decisions for the research team (20).

2.3.3. Quality assessment:

GRIPP2-short form checklist (16) was used by primary reviewer (SKA) and verified by a second reviewer (AHK) to assess the quality of patient and public reporting in the included studies.

2.3.4. Data analysis:

In this review, we identified studies involving children and/or their parents/guardians in the process of development of pediatric PROMs. We descriptively reported how and in what stage this population was engaged. Count data were presented using proportions.

2.4 Results

Retrieved references from electronic and hand searches (n=8302) went through title and abstract screening after removing duplicates. Of 7450 references, 304 were considered potentially relevant and reviewers screened the full texts for final inclusion. Eventually, 131 studies (21-151) were included in this review reporting child and/or parent/guardian engagement in the development of 118 pediatric PROMs (Figure 2.2).

2.4.1. General characteristics of the included studies:

The earliest study we identified was published in 1994. As the years progressed, the number of studies with pediatric/parent engagement increased (Appendix B)

Most studies were conducted in the USA (n=58, 44%) followed by Europe (N=41, 31%), and Canada (n=16, 12%). Children as young as 4 years of age were engaged in PROM development activities as well as parents of children from birth to adolescence. Out of 118 PROMs, 52 (44%) were developed by engaging both parents/children, while 39 (33%) only engaged children/adolescents. Most studies had mixed gender participation except those focused-on gender-specific clinical conditions (e.g., Duchenne muscular dystrophy, hypospadias). The number of children and/or parents/guardians engaged ranged from 1 to146. (Table 2.1.)

Among 118 PROMs, 13 were generic (11%); most were developed to be self-reported by the child (n=55, 47%) or reported by both patient and their parent/proxy (n=48, 40%). The clinical conditions were heterogeneous, however, the health outcomes measured by the 118 PROMs were mainly related to different aspects of health-related quality of life (n=63, 53%). (Table 2.1)

2.4.2. Patient engagement

The method and stage of engagement:

Different methods of interview (n=97, 74%) and focus groups (n=36, 27%) were most often used by the researchers to engage children and families in the 131 studies included in this review. Concept elicitation, item generation and selection, relevance, and comprehensibility testing (content validity) were the stages for which patient/family input were mostly sought. The investigators usually used in-depth interview methods and focus groups for concept elicitation and item generation phases, and cognitive debriefing techniques for items/scales refinement and content validity testing. (Table 2.2)

The level of engagement (*consult, involve, collaborate, lead/support*):

All but six studies engaged patients/families at the *consult* level, whereby patients/families provided feedback at different stages of PROM development (e.g., concept elicitation, item generation, content validity testing) when needed, using qualitative methodology.

There were four studies in which children or parents were members of advisory groups/councils (i.e., *involve* level). Ardelt et al., 2017 (91) involved one 14-year-old patient representative in a standing group to identify items for a questionnaire measuring psychosexual satisfaction after genital hypospadias treatment. In a study by Klingels et al., 2017 (94), a working group including medical doctors, researchers, physiotherapists, and representatives from advocacy groups, industry, and patients with lived experience were involved in an iterative process using focus groups to identify a conceptual framework and select/refine items according to their relevance and applicability for a questionnaire measuring activities of daily living in Duchenne muscular dystrophy. Sperling et al., 2017 (104), conducted a study to develop a questionnaire to

measure perspectives of adolescents/young adults (AYAs) about cancer treatment and survivorship. In this study, a youth panel including nine AYAs with cancer were involved in the entire process along with a professional panel including experts in primary care, pediatric oncology, and adolescent medicine. Through group and individual meetings, they prioritized themes, generated items, and commented on the format/structure of the questionnaire. Another study on Duchenne muscular dystrophy was conducted in 2021 by Powell et al. (147) to develop a new quality of life measure in these patients. Patients and parents as members of an advisory group were involved to endorse themes derived from qualitative interviews and rank/refine the generated items.

Two studies engaged children and parents at the *collaborate* level. McErlane et al., 2018 (113), collaborated with a group of parents and children/young people (CYP) with juvenile idiopathic arthritis (JIA) as members of a scientific steering committee to select outcomes, identify and prioritize themes, generate items, and test the face validity of their questionnaire measuring physical, social, and emotional wellbeing of CYP with JIA. Schwartz et al., 2021 (149), developed the response scales for a questionnaire called Pediatric Evaluation of Disability Inventory-Patient Reported Outcome (PEDI-PRO) in adolescents with developmental/intellectual disabilities. They reported collaboration with eight youth (14-21 years) as co-researchers (*collaborate* level). They collaborated in developing potential response options, conducting focus groups for content validity testing, and interpreting the data to refine response options. (Table 2.2)

2.4.3. Quality of PPI reporting assessment (according to GRIPP2-SF checklist)

Out of 131 included studies, 125 reported the aim of engagement (95%). Methods and results were described in most of the studies (n=128, 98%), and the impact of engagement (n=95, 72%) were mentioned. Critical reflection on positive and negative experiences of engagement was only discussed in 52 (40%) studies. (Table 2.3)

2.5 Discussion

This review found 131 studies with some level of pediatric and/or parent/guardian engagement in the development of 118 pediatric PROMs. The level of engagement was at the *consult* level in almost all studies. Child/parent opinions were usually sought through qualitative research methods such as focus group, in-person, in-depth interviews, or cognitive debriefing. Developing a conceptual framework, item generation, and testing the content validity (including relevance, comprehensibility, and ease of administration) were the main stages in which child/parent input was obtained. The quality of reporting according to the GRIPP-2 checklist was described.

Many more studies have been published with some level of child/parent engagement in developing pediatric PROMs than what was described by Wiering et al. (13) just 5 years ago in 2017 (131 vs. 8). This could be the result of highlighting the necessity and significance of POR among research community members in the recent years. For example, many funding agencies, policy makers, research ethics boards, and even some peer-reviewed journals now require submissions to include a patient engagement strategy plan/activity. Considering the many benefits of POR, this novel trend is promising. However, as with any new strategy, learning from previous experience (e.g., knowledge synthesis through systematic reviews), is essential for all stakeholders (i.e., policy makers, funding agencies, investigators, health-care providers, patients, and their families).

Based on the levels of patient engagement in health research spectrum used in our study (20), the level of engagement identified in the included studies was most often consulting, i.e., obtaining child/parent feedback as needed throughout the development process. Only in six studies were they actively engaged as members of an advisory group (involve level, n=4), or as co-researchers/steering committee members (collaborate level, n=2). The Canadian Institutes of Health Research (CIHR) defines patient engagement as "meaningful and active collaboration in governance, priority setting, conducting research and knowledge translation" (19). According to this definition, only these six studies are considered as children/families engagement in PROM development process and all the other ones which used patient feedback through focus groups or interviews (i.e., consult level) should not be considered as active patient engagement. This has been highlighted by some researchers who argue that patients/families involved in qualitative studies being conducted to elicit concepts and to test the validity of an instrument, are still considered as "research participants" (12) and they are not truly engaged as "research partners". The fact that patient engagement employs the same methodology (e.g., focus groups, in-depth interviews, cognitive debriefings) as these qualitative studies, makes the distinction more challenging. Doria et al., 2018, (152) highlighted this confusion in their commentary and introduced a guideline which addresses how to distinguish between a focus group as a technique to gather data for a qualitative study and as a method to engage patients, i.e., "discussion group", in the process of planning and designing research." Investigators are encouraged to use these guidelines and clearly report patient engagement activities in their research projects.To improve clarity and avoid discrepancies, Carlton et al., (153) has established a framework for full incorporation of public involvement in PROM development. They suggest 11 stages where "public involvement" could be implemented in the process of PROM development and

differentiate patient participation from engagement in these stages. For instance, when generating the items, patient partners could help to conduct, analyze, and interpret the data gathered from the qualitative interviews and advise on wording of potential items and questions. In testing the content validity of the instrument, they could be engaged to design the study, plan, and recruit participants, design the format and content of the documents, and manage the studies (for more details refer to Figure 1, Carlton et al., 2020(153)).

To our knowledge, there is only one other review focusing on engagement of children and families in developing pediatric PROMs. McNelli et al. (154) restricted their search to studies published 2009 through 2018 with the objective to assess child and family engagement in both selecting the outcomes and developing PROMs and PREMs. They included 29 studies in their review. Employing the original version of IAP2 spectrum to assess the level of engagement, they concluded that most studies engaged child/family in the low-mid levels of the spectrum. The quality of reporting was not assessed in their review.

Although we employed a comprehensive search strategy in multiple databases, since this field is evolving and the terminology is not consistent among researchers, it is possible that we have missed some relevant citations. Regardless, child/family engagement in pediatric PROM development is currently at a basic level and significant steps should be taken for improvement.

Conclusions

This review showed child and parent engagement in pediatric PROM development is at the basic levels of the engagement continuum. Child/parent views were mainly obtained by focus group or qualitative and cognitive interviews in the stages of concept elicitation, item generation and content validity testing. Active engagement of children/parents as co-researchers is

recommended in all stages of pediatric PROM development from designing the study to dissemination of its findings.

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2.7. Tables and figures

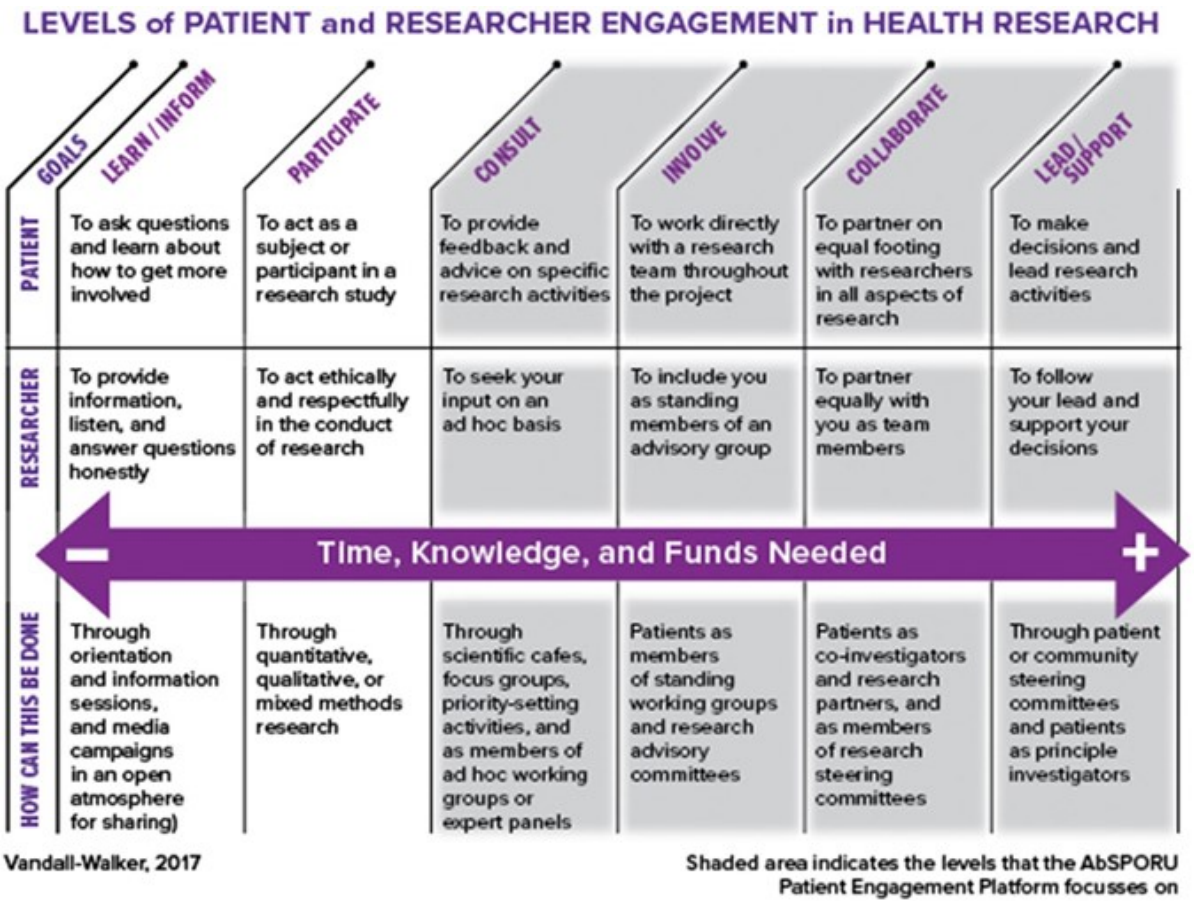

Figure 2. 1 Levels of patient and researcher engagement in health research [adapted with permission (20)]

Figure 2. 2 Adapted version of PRISMA flow diagram of study selection for the parents and children engagement in developing PROMs systematic review

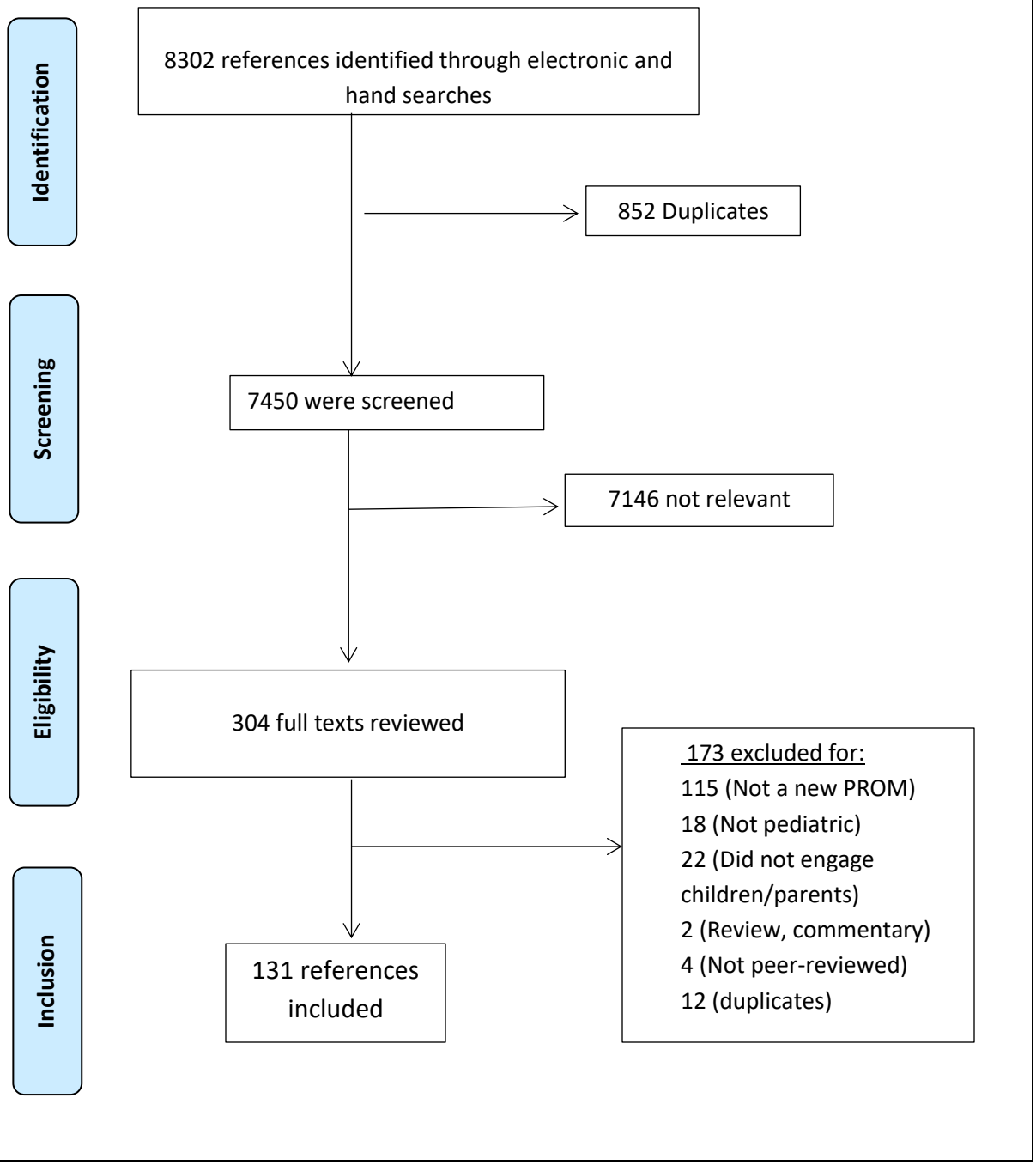

Table 2. 1 General characteristics of the included studies*

Author Publication year Country	Population characteristics			PROM characteristics				
	Sample size	Age group	Sex (male, female, both)	Name	Specific/generic	Patient-reported/ parent/proxy reported/both	Clinical condition	Health outcome
Juniper EF, 1994, Canada[21]	83 adolescents	12-17 years	Both	Quality of life in children with allergic rhino conjunctivitis	Condition-specific	Patient-reported	Seasonal allergic rhino conjunctivitis	Quality of life
Juniper EF, 1996, Canada[22]	100 in item generation, 10 in pretesting	7-17 years	Both	Paediatric Asthma Quality of Life Questionnaire	Condition-specific	Patient-reported	Asthma	Quality of life
Armstrong FD, 1999, USA[23]	30 families	10 of preschool age, 10 of school age and 10 of adolescent age	Both	The Miami Pediatric Quality of Life Questionnaire	Condition-specific	Parent/proxy-reported	Cancer	Health-related quality of life
Ravens-Sieberer U, 2001, Multisite Europe[24]	24	8-17 years	Both	KIDSCREEN	Generic	Patient-reported	General children population	Health-related quality of life
Bullinger M, 2002, Multisite Europe[25]	58 children 57 parents	4-16 years	Both	Haemo-Qol	Condition-specific	Both	Hemophilia	Health-related quality of life

Jokovic A, 2002, Canada[26]	33 parents and 11 children in item generation and content validity testing, 83 children in item selection	11-14 years	Both	CPQ (Child Perceptions Questionnaire)	Condition-specific	Patient-reported	Dental and oro-facial disorders	Oral health-related quality of life
Barnard D, 2003, Canada[27]	88 children, 90 parents	1-17 years	Both	ITP-Child Quality-of-Life Questionnaire, ITP-Parental Burden Quality-of-Life Questionnaire	Condition-specific	Both	ITP	Health-related quality of life
Ronen GM, 2003, Canada[28]	29 child-parent dyads in item generation, 50 child-parent dyads in pilot testing	6-15 years	Both	HRQL measures for children with epilepsy	Condition-specific	Both	Epilepsy	Health-related quality of life
Moorthy LN, 2004 and 2007, USA [29, 30]	21 children and 16 parents in qualitative research	≤18 years	Both	Simple Measure of the Impact of Lupus Erythematosus in Youngsters (SMILEY)	Condition-specific	Both	SLE	Health-related quality of life
Petersen C, 2005, Multisite Europe[31]	154 children-adolescents, 142 parents	4-16 years	Both	DISABKIDS chronic generic measure for children and adolescents with disabilities and chronic conditions	Generic (chronic generic)	Patient-reported	Chronic health conditions	Health-related quality of life
Waters E, 2005 and 2007,	28 families	Families of 4-12 years children	Both	CP QOL-Child	Condition-specific	Both	CP	Health-related quality of life

Australia[32, 33]								
Adair CE, 2007, Canada[34]	Item generation:12 patients, narretaives:31, focus group:5 Pre-testing: 17 patients and 10 family members	≥14 years and adults	Both	The Eating Disorders Quality of Life Scale (EDQLS)	Condition-specific	Patient-reported	Eating disorder	Quality of life
Buck D, 2007, UK[35]	16 parents	18 months - 21 years	Both	Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale	Condition-specific	Parent/proxy-reported	Epilepsy and learning disabilities	Health-related quality of life
Christie G, 2007, New Zealand[36]	61 adolescents	13-18 years	Both	The Substances and Choices Scale (SACS)	Condition-specific	Patient-reported	Alcohol and other drug (AOD) use	Screening and outcome measurement in AOD treatment
Cochrane G, 2008, Australia[37]	102 participants (students, parents, class teachers)	8-18 years	Both	The Impact of Vision Impairment on Children: IVI_C	Condition-specific	Patient-reported	Low vision	Health-related quality of life
Kintner E, 2008, USA[38]	4 adolescents, 3 parents in face validity testing	9-15 years	Both	Participation in Life Activities Scale (PLA) for children and adolescents with asthma	Condition-specific	Patient-reported	Asthma	Involvement in chosen life activities (one aspect of QOL)

Walsh TR, 2008, USA[39]	21 children with asthma and 21 children from the general population	8-17 years	Both	PROMIS pediatric item bank	Both	Patient-reported	Asthma and general population	Some aspects of health-related quality of life
Bourke-Taylor H, 2009 and 2010, Australia [40, 41]	8 mothers	5-18 years	Both	Assistance to Participate Scale (APS)	Condition-specific	Parent/proxy-reported	School-aged child with a disability	Participation in play and leisure activities
Irwin DE, 2009, USA[42]	77 children and adolescents	8-17 years	Both	PROMIS pediatric item bank	Both	Patient-reported	Asthma and children from general population	Some aspects of health-related quality of life and symptoms
Markham C, 2009, UK[43]	29 children and adolescents	6-18 years	Both	"Paediatric Speech and Language QoL" Scale (Ped SaL QoL)	Condition-specific	Patient-reported	Children with speech, language and communication needs	Quality of life
Shaikh N, 2009, USA[44]	18 children and 30 parents in item selection, 11 children in content validity testing	5-15 years	Both	A patient-reported outcome measure for assessing symptoms of streptococcal pharyngitis (Strep-PRO)	Condition-specific	Patient-reported	Streptococcal pharyngitis	Symptoms
Aparicio López C, 2010, Spain[45]	Not reported	Children over 9 and their parents	Both	TECAVNER (Test of Quality of Life in Children with kidney disease) in Spanish	Condition-specific	Both	Chronic kidney disease	Health-related quality of life

Arbuckle R, 2010, USA[46]	33 children/adolescents and 33 parents in concept elicitation, 21 children/adolescents and 15 parents in content validity testing	6-17 years	Both	Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS)	Condition-specific	Patient-reported	RLS	Symptoms and impact of disease
Barker D, 2010, USA[47]	Not reported	Parents of children 2-16 years	Both	Preschool Outcome Questionnaire (POQ)	Generic	Parent/proxy-reported	Preschool children	Psychological treatment impact
Liu WY, 2010, Taiwan[48]	1 parent	8-11 years	Both	A caregiver questionnaire for HRQL in children with CP (CQ-HRQL-CP)	Condition-specific	Parent/proxy-reported	CP	Health-related quality of life
Mulcahey MJ, 2010, USA[49]	33 children and 13 caregivers	7-18 years	Both	A PROM (in the form of computer adaptive testing) to evaluate activity performance and participation after spinal cord injury (SCI)	Condition-specific	Both	SCI	Performance and participation
Roodra LD, 2010, Netherland [50]	44 caregivers	Caregivers of children 2-13 years	Both	Mobility Questionnaire, 47-item (MobQues47)	Condition-specific	Parent/proxy-reported	Cerebral palsy	Mobility limitation
Akram A J, 2011, UK[51]	22 children	11-18 years	Both	Quality of life in patients with hypodontia	Condition-specific	Patient-reported	hypodontia	Quality of life

Angeles-Han, ST, 2011, USA[52]	? (Not reported) in item generation, 13 in content validity testing	8-18 years	Both	The Effects of Youngsters' Eyesight on Quality of Life (EYE-Q)	Condition-specific	Patient-reported	juvenile idiopathic arthritis-associated uveitis	Vision-related quality of life
Lai JS, 2011, USA[53]	20 parent/child in item generation and 27 parent/child in content validity testing	Parents and children 7-21 years	Both	Perceived cognitive function (pedsPCF) item bank	Generic	Parent/proxy-reported	Brain tumor and neurocognitive impairment	Cognitive function
Punpanich W, 2011, Thailand[54]	34 children and 35 caregivers in item generation and 10 children in content validity testing	Caregivers and children 8-16 years	Both	Thai Quality of Life for HIV-infected Children instrument (ThQLHC)	Condition-specific	Patient-reported	HIV infection	Health-related quality of life
Rahi JS, 2011, UK[55]	15 children and young people in concept elicitation, 32 in item generation	10-15 years	Both	A questionnaire for assessing vision-related quality of life (QoL) of visually impaired (VI) or blind (BL) children and young people	Condition-specific	Patient-reported	Visual impairment or blind	Vision-related quality of life
DeCarlo DK, 2012, USA[56]	24 children and 23 parents	6-12 years	Both	A vision-targeted health-related quality of life questionnaire designed for children ages 6-12	Condition-specific	Both	Visual impairment	Vision-related quality of life
Panepinto JA, 2012, USA[57]	13 children and 18 parents in in-depth interview, 33 children and 39	Children 5-18 and parents of	Both	PedsQL™ Sickle Cell Disease Module	Condition-specific	Both	Sickle cell disease	Health-related quality of life

	parent in cognitive interview	children 2-18 years						
Tsakos G, 2012, UK[58]	8 parents/guardians	Parents of 5-year-olds	Both	Scale of Oral Health Outcomes for 5-year-old children (SOHO-5)	Condition-specific	Patient-reported	General children population	Oral health-related quality of life
Varni JW, 2012, USA[59]	46 children 5-18 and 52 parents of children 2-18	2-18 years	Both	Pediatric Quality of Life Inventory (PedsQL) Gastrointestinal Symptoms Module	Condition-specific	Both	Gastrointestinal disorders	Health-related quality of life
Bevans KB, 2013, USA[60]	17 children and 6 parents in item generation, 39 children in content validity testing	Children 8-17 and parents of children 5-12 years	Both	PROMIS Pediatric Stress Response item banks	Generic	Both	General children population	Stress response
Bokhary KA, 2013, Saudi Arabia[61]	30 children and their parents	5-12 years	Both	'Children's Vision for Living Scale' (CVLS) (Arabic)	Condition-specific	Patient-reported	Children with or without amblyopia	Vision-related quality of life
Carlton J, 2013, UK[62]	32 children	4-7 years	Both	Child amblyopia treatment questionnaire (CAT-Qol)	Condition-specific	Patient-reported	Amblyopia	Health-related quality of life
Dufresne H, 2013, France[63]	94 families	Families of children less than 18 years	Both	Family Burden Ichthyosis questionnaire ("FBI") (French)	Condition-specific	Parent/proxy-reported	Inherited ichthyosis	Family burden
Fabricant PD, 2013, USA[64]	40 in item generation and selection, 20 in	Children 10-18 years	Both	Hospital for Special Surgery Pediatric	Condition-specific	Patient-reported	Adolescent athletes	Activity level

	content validity testing			Functional Activity Brief Scale (HSS Pedi-FABS)				
Kerfeld CI, 2013, USA[65]	14 children	8-12 years	Both	PROMIS pediatric physical function related to mobility items for children who use wheelchairs (WCs)	Condition-specific	Patient-reported	children who use wheelchairs (WCs)	Physical function
Forrest CB, 2014, USA[66]	21 children, 15 parents in concept elicitation	Children 8-17 and parents of children 5-17	Both	Pediatric global health (PGH) measure	Generic	Both	Children from general population	Global health
Geister TL, 2014, USA[67]	21 children and their caregivers in concept elicitation, 12 in content validity testing	Children 2-17 years	Both	Questionnaire on Pain caused by Spasticity (QPS)	Condition-specific	Both	CP	Pain
Izaguirre MR, 2014, USA[68]	19 children and 5 parents	10-22 years	Both	A self-efficacy scale for adolescents and young adults with IBD	Condition-specific	Patient-reported	IBD	Self-efficacy
Morley TE, 2014, Canada[69]	A total of 74 children/adolescents and parents	2-18 years	Both	Pediatric Advanced Care-Quality of Life Scale (PAC-QoL)	Condition-specific	Both	Advanced cancer	Health-related quality of life
Ng V, 2014, Multi-country[70]	146 children and/or parents	8-18 years	Both	Pediatric Liver Transplantation Quality of Life (PeLTQL) questionnaire	Condition-specific	Both	Liver transplant	Health-related quality of life

Ravens-Sieberer U, 2014, Germany and USA[71]	20 children and 5 parents in item generation, 37 children in content validity testing	Children 8-17 years and their parents	Both	Pediatric PROMIS subjective well-being (the eudaimonic component)	Generic	Both	General population	Subjective well-being (eudaimonic aspect)
Tucker CA, 2014, USA[72, 73]	20 children in concept elicitation and item generation, 37 children in content validity testing	Children 8-17 years	Both	Pediatric Measures of Physical Activity, Sedentary Behavior and Strength Impact for PROMIS	Generic	Patient-reported	General population	Activity level
Costa-Tutusaus L, 2015, Spain[74]	13 in focus group (item generation), 67 in comprehensibility testing	Adolescents	Both	A scoring questionnaire to assess healthy lifestyles among adolescents called VISA-TEEN (Spanish)	Generic	Patient-reported	Adolescents from the general population	Healthy lifestyle
Jacobson jr. CJ, 2015, USA[75]	40 children and 26 parents in item generation, 15 children and 15 parents in content validity testing	Children 8-17 and parents	Both	Pediatric pain behavior and pain quality item banks for the PROMIS	Generic	Both	Chronic/recurrent pain	Pain
Parslow R, 2015, 2019, and 2020, UK[76, 77, 78]	25 children/parents in concept elicitation, 43 in item generation, 24	8-18 years	Both	A PROM for pediatric chronic fatigue syndrome/ myalgic encephalopathy (CFS/ME)	Condition-specific	Patient-reported	CFS/ME	Health-related quality of life

	in content validity testing							
Young NL, 2015, Canada[79]	9 children and 9 caregivers	8-18 years	Both	Aboriginal Children's Health and Well-Being Measure (ACHWM)	Generic	Patient-reported	Children from general population	Health and well-being
Adams M, 2016, UK[80]	Children: 8 Parents: 8	8-24 years	Both	QoL measure for children and young adults with ALL receiving corticosteroids (the QuESt tool)	Condition-specific	Both	ALL	Quality of life
Bearss K, 2016, USA[81]	48 parents of 45 children	3-17 years	Both	A parent-rated instrument of anxiety symptoms in youth with ASD	Condition-specific	Parent/proxy-reported	Autism spectrum disorder	Symptoms (anxiety)
Benson PE, 2016, UK[82]	13 children	10-16 years	Both	Malocclusion Impact Questionnaire (MIQ)	Condition-specific	Patient-reported	Malocclusion	Oral health related quality of life
Bramhagen AC, 2016, Sweden[83]	18 children	4-12 years	Both	Postoperative Recovery in Children (PRiC)	Condition-specific	Patient-reported	Post surgery recovery	Quality of postoperative recovery
Dell SD, 2016, multi-country[84]	20 patients/parents in focus group, 69 in open ended interview, 57 in survey, 47 in cognitive testing	6-17 years	Both	A health-related quality-of-life questionnaire for primary ciliary dyskinesia (QOL-PCD)	Condition-specific	Both	Primary ciliary dyskinesia	Health-related quality of life

Dellenmark-Blom M, 2016, Sweden[85]	18 children and 32 parents	Children: 8-17 years, parents of children 2-17 years	Both	A health-related quality-of-life questionnaire for esophageal atresia	Condition-specific	Both	Esophageal atresia	Health-related quality of life
Follansbee-Junger KW, 2016, USA[86]	10 children and 11 parents in focus group, 13 children and 17 parents in cognitive interview	4-17 years	Both	PedsQL™ Epilepsy Module	Condition-specific	Both	Epilepsy	Health-related quality of life
Keays MA, 2016, Canada and USA[87]	5 patients/care givers in open ended interview	Children older than 8 years and caregivers of boys younger than 8	Males	A PROM for hypospadias	Condition-specific	Both	Hypospadias	Assessment of treatment
Newcombe PA, 2016, Australia[88]	? (Not reported) in focus group	7-17 years	Both	Child chronic cough-specific quality of life (CC-QoL) measure	Condition-specific	Patient-reported	Chronic cough	Quality of life
Olivieri I, 2016, Italy[89]	? (Not reported) in focus group	7-11 years	Both	SOLE VLBWI Questionnaire	Condition-specific	Patient-reported	Very low birthweight (VLBL)	Quality of life
Vande Velde S, 2016, Belgium[90]	10 patients and their parents in comprehensibility testing	6-18 years	Both	Spina Bifida Pediatric Questionnaire (SBPQ)	Condition-specific	Both	Spina bifida	Health-related quality of life

Ardelt PU, 2017, Germany[91]	1 patient representative, 9 in pilot testing	≥14 years	Males	Satisfaction In Genital Hypospadias Treatment (SIGHT)	Condition-specific	Patient-reported	Hypospadias	Psychosexual satisfaction
Bevans KB, 2017, USA[92]	24 children and 8 parents in concept elicitation, 43 in item generation and content validity	5-17 years	Both	The PROMIS pediatric Family Relationships measure	Generic	Both	General population	Family relationships
Elsman EB, 2017, Netherland[93]	30 in content validity testing	7-25 years and parents of children 0-17 years	Both	Participation and Activity Inventory for Children and Youth (PAI-CY) and Young Adults (PAI-YA) with a visual impairment	Condition-specific	Both	Visual impairment	Participation and activity measurement
Klingels K, 2017, multi-country[94]	? (Not reported)	≥ 7 years	Males	DMD Upper Limb PROM	Condition-specific	Both	Duchenne muscular dystrophy	Activities of daily living (ADL)
Longmire NM, 2017, Multi-country[95] Tassi A, 2021, Canada[96]	84 patients in concept elicitation and 15 in content validity testing	8-29 years	Both	FACE-Q Craniofacial Module for children and young adults	Condition-specific	Patient-reported	Facial conditions including ear anomalies, facial paralysis, skeletal conditions, and soft tissue conditions	Appearance and facial function
Oluboyede Y, 2017, UK[97]	31 adolescents	11-18 years	Both	Weight-specific Adolescent Instrument for Economic-evaluation (WAItE)	Condition-specific	Patient-reported	Obesity	Weight management

Reeve BB, 2017, USA[98, 99]	132 children in total and 114 parents/proxies	Children 7-20 and parent/proxies	Both	Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	Condition-specific	Both	Symptomatic adverse event in cancer patients	Adverse events
Samuels-Kalow ME, 2017, USA[100]	37 parents	Parents of 2–11-year-olds and adults	Both	A PROM for asthma patients discharged from emergency department (ED)	Condition-specific	Parent/proxy reported	Post-ED asthma	Post-ED care
Skjerning H, 2017, Denmark and Ireland[101]	26 in focus group (item generation), 76 in cognitive interview (comprehensibility)	Children and parents of children 0-18 years and adults	Both	Coeliac Disease Quality of Life questionnaire (CDQL)	Condition-specific	Both	Coeliac Disease	Health-related quality of life
Somer R, 2017, Germany[102] Bloemeke J, 2019, Germany and Spain[103]	34 patients and 21 parents in item generation (focus group) 14 patients and 28 parents in content validity testing	Children and adolescents/ young adults 8-28 years and parents of children 5-14 years	Both	Achondroplasia Personal Life Experience Scale (APLES)	Condition-specific	Both	Achondroplasia	Health-related quality of life
Sperling CD, 2017, Denmark[104]	21 in youth panel and 11 in content validity testing	Adolescents and young adults (15-29)	Both	A questionnaire to evaluate AYAs' perspectives of cancer treatment and survivorship	Condition-specific	Patient-reported	Cancer	Perspectives about cancer treatment and survivorship

Tapia VJ, 2017, USA[105]	47 patients, 80 parents	Patients 7-18 and parents of patient 0-18 years or older	Both	Quality of Life Outcomes Measure for Pediatric Patients With Craniofacial Conditions (bilingual-English and Spanish)	Condition-specific	Both	Diverse craniofacial conditions	Health-related quality of life
Wong Riff KW, 2017 and 2018, multi-country[106, 107]	136 patients	6-22 years	Both	A cross-cultural patient-reported outcome instrument for children and young adults with cleft lip and/or palate (CLEFT-Q)	Condition-specific	Both	Cleft lip and/or palate	Treatment outcomes regarding physical, psychological, and social health
Wright WJ, 2017, USA[108]	22 in item generation, 40 in face and content validity	Children 13-18 years	Both	Teen Oral Health-Related Quality of Life instrument (TOQOL)	Condition-specific	Patient-reported	Children from general population	Oral health related quality of life
Basra MKA, 2018, UK[109]	50 adolescents in item generation, 20 in content validity testing	12-19 years	Both	Teenagers' Quality of Life (T-QOL)	Condition-specific	Patient-reported	Skin disease	Dermatology-related quality of life
Fiume A, 2018, Canada[110]	Parents of 44 children and 6 adolescents in item generation, 10 parents in content validity testing	Children 2-18 years	Both	Pediatric Stroke Quality of Life Measure (PSQLM)	Condition-specific	Both	Pediatric stroke	Health-related quality of life
Heyworth B, 2018, USA[111]	40 in item generation, 10 in content validity testing	Children 10-18 years	Both	Pediatric and Adolescent Shoulder and Elbow Survey (Pedi-ASES)	Condition-specific	Patient-reported	Shoulder and elbow disorders	Physical function

Lewis S, 2018, USA[112]	39 caregivers	≤2 years	Both	An observer-reported outcome measure to assess observable RSV symptoms	Condition-specific	Parent/proxy reported	Respiratory syncytial virus infection	Symptoms
McErlane F, 2018, UK[113] Lunt LE, 2020, UK[114]	14 in scientific steering committee, 10 in face and content validity testing	Parents and children older than 1 year	Both	CAPTURE-JIA PROM and PREM	Condition-specific	Both	Juvenile idiopathic arthritis (JIA)	Aspects of healrh-related quality of life
Niemitz M, 2018, Germany[115]	? (not reported) in focus group for item generation	Children 8-18 and parents of children 0-18 years	Both	A health-related quality of life questionnaire for pediatric patients with interstitial lung disease (chILD-QOL)	Condition-specific	Both	Interstitial lung disease	Health-related quality of life
Santucci NR, 2018, USA[116]	10 children and their parents	Parents and children 8-16 years	Both	Self-efficacy for functional constipation questionnaire (SEFCQ)	Condition-specific	Both	Functional constipation	Self-efficacy
Bevans KB, 2019, USA[117]	64 children, and 54 parents	children 8–17 years, and parents of children 5–17 years	Both	PROMIS pediatric sleep health items	Generic	Both	Not specified (general)	Sleep health
Chhina H, 2019 and 2021, multi-country[118, 119]	39 children and 40 parents in concept elicitation	Children 8-18 years and their parents	Both	A PROM for children and adolescents with lower limb deformities (LIMB-Q kids)	Condition-specific	Patient-reported	Lower limb deformities	Health-related quality of life

Halleran DR, 2019, USA[120]	36 families in item generation and 20 in face validity	Families of children 3-18 years	Both	Patient-Reported Experience and utcome Measure in a Bowel Management Program (PREOM-BMP),	Condition-specific	Parent/proxy reported	Constipation and fecal incontinence undergoing bowel management	Impact of treatment
Heidi M, 2019, UK[121]	12 families in focus group, 57 in interview	Preschool children	Both	A tool for preschool children with recurrent wheeze	Condition-specific	Parent/proxy reported	Recurrent wheeze	Impact of episode and management on family
Hoffman MF, 2019, USA[122]	21 child/parents in open ended interview (item generation), 20 in cognitive interview (content validity testing)	Children 6-12 years and their parents	Both	Health-Related Quality of Life Instruments for Children with Cochlear Implants (CI-QOL)	Condition-specific	Both	Cochlear implant	Health-related quality of life
Jaudszus A, 2019, Germany[123]	Not reported	Older than 6 years	Both	Multimodal Questionnaire for the Assessment of Abdominal Symptoms in People with Cystic Fibrosis (CFAbd-Score)	Condition-specific	Both	Abdominal symptoms in cystic fibrosis	Symptom
Klassen AF, 2019, Canada and USA[124]	21 in concept elicitation, 10 in scale refinement	Older than 12 years	Both	A PROM for acne and acne scarring (ACNE-Q)	Condition-specific	Patient-reported	Acne and acne scarring	Appearance, symptoms, and related psychological concerns
Nelson LM, 2019, USA[125]	8 children/adolescents	10-17 years	Both	Axillary Sweating Daily Diary (ASDD)	Condition-specific	Patient-reported	Axillary hyperhidrosis	Symptom severity

Newton L, 2019, USA[126]	24 adolescents	12-17 years	Both	Tools for itch and skin pain in atopic dermatitis	Condition-specific	Patient-reported	Atopic dermatitis	Symptom severity and its impact on health-related quality of life
Piscione J, 2019, Canada[127]	17 children/adolescents	7-18 years	Both	The Pediatric Toronto Extremity Salvage Score (pTESS) [arm and leg questionnaire]	Condition-specific	Patient-reported	Extremity tumors	Physical function
Propp R, 2019, Canada[128]	19 children and 20 parents	Children 5-18 years and their caregivers	Males	Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD)	Condition-specific	Both	Duchenne muscular dystrophy	Health-related priorities
Sarda SP, 2019, USA[129]	4 children/adolescents, 10 parent/caregivers, 4 child/parent dyads	Children older than 8 years and parents/caregivers of children 1-10 years	Both	Instruments to assess symptoms of ocular discomfort associated with viral or bacterial conjunctivitis	Condition-specific	Both	Viral or bacterial conjunctivitis	Symptoms
Tingsgaard JK, 2019, Denmark[130]	9 parents/caregivers	Parents/caregivers of children less than 12 years	Both	Danish National Tympanostomy Tube Insertion Questionnaires (DANTIQ)	Condition-specific	Parent/proxy reported	Otitis media undergoing tube insertion	Symptoms and adherence to treatment
Tsangaris E, 2019, Canada[131]	45 adolescents and young adults	15-39 years	Both	Cancer Distress Scales for AYA (CDS-AYA)	Condition-specific	Patient-reported	Cancer	Distress

Bevans KB, 2020, USA[132]	27 children/adolescents and 21 parents	Children 8-17 and parents of children 5-17 years	Both	PROMs of oral health aesthetics	Condition-specific	Both	Oral appearance	Oral health aesthetics
De Zwaan M, 2020, Germany[133]	29 patients and 22 parents	Patients 8-18 years and parents	Both	Instrument assessing Barriers to Growth Hormone Treatment (BAR-GHT)	Condition-specific	Both	Growth hormone deficiency	Treatment barriers and problems
Halstead P, 2020, USA[134]	39 children and 10 parents	Children 6-11 years	Both	A PROM to self-assess symptoms of the common cold	Condition-specific	Patient-reported	Common cold	Symptoms
Martin SA, 2020, USA[135]	17 adolescents in item generation and 9 in content validity testing	Adolescents 12-18 years	Both	The atopic dermatitis itch scale (ADIS)	Condition-specific	Patient-reported	Pruritis in atopic dermatitis	Symptoms
McCarrier KP, 2020, USA[136]	22 children/adolescents and their parents	Children/adolescents 6-18, parents, and adults	Both	Cystic Fibrosis Impact Questionnaire (CF-IQ)	Condition-specific	Patient-reported	Cystic fibrosis	Quality of life
Robertson AO, 2020, UK[137]	29 in item generation, 28 in content validity testing	Children 8-12 and young people aged 13-18 years	Both	A PROM of functional vision for children and young people (FVQ-C, FVQ-Y)	Condition-specific	Both	Visual impairment	Functional vision
Wyrwich KW, 2020, USA[138]	5	15-17 years	Both	The Scalp Hair Assessment PRO ™	Condition-specific	Patient-reported	alopecia areata	Symptom
Zigler CK, 2020, USA[139]	? (not reported) in concept elicitation, 17 in content validity tetsing	8-18 and their caregivers	Both	Localized Scleroderma Quality of Life Instrument	Condition-specific	Patient-reported	Localized Scleroderma	Health-related quality of life

Cejas I, 2021, USA[140]	43 parents and 36 adolescents/young adults	Children ages birth through 22 years	Both	QoL-cochlear implant (CI) for early childhood (0-5 years) and adolescents (13-22 years)	Condition-specific	Both	Cochlear implant	Quality of life
Dermott JA, 2021, Canada[141]	25 children/adolescents and 20 parents	9-18 years and parents	Both	Gait outcome Assessment List (GOAL) questionnaire	Condition-specific	Both	Lower limb differences	Health-related quality of life
Griffiths C, 2021, UK[142]	12 parents in concept elicitation, 18 in content validity testing	Parents of children aged 8 years and less	Both	CARe burn scale: Child form	Condition-specific	Parent/proxy reported	Burn injury	Quality of life
Gwaltney C, 2021, USA[143]	18 children/adolescents and caregivers in concept elicitation, 12 in content validity testing	Children/adolescents <16 years and adults	Both	Barth Syndrome Symptom Assessment (BTHS-SA)	Condition-specific	Both	Barth Syndrome	Symptoms
Hall R, 2021, USA[144]	20 adolescents	Adolescents older than 12 years and adults	Both	Pruritis and Symptoms Assessment for Atopic Dermatitis (PSAAD)	Condition-specific	Patient-reported	Atopic dermatitis	Symptoms
Meltzer LJ, 2021, USA[145]	28 children/adolescents in concept elicitation, 32	Youth 8–17 years	Both	Pediatric Sleep Practices Questionnaire (PSPQ).	Condition-specific	Patient-reported	Sleep practices	Sleep health

	in content validity testing							
Pandina G, 2021, USA[146]	50 caregivers	Caregivers of patients of 2-40 years of age	Both	Autism Behavior Inventory (ABI)	Condition-specific	Parent/proxy reported	Autism spectrum disorder (ASD)	Symptoms
Powell PA, 2021, UK[147]	18 patients in item generation, 8 in item selection and 10 parents	Children older than 7 years and parents	Male	Quality of Life Measure for Duchenne Muscular Dystrophy (DMD-QoL)	Condition-specific	Both	Duchenne Muscular Dystrophy	Quality of life
Ramchandren S, 2021, Multi-country[148]	31 in focus group	4-17 years	Both	CMT-specific QOL outcome measure (pCMT-QOL)	Condition-specific	Patient-reported	Charcot–Marie–Tooth disease	Health-related quality of life
Schwartz AE, 2021, USA[149]	8 youth co-researchers 62 in focus group	14-21 years	Both	Pediatric Evaluation of Disability Inventory-Patient Reported Outcome (PEDI-PRO)	Condition-specific	Patient-reported	Intellectual/developmental disabilities	Functional performance in daily activities, social/cognitive, and mobility
Winnette R, 2021, USA[150]	7 adolescents	12-17 years	Both	Alopecia Areata Patient Priority Outcomes Instrument (AAPPO)	Condition-specific	Patient-reported	Alopecia areata	Priority treatment outcomes
Zizzi CE, 2021, USA[151]	5 patients and their caregivers	Children/adolescents 8-15 years and their caregivers, and adults	Both	The Spinal Muscular Atrophy Health Index (SMA-HI)	Condition-specific	Both	Spinal Muscular Atrophy	Disease burden

*Each row represents a PROM which its development process may have been reported in more than one study.

ALL: Acute lymphoblastic leukemia, AOD: Alcohol and other drug use, CFS/ME: Chronic fatigue syndrome/ myalgic encephalopathy, CMT: Charcot–Marie–Tooth disease, CP: Cerebral palsy, ED: Emergency department, HIV: Human immunodeficiency virus, HRQL: Health-related quality of life, IBD: Inflammatory bowel disease, ITP: Idiopathic thrombocytopenic purpura, PROM: Patient-reported outcome measure, PROMIS: Patient-Reported Outcomes Measurement Information System, QOL: quality of life, RLS: Restless leg syndrome, SCI: Spinal cord injury, SLE: Systemic lupus erythematosus

Table 2. 2 Patient engagement in the development of PROMs*

Author Publication year Country	Method of involvement (survey, interview, focus group, etc.)	Stage of involvement (concept elicitation, item generation, comprehensibility testing, validity testing, etc.)	Level of involvement (consult, involve, collaborate, patient-led)
Juniper EF, 1994, Canada[21]	Interview and survey	Item generation and selection	Consult
Juniper EF, 1996, Canada[22]	Survey	Item generation and selection, content validity testing	Consult
Armstrong FD, 1999, USA[23]	Interview	Item generation and selection	Consult
Ravens-Sieberer U, 2001, Multisite Europe[24]	Focus group	Content validity testing	Consult
Bullinger M, 2002, Multisite Europe[25]	Survey, cognitive debriefing	Content validity testing	Consult
Jokovic A, 2002, Canada[26]	In-depth interview	Item generation and selection, content validity testing	Consult
Barnard D, 2003, Canada[27]	Interview	Item generation and selection	Consult
Ronen GM, 2003, Canada[28]	Focus group in item generation	Item generation	Consult
Moorthy LN, 2004 and 2007, USA [29, 30]	Interview (single open-ended question)	Domain identification and item generation	Consult
Petersen C, 2005, Multisite Europe[31]	Focus group and interview, Cognitive debriefing	Item generation and content validity testing	Consult
Waters E, 2005 and 2007, Australia[32, 33]	Qualitative interview	Item generation	Consult
Adair CE, 2007, Canada[34]	Semi-structured in-depth interviews,	Item generation and selection, content validity testing	Consult

	narratives, focus group		
Buck D, 2007, UK[35]	Cognitive in-depth interview	Item selection and content validity testing	Consult
Christie G, 2007, New Zealand[36]	Interview and focus-group	Item selection and content validity testing	Consult
Cochrane G, 2008, Australia[37]	Focus group, In-depth interview	Domain identification	Consult
Kintner E, 2008, USA[38]	Qualitative interview	Domain identification, item generation and face validity testing	Consult
Walsh TR, 2008, USA[39]	Focus group	Item generation	Consult
Bourke-Taylor H, 2009 and 2010, Australia [40, 41]	In-depth interview	Item generation	Consult
Irwin DE, 2009, USA[42]	Cognitive interview	Content validity (comprehensibility)	Consult
Markham C, 2009, UK[43]	Modified focus group	Concept elicitation	Consult
Shaikh N, 2009, USA[44]	In-depth interview, survey	Item selection, content validity testing	Consult
Aparicio López C, 2010, Spain[45]	Survey	Content validity testing	Consult
Arbuckle R, 2010, USA[46]	Open ended qualitative interview and cognitive debriefing interview	Concept elicitation, item generation, content validity testing	Consult
Barker D, 2010, USA[47]	Focus group	Item generation	Consult
Liu WY, 2010, Taiwan[48]	Survey	Face validity testing	Consult

Mulcahey MJ, 2010, USA[49]	Cognitive testing interview	Item generation	Consult
Roodra LD, 2010, Netherland [50]	Interview	Content validity testing	Consult
Akram A J, 2011, UK[51]	Focus group, survey	Item generation, ease of administration, face, and content validity testing	Consult
Angeles-Han, ST, 2011, USA[52]	Interview, questionnaire	Item generation, Face, and content validity	Consult
Lai JS, 2011, USA[53]	Interview, cognitive interview	Item generation, content validity testing	Consult
Punpanich W, 2011, Thailand[54]	In-depth structured interview, cognitive interview	Item generation, content validity testing	Consult
Rahi JS, 2011, UK[55]	Focus group, in-depth interview	Concept elicitation, Item generation	Consult
DeCarlo DK, 2012, USA[56]	Focus group	Domain identification and item generation	Consult
Panepinto JA, 2012, USA[57]	In-depth interview, cognitive interview (cognitive debriefing and think aloud)	Domain identification and item generation, content validity testing	Consult
Tsakos G, 2012, UK[58]	Focus group	Item selection and content validity testing	Consult
Varni JW, 2012, USA[59]	Focus and cognitive interview	Item generation and content validity testing	Consult

Bevans KB, 2013, USA[60]	Semi-structured interview and cognitive interview	Conceptual framework, item generation and content validity testing	Consult
Bokhary KA, 2013, Saudi Arabia[61]	Individual interview	Item generation and content validity testing	Consult
Carlton J, 2013, UK[62]	Semi-structured interview, cognitive debriefing interview	Item generation, content validity testing	Consult
Dufresne H, 2013, France[63]	One-to-one sessions, cognitive debriefing interview	Item generation and content validity testing	Consult
Fabricant PD, 2013, USA[64]	Survey	Item generation and selection, content validity testing	Consult
Kerfeld CI, 2013, USA[65]	Cognitive interview	Content validity testing	Consult
Forrest CB, 2014, USA[66]	Cognitive debriefing interview	Concept elicitation, content validity testing	Consult
Geister TL, 2014, USA[67]	Semi-structured and cognitive interview	Concept elicitation, content validity testing	Consult
Izaguirre MR, 2014, USA[68]	Semi-structured and cognitive interview	Concept elicitation and content validity testing	Consult
Morley TE, 2014, Canada[69]	Cognitive probing interview	Comprehensibility testing	Consult
Ng V, 2014, Multi-country[70]	Semi-structured interview and focus group	Item generation	Consult
Ravens-Sieberer U, 2014, Germany and USA[71]	Semi-structured interview and cognitive interview	Item generation, content validity testing	Consult

Tucker CA, 2014, USA[72, 73]	Semi-structured interview and cognitive interview	Concept elicitation and item generation, content validity testing	Consult
Costa-Tutusaus L, 2015, Spain[74]	Focus group	Item generation	Consult
Jacobson jr. CJ, 2015, USA[75]	Semi-structured interview, focus group, cognitive debriefing	Concept elicitation, item generation, content validity testing	Consult
Parslow R, 2015, 2019, and 2020, UK[76, 77, 78]	Cognitive interview, focus group	Concept elicitation and item generation, content validity testing	Consult
Young NL, 2015, Canada[79]	Cognitive interview and community consultation	Face validity and interpretability	Consult
Adams M, 2016, UK[80]	Focus group, cognitive interviewing	Item generation, Face validity testing	Consult
Bearss K, 2016, USA[81]	Focus group	Item generation	Consult
Benson PE, 2016, UK[82]	Interview	Content validity and item reduction	Consult
Bramhagen AC, 2016, Sweden[83]	Not reported	Content validity and comprehensibility testing	Consult
Dell SD, 2016, multi-country[84]	Focus group, open ended interview, survey, cognitive interview	Item generation, content validity testing	Consult
Dellenmark-Blom M, 2016, Sweden[85]	Focus group	Item generation	Consult
Follansbee-Junger KW, 2016, USA[86]	Focus group, cognitive debriefing interview	Item generation, content validity testing	Consult

Keays MA, 2016, Canada and USA[87]	Open ended interview, survey	Item generation, face validity	Consult
Newcombe PA, 2016, Australia[88]	Focus group	Item generation and selection	Consult
Olivieri I, 2016, Italy[89]	Focus group	Item generation	Consult
Vande Velde S, 2016, Belgium[90]	Interview	Item generation and comprehensibility testing	Consult
Ardelt PU, 2017, Germany[91]	Open session, survey	Item generation and pilot testing	Involve and consult
Bevans KB, 2017, USA[92]	Semi-structured interview, cognitive interview	Concept elicitation, item generation and content validity testing	Consult
Elsman EB, 2017, Netherland[93]	Survey, focus group, semi-structured interview, concept mapping workshop	Concept elicitation, item generation, face, and content validity testing	Consult
Klingels K, 2017, multi-country[94]	Focus group	Concept elicitation, item generation and selection, relevance and content validity testing, interpretation of findings	Involve
Longmire NM, 2017, Multi-country[95] Tassi A, 2021, Canada[96]	Semi-structured interview, cognitive interview	Concept elicitation, content validity testing	Consult
Oluboyede Y, 2017, UK[97]	One-to-one and focus groups interviews	Item generation, content validity testing	Consult

Reeve BB, 2017, USA[98, 99]	Cognitive interview	Refinement and content validity testing	Consult
Samuels-Kalow ME, 2017, USA[100]	Free-listing, semi-structured interview, cognitive interview	Concept elicitation, item generation	Consult
Skjerning H, 2017, Denmark and Ireland[101]	Focus group, Cognitive interview	Item generation, comprehensibility, and content validity testing	Consult
Somer R, 2017, Germany[102] Bloemeke J, 2019, Germany and Spain[103]	Focus group, cognitive debriefing	Concept elicitation and item generation, content validity testing	Consult
Sperling CD, 2017, Denmark[104]	Qualitative interview youth panel meetings, cognitive interview	Theme identification, item generation, content validity testing	Involve and consult
Tapia VJ, 2017, USA[105]	In-depth interview	Theme identification, item generation, content validity testing	Consult
Wong Riff KW, 2017 and 2018, multi-country[106, 107]	In-depth interview (interpretive description)	Concept elicitation, item generation	Consult
Wright WJ, 2017, USA[108]	Focus group, one-on-one interview	Item generation, face and content validity	Consult
Basra MKA, 2018, UK[109]	Semi structured interview, cognitive debriefing	Concept elicitation and Item generation, content validity testing	Consult
Fiume A, 2018, Canada[110]	In-depth semi-structured interview	Concept elicitation and Item generation,	Consult

		content validity testing	
Heyworth B, 2018, USA[111]	Cognitive interview, survey	Item generation, content validity testing	Consult
Lewis S, 2018, USA[112]	In-depth individual interview and cognitive debriefing	Concept elicitation and item generation and selection, content validity testing	Consult
McErlane F, 2018, UK[113] Lunt LE, 2020, UK[114]	Scientific steering committee workshops, survey, cognitive interview	Concept elicitation, item generation and selection, face and content validity testing	Collaborate and consult
Niemitz M, 2018, Germany[115]	Focus group	Item generation	Consult
Santucci NR, 2018, USA[116]	Interview	Face and content validity	Consult
Bevans KB, 2019, USA[117]	Semi-structured interview, cognitive interview	Concept elicitation and item generation, content validity testing	Consult
Chhina H, 2019 and 2021, multi-country[118, 119]	Semi-structured interview, cognitive debriefing	Concept elicitation, item generation and selection	Consult
Halleran DR, 2019, USA[120]	Open ended questions via email or in person interview, cognitive interview	Item generation, face validity	Consult
Heidi M, 2019, UK[121]	Focus group, semi-structured interview	Theme identification and item generation	Consult
Hoffman MF, 2019, USA[122]	Open ended questions interview	Item generation, content validity testing	Consult

	and cognitive interview		
Jaudszus A, 2019, Germany[123]	In-depth cognitive interview	Concept elicitation	Consult
Klassen AF, 2019, Canada and USA[124]	Individual and cognitive interview	Concept elicitation, item generation and selection	Consult
Nelson LM, 2019, USA[125]	Semi-structured interview and cognitive debriefing	Concept elicitation, content validity testing	Consult
Newton L, 2019, USA[126]	In-person interview and cognitive debriefing	Concept elicitation, content validity testing	Consult
Piscione J, 2019, Canada[127]	Cognitive interview	Item selection and content validity testing	Consult
Propp R, 2019, Canada[128]	Semi-structured interview	Item selection and content validity testing	Consult
Sarda SP, 2019, USA[129]	Open ended questions and cognitive interview	Concept elicitation, item selection and content validity testing	Consult
Tingsgaard JK, 2019, Denmark[130]	Semi-structured single-person interview	Face and content validity testing	Consult
Tsangaris E, 2019, Canada[131]	Cognitive interview	Content validity testing	Consult
Bevans KB, 2020, USA[132]	Semi-structured interview and cognitive interview	Item generation and content validity testing	Consult
De Zwaan M, 2020, Germany[133]	Open-ended questions and cognitive debriefing	Concept elicitation and item generation, content validity testing	Consult
Halstead P, 2020, USA[134]	Open-ended qualitative questions	Concept elicitation, item generation and	Consult

	and tasks and cognitive debriefing	content validity testing	
Martin SA, 2020, USA[135]	Focus group, cognitive debriefing	Concept elicitation and item generation, content validity testing	Consult
McCarrier KP, 2020, USA[136]	Semi-structured interview and cognitive interview	Concept elicitation and item generation, content validity testing	Consult
Robertson AO, 2020, UK[137]	Semi-structured in-depth interview, cognitive interview	Item generation and selection, content validity testing	Consult
Wyrwich KW, 2020, USA[138]	Cognitive debriefing interview	Content validity testing	Consult
Zigler CK, 2020, USA[139]	Focus group, survey, cognitive interview	Concept elicitation and item generation, content validity testing	Consult
Cejas I, 2021, USA[140]	Open-ended interview, cognitive interview	Item generation and selection, content validity testing	Consult
Dermott JA, 2021, Canada[141]	Cognitive interview	Item selection and content validity testing	Consult
Griffiths C, 2021, UK[142]	Semi-structured interview and cognitive interview	Conceptual framework, item generation, and content validity testing	Consult
Gwaltney C, 2021, USA[143]	Semi-structured interview, cognitive debriefing	Concept elicitation, item generation and selection, content validity testing	Consult
Hall R, 2021, USA[144]	Semi-structured (open ended questions) interview	Concept elicitation and item generation,	Consult

	and cognitive debriefing	content validity testing	
Meltzer LJ, 2021, USA[145]	Face to face interview and cognitive interview	Concept elicitation, content validity testing	Consult
Pandina G, 2021, USA[146]	Cognitive interview	Content validity testing	Consult
Powell PA, 2021, UK[147]	Advisory group meetings, Semi-structured interview, cognitive debriefing	Item generation, item selection	Involve and consult
Ramchandren S, 2021, Multi-country[148]	Focus group	Content and face validity	Consult
Schwartz AE, 2021, USA[149]	Team meetings, focus group	Content validity of response scales	Collaborate and consult
Winnette R, 2021, USA[150]	Cognitive debriefing	Content validity testing	Consult
Zizzi CE, 2021, USA[151]	Semi-structured qualitative interview	Content validity testing	Consult

*Each row represents a PROM which its development process may have been reported in more than one study.

PROMs: Patient-reported outcome measure

Table 2. 3 Quality of PPI reporting assessment using GRIPP2-SF checklist*

Author Publication year Country	**Aims—Report the aim of PPI in the study**	**Methods—Provide a clear description of the methods used for PPI in the Study**	**Study Results—Outcomes: Report the results of PPI in the study, including both positive and negative outcomes**	**Discussion and Conclusions—Outcomes: Comment on the extent to which PPI influenced the study overall; Describe positive and negative effects**	**Critical Perspective—Comment critically on the study, reflecting on the things that went well and those that did not so others can learn from this experience**
Juniper EF, 1994, Canada[21]	✓	✓	✓	✓	

Juniper EF, 1996, Canada[22]		✓	✓	✓	
Armstrong FD, 1999, USA[23]	✓	✓	✓	✓	
Ravens-Sieberer U, 2001, Multisite Europe[24]	✓	✓			
Bullinger M, 2002, Multisite Europe[25]	✓	✓	✓		
Jokovic A, 2002, Canada[26]	✓	✓	✓	✓	
Barnard D, 2003, Canada[27]	✓	✓	✓	✓	
Ronen GM, 2003, Canada[28]	✓	✓	✓	✓	
Moorthy LN, 2004 and 2007, USA [29, 30]	✓	✓	✓	✓	
Petersen C, 2005, Multisite Europe[31]	✓	✓	✓	✓	✓
Waters E, 2005 and 2007, Australia[32, 33]	✓	✓	✓	✓	✓
Adair CE, 2007, Canada[34]	✓	✓	✓		
Buck D, 2007, UK[35]	✓	✓	✓	✓	
Christie G, 2007, New Zealand[36]	✓	✓	✓	✓	
Cochrane G, 2008, Australia[37]	✓	✓	✓	✓	✓

Kintner E, 2008, USA[38]	✓	✓	✓	✓	
Walsh TR, 2008, USA[39]	✓	✓	✓	✓	✓
Bourke-Taylor H, 2009 and 2010, Australia [40, 41]	✓	✓	✓	✓	
Irwin DE, 2009, USA[42]	✓	✓	✓	✓	✓
Markham C, 2009, UK[43]	✓	✓	✓	✓	✓
Shaikh N, 2009, USA[44]	✓	✓	✓		
Aparicio López C, 2010, Spain[45]	✓	✓			
Arbuckle R, 2010, USA[46]	✓	✓	✓	✓	
Barker D, 2010, USA[47]		✓			
Liu WY, 2010, Taiwan[48]	✓	✓	✓		
Mulcahey MJ, 2010, USA[49]	✓	✓	✓	✓	✓
Roodra LD, 2010, Netherland [50]	✓	✓	✓		
Akram A J, 2011, UK[51]	✓	✓	✓	✓	✓
Angeles-Han, ST, 2011, USA[52]	✓	✓	✓		
Lai JS, 2011, USA[53]	✓	✓	✓		
Punpanich W, 2011, Thailand[54]	✓	✓	✓		

Rahi JS, 2011, UK[55]	✓	✓	✓	✓	✓
DeCarlo DK, 2012, USA[56]	✓	✓	✓	✓	✓
Panepinto JA, 2012, USA[57]	✓	✓	✓	✓	✓
Tsakos G, 2012, UK[58]	✓	✓	✓	✓	✓
Varni JW, 2012, USA[59]	✓	✓	✓	✓	✓
Bevans KB, 2013, USA[60]	✓	✓	✓	✓	✓
Bokhary KA, 2013, Saudi Arabia[61]		✓	✓		
Carlton J, 2013, UK[62]	✓	✓	✓	✓	✓
Dufresne H, 2013, France[63]	✓	✓	✓		
Fabricant PD, 2013, USA[64]	✓	✓	✓		
Kerfeld CI, 2013, USA[65]	✓	✓	✓	✓	✓
Forrest CB, 2014, USA[66]	✓	✓	✓		
Geister TL, 2014, USA[67]	✓	✓	✓	✓	✓
Izaguirre MR, 2014, USA[68]	✓	✓	✓		
Morley TE, 2014, Canada[69]	✓	✓	✓	✓	✓
Ng V, 2014, Multi-country[70]	✓	✓	✓		
Ravens-Sieberer U, 2014, Germany and USA[71]	✓	✓	✓	✓	✓

Tucker CA, 2014, USA[72, 73]	✓	✓	✓	✓	✓
Costa-Tutusaus L, 2015, Spain[74]	✓	✓	✓	✓	
Jacobson jr. CJ, 2015, USA[75]	✓	✓	✓	✓	✓
Parslow R, 2015, 2019, and 2020, UK[76, 77, 78]	✓	✓	✓	✓	✓
Young NL, 2015, Canada[79]	✓	✓	✓	✓	✓
Adams M, 2016, UK[80]	✓	✓	✓	✓	✓
Bearss K, 2016, USA[81]	✓	✓	✓	✓	
Benson PE, 2016, UK[82]	✓	✓	✓	✓	
Bramhagen AC, 2016, Sweden[83]	✓	✓	✓	✓	
Dell SD, 2016, multi-country[84]	✓	✓	✓	✓	✓
Dellenmark-Blom M, 2016, Sweden[85]	✓	✓	✓		✓
Follansbee-Junger KW, 2016, USA[86]	✓	✓	✓	✓	✓
Keays MA, 2016, Canada and USA[87]	✓	✓	✓	✓	✓
Newcombe PA, 2016, Australia[88]	✓	✓	✓	✓	
Olivieri I, 2016, Italy[89]		✓	✓		

Vande Velde S, 2016, Belgium[90]		✓	✓		
Ardelt PU, 2017, Germany[91]	✓	✓	✓		
Bevans KB, 2017, USA[92]	✓	✓	✓	✓	✓
Elsman EB, 2017, Netherland[93]	✓	✓	✓		
Klingels K, 2017, multi-country[94]	✓	✓	✓	✓	
Longmire NM, 2017, Multi-country[95] Tassi A, 2021, Canada[96]	✓	✓	✓	✓	✓
Oluboyede Y, 2017, UK[97]	✓	✓	✓		✓
Reeve BB, 2017, USA[98, 99]	✓	✓	✓	✓	✓
Samuels-Kalow ME, 2017, USA[100]	✓	✓	✓	✓	
Skjerning H, 2017, Denmark and Ireland[101]	✓	✓	✓		
Somer R, 2017, Germany[102] Bloemeke J, 2019, Germany and Spain[103]	✓	✓	✓	✓	✓
Sperling CD, 2017, Denmark[104]	✓	✓	✓	✓	✓
Tapia VJ, 2017, USA[105]	✓	✓	✓	✓	✓

Wong Riff KW, 2017 and 2018, multi-country[106, 107]	✓	✓	✓	✓	✓
Wright WJ, 2017, USA[108]	✓	✓	✓		
Basra MKA, 2018, UK[109]	✓	✓	✓	✓	
Fiume A, 2018, Canada[110]	✓	✓	✓	✓	
Heyworth B, 2018, USA[111]	✓	✓	✓	✓	
Lewis S, 2018, USA[112]	✓	✓	✓	✓	
McErlane F, 2018, UK[113] Lunt LE, 2020, UK[114]	✓	✓	✓	✓	✓
Niemitz M, 2018, Germany[115]	✓	✓	✓	✓	✓
Santucci NR, 2018, USA[116]	✓	✓	✓		
Bevans KB, 2019, USA[117]	✓	✓	✓	✓	
Chhina H, 2019 and 2021, multi-country[118, 119]	✓	✓	✓	✓	✓
Halleran DR, 2019, USA[120]	✓	✓	✓		
Heidi M, 2019, UK[121]	✓	✓	✓		
Hoffman MF, 2019, USA[122]	✓	✓	✓	✓	✓
Jaudszus A, 2019, Germany[123]	✓	✓			

Klassen AF, 2019, Canada and USA[124]	✓	✓	✓	✓	
Nelson LM, 2019, USA[125]	✓	✓	✓		
Newton L, 2019, USA[126]	✓	✓	✓	✓	
Piscione J, 2019, Canada[127]	✓	✓	✓	✓	
Propp R, 2019, Canada[128]	✓	✓	✓	✓	✓
Sarda SP, 2019, USA[129]	✓	✓	✓	✓	✓
Tingsgaard JK, 2019, Denmark[130]	✓	✓	✓	✓	✓
Tsangaris E, 2019, Canada[131]	✓	✓	✓	✓	✓
Bevans KB, 2020, USA[132]	✓	✓	✓	✓	
De Zwaan M, 2020, Germany[133]	✓	✓	✓		
Halstead P, 2020, USA[134]	✓	✓	✓	✓	✓
Martin SA, 2020, USA[135]	✓	✓	✓	✓	✓
McCarrier KP, 2020, USA[136]	✓	✓	✓	✓	✓
Robertson AO, 2020, UK[137]	✓	✓	✓		
Wyrwich KW, 2020, USA[138]	✓	✓	✓		
Zigler CK, 2020, USA[139]	✓	✓	✓	✓	✓
Cejas I, 2021, USA[140]	✓	✓	✓	✓	

Dermott JA, 2021, Canada[141]	✓	✓	✓	✓	
Griffiths C, 2021, UK[142]	✓	✓	✓		
Gwaltney C, 2021, USA[143]	✓	✓	✓	✓	✓
Hall R, 2021, USA[144]	✓	✓	✓	✓	
Meltzer LJ, 2021, USA[145]	✓	✓	✓	✓	✓
Pandina G, 2021, USA[146]	✓	✓	✓	✓	
Powell PA, 2021, UK[147]	✓	✓	✓		
Ramchandren S, 2021, Multi-country[148]	✓	✓	✓		
Schwartz AE, 2021, USA[149]	✓	✓	✓	✓	✓
Winnette R, 2021, USA[150]	✓	✓	✓	✓	✓
Zizzi CE, 2021, USA[151]	✓	✓	✓		

*Each row represents a PROM which its development process may have been reported in more than one study.

PPI: Patient and public involvement, GRIPP2-SF: Guidance for Reporting Involvement of Patients and Public2-Short form

Chapter 3: Patient involvement in determining minimal important difference: A scoping review

3.1 Abstract

Objectives: The goal was to investigate the involvement of patients and parents/guardians in defining minimal important difference (MID). We also aimed to elaborate on how they have been involved in determining MID and the methods used to obtain MID.

Methods: MEDLINE, EMBASE, CINAHL, PsycINFO, and Cochrane CENTRAL were searched (1989 to September 2021). Hand searches of the reference lists of included studies were also performed. Studies reporting patient involvement regarding MID of any intervention were eligible for inclusion. The patient could be an adult, child or parent/guardian. Studies were excluded if they used only distribution and/or anchor-based methods or pre-established MIDs, sought opinions of healthcare providers or stakeholders other than patients, or reported only patient satisfaction with, or preference for, the health care system, products and/or services. Characteristics and findings of the included studies were reported descriptively.

Results: Of 6044 screened titles, 45 studies were included. Of these, 41 involved adults and 4 studies sought adolescents/parents' opinions. The most common MID outcomes were survival time, survival rate and symptom relief. Trade-off techniques were the most frequently used method to elicit patients' perspectives.

Conclusion: Most of the studies found in this review were focused on adults and there was a paucity of evidence regarding involvement of children/adolescents and their parents/guardians in determining MID. Heterogeneity in terminology, interventions, outcomes, and estimated MIDs,

even for the same clinical conditions, was notable. Mixed method studies and finding the best approach to incorporate patient priorities to generate a narrow range of MIDs are required.

3.2 Background

As the gold standard for determining treatment efficacy (1), randomized controlled trials (RCTs) are powered to detect the difference or change in the outcome of interest between study groups (2). However, this difference/change must outweigh risks, costs and inconvenience of the intervention in order to warrant its implementation. The smallest difference/change that meets these criteria was originally called minimal clinically important difference (MCID) (3, 4). The terminology has since been updated to minimal important difference (MID) to accommodate both patient and clinician perspectives. In the design phase of RCTs, trialists can calculate the sample size by ensuring that the study is powered to detect the estimated MID. In addition, MID helps researchers, clinicians, decision makers and guideline developers to interpret the findings of studies by comparing the magnitude of actual treatment effects with the estimated MID (5, 6).

Since 1989, when the concept was first introduced by Jaeschke et al. (3), several methods have been used to measure MCID, although most do not directly seek patient preferences. These methods include anchor-based, distribution-based, and opinion- seeking methods. Anchor-based methods relate the change in the measure of interest to an external measure of change, the "anchor", usually patient or clinical judgment (7). Distribution-based methods compare the change in the outcome of interest, whether continuous or ordinal, to some other statistical parameters of variability (e.g., standard error of measurement, standard deviation, effect size, and smallest detectable change) (2, 8). Opinion-seeking methods, such as surveys, Delphi methods,

and interviews can be used to elicit patients and/or clinicians' opinions about the change or difference they perceive as important (2).

Historically, health care providers have dominated the determination of MID. More recently, as patient-oriented research has been emphasized, patient input on MID is also being sought (4). In 2011, Cook et al. (2) conducted a systematic review (SR) to identify different methods for specifying a MID. Of 60 studies that sought opinions from patients, health care providers, and multidisciplinary experts, only 10 involved patients and none involved children or their parents/guardians (2).

Patient involvement in all aspects of research design has progressed significantly since the Cook study in 2011. Therefore, it is worthwhile to explore whether this is reflected in research regarding MID. Similar to adults, children have also the right to be involved in research about them and to be heard and valued (9). The goal of the present review was to investigate the involvement of patients in defining MID. We also aimed to elaborate on how they have been involved in determining MID and the methods used to obtain MID.

Objectives: 1) To review studies seeking adult patient opinions regarding MID for any disease, 2) To review studies seeking children/adolescents' and parents/guardians' opinions regarding MID for any disease.

Outcomes:

To quantify i) whether and, ii) how patients have been involved in determining MID.

3.3 Methods

We followed the PRISMA extension for scoping reviews (PRISMA-ScR) (10) guidelines for conducting and reporting this scoping review. (10). The protocol of this review was registered at PROSPERO (CRD42018085981).

3.3.1. Search strategy: With the help of a health research librarian, the following sources were searched from 1989 (the time in which the concept of MID was first introduced in the medical literature (3)) to September 2021: 1) Electronic literature search in the following databases: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, PsychINFO. 2) Hand-searching reference lists of included studies. No publication type, population, or language restrictions were applied.

Search terms related to minimal important difference were combined with search terms related to seeking patient opinions (Appendix C for search strategy in MEDLINE).

3.3.2. Study selection and data extraction:

We included studies reporting patient preferences with regard to MID of any intervention whether or not clinician/health care provider opinion was also reported. The patient could be adult, child/adolescent, or parent/guardian. Studies were not restricted by design, population, or interventions.

Studies that did not seek patient opinions, studies that only used distribution-based and/or anchor based methods to estimate MID or used pre-established MIDs, studies that only sought opinions of healthcare providers or stakeholders other than patients, studies that reported only patient satisfaction with, or preference for, the health care system, products and/or services, non-human

or non-clinical studies, review studies including systematic, narrative, and opinion pieces, or publications that lacked peer-review (e.g., conference abstracts, dissertations) were excluded.

Two reviewers (SKA, AC) screened titles and abstracts for relevant studies and then reviewed full texts of potentially relevant articles independently. Studies fulfilling the inclusion criteria were selected and any disagreements were resolved by a senior reviewer (SV). Data were extracted using an *a priori* data extraction form by one reviewer (SKA) and verified by a second reviewer (AC).

Demographics of the studies (publication year, title, first author, country), design, population characteristics (age, gender, sample size), interventions, outcomes, methods used to obtain MID from patients and clinicians/health care providers [if reported], and the overall value of the MIDs (if reported) were extracted.

3.3.3. Data analysis:

We narratively reported the methods used for obtaining MID and the overall values of MID. If studies obtained both patient and health care provider opinions, we reported both overall values.

3.4 Results

Of 6044 retrieved references from electronic and hand searches, 850 duplicates were removed and 5194 were screened using title and abstracts. Of these, 818 underwent full text screening of which 45 were included (11-55) (Figure 3.1).

3.4.1. General characteristics of the included studies

Most studies were conducted in Australia (N=9), UK (N=9), USA (N=9), and Canada (N=7). Almost all studies used either interviews or questionnaires to obtain patient opinions. Forty-one studies involved adults (Table 3.1). Four studies involved parents/guardians and three of these four also involved adolescents (Table 3.2). In addition to patient perspectives, 11 studies also obtained clinicians, nurses, or other health professionals' perspectives. Eight studies only included female participants.

3.4.2. Interventions/Outcomes and methods to obtain MID

The included studies acquired patient input for heterogenous interventions and outcomes. Chemotherapy, anti-hypertensive or cardioprotective therapies, physiotherapy, exercise programs, and surgeries were among the interventions specified. In eight studies, however, no specific intervention was mentioned. MID was most often calculated for outcomes related to survival time, survival rate, and symptom relief.

More than half of the included studies (24/45) used trade-off techniques to elicit patients' opinions about MID. Other methods included qualitative interviews, direct questions, standard gamble method, etc. (Table 3.1 and Table 3.2)

3.5 Discussion

In this review, we surveyed studies in which patients' opinions were sought regarding determination of MID. We found 41 studies involving adults and 4 studies involving adolescents and/or parents/guardians. Most of these studies used trade-off methods to elicit patients' views.

Estimation of MID has been a challenge since its introduction. We excluded studies that only used distribution- and/or anchor-based methods, which are the most common approaches used in

the current literature (8, 56). A common criticism of the distribution-based approach is that the measured change is not necessarily clinically important or based on the patient's perspective (4, 57). Standard error of measurement and smallest detectable change are considered measurement properties of the outcome measure which are independent of intervention (4). Therefore, they are mostly recommended to be used as supportive information alongside other estimates (2).

Anchor-based methods are the most common and accepted approaches used to determine MID, especially for patient-reported outcomes and health-related quality of life measures (2, 4, 8, 58). The majority of excluded studies in our review used this approach alone or in combination with distribution methods. While multiple anchors have been examined, the most frequently used is the patient global rating of change (6, 57). The anchor should be independent, interpretable, and relevant to patients (8, 57) but, although many anchor-based methods use patients' perceptions to recognize whether change has occurred, the threshold used for MID estimates is usually determined by the researcher (4, 59). Furthermore, this method relies mostly on within-patient change over time rather than differences between patients with and without intervention (59, 4). Lastly, the choice of anchor (e.g., the magnitude of correlation between anchor and the outcome measure), and the type of statistical method used to quantify the MID both affect the resulting MID estimates, yet neither are patient-driven (60, 61).

Various opinion-seeking methods have been developed to directly elicit patients' and/or health professionals' opinions about the change or difference they perceive as important (2). These methods are useful for any type of outcome and can be designed for any degree of difficulty (2).

Trade-off methods were the most common opinion-seeking methods in the studies included in this review. Barret et al. (2005) (59) developed a benefit-harm trade-off method that is well

accepted among researchers. In this method, a scenario including benefits, harms, costs, and inconvenience associated with the intervention of interest is described, and the participants are asked if they accept the intervention. This process is repeated using larger or smaller effect until the minimum benefit is determined. According to Ferreira et al. (2012) (4), this method is directly patient-driven and intervention specific. It focuses on the effect with and without the intervention, and not the change over time. However, the estimate of MID can be influenced by how scenarios are presented, methods of elicitation, and individual preferences (2).

In recent years, qualitative interviews have been used to determine MID. Semi-structured interviews using concept elicitation or cognitive debriefing, focus groups, Delphi panel methods and vignettes are among the methods that are used in an independent study or embedded as exit interviews in the clinical trials (58). In a study by Staunton et al., (2019) (58), they recommend using triangulation methods in which estimates calculated by anchor and distribution methods are supported by the findings of qualitative studies to generate a single MID or a narrow range.

Strengths of the review

In the review by Cook et al. (2011) (2), 60 studies used opinion-seeking methods, of which only 10 focused on patients. However, in our review, we found 27 studies obtaining patients' opinions before 2011. It should be noted that the review by Cook et al. was conducted to find studies determining the "target difference" using all known methods, whilst our review has only focused on patient involvement in MID determination. We also hand searched the reference lists of the included studies which enabled us to find more articles. As another strength of this review, we used a comprehensive search strategy and did not restrict our search to any specific population, condition, or language.

Limitations

As in other reviews (60, 61), the heterogeneity in data such as terminology, interventions and outcomes, were noticeable in our review. Even for the same clinical condition, different MIDs were estimated. Hence, challenges remain to reconcile these heterogenous data and how to interpret them. Multiple MIDs hamper sample size calculation and interpretation of clinical trials findings. Moreover, disease severity, the specific intervention under study, and patient characteristics could all impact the final MID estimate (62).

Conclusion and future research

This review was conducted to show whether and how patients' opinions have been sought in the determination of MID. Most of the studies found in this review were focused on adults and there was a paucity of evidence regarding involvement of children/adolescents and their parents/guardians in determining MID. Heterogeneity in terminology, interventions, and outcomes, and estimated MIDs even in the same clinical conditions was notable. Patient-oriented research emphasizes the involvement of patients in the design stage of research and interpretation of findings. Hence, estimation of MID, which should be patient-driven according to its definition, underscore the need for more studies to seek patients' perspectives directly. Future research will benefit from mixed method studies. In addition, studies for finding the best method to reconcile the distribution, anchor and qualitative data resulting in a narrow range of MIDs for specific interventions and outcomes are warranted.

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3.7 Tables and figures

Figure 3. 1 Adapted version of PRISMA flow diagram of study selection for the MID scoping review

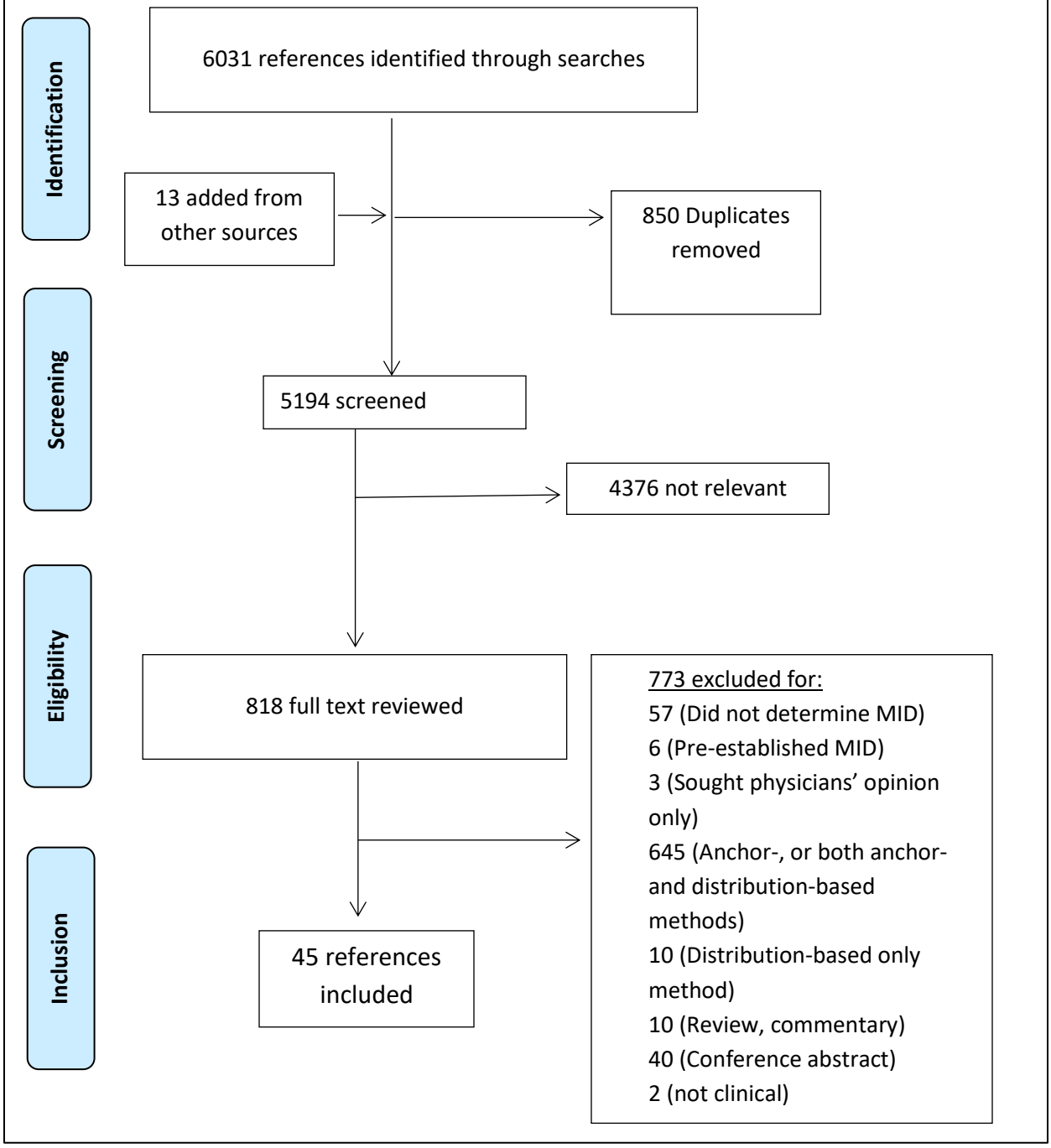

Table 3. 1 General characteristics and results of studies seeking opinions of adults regarding MID

Authors Publication Year Country	Study design	Sample size	Age	Gender (F/M)	Study objective	Intervention	The outcome that MID calculated for	How they asked about MID	Reported MID value
Bryce RL, 1989, Australia[11]	Interview	Pregnant women: 66, Clinicians: 46	Patients: mean 29, 50% between 25-35, Clinicians: 50% between 35-45 years	Patients: All female, Clinicians: 22% female	"what excess miscarriage rate would women tolerate in order to gain the perceived advantages of their preferred procedure? (CVS vs. amniocentesis)"	Chorionic villus sampling (CVS)	The risk of miscarriage	Standard gamble method	Pregnant women: median utility for CVS of a miscarriage rate of 0.9%, Clinicians: 1.2%
Reed W, 1993, USA[12]	Interview	35	Median: 53, range 40-65 years	22/13	"To assess variability in patients' values and preferences regarding cholesterol-lowering therapy"	Cholesterol lowering therapy	Life expectancy	Time trade-off, Standard reference gamble	Time trade-off (The amount of additional life patients required) median 3 months, range: 1-81 months The standard reference Gamble (Risk of painless death in 30 days vs. chance of normal life expectancy off therapy) median :0.1%, range: 0.1-22%

Bremnes RM, 1995 Norway[13]	Questionnaire	Cancer patients: 98 Healthy individuals (control): 42 Clinicians (surgeon, oncologists): 79 Nurses (surgical and oncology): 102	Mean: patients 55, Controls 37, Clinicians: surgeons, oncologist s: 41, 42, Nurses: oncology, surgical 29,35 years	Patients (55% male), Controls (34% male), Clinician s (78-80 % male), Nurses (0-6% male)	"To indicate the minimal benefit with respect to chance of cure, life prolongation and symptom relief they would demand to accept the treatment."	Cancer chemotherapy	Chance of cure, life prolongation, symptom relief	Presenting a hypothetical situation and then asking about the minimal benefit they would require from treatment	Patients: median chance of cure: 43%, prolongation of life: 12 months, symptom relief: 50% Controls: median chance of cure: 20%, prolongation of life: 9 months, symptom relief: 50% Clinicians: median chance of cure: (surgeons 25%, oncologists 10%), prolongation of life: surgeons:12 months, oncologists: 6 months, symptom relief: both 50% Nurses: median chance of cure: (surgical 40%, oncology 25%), prolongation of life: surgical:12 months, oncology: 12 months, symptom relief: both 50%
Man-Son-Hing M, 1996, Canada[14]	Interview (face-to-face)	64	Mean (SD): 68.9 (9)	19/45	"To determine the minimal clinically important difference (MCID) of warfarin therapy for the treatment of nonvalvular	Warfarin therapy	Risk of stroke in non valvular atrial fibrillation	Probability trade-off techniques (ping-pong methods, known efficacy method)	Given a 10% baseline risk of having a stroke in the next 2 years if not taking warfarin, the mean MCID was 2.01% (95% CI 1.60-2.42), meaning they would take warfarin if the risk of stroke were

					atrial fibrillation"				increased by 2% on average
Silvestri G, 1998, USA[15]	Interview	81	31 patients:< 60 years, 30 patients: 60-70, 20 patients: >70 years	27/54	"To determine how patients with lung cancer value the trade off between the survival benefit of chemotherapy and its toxicities"	Chemotherapy	Survival threshold for accepting chemotherapy	Modified time trade-off	The median survival threshold for accepting chemotherapy: 4.5 months for mild toxicity and 9 months for severe toxicity. Choice between supportive care and chemotherapy: 18 (22%) patients chose chemotherapy for a survival benefit of 3 months. 55 (68%) patients chose chemotherapy if it substantially reduced symptoms without prolonging life.
McAlister F, 2000, Canada[16]	Interview (face-to-face)	Patient: 72 family physicians: 74	Mean (SD): Patients: 49.4 (8) Clinicians: 45 (7.6)	Patients: 39/33 Clinicians: 28/46	"to determine the treatment thresholds of family physicians and hypertensive patients for mild, uncomplicated essential hypertension"	Anti-hypertensive therapy	Cardiovascular risk in patients with hypertension	Probability trade-off tool	The minimum risk of a CV event which makes patients would want to take the therapy in different scenarios: (2% risk in 5 yr): 1.5 (1.3–1.7) (5% risk in 5 yr): 2.8 (2.3–3.3)

									(10% risk in 5 yr): 4.0 (3.2–4.9) (15% risk in 20 yr): 6.1 (4.8–7.4) (30% risk in 20 yr): 7.8 (6.0–9.7) (50% risk in 20 yr): 9.8 (7.1–12.6)
Steel N, 2000, UK[17]	Postal questionnaire	Public:58 Practice nurses:32 GPs:30 Consultant physicians: 29	Public:45 % 41-65 years, Practice nurses:50 % 41-65 years, GPs:53% 41-65 years, Consultant physicians :76% 41-65 years	Public:58 % female, Practice nurses:97 % female, GPs:30% female, Consultant physicians:14% female	" The study compared the threshold at which consultant physicians, general practitioners, nurses attached to a general practice, and the general population would start taking antihypertensive drugs."	Anti-hypertensive therapy	Number needed to treat (NNT) to prevent mortality in 5 years	A questionnaire presenting a hypothetical situation and asking whether respondents would take therapy	Median (IQR) NNT: Public: 33-(12-250) Practice nurses: 33 (<12-250) GP: 50 (33-100) Consultant physicians: 100 (50-250)
Devereaux PJ, 2001, Canada[18]	Prospective observational study (face to face interview)	Patients: 61, Physicians: 63	Patients: 52% <75 years Physicians : Not reported	Patients: 26/37 Physicians: Not reported	" To determine and compare physicians' and patients' thresholds for how much reduction in risk of stroke is necessary and how much risk of excess	Antithrombotic therapy	Risk of stroke and bleeding	Probability trade-off tool	The minimum number of strokes that needed to be prevented in 100 patients over two years Warfarin: Patients: 1.8 (SD 1.9) Physicians: 2.5 (1.6) Aspirin: Patient:1.3 (1.3) Physicians: 1.6 (1.5) The maximum number of acceptable excess bleeding in

					bleeding is acceptable with antithrombotic treatment in people with atrial fibrillation."				100 patients over two years Warfarin: Patients: 17.4 (7.1) Physicians: 10.3 (6.1) Aspirin: Patient: 14.7 (8.5) Physicians: 6.7 (6.2)
Jansen SJT, 2001, Netherland [19]	Interview	Chemotherapy group: 38, no-chemotherapy group: 38	Chemotherapy: mean (SD): 42 (5.5), No-chemotherapy: 55 (9.3)	All female	" to determine the minimum benefits that patients need to find chemotherapy acceptable"	Adjuvant chemotherapy for early-stage breast cancer	Improved 5-year disease-free survival	Adapted version of the decision board described by Levine et al., (1992).	In the chemotherapy group, the median benefit was 1%, in the no-chemotherapy group: 12-15%
Trewby PN, 2002, UK[20]	Questionnaire and interview	307 (group 1(102): recent MI, group 2 (105): on preventive drugs but no recent MI, group 3 (100): control)	Mean (SD): Group 1: 62 (11.4), group 2: 64.1 (9.4), group 3: 57.5 (15) years	Group 1: 75.5 % male, Group 2: 53.3% male, Group 3: 45% male	" to find the threshold of benefit for a hypothetical cholesterol-lowering drug below which the subject would not be prepared to take the drug."	Cholesterol lowering therapy	Risk of CVD, prolongation of life	Presenting scenario and then asking about the minimum acceptable benefit patients require.	Median values for the threshold of benefit below which the subject would not take the preventive drug: Group 1 (20%), group 2 (20%), and group 3 (30%) absolute risk reduction for a CVD event. Median values for expectation of average prolongation of life: Group 1 (12 months), group 2 (12 months) and group 3 (18 months).
Wong RK, 2002, Canada[21]	Interview	43	Mean (SD): 62 (15)	14/29	"To measure patient-based minimal clinically important	Short (5 days) and long (20 days) terms radiotherapy regimens	Pain relief in unresectable painful pelvic recurrences	Decision aid– facilitated trade-off exercises	When the probability of pain relief was unchanged, the median switch point from short term (5

					effect sizes for pain relief between two contrasting palliative radiotherapy regimens for painful pelvic recurrences from rectal cancer."		from rectal cancer		days) to long term (20 days) treatment for the duration of pain relief was 6.7 and 7.2 months for severe and mild pain, respectively
Lewis DK, 2003, UK[22]	Questionnaire	Patients: 163, Health professional: 155	Mean age: Patient:52 Health professional: 38	147/170	" This study compared the absolute benefits of treatment different groups would require before starting treatment themselves."	Tablet reducing the risk of heart attack	% saved from myocardial infarction over 5 years	Presenting a question asking about the minimum absolute benefit they require.	Patients: 50 (10-75) Health professionals: 10 (5-38)
Barrett B, 2005, USA[23]	Interview (in person and telephone)	460 (149 in person, 162 telephone interview)	Mean (SD): 35.5 (14.7) Range: 18-80 years	104/45	"To develop methods to assess SID and to estimate SID for common cold"	Vitamin C, Echinacea, Zinc, Pleconaril	Common cold: Reduction in length of illness (duration)	Benefit-harm trade-off method	Overall: 52.6 h, Vitamin C: 26.1 h, Echinacea: 36.8h, Zinc: 64.8 h, anti-viral: 82.6 h
Duric VM, Fallowfield, LJ, 2005, Australia[24]	Interview	85	Median: 45 years	All female	" to determine the preferences of premenopausal women who had adjuvant endocrine therapy in a randomised trial."	Adjuvant endocrine therapy in early breast cancer	Survival times and rates	Trade-off method	More than half the women required gains of at least 5% in survival rates or 3 years absolute survival time

Duric VM, Stockler MR, 2005, Australia[25]	Interview	97	Median: 55 years	All female	" We sought the preferences of contemporary women who received chemotherapy. "	Adjuvant chemotherapy for early breast cancer	Survival rate and life expectancy	Trade-off method	68-84% women required improvements of an additional year in life expectancy or 3% in survival rates
Hirose T, 2005, Japan[26]	Face-to-face interview (questionnaire)	Chemotherapy group: 73 Control group: 120	40-80 years	Chemotherapy group: 16/57 Control group: 55/65	" to determine how Japanese patients with lung cancer weigh potential survival, response rate, and symptom relief against the potential toxicity of different treatment strategies."	Intensive and less intensive chemotherapy for advanced non-small cell lung cancer	"Chance of cure," "Response but not cure," "Symptom relief", "prolonging life"	Questionnaire presenting a scenario and then asking about the minimal benefit patients would accept	3 months additional life required by 19% and 21% of patients with lung cancer to receive intensive and less-intensive treatment, respectively. When the chance of symptom relief was 70%, 73% of patients with lung cancer were willing to choose intensive chemotherapy
Yelland MJ, 2006, Australia[27]	Descriptive study nested within RCT	110	Median (IQR): 50 (44, 59) years	63/47	" To describe patients' perceptions of minimum worthwhile and desired reductions in pain and disability upon commencing treatment for chronic low back pain."	Prolotherapy injections and exercises	Pain and disability in chronic low back pain	Question asking about the minimum percentage improvement	Median (inter-quartile range) minimum worthwhile reductions were 25% (IQR 20%, 50%) for pain and 35% (20%, 50%) for disability. Desired reductions of 80% (60%, 100%) for pain and 80% (50%, 100%) for disability

Barrett B, 2007, USA[28]	Interview (in person and telephone)	253 (182 in-person, 162 telephone interview)	Mean (SD): 34.8 (13.3) Range: 18-74 years	139/66	"to estimate the sufficiently important difference (SID) for the common cold"	Vitamin C, Echinacea, Zinc, Pleconaril (anti-viral)	Common cold: Severity reduction	Benefit-harm trade-off method	Vitamin C: 25%, Echinacea: 32%, Zinc: 47%, Anti-viral: 57%
Johnson FR, 2007, USA[29]	Survey	523	Mean (SD): 52 (4.37)	All female	"to estimate the maximum acceptable risk (MAR) of long-term treatment side effects that women are willing to bear in exchange for relief of vasomotor symptoms"	Hormone therapy	Improvement in vasomotor symptoms	Choice-format conjoint analysis (discrete choice experiment) employing benefit-harm trade-off tasks	Women were willing to accept greater risks in exchange for greater relief in their symptoms
Aarabi M, 2008, UK[30]	Cross-sectional face-to-face interview	262 both groups South Asians: 110, Caucasian: 152	Mean: South Asians men: 50.2 (11.6), women: 52.0 (11.2), Caucasians men: 52.2 (12.0), women: 51.7 (10.7) Range: 35-74 years	South Asians: 52/58, Caucasians: 77/75	"To establish people's willingness to receive antihypertensive drug treatment as primary prevention of CVD"	Anti-hypertensive therapy	CVD risk	Benefit-harm trade-off method	The minimum CVD risk which makes patients would want to take the therapy in different scenarios: South Asians: Scenario 1 (10% CHD risk without treatment in 10 yrs): 1%, Scenario 2 (20% CHD risk in 10 yrs): 2%, Scenario 3 (40% CHD risk in 10 yrs): 1%Caucasians: 4% in all scenarios

Duric VM, 2008, Australia[31]	Interview	46 women and their partners	Mean (SD): Women: 57, Partners: 60 Range: Women: 37-71, partners: 40-74 years	Women and their partners	"To compare women and their partners' preferences for adjuvant chemotherapy in early breast cancer."	Adjuvant chemotherapy	Survival times (5 and 15 yrs) and survival rates (65% and 85% at 5 years) in early breast cancer	Benefit-harm trade-off method	Most couples: extra 1 year in life expectancy or 3% i survival, An extra 1 day or 0.1% survival were judged sufficient to make adjuvant chemotherapy worthwhile by 59–72% of women and 54–59% of partners
Ferreira ML, 2009, Australia[32]	Cross-sectional, observational study (interview)	77	Mean (SD): 53.2 (15.1) years	51/26	" How much of an effect do five common physiotherapy interventions need to have for patients with low back pain to perceive they are worth their cost, discomfort, risk, and inconvenience ?"	Physiotherapy for low back pain	global perceived change (0 to 4) and percentage perceived change	Benefit-harm trade-off method	Participants perceived that intervention would have to make them 'much better', which corresponded to 1.7 (SD 0.7) on the 4-point scale, or improve their symptoms by 42% (SD 23), to make them worthwhile
Lauridsen HH, 2009, Denmark[33]	Prospective observational study (questionnaire)	147	Mean (SD): 46 Range: 19-82 years	82/65	"to determine the reproducibility and validity of a novel method for estimating low back pain (LBP) patients' view of an acceptable	Standard conservative treatment	Low back pain outcome measures (The Oswestry disability index (ODI), the Bournemouth questionnaire (BQ), the 11-	A question asking about the acceptable level of pain and disability after treatment	The MCIDpre for chronic LBP patients scoring the ODI is a 26.1 points reduction (26%), 25.6 points (37%) for the BQ and 4.2 points (42%) for the NRSpain.

					change (MCIDpre) before treatment begins"		box numeric pain rating scale (NRSpain))		
Oliveira VC, 2009, Brazil[34]	Cross-sectional observational study (questionnaire)	86	Mean (SD): 36.9 (11.5)	60/26	"Does health locus of control predict the smallest worthwhile effect of motor control exercise or spinal manipulative therapy when adjusted for severity of pain?"	Motor control exercises and spinal manipulative therapy	Non-specific low back pain	Benefit-harm trade-off method	Mean (SD) of Smallest worthwhile effect (%) for exercise was 63 (22) and for spinal manipulation was 62 (28)
Allison DB, 2010, USA[35]	Survey	74	Mean (SD): Men: 46.4 (14), Women: 48.9 (11.4) Range: 24-73 years	66/8	"Evaluate patient opinions on acceptable risks in exchange for a given degree of weight loss"	Weight loss	The added risk of serious adverse events (SAEs) or death in obesity	Benefit-harm trade-off method	3.5% risk for death for 5% and 10% weight loss, SAEs risk: 7.2% for 5% and 6.7% for 10% weigh loss
Mullis R, 2010, UK[36]	Semi-structured interview	15	Mean: 50 Range: 24-78 years	6/9	"The aim of this project was to develop a goal-based individualized assessment tool capable of defining meaningful change in condition from the patient	Not specified	Problems associated with low back pain	Modified goal attainment scaling method	59 problem areas were identified, and then reduced to the 45 most important goals (three for each patient). The minimal significant improvement was identified on 31 (69%) of these.

					perspective for use in longitudinal clinical studies"				
Carragee EJ, 2010, USA[37]	Descriptive study (questionnaire)	165	Mean (SD): Spondylolisthesis: 42.6 (12.2), degenerative disc disease: 40.9 (10.1)	Spondylolisthesis: 43.7% female, Degenerative disc disease: 59.6% female	"to describe a method of assessing treatment success based on prospective, patient-reported ''minimum acceptable'' outcome for which they would undergo a procedure"	Lumbar fusion	Pain intensity, functional outcome (Oswestry Disability Index [ODI]), medication usage, and work status in Isthmic spondylolisthesis or disc degeneration	Benefit-harm trade-off method	At least a decrease in pain intensity to 3/10 or less, an improvement in ODI of 20 or more, discontinuing opioid medications, and return to some occupational activity
Mullis R, 2011, UK[38]	Observational cohort study (Interview, questionnaire)	35	Mean (SD): 50 (14.4)	26/9	"The aim of this study was to explore the associations between goal attainment scores and disability, general health and global change in condition, with particular reference to minimal important change"	Not specified	Unresolving acute low back pain	Modified goal attainment scaling method	Minimal important change was identified on 67% of the goals

Chappell LC, 2012, UK[39]	Survey	Pregnant Women: 100, Clinicians: 100	Not reported	Patients: All female, Clinicians: Not reported	"to determine what reduction in score on the visual analogue scale would be a clinically meaningful difference among clinicians involved in treating women with intrahepatic cholestasis of pregnancy and among women who had previously experienced the condition"	Ursodeoxycholic acid	Itching in women with Intrahepatic cholestasis of pregnancy	Benefit-harm trade-off method	Women: Median: 30 mm reduction in itching, 95% CI: 10-60, Clinicians: Median: 30, 95% CI: 15-50
Hudson B, 2012, New Zealand[40]	Questionnaire	354	156/198	Mean (SD): 59.7 (5.7) years	"This study assessed participants' estimates of the benefit, as well as minimum acceptable benefit, of screening for breast and bowel cancer and medication to prevent hip fracture and	Breast and bowel cancer screening, and medications to prevent hip fracture and cardiovascular disease	the number of events (fractures or deaths) prevented in a group of 5,000 patients undergoing each intervention over a period of 10 years, and the minimum number of	Presenting a scenario and asking patient to indicate the minimum benefit they require from the interventions	Respondents required the minimum benefit greater than the actual benefit these interventions could achieve in reality except for cardiovascular mortality prevention.

					cardiovascular disease."		events avoided by the intervention		
Ferreira ML, 2013, Australia[41]	Telephone interview	102	Mean (SD): 45.2 (12.8)	78/24	"To determine the smallest worthwhile effects of two treatments for nonspecific low back pain (LBP)"	NSAIDs and physiotherapy	Pain, disability in chronic non-specific Low back pain	Benefit-harm trade-off method	For NSAIDs: 30% (10-40) greater improvement in pain and 20% (10-40) decrease in disability, For Physiotherapy: 20% (0-30%) improvement in pain and disability
Epstein RS, 2014, US, UK, Canada, Germany, Sweden, Norway[42]	Cross sectional survey	513	Mean (SD): 46.1 (13)	282/231	"to determine those symptoms of OIC that most patients ([80%) would prefer to improve, and to determine whether one more bowel movement per week was considered 'extremely' or 'very' important to them"	Not specified	Bowel movement per week in OIC	A question asking patient's opinion of what they consider important	"When asked 'how important is it you to have 1 more bowel movement per week'', over 90% endorsed it was 'somewhat', 'very', or 'extremely important' with nearly 70% (n = 354) endorsing the 'extremely' or 'very important' response options."
Lahaye S, 2014, Canada[43]	Cross-sectional (iPAD questionnaire)	172	Mean (SD): 72 (12)	56/116	"to determine the minimal clinically important difference (Treatment Threshold)	Anticoagulant therapy for stroke prevention	Risk of stroke, Risk of major bleeding event in non-valvular	Standard gamble method and an adaptation of the probability	At least a 0.8% (NNT=125) annual absolute risk reduction and 15% relative risk reduction in the risk of stroke in order to agree to

					and the maximum number of major bleeding events that a patient would be willing to endure in order to prevent one stroke (Bleeding Ratio) for the initiation of antithrombotic therapy"		atrial fibrillation	trade-off technique	initiate antithrombotic therapy, and patients were willing to endure 4.4 major bleeds in order to prevent one stroke
McNamara RJ, 2015, Australia[44]	Computer application	100	Mean (SD): 72 (9)	57/43	"to determine the smallest worthwhile effect of land-based and water-based pulmonary rehabilitation on 6-min walk distance among people with chronic obstructive pulmonary disease (COPD)"	Land-based and water-based pulmonary rehabilitation	6-min walk distance in patients with COPD	Benefit-harm trade-off method	For land-based pulmonary rehabilitation, the median smallest worthwhile effect was 20 m (95% CI 15–37 m). For water-based pulmonary rehabilitation, the median smallest worthwhile effect was 26 m (95% CI 15–33 m). The pulmonary rehabilitation would be worthwhile if it increased the 6-min walk distance by about 6%.
Franco MR, 2016, Australia[45]	Survey (On-line and face-to-face)	Discrete choice group: 220, trade-	Mean (SD): Discrete choice	Discrete choice group: 115/105,	"to estimate the smallest worthwhile effect of	A proposed exercise program	Risk of falling in community-dwelling	Discrete choice experiment and benefit-	The average smallest worthwhile effect of participation in an exercise program for

		off group: 66	group: 68 (6), trade-off group: 68 (6)	trade-off group: 37/29	exercise programs designed to prevent falls among older people"		older people who reported a past fall or a mobility limitation	harm trade-off method	discrete choice group: an absolute reduction in the risk of falling of 35% (standard deviation [SD] = 13) and for the benefit–harm trade-off group: 16% (SD = 11)
Ziai H, 2017, Canada[46]	Prospective cohort questionnaire	76	Mean (SD): 39.0 (13.7)	20/56	"to determine the patient-identified MID in the NOSE scale in patients with nasal obstruction due to a septal deviation who are planning on undergoing a septoplasty"	Nasal airway surgery	Nasal Obstruction Symptom Evaluation (NOSE) score in patients with septal deviation	A question asking patient opinion of smallest change in their score they require to consider surgery successful	Mean (SD) patient-identified MID: 5.3 (2.1) corresponding to a 41.1% change (95% confidence interval, 37.2-41.3) from baseline.
Anthony L, 2017, Multisite (USA, Canada, Australia, England, Germany) [47]	Telephone Interview (Exit interview of an RCT)	35	Mean (SD): 62	51% female	"to provide insight into the patient experience in TELESTAR and to help understand whether reductions in BM frequency (the primary end point) and other symptoms were clinically meaningful."	Telotristat ethyl therapy	Improvements in carcinoid syndrome symptoms	Qualitative interview	Most participants (60%) were satisfied with ≤30% reductions in bowel movement frequency

Christiansen D, 2018, Denmark[48]	Telephone interview	160	Mean (SD): 50.8 (14.2)	90/70	"To determine and compare estimates of the smallest worthwhile effect (SWE) for physiotherapy in neck, shoulder, and low-back pain patients"	Physiotherapy	Pain and disability, time to recovery in patients with neck, shoulder, and low back pain	Benefit-harm trade-off method	The median for improvements in pain and disability: 20% (95%CI; 10-30%) and time to recovery: 10 (95%CI; 7-14) days over a period of 6 weeks
Sully K, 2019, UK and USA[49]	Mixed-methods study (semi-structured interview)	20	11(55%) < 65 years	9/11	" to establish MID and RD for the European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma questionnaire (EORTC QLQ-MY20)."	Not specified	Health-related quality of life in patients with MM	Qualitative interview	Disease Symptoms Scale: improvement of 20 points, deterioration:10-point Side effects of Treatment scale: improvement of 10, 20 or 30 points improvement, deterioration of 5-10 points Estimates for the Body Image scale: improvement of 20-points, deterioration of 10-20 points Future Perspective scale: improvement of 10-points, deterioration of between 10-20 points
Crichton M, 2021, UK[50]	Prospective observational study (questionnaire)	173	69 (11.43)	99 (57%) female	" We developed a simple patient reported visual analogue	Not specified	Disease impact in patients with bronchiectasis	A question asking the improvement they consider	A median of 1.5 points in each domain on a 10-point scale

					outcome measure, the Bronchiectasis Impact Measure (BIM), for use in clinical research, including clinical trials."			clinically meaningful	
Kitchen H, 2021, Germany, US[51]	Semi-structured interview	Patients: 25. Clinicians: 4	Patients: 33 (6), Clinicians: not reported	Patients: All female, Clinicians: not reported	" This study explored the importance of symptoms (ESD items) and impacts (EIS domains), perspectives on scoring algorithms, and clinically important difference (CID) thresholds to inform clinical trial score interpretation. "	Not specified	Symptom change in the Endometriosis Symptom Diary (ESD) and Endometriosis Impact Scale (EIS)	Qualitative interview (cognitive exploration tasks)	2 or 3 points reduction in pain

CI: confidence interval; CVD: Cardiovascular diseases, CVS: Chorionic villus sampling, MM: Multiple myeloma, OIC: Opioid-induced constipation, NNT, Number needed to treat, SD: Standard deviation, SID: Sufficiently important difference, RD: Responder definition

Table 3. 2 General characteristics and results of 4 studies seeking opinions of pediatric/parents' population regarding MID

Authors Publication Year Country	Study design	Population			Study objective	Intervention	The outcome that MID calculated for	How they asked about MID	Reported MID value
		Sample size	Age Mean (SD) Range	Gender (F/M)					
Thissen D, 2016, USA[52]	Questionnaire, Interview	246 (78 adolescents, 85 parents, 83 clinicians)	Mean (SD): Adolescents: 14.9 (1.5), parents: 42.9 (7.9), Clinicians: 41.6 (9.2) Range: Adolescents: 13-18, parents: 25-82, Clinicians: 28-68 years	Adolescents: 31/47, parents: 69/16, Clinicians: 60/23	"To assess minimally important differences (MIDs) for several pediatric self-report item banks from the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS)."	Not specified	Depressive symptoms, Pain interference, Fatigue, Mobility	Scale-judgment method	The point at which 50% of judges would declare an important change. The MID estimated with adolescent and parent data: 3 points on the PROMIS T-score scale. The MID estimated with clinician's data: 2 points on the PROMIS T-score scale
Morgan E, 2017, USA[53]	Panel discussion	Adolescents: 4, Parents: 5, Clinicians: 7	Range: Adolescents: 15-20, parents of kids between 13-20	Adolescents and parents: all female, Clinicians: 4/3	"we conducted a novel exercise to ascertain the magnitude of change, or differences in scores, that were deemed clinically	Not specified	Mobility, upper extremity function (UE), fatigue, and pain interference in patients	"To define MIDs, panelists reviewed a full score report for the vignettes and indicated which items	Fatigue: Severe (3-9.4), mild (3-4.8) Pain interference: Severe (5.3-12.7), mild (2.1-5.5) Mobility: Severe (2.2-4.4), mild (1.6-5.4)

					significant by stakeholders."		with juvenile idiopathic arthritis	would need to change and by how much to represent ''just enough improvement to make a difference.'' "	UE function: Severe (1.8-2.8), mild (1.5-3.5)
Brigden A, 2018, UK[54]	Interview	21 children and their parents	Children: mean: 14.5, Range: 12-17	16 (76.2%) female	"to identify the MCID of the SF-36-PFS for children and adolescents with CFS/ME."	Not specified	Physical function sub-scale of SF-36 in pediatric patients with CFS/ME	Qualitative interview	10-point improvement
Ardestani SK, 2019, Canada[55]	Survey	Parents: 127 Clinicians: 45	Parents: 57 (46%) between 31-40	Parents: 98 (77.8%) female, Clinicians: 19 (49%)	"To establish the minimally important difference (MID) that would prompt parents and clinicians to use probiotics for prevention of paediatric antibiotic associated diarrhoea (AAD)"	Probiotic therapy	Risk of AAD in children	Trade-off method	39% reduction in the risk of AAD

AAD: Antibiotic-associated diarrhea, CFS/ME: Chronic fatigue syndrome/myalgic encephalomyelitis, JIA: Juvenile idiopathic arthritis

Chapter 4: Surveys of parents and clinicians concerning the minimal important difference of probiotic therapy for prevention of pediatric antibiotic-associated diarrhea

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4.1 Abstract

Objectives: To establish the minimally important difference (MID) that would prompt parents and clinicians to use probiotics for prevention of pediatric antibiotic-associated diarrhea (AAD) and to obtain parent and clinician opinion about the most important outcomes in clinical trials of AAD.

Methods: In this survey, parents of children presenting to the emergency department of a Canadian tertiary care children's hospital and pediatricians working in that hospital were approached. A range of potential MIDs were presented and participants selected one that they would require to use probiotics for AAD prevention. Additionally, participants were asked to rate a list of outcomes they would consider to be important in clinical trials of AAD.

Results: In total, 127 parents and 45 pediatricians participated. 51% (64/125) of parents and 51% (21/41) of clinicians responding to the MID question reported they would use probiotics if it reduced the risk of AAD by 39% (i.e., reduce the risk of AAD from 19% to 12%). The most important outcomes to parents, in descending order, were need for hospitalization, prevention of dehydration, disruption of normal daily activities, diarrhea duration and physician revisit. Pediatricians considered need for hospitalization along with physician revisit as the most important outcomes. They rated prevention of dehydration, diarrhea duration and stool frequency as important outcomes as well.

Conclusion: There is good agreement between parents and clinicians regarding how effective probiotics would need to be in preventing AAD in order to warrant use. This information, along with outcomes perceived to be most important, will help in the design of future clinical trials.

4.2 Background

Probiotics are defined as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host". (1, 2) Research shows a substantial increase in probiotic use in clinical and research settings and among the general public in the last three decades. (3)

According to a 2015 Cochrane systematic review,(4) probiotics may be effective for prevention of antibiotic associated diarrhea (AAD) in children (pooled relative risk (RR) = 0.46, 95% CI: 0.35-0.61), AAD can be delayed up to eight weeks after initiation of antibiotics.(5) Its incidence varies considerably (5-62 %) depending on the patient population, setting, type and duration of antibiotics.(6-12) Although mild-to-moderate diarrhea is more common, serious complications such as dehydration and *Clostridium difficile* infection can result.(11, 12) The proposed mechanism for the development of AAD is that antibiotics influence the gut microbial balance, altering its protective functions and leading to diarrhea.(13) AAD is particularly important in children as antibiotics are frequently prescribed in this population (14) and they are more likely to develop dehydration from diarrhea than are adults.

As the gold standard for determining treatment efficacy, (15) randomized clinical trials (RCTs) are powered to detect the difference or change in the outcome of interest between study groups. (16) However, this difference or change must outweigh the risks, costs and inconvenience of the intervention in order to warrant implementation. The smallest difference or change that meets

these criteria is called the minimally important difference (MID). (17, 18) MID also informs the sample size calculation of RCTs. (17)

Historically, MID was determined by health care providers; more recently, patient or parent input on MID is being sought. (18, 19) Recent calls to establish patient-determined MID are especially relevant for therapies that are accessed by consumers without a prescription (e.g., probiotics).

To date, more than 20 RCTs (20-39) have studied the effectiveness and safety of probiotics for prevention of AAD in children. None of these studies reported seeking the perspective of children or parents about the most relevant outcomes and associated MID.

Different methods, including surveys, Delphi methods, and interviews, can be used to elicit opinions about the change or difference in an outcome that is perceived to be Important. (16, 40) Accordingly, we conducted a survey to establish the MID in diarrhea incidence that would lead parents/guardians to use probiotic therapy for prevention of AAD in their children.

As our secondary objective, we also obtained the opinions of clinicians and compared them to the opinions of parents/ guardians. Factors associated with the size of MID (demographics, previous familiarity and experience with probiotics and AAD) in each group were explored. Furthermore, parents/guardians and clinicians rated the importance of outcomes that should be measured in AAD trials, other than risk of AAD.

4.3 Methods

The Health Research Ethics Board of University of Alberta, Canada approved this study.

4.3.1. Sampling frame and administration:

1) Parents/guardians:

We approached parents/guardians of children in the waiting room of the emergency department at the Stollery Children's Hospital, a large urban tertiary care hospital in Edmonton, Canada. They were eligible if their children were less than 17 years old and had taken antibiotics at least once in their lives. Exclusion criteria were inability to communicate in English or previous participation in the study. Participants were provided a paper-based survey (Appendix D) by a study team member (SKA) who obtained consent for participation and provided help to understand the questions as required.

2) Clinicians:

We approached a convenience sample of general pediatricians and all sub-specialists from gastroenterology, infectious diseases, and emergency medicine in active practice at the Stollery Children's Hospital. Clinicians were given electronic surveys (Appendix E) using REDCap; (41) paper surveys were provided to those who did not respond to the electronic surveys.

4.3.2. Development of survey:

Validated surveys were developed based on the literature, discussion with experts, and consultation with parents and pediatricians. Clinical sensibility and pilot testing were performed on a group of parents (n=5) and clinicians (n=5) with diverse demographic characteristics to ensure face validity, comprehensiveness, clarity, acceptability and ease of administration of the surveys. The surveys (Appendices D and E) consisted of two sections: in the first section, we asked participants for their opinions and behavior about probiotics. In the second section, we

introduced a trade-off tool consisting of potential advantages and disadvantages of probiotic therapy. (4, 12, 42) For parents/guardians, this was complemented by presentation of a scenario wherein the risk of developing AAD in children was shown to be 19% as stated in a 2015 systematic review. (4) Then, a range of higher and lower MIDs were presented. These options were calculated based on the pooled RR of probiotics to reduce the incidence of pediatric AAD and the corresponding lower and upper limits of 95% confidence interval (pooled RR = 0.46, 95% CI: 0.35-0.61). We asked participants to select the MID that was closest to what they would require in order to use probiotics for AAD prevention. The rationale of presenting limited response options was to obtain the opinions of parents and clinicians for the range of treatment effect that was realistic and in keeping with the published literature. A research team member was available to respond to any questions that parents/guardians might have had and to make sure that they had a good understanding of the concept of the question. For parents/guardians, risks were expressed as frequencies per 100 patients to facilitate ease of understanding. (43) Positive and negative wording with corresponding visual illustration (i.e., happy and sad faces) were used to promote clarity. (44) Format and questions of clinician survey were mainly adapted from the survey study carried out by Li et al. (45)

Finally, we asked participants to score a list of outcomes they would consider important to be measured in clinical trials of AAD. We used the 9-point scale suggested by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) group to score the importance of outcomes. (46) In this scale, scores of 1-3 represents outcomes of limited importance, 4-6 important but not critical, and 7-9 indicates outcomes that are of critical importance.

4.3.3. Sample size justification:

A sample size of 122 parents/guardians and 44 clinicians would achieve 80% power to detect an effect size of 0.3 (medium effect) and 0.5 (large effect) respectively using a 3 degrees of freedom Chi-Square test with a significance level (alpha) of 0.05, two sided. (47) According to Cohen et al (47), effect size is the measure of the magnitude of the Chi-square that is to be detected.

4.3.4. Statistical Analysis:

Frequencies of MID estimates of parents/guardians and clinicians were reported as n (%). MID estimates derived from clinicians and parents/guardians were compared using Chi-square test. Participant opinions and behaviors were reported as frequencies for each question. A multinomial logistic regression model was conducted to determine factors associated with the size of MID in clinicians and parents/guardians. P value < 0.05 was considered statistically significant. Data were analyzed using SPSS 16.0.(48)

4.3.5. Patient and public involvement:

Parents were involved in the comprehensibility and feasibility testing of the surveys. The results of the study reflects parents and clinicians views which can be used to designing and interpreting the findings of intervention studies of probiotic therapy for prevention of AAD.

4.4 Results

We approached 145 families and 125 clinicians of which 127 parents/guardians (87.5%) and 45 pediatricians (36%) responded. Lack of time or interest was the main reason of refusal among families**,** and respondents did not answer all questions (1-13% missing values across different questions and participants). The mean age of children presenting to the emergency room on whose behalf their parents/guardians completed our survey was 6.5 years (66/124, 53% female).

According to the parents/guardians, 39 out of 127 (31%) of the children had previous experience of AAD. Most of the responding clinicians were general pediatricians (17/39, 44%) or pediatric emergency medicine sub-specialists (15/39, 38%). Tables 4.1 and 4.2 show the general characteristics of responding parents/guardians and pediatricians, respectively.

4.4.1. Parent/guardian and clinician knowledge and behavior regarding probiotics

Parents/guardians

One hundred and twelve (88%) of the 127 parents/guardians were familiar with probiotics before doing the survey and 106/127 (84%) had previously given their children probiotics, mostly as foods containing naturally occurring probiotics (e.g., regular yogurt, kefir, sauerkraut, kimchi) (81/106; 64%) and foods containing supplemental probiotics (e.g., yogurts and drinks containing added probiotics) (64/106; 50 %). Thirty-two of 106 parents (25%) had given their children probiotics in the form of supplements (e.g., powder, capsule, chewable pill, drop/liquid). When asked which formulation their child would prefer (choose all that apply), most parents favored drops/liquid form (63%) of probiotic supplements. Chewable pills (48%) and powder/sachet (42%) were the next favorite options, followed by capsules (26%); 3% selected none of the options.

Clinicians

Thirty two of the 45 (71%) pediatricians recommended probiotics for specific indications, 9/45 (20%) selected "other" (e.g., "If they want to take them I do not object", "I state that the current evidence for its use is limited and that there is a cost associated with their use. It could help and likely would not harm their child but could harm their pocket book."), 3/45 (7%) did not know

enough about probiotics to make any recommendations, and 1/45 (2%) did not recommend probiotics at all. Thirty-eight of the 45 pediatricians (84%) stated that they recommended probiotics without parents asking them. Pediatricians mainly recommended probiotic supplements (29/45, 64%) or foods containing supplemental probiotics (23/45, 51%). The commonest indication for which they had recommended probiotics was prevention and treatment of AAD (31/45, 69%). Other indications were treatment (23/45, 51%) and prevention (12/45, 27%) of non-specific diarrhea, prevention of necrotizing enterocolitis (2/45, 4%) and other conditions (10/45, 22%) (e.g., functional abdominal pain, functional constipation, inflammatory bowel disease, irritable bowel syndrome, infantile colic, cold).

4.4.2. Parent/guardian and clinician opinions regarding probiotics for prevention and treatment of AAD

Compared to parents, pediatricians more frequently agreed or strongly agreed that probiotics were effective (77 vs. 48%, p=0.001) and safe (98 vs. 62%, p<0.001) for prevention of AAD. Three (2%) parents and none of the clinicians disagreed or strongly disagreed that probiotics were safe for prevention of AAD (table 4.3).

4.4.3. Minimally important difference

Sixty four out of 125 responding parents (51%) and 21 out of 41 responding clinicians (51%) reported they would use probiotics if it could reduce the relative risk of AAD by 39% (i.e., reduce the absolute risk of AAD from 19% to 12%; yielding a number needed to treat of 13 and a relative risk of 0.61) (Table 4.4). Pediatricians were most likely to choose a relative risk reduction of 54% or less as compared to parents (85 vs. 65%; odds ratio=3, 95% CI:1.14-9.54, P=0.02)

There was no association between parental age, gender, ethnicity, education, previous familiarity with probiotics, previous use of probiotics, child's previous experience of AAD, and parental opinion about the safety of probiotics with the choice of MID ($p>0.05$) (Appendix F). In addition, there was no association between clinician's gender, specialty, years since graduation, number of AAD patients seen per month, previous familiarity and recommendation of probiotics, and clinician's opinion about the safety of probiotics with the choice of MID ($p>0.05$) (Appendix F).

4.4.4. Important outcomes

According to GRADE (46), outcomes should be measured in clinical trials if more than 70% of respondents rate them between 7-9 (critical) and less than 15% rate them between 1-3 (limited importance) on a scale of 1-9.

In our study, the most important outcomes to parents in descending order were - need for hospitalization, prevention of dehydration, disruption of normal daily activities, diarrhea duration and physician revisit (Table 4.5). Pediatricians considered the need for hospitalization along with physician revisit as the most important outcomes. Moreover, they also rated prevention of dehydration, diarrhea duration, and stool frequency as critical outcomes to be measured in clinical trials (Table 4.5).

4.5 Discussion

Our study showed that half of the parents of children presenting to the emergency department of a Canadian tertiary care children's hospital and half of the pediatricians working in that hospital required at least a 39% reduction in the relative risk of pediatric antibiotic-associated diarrhea (i.e., decrease the absolute AAD risk from 19% to 12%) to consider it worthwhile to

consume/recommend probiotics. No associated factors (e.g., demographic characteristics, previous experience of AAD and familiarity with probiotics) were found to be related with the choice of MID in either group.

There are multiple approaches to establish MID in the current literature: anchor-based, distribution-based, health economic, pilot studies, review of the existing evidence, and opinion-seeking. (16) However, most of them are not considered patient-centered approaches. Although anchor-based methods reflect patients' views about the amount of experienced change, most often researchers decide on the threshold scores for MID. Additionally, this method usually relies on change of symptoms over time rather than differences between patients with and without intervention. (19)

To obtain parent preferences about MID, we used the benefit-harm trade off tool providing advantages and disadvantages (e.g., side effects, costs, inconvenience) of the intervention. This method has been used in various studies in other settings. (49-54) In addition to considering the patient's perspective, this method is specific to the intervention and is based on between-group comparisons. (18, 19)

In the majority of the previous studies comparing patient and health care provider opinions, patients wanted larger effect sizes before opting for an intervention than did health care providers. (55-60) In our study, although clinicians were more convinced than were parents that probiotics are safe and effective, the MIDs were relatively similar. Only 8% of parents and none of the clinicians were unwilling to use probiotics for AAD. The high rates of familiarity and use of probiotics, limited costs and inconvenience, and the favorable safety profile of probiotics may explain this preference.

The level of familiarity (88%) and use of probiotics (84%) by parents/guardians were high in our study compared to others. Chin-Lee et al in 2014, (61) reported that 65% of their respondents were familiar with the term "probiotics" and only 30% had used them before. Another study in New Zealand (2011) (62) also showed a low rate (25%) of probiotic use. Studies in the Netherlands in 2013 (50%), (63) Brazil in 2008 (29%),(64) and Greece in 2005 (18-29%) (65) reported even less familiarity with the term and meaning of probiotics. It is possible that the general population has greater awareness about the potential health benefits of probiotic products over time, but it also seems parents in Canada have a more positive attitude towards probiotics than do those in other countries.

In 2014, a core outcome set (COS) was developed for clinical trials of acute diarrhea in children. (66) Outcomes included prevention of hospitalization, diarrhea and dehydration, similar to the outcomes of greatest importance to our participants. Employing outcomes that reflect patient/parent and clinician opinions will increase the acceptability and relevance of these studies.

Strengths and limitations

Our study is the first to seek parent and clinician opinions about MID of probiotic therapy for preventing pediatric AAD. Before recruitment, a pilot and clinical sensibility testing were conducted to ensure the comprehensibility and feasibility of the surveys, and revisions were made based on the results. Response rate of parents/guardians was very high since the survey was conducted in the emergency department waiting room with in-person support.

Our study has some limitations. It was restricted to individuals who could communicate in English. Additionally, we only recruited parents of children presenting to a children's hospital emergency department, which represent a small fraction of children who are prescribed antibiotics. These might affect the generalizability of our findings. The level of education in our participating parents was higher than the level of education in people living in Alberta (Canada) (67). Although, education level and previous familiarity with probiotics were not correlated with the choice of MID in our study, these characteristics might affect the generalizability of our findings. In addition, all our participating clinicians were pediatricians who may be more familiar with probiotics than other medical specialists. Similar to previous studies, (68) there was a low response rate from clinicians despite sending two reminders after the first invitation. According to VanGeest et al., (69) the most common reasons for non-responders are being busy and considering surveys as a low priority task compared to their other duties. Moreover, in our study, the administration method was different for parents/guardians (in-person) and clinicians (online) which might have an effect on their response rate.

Implication

Findings of our study regarding MID will inform future RCTs to calculate sample size and interpret findings informed by parental and clinician perspectives. Given that parents/caregivers are the ultimate decision-makers about their child's health, especially for treatments that are easily available without a prescription, employing the outcomes that are most important to them will also improve the applicability and relevance of future studies.

Conclusion

There is a good agreement between parents and clinicians regarding how effective probiotics need to be in preventing AAD in order to warrant use. This information, along with the outcomes they perceived important, will help designing future clinical trials.

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4.7 Tables and figures

Table 4. 1 Responding parent/guardian general characteristics

Child's age (years), n=126 Mean (SD)	 6.5 (4.9)
Child's gender, n=124 Female	 66 (53%)
Parent's age (years), n=125 20 or less 21-30 31-40 41-50 Over 50	 8 (6%) 20 (16%) 57 (46%) 31 (25%) 9 (7%)
Parent's gender, n=126 Female	 98 (77.8%)
Parent's ethnicity, n=123 White/European/ Caucasian Asian (East, Southeast) Middle Eastern/ South or West Central Asian Black Latin American North American Aboriginal Other	 80 (65%) 15 (12%) 8 (7%) 6 (5%) 4 (3%) 5 (4%) 5 (4%)
Parent's education, n=124 Did not finish high school High school diploma Post-secondary education without a bachelor's degree Bachelor's degree or higher	 6 (5%) 22 (18%) 39 (31%) 57 (46%)

Categorical variables are presented as n (%)

Table 4. 2 Clinicians general characteristics

Gender, n=39 Female	 19 (49%)
Specialty, n=39 General pediatricians Sub specialists Pediatric emergency medicine Pediatric gastroenterology Pediatric infectious disease	 17 (44%) 15 (38%) 5 (13%) 2 (5%)
Years since graduation, n=39 Mean (SD) Median (Q1, Q3)	 10.05 (6.3) 10 (5, 15)

Number of AAD patients in a typical month, n=39 Mean (SD) Median (Q1, Q3)	 4.5 (3.8) 4 (2, 5)

Categorical variables are presented as n (%)

Table 4. 3 Parent/guardian and clinician opinions about effectiveness and safety of probiotics for prevention and treatment of AAD

			Strongly agreed	Agreed	Neutral	Disagreed	Strongly disagreed	Do not know	P value
Prevention	**Effective**	Parents N=126	19 (15%)	41(33%)	22 (17%)	5 (4%)	6 (5%)	33 (26%)	0.001
		Clinicians N=44	10 (23 %)	24 (54%)	6 (14%)	4 (9%)	0	0	
	Safe	Parents N=123	38 (31%)	38 (31%)	26 (21%)	0	3 (2%)	18 (15%)	0.000
		Clinicians N=44	17 (39%)	26 (59%)	1 (2%)	0	0	0	
Treatment	**Effective**	Parents N=126	17 (14%)	37 (29%)	23 (18%)	3 (2%)	6 (5%)	40 (32%)	0.000
		Clinicians N=43	6 (14%)	23 (53%)	11 (26%)	3 (7%)	0	0	
	Safe	Parents N=123	34 (28%)	39 (32%)	21 (17%)	1 (1%)	4 (3%)	24 (19%)	0.000
		Clinicians N=43	13 (30%)	28 (65%)	2 (5%)	0	0	0	

AAD: Antibiotic-associated diarrhea, NS: Non-significant
Data are presented as n (%)

Table 4. 4 Parent/guardian and clinician opinions about minimally important difference

MID options – Absolute risk of diarrhea in probiotic group, assuming 19% in control group	**Parents (n=125)**	**Clinicians (n= 41)**
12% (NNT=13, RRR=0.39)	64 (51%)	21 (51%)
9% (NNT=10, RRR= 0.54)	18 (14%)	14 (34%)
7% (NNT=8, RRR=0.65)	33 (27%)	6 (15%)
I would not give (recommend) probiotics for AAD prevention	10 (8%)	0

MID: Minimally important difference, NNT: Number needed to treat, RRR: Relative risk reduction

Table 4. 5 Parent/guardian and clinician opinions regarding importance of outcomes in clinical trials of AAD

Outcomes		Limited importance	Important but not critical	Critical	P value*
Stool frequency	Parents (N=125)	17 (14%)	50 (40%)	58 (46%)	0.002
	Clinicians (N=40)	1 (2%)	8 (20%)	31 (78%)	
Stool consistency	Parents (N=125)	6 (5%)	38 (30%)	81 (65%)	0.03
	Clinicians (N=40)	2 (5%)	21 (53%)	17 (42%)	
Duration of diarrhea	Parents (N=125)	3 (2%)	26 (21%)	96 (77%)	NS
	Clinicians (N=40)	1 (2%)	7 (18%)	32 (80%)	
Dehydration	Parents (N=125)	3 (2%)	15 (12%)	108 (86%)	NS
	Clinicians (N=40)	1 (2%)	7 (18%)	32 (80%)	
Effect on normal daily activities (e.g. eating, sleeping, playing)	Parents (N=125)	0	19 (15%)	106 (85%)	0.004
	Clinicians (N=40)	1 (2%)	14 (35%)	25 (63%)	
Child absence from day care or school	Parents (N=125)	19 (15%)	31 (25%)	75 (60%)	NS
	Clinicians (N=40)	3 (7%)	16 (40%)	21 (53%)	
Parental absence from work	Parents (N=125)	30 (24%)	31 (25%)	64 (51%)	NS
	Clinicians (N=40)	4 (10%)	14 (36%)	21 (54%)	
Need for hospitalization	Parents (N=125)	3 (2%)	8 (7%)	113 (91%)	NS
	Clinicians (N=40)	1 (2%)	4 (10%)	35 (88%)	
Need for outpatient or emergency department visit	Parents (N=125)	7 (6%)	23 (18%)	95 (76%)	NS
	Clinicians (N=40)	1 (2%)	4 (10%)	35 (88%)	

*For the comparison between parents and clinicians, AAD: Antibiotic-associated diarrhea, NS: Non-significant

Chapter 5: Development of a patient/proxy-reported instrument for pediatric antibiotic-associated diarrhea

5.1 Abstract

Objective: To develop and validate a patient/proxy-reported measure of the incidence and severity of pediatric antibiotic-associated diarrhea (PAAD) in inpatient and outpatient settings.

Methods: A patient advisory group, consisting of five parents and two children, was engaged as a research partner. Instrument items were developed from three sources: relevant items from two previously validated instruments; relevant constructs from a newly developed core outcome measurement set; and outcomes identified by parents and clinicians as being the most important. In a prospective observational study, children (birth to 17 years old) newly prescribed antibiotics or on antibiotics for ≤ 7 days, were included and assessed at the time of presentation and daily thereafter until two weeks after antibiotic therapy was completed. Internal consistency and convergent validity of the instrument were examined.

Results: Of 80 patients who agreed to participate and met the eligibility criteria, 32(40%) were lost to follow-up; data from the remaining 48 were analyzed. By applying four different definitions of diarrhea, we found a broad range of incidence risks of PAAD (27%-83%). PAAD was more likely to develop in younger age groups (≤ 3 years old). Cronbach's α for the severity scale was less than 0.7. A high correlation was found between the PAAD severity score and numerical rating score of diarrhea severity reported by parents ($r>0.5$).

Conclusion: The PAAD instrument is the first designed to measure the incidence and severity of PAAD. The instrument has content and construct validity. For reliability analyses of the severity scale, larger studies are required.

5.2 Background

Interventional studies of pediatric acute diarrhea have used heterogeneous outcome measures, often with poor reporting of their measurement properties [1]. Use of different definitions and measures, or use of measures that lack sound measurement properties, in trials with similar primary outcomes hampers comparison of results and knowledge synthesis [1, 2].

Antibiotic-associated diarrhea (AAD) is a complication of antibiotic use, likely due to resulting dysbiosis [3]. Clinical trials on prevention of AAD have mainly used probiotics as the intervention. A recent review reporting the outcomes related to pediatric antibiotic-associated adverse events in probiotic trials showed that diarrhea was only clearly defined in 21 of 37 studies. Among these 21 studies, 16 different definitions of diarrhea were documented [4]. Additionally, in a previous systematic review [5], we showed that there is a disturbing lack of evidence evaluating the validity and reliability of the most commonly used pediatric diarrhea severity scales.

The Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials was established in 2012 to reach consensus on common definitions for relevant outcome measures, including acute diarrhea [6]. They developed a core outcome set (COS) and a core outcome measurement set (COMS) for clinical trials evaluating strategies for prevention and treatment of pediatric acute diarrhea and gastroenteritis [7, 8]. Although their work was novel and valuable, they did not derive a specific definition or measurement instrument for AAD.

Since existing instruments were designed to measure pediatric acute diarrhea or gastroenteritis and not specifically AAD, the primary objective of this study was to develop and validate a patient/proxy-reported measure of the incidence and severity of pediatric AAD in inpatient and outpatient settings, the Pediatric Antibiotic-Associated Diarrhea (PAAD) instrument.

5.3 Methods

This study was approved by the University of Alberta Health Research Ethics Board. Informed consent was obtained from all participants, and assent was obtained from children old enough to write their name.

5.3.1. Derivation of the PAAD instrument

Aim of the instrument: To determine the incidence and severity of AAD in children (birth to 17 years of age) who were prescribed antibiotics in inpatient and outpatient settings.

Diarrhea incidence

To determine the incidence of AAD, objective definitions of diarrhea are required. Given the previous lack of consensus, we performed a sensitivity analysis comparing the incidence of AAD in our study population using the following four common definitions:

1. Core Outcome Measurement Set for acute diarrhea (COMS) [8]: a decrease in the consistency of loose or liquid stools and, or an increase in the frequency of evacuations, typically three in 24 hours, with or without fever or vomiting.

2. World Health Organization (WHO): the passage of unusually loose or watery stools, usually at least three times in a 24-hour period.

3. Numerical Rating Scale (NRS): a 0-10 scale where 0 indicates normal bowel movement (middle of the line) and moving to the right or left indicates progressive diarrhea or constipation, respectively (Appendix G). NRS scores of 1 on the right side indicate mild diarrhea while 10 is severe diarrhea. Daily NRS scoring reflects parental opinions without the interference of recall bias.

4. Parental global report: At the end of the follow-up period, parents/guardians were asked whether, in their opinion, their child developed diarrhea during the study period.

To assess stool consistency for the first two definitions, we used the Modified Bristol Stool Form Scale (Appendix H). The original Bristol stool form scale was modified first by Chumpitazi et al. (2010) [9]. The modified scale depicts 5 categories of stool consistency using drawings with descriptive captions and has high interrater (intra-class correlation coefficients (ICC)= 0.85) and intra-rater reliability (ICC=0.87) [9] and high interobserver reliability in children 8 years and older [10]. In our study, parents of children younger than 8 years old provided proxy ratings, and we considered drawings 4 and 5 (“loose” or “watery”) in the Modified Bristol Stool Form scale to be diarrhea.

Diarrhea severity

To develop items for AAD severity, we reviewed the published literature on pediatric acute diarrhea measurement. To our knowledge, two more recent scales, the 20-point Modified Vesikari Score (MVS) [11] and the International Pediatric Acute Diarrheal Diseases Scale (IPADDS) [Johnston 2009], are the only instruments for which measurement properties have been examined. The MVS was developed in Canada [11] for outpatient settings and was validated in a US population [12]. IPADDS developed by Johnston et al (2009) and its content

validity was established through a modified international Delphi study. Both scales were developed to measure the severity of acute gastroenteritis (AGE) or acute pediatric diarrhea and included vomiting and fever in the final score.

To develop our PAAD instrument, we adapted relevant items from these two scales. Vomiting and fever were not included in the calculation of total score but were collected to help distinguish between AAD and AGE. We also added the relevant constructs of the recommended COS [7] and COMS [8] in order to be consistent with other studies in this area. Lastly, we included items from our previous survey [13] that parents/guardians and pediatricians identified as key PAAD outcomes: stool frequency and consistency, diarrhea duration, prevention of dehydration, hospitalization, physician or emergency department visit, and disruption of normal daily activities (eating, sleeping, playing).

Final components of PAAD instrument

Initially, we developed different PAAD instruments for inpatient and outpatient settings. In outpatient settings, AAD severity was assessed by diarrhea duration and frequency, physician and/or nurse practitioner visits as a substitution for the dehydration item (adapted from MVS), the need for rehydration treatment (adapted from MVS) and ability to participate in normal daily activities (adapted from IPADDS). In inpatient settings, AAD severity was assessed by diarrhea duration and frequency, the need for rehydration treatment and estimated prolongation of hospital stay due to AAD.

Ultimately, we decided to use the outpatient form for all participants as none of the inpatients were treated for dehydration or had their hospital stay prolonged by AAD.

A committee of experts in clinimetrics, clinical epidemiology, general pediatrics, pediatric emergency medicine, pediatric infectious disease and pediatric gastroenterology approved the final structure and content of the PAAD instrument (Appendix H).

5.3.2. Patient engagement

In the design stage of this study, five parents and two children who were diverse in gender, education and ethnicity were engaged as part of an advisory council. They were recruited through patient/family registry invitations and word of mouth and interacted through in-person meetings and email communications with the academic research team. They reviewed the items, response options and formatting of our measurement instrument and the data collection forms and provided perspectives on the best recruitment and follow-up strategies. Study methods and data collection forms were approved by them before deployment.

5.3.3. Validation of the PAAD instrument

Study design, setting and population

A prospective observational study was conducted in the Emergency Department and ambulatory clinics of a tertiary care children's hospital in Edmonton, Canada.

We approached parents of inpatient or outpatients, birth to 17 years old, who were newly prescribed antibiotics for any reason or who were on antibiotics for fewer than seven days at the time of presentation. We asked for participation until 2 weeks after antibiotic therapy was finished (the time interval in which the incidence of AAD is highest).

Exclusion criteria:

1. Parental report of current diarrhea or diarrhea within the last week.

2. Anticipated antibiotic use for ≤ 2 days or at sub-therapeutic doses (e.g., prophylaxis).

3. Inflammatory bowel disease, irritable bowel syndrome or other causes of diarrhea.

4. Parent/guardians without phone or email access or who could not communicate in English.

5. No parents/guardians who could complete the baseline measurement.

6. Previously enrolled in this study.

Administration

The initial screening visit took place in the pediatric emergency department and ambulatory clinics of the participating hospital. After meeting the eligibility criteria and providing written informed consent, demographic information and baseline stool frequency and consistency were recorded (Appendix I and J-1). Parents/guardians were asked to record their child's stool frequency and consistency daily until two weeks after antibiotic therapy was finished (Appendix J-1). For stool consistency, they were instructed to compare their child's most abnormal stool appearance over the preceding 24 hours to the categories on the Modified Bristol Stool Form Scale. They also rated their child's most abnormal stool using the NRS. For outpatients, an additional question regarding child's normal activities (e.g., eating, sleeping, playing) was asked every day. Vomiting and fever were recorded by parents daily, and if either was present, the child was presumed to have infectious diarrhea rather than AAD. At the end of the follow-up period, parents/guardians were asked to report whether they thought that the child had diarrhea, the duration of diarrhea and if any physician/nurse practitioner visit or treatment were sought (Appendix J-2). For uniformity, every effort was made to have the parent/guardian form filled

out by the same person. All parents/guardians were contacted daily by email or text message, based on their preference, for the duration of treatment and the next two weeks. Older children were encouraged to rate their own stool.

5.3.4. Sample size

A minimum of 50 patients is recommended to calculate correlation coefficients for construct validation. For factor analysis, a minimum of 4-10 cases per item is suggested [14]. Considering that PAAD instrument had 5 items adapted from two validated instruments, we aimed to include at least 50 patients in our study.

5.3.5. Analysis

Content validity

Content validity is defined as "the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured" [15]. To ensure its relevance and comprehensiveness, we developed the items in the PAAD instrument based on previous measures for which face and content validity had been established. Items were also chosen based on our previous survey of parents and clinicians [13]. Finally, a committee of experts and patient partners approved its content and structure.

Construct validity (hypothesis testing)

- *Hypothesis testing:*

o We expected to observe high correlation (0.5 or higher) between the PAAD instrument severity score and NRS severity score (convergent validity).

o Information about child absenteeism from day care/school and parental absenteeism from work were gathered to assess the correlation between disease severity and its impact on family life. We expected to observe high correlation (0.5 or higher) between the PAAD instrument severity score and child absenteeism from day care/school and parental absenteeism from work.

Internal consistency

Internal consistency is defined as the degree of correlation among items of a uni-dimensional multi-item instrument, therefore measuring the same concept [15]. We performed exploratory factor analysis to identify the dimensions of the PAAD instrument. Internal consistency was examined separately for each dimension (subscale) by Cronbach's α [14]. Cronbach's α between 0.70 and 0.95 is considered to indicate good internal consistency [16].

5.4 Results

5.4.1. Population characteristics

Parents of 104 children were approached from August 2019 through March 2020 of which 95 agreed to participate. Eighty-five patients met eligibility criteria, of whom five were eventually excluded (3 received antibiotics for less than 2 days, and 2 received polyethylene glycol (a laxative which can cause diarrhea)). No study participants were excluded for having presumed infectious diarrhea.

Of the remaining 80 participants, 32 (40%) were lost to follow-up (never responded or responded for only one or two days), hereafter referred to as "non-respondents". The remaining 48 participants responded for at least the duration of their antibiotic therapy and were included in

data analysis. The only significant difference between respondents and non-respondents was parental age (Table 5.1).

5.4.2. Incidence of AAD

The incidence of AAD based on the four definitions of diarrhea was as follows: The COMS definition: 40/48 (83%), the WHO definition: 24/48 (50%), the NRS definition: 37/48 (77%), and the parental global report at the end of the study: 13/39 (27%).

Gender, ethnicity, antibiotic type and duration were not risk factors for developing AAD by any of the definitions (Appendix K). We categorized children into three age groups [group 1 (0-3 years old), group 2 (4-6 years old), and group 3 (>6 years old)] as a post-hoc analysis and found the youngest age group (0-3 years old) had the highest risk of developing AAD according to three of the four definitions - parental global report was the exception (P=0.07) (Appendix K).

5.4.3. Severity of AAD

Scoring

Table 5.2 shows the PAAD instrument severity components. The instrument has a minimum of 0 and maximum of 15 points. To define cut-points for mild, moderate, and severe AAD, we looked at the distribution of item scores among our population. Considering that most patients scored zero in the “daily activities”, “physician/nurse practitioner visit”, and “treatment” items, we defined severity categories as follows: 0 as no-diarrhea, 2-3 as mild, 4-5 as moderate and >= 6 as severe.

Distribution of scores

Figure 5.1 shows the distribution of severity scores based on different definitions. As shown, skewness and kurtosis are minimal in COMS and NRS definitions. The severity scores distribution based on the WHO definition is slightly right skewed but still in the acceptable range. The parent reported distribution, however, is more skewed towards the right tail and kurtosis is also high, both showing less severe scores based on this definition.

Reliability analysis

Most patients scored zero for "daily activities", "physician/nurse practitioner visit" and "dehydration treatment" in the PAAD instrument. As a result, we were not able to conduct factor analysis. Cronbach's α was less than 0.7 for all definitions, indicating low internal consistency (Appendix L). In the inter-item correlation matrix (Appendix M), only "diarrhea frequency" showed acceptable correlation with other items of the severity scale. The corrected item-total correlation shows the correlation between that item score and sum of the scores of the remaining items. If the correlation is more than 0.3, it shows the item can discriminate between patients with different severities and should remain in the scale [14]. Appendix N shows "diarrhea duration" and "diarrhea frequency" meet these criteria.

Construct validity (hypothesis testing)

We observed high correlation (0.5 or higher) between the PAAD instrument severity score and worst NRS score, confirming our a priori hypothesis and demonstrating convergent validity (Table 5.3).

Since only one child missed daycare/school because of diarrhea, we were unable to analyze the correlation between the PAAD instrument severity score and child absenteeism from daycare/school and parental absenteeism from work. Out of 34 children with AAD according to

the COMS definition, 19 (56%) did not miss daycare/school and the question was not applicable in the remaining 14 (41%) participants. For parents, 30/34 (88%) did not miss work and the question was not applicable in the other 4 (12%).

5.5 Discussion

To our knowledge, this is the first study to develop an instrument to measure the incidence and severity of AAD in children. Engagement of parents and children in this process was a highlight of this study. Content and construct validity, and internal consistency were examined, and promising results were obtained for the PAAD instrument.

The incidence of AAD reported by observational and clinical trials varies significantly, depending on the sample size, the definition and diagnostic criteria used. For broad spectrum antibiotics, the risk of developing AAD has been reported to be 11 to 40% in children [3]. Other studies report an even wider 5 to 62% risk [3].

In our study, despite daily recording and using a standardized validated instrument to assess stool consistency (modified Bristol stool form scale), we found a broad range in incidence of AAD using four different definitions of diarrhea. When a change in stool consistency from baseline was considered the main indication of diarrhea (COMS definition), the incidence observed was very high (83%). Conversely, only about one-quarter of parents thought that their child had diarrhea, suggesting that parents only considered it to be diarrhea if their child developed a marked change in stool consistency and/or frequency.

In contrast, applying the definition of three or more loose or liquid/watery bowel movements per day (WHO definition), showed a 50% incidence of diarrhea. Using the same definition an

observational study of 75 children up to 12 years old with acute respiratory tract infections also showed a 52% prevalence of AAD [17] although a prospective study of 289 children up to 17 years old showed a 20% incidence of AAD [18].

In our study, children in the youngest age group (0-3 years old) were most likely to have AAD as shown in previous studies [17, 18]. This is thought to be related to immaturity of the gastrointestinal tract and microbiota alterations in younger children [18]. Antibiotic type and duration did not affect the risk of developing AAD in our study. However, as the majority of participants were exposed to relatively few antibiotic types, our ability to comment on antibiotic type as a risk factor for AAD was constrained.

Regarding the PAAD instrument severity scores, the distributions seemed symmetrical for all diarrhea definitions except the parental global report. Consistent with results of a previous study [19], our results showed that most patients developed AAD of mild to moderate severity.

We were unable to run the reliability analyses (factor analysis and internal consistency) for the severity scale of the PAAD instrument because most of our patients scored zero for the three items of "daily activities", "physician/nurse practitioner visit" and "dehydration treatment". This also could explain the low Cronbach's α shown in our study according to the different diarrhea definitions. Furthermore, low Cronbach's α could be due to low correlation between the items of an instrument, heterogenous constructs or low number of items (20). The PAAD instrument only has five items, and the constructs could be diverse. It should be noted that the MVS from which some items of the PAAD instrument were adapted, also showed low Cronbach's α. The authors attributed this finding to the low number of items (seven items) and possibly distinct constructs but mentioned that it did not affect the validity of their scale (11). Studies with larger sample

sizes may include children with different severities of AAD which therefore enables a more accurate examination of internal consistency of the PAAD severity instrument.The high correlation found between the PAAD instrument severity score and the worst NRS score confirmed the convergent validity of the PAAD instrument. However, there was insufficient data to determine the impact of AAD on family life.

Small sample size was the main limitation of our study. Although we reached the minimum number of participants required [14] despite the unexpectedly high attrition rate and restrictions in doing clinical research at the hospital due to the COVID pandemic, many references recommend 100 participants in validation studies to reflect the full spectrum of illness severity. Future larger studies with children who are more severely affected are required to enable accurate examination of the internal consistency as well as the impact of disease severity on family life.

Conclusion

The first instrument to measure the incidence and severity of pediatric AAD was successfully designed and assessed for its measurement properties with the engagement of parents/children in the process of development. The PAAD instrument has content and construct validity. For reliability analyses, larger studies are needed, including children with more severe AAD.

5.6 References

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5.7 Tables and figures

Table 5. 1 General characteristics of children enrolled in a study to validate a measure of antibiotic associated diarrhea (PAAD)

	Respondents (N=48)	Non-respondents (N=30)	P value
Outpatient, n (%) **Inpatient, n (%)** Duration of hospitalization	40 (83%) outpatients 8 (17%) inpatients 2-7 days	26 (87%) outpatients 4 (13%) inpatients 1-3 days	0.75
Patient's Age (years) Range Mean (SD)	 1 month- 16 y 4.2 (3.9) years	 4 months-17 y 5.1(5.1) years	0.39
Sex, n (%)	25 (52%) Male	15 (50%) Male	0.85
Ethnicity, n (%) White/ European/ Caucasian East and South East Asians South Asians Middle Eastern Black Latin American North American Indigenous Other (Mixed, Pacific Islander)	 25 (52.1%) 3 (6.2%) 4 (8.3%) 6 (12.5%) 1 (2.1%) 2 (4.2%) 1 (2.1%) 6 (12.5%)	 12 (42.9%) 1 (3.6%) 2 (7.1%) 0 3 (10.7%) 0 3 (10.7%) 7 (25%)	0.09
Primary diagnosis, n (%) Pneumonia Acute otitis media Urinary tract infection Cellulitis Abscess Sepsis Animal bite Other (Febrile neutropenia, lymphadenitis, conjunctivitis, sinusitis, pharyngitis, balanitis)	 11 (22.9%) 6 (12.5%) 8 (16.7%) 9 (18.8%) 2 (4.2%) 3 (6.2%) 3 (6.2%) 6 (12.5%)	 9 (30%) 6 (20%) 1 (3.3%) 6 (20%) 2 (6.7%) 0 3 (10%) 3 (10%)	0.5
Antibiotic name, n (%) Amoxicillin Amoxicillin-clavulanate Cephalosporins Combination of penicillin and cephalosporin class Macrolides Other (TMP/SMX, Piperacillin-tazobactam, clindamycin, other combinations)	 14 (29.2%) 5 (10.4%) 21 (43.8%) 3 (6.2%) 1 (2.1%) 4 (8.3%)	 9 (30%) 4 (13.3%) 6 (20%) 1 (3.3%) 5 (16.7%) 5 (16.7%)	0.07
Duration of antibiotic therapy, days Range Mean (SD)	 3-28 days, 8.3 (4.29)	 5-14 days, 7.5 (2.2)	0.33

Parent age n (%) < 20 or younger 21-25 26-30 31-35 36-40 41-45 46-50 >51	 0 2 (4.3%) 5 (10.9%) 14 (30.4%) 16 (34.8%) 8 (17.4%) 1 (2.2%) 0	 0 3 (11.5%) 7 (26.9%) 3 (11.5%) 8 (30.8%) 2 (7.7%) 0 3 (11.5%)	**0.03**
Parent gender, n (%)	37 (78.7%) female	20 (69%) female	0.34
Parental education, n (%) Bachelor's degree Post-secondary education without bachelor's degree High school diploma Did not finish high school	 28 (59.6%) 11 (23.4%) 7 (14.9%) 1 (2.1%)	 11 (47.8%) 5 (21.7%) 4 (17.4%) 3 (13%)	 0.34

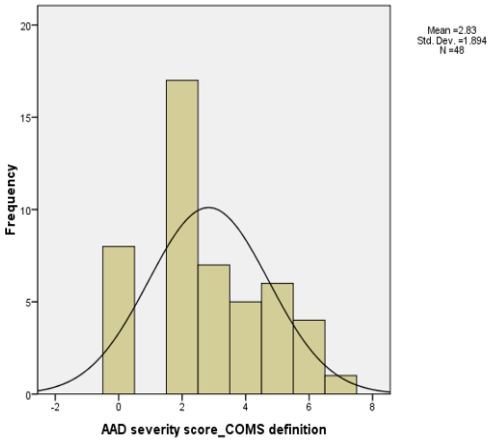
Table 5. 2 Pediatric antibiotic-associated diarrhea (PAAD) instrument severity components

	0 point	1 point	2 points	3 points
Diarrhea duration, days	0	1-4	5	>=6
Diarrhea frequency (maximum number of diarrheal stools in 24 hours)	0	1-3	4-5	>=6
Daily activities	Normal	Reduced	Not able to participate	Hospitalized due to diarrhea
Physician/nurse practitioner visit	None	Outpatient	Emergency department visit	Hospitalized due to diarrhea
Treatment	None	Oral Rehydration	IV Rehydration	Hospitalized due to diarrhea

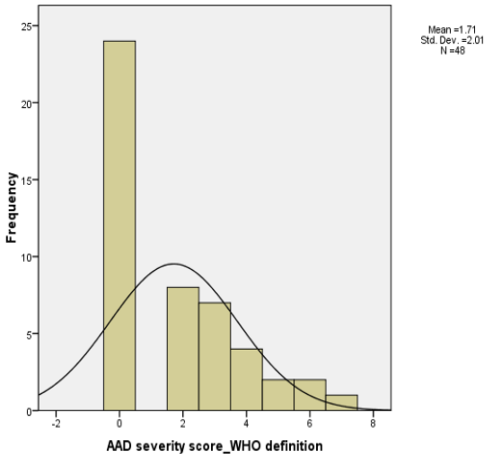
Table 5. 3 Correlation between PAAD severity score and worst NRS reported by parents

	COMS (n=47)	WHO (n=47)	NRS (n=47)	Parent (n=36)	Worst recorded NRS severity score (n=47)
Worst recorded NRS severity	0.66*	0.6*	0.79*	0.52*	1

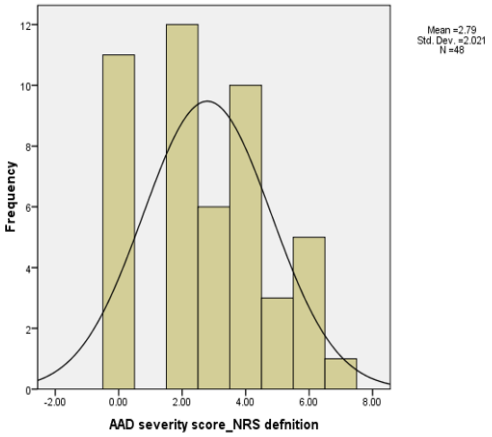
*Correlation is significant at the 0.01 level (2-tailed)
** Spearman's rho correlation coefficients were calculated.
COMS: Core Outcome Measurement Set; NRS: Numerical Rating Scale, WHO: World Health Organization



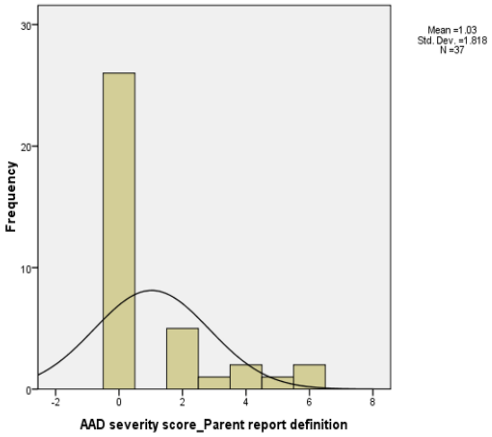
Distribution of severity scores according to COMS definition
Skewness (SE): 0.25 (0.34), Kurtosis (SE): -0.63 (0.67), Median: 2, Range: 0-7
Severity categories: No diarrhea: 8(17%), Mild: 24(50%), Moderate: 11(23%), Severe: 5(10%)



Distribution of severity scores according to WHO definition
Skewness (SE): 0.88 (0.34), Kurtosis (SE): -0.19 (0.67), Median: 1, Range: 0-7
Severity categories: No diarrhea: 24(50%), Mild: 14(29%), Moderate: 7(15%), Severe: 3(6%)



Distribution of severity scores according to NRS definition
Skewness (SE): 0.12 (0.34), Kurtosis (SE): -0.86 (0.67), Median: 3, Range: 0-7
Severity categories: No diarrhea: 11(23%), Mild: 18(37.5%), Moderate: 13(27%), Severe: 6(12.5%)



Distribution of severity scores according to parent report
Skewness (SE): 1.69 (0.39), Kurtosis (SE): 1.77 (0.76), Median: 0, Range: 0-6
Severity categories: No diarrhea: 26(54%), Mild: 6(13%), Moderate: 3(6%), Severe: 2(4%), Missing: 11(23%)

Figure 5. 1 Distribution of severity scores according to different definitions

Chapter 6. Conclusion

6.1 Summary of key findings

This doctoral dissertation was performed to investigate the role of patient engagement with a focus on children and their parents/guardians in developing pediatric patient-reported outcome measures (PROMs) and determining minimal important difference (MID). The four chapters consist of two review studies, one survey and one validation study.

In chapter 2, the engagement of children and parents/guardians in developing pediatric PROMs was explored in the published literature through a systematic review. In most studies found by this review, feedback from children and/or parents/guardians was sought on specific research activities when needed (*consult* level). Only six studies engaged children and/or their parents/guardian as members of advisory groups/councils (*involve* level) or as co-researchers and members of scientific steering committees (*collaborate* level). Qualitative research methods such as focus groups and interviews were the most common methods of obtaining opinions. Child/parent input was mainly employed in developing a conceptual framework, item generation, and testing the content validity (including relevance, comprehensibility, and ease of administration) of the PROMs.

In chapter 3, we reviewed studies to reveal the engagement of patients of any age in determining MID for any intervention in any clinical condition. This review highlighted the scarcity of studies involving adolescents and/or parents/guardians. Trade-off techniques were used most often for direct elicitation of patients' views. We observed considerable heterogeneity in the terminology used for MID, the interventions and outcomes that MID were calculated for, and the different MID estimates for the same clinical condition.

In chapter 4, we conducted a survey to sample parent and clinician opinions about probiotic consumption, MID of probiotics for prevention of pediatric AAD, and important outcomes to be measured in clinical trials of AAD. For the MID question, we employed a trade-off technique. According to the half of the participants, risk of developing AAD needed to be decreased at least 40% for parents or clinicians to consider it worthwhile to consume/recommend probiotics. In our study participants, demographic characteristics, previous experience of AAD and familiarity with probiotics were (surprisingly) not found to be related with the choice of MID. To support future instrument development to measure pediatric AAD, specific outcomes were also rated for their importance to parents and clinicians.

Chapter 5 describes our final study in which we developed, and validity tested a novel instrument to measure the incidence and severity of pediatric AAD (PAAD instrument). Parents and children were engaged in the process of development as members of our advisory council ("involve" level). Their opinions were sought to develop the items and response options, format the instrument and data collection forms, and develop strategies to improve recruitment and follow-up of the participants. The items of the PAAD instrument were based on i) the outcomes identified by parents and clinicians as being most important (Chapter 4); ii) relevant constructs of a core outcome measurement set for pediatric acute diarrhea; and iii) relevant items of two previously validated instruments of pediatric acute diarrhea. Internal consistency and convergent validity of the instrument were examined. This study revealed a broad range of AAD incidence when using different definitions, emphasizing the need for a consistent definition of AAD across studies.

6.2 Limitations

Review studies (Chapters 2 and 3):

Patient-oriented research (POR) and patient engagement have been emerging issues in the last decade, but further work is required to address several challenges. For instance, inconsistent terminology used in the literature may have limited the ability of our search strategies to be as comprehensive as possible.

While some POR guidelines for researchers and patients exist, the current evidence lacks homogeneous frameworks for patient engagement which hamper comparison and interpretation of findings.

Survey study (chapter 4):

The generalizability of our findings in the survey study might have been limited by recruitment from a single site (patients and their parents in a pediatric emergency department and pediatricians at the associated Children's hospital) which represent a small fraction of the target population. Participating parents had a higher level of education than the provincial average. Additionally, clinicians who participated in our survey were all hospital-based academic pediatricians who may have been more familiar with probiotics than other medical specialists or community-based providers. Although our study did not find any correlation between parental education and previous familiarity with probiotics (for both parents and clinicians) with the choice of MID, these characteristics may also have affected the generalizability of our findings.

Validation study (chapter 5):

Considering the longitudinal design of the validation study, the main limitation was the small sample size due to the high attrition rate. Except for parental age, no significant difference was

found between respondents and non-respondents. Daily reporting for at least three weeks was difficult for many participants to sustain, and our access to them was limited to email or phone reminders. Most participants in our study developed mild symptoms, which is typical for AAD. Increasing the sample size may have enhanced the possibility of capturing the full spectrum of illness severity and thus enabled more accurate examination of the PAAD instrument measurement properties.

While invaluable, engagement with patients had its own challenges in this study. First, recruitment was both time and energy intensive. We tried different recruitment strategies; however, word of mouth was the most efficient. Second, due to the COVID pandemic and time limitations, meetings were logistically difficult to arrange with parents/children on our advisory council. Despite this, we received valuable feedback from patient partners regarding potential ethical or feasibility issues, which was used to modify the study until concerns were resolved.

6.3 Implications for research

According to the principle of "nothing about me without me", the importance of patient engagement in developing PROMs is apparent in both research and clinical care. While this has been addressed in some pediatric PROMs, our systematic review showed the low level of engagement in most studies. Moreover, conflating patients as participants of qualitative studies versus patients as research partners remains controversial and ambiguous. Future research should be transparent in terms of the methodology used and require adherence to standard guidelines developed to facilitate the engagement of patients in the process of PROM development. Furthermore, most studies overlook reporting the impact of patient engagement throughout the research enterprise. Using the Guidance for Reporting Involvement of Patients and Public-2

(GRIPP-2) checklist at the initial stages of the research cycle would help ensure all aspects of patient engagement have been addressed and facilitate manuscript preparation.

Obtaining patient perspectives for the interpretation of research findings is also worthwhile. This was highlighted in our scoping review in which we showed the paucity of evidence regarding estimation of MIDs with direct patient input, especially in the pediatric population. Recent trends of conducting mixed method studies for MID determination, in which estimates calculated by anchor and distribution methods are supported by the findings of qualitative studies, are promising. These methods are helpful to overcome the considerable heterogeneity of MID estimates by generating a single MID or a narrow range of MID for a specific clinical condition.

In our survey study, we actively involved the target population (parents and clinicians) to establish MID for use of probiotics in preventing pediatric AAD. This patient-driven MID can be used to calculate sample size in future RCTs and interpret their findings. As parents/caregivers are the ultimate decision-makers about their child's health, identifying the outcomes that are most important to them will improve the applicability and relevance of future studies.

Our novel PAAD instrument can be used in future studies to provide a standardized measure of the incidence and severity of AAD in children. By developing this specific outcome instrument with the active engagement of parents and children, accurate measurement of outcomes that are most important and relevant to them are enabled. Our goal is for results of clinical studies using the PAAD instrument to be comparable, facilitating knowledge synthesis.

6.4 Implications for clinical practice

Integrating PROMs into routine clinical practice is on the rise (1). Having patient perspectives about the physical, psychological, social, and emotional aspects of their health is essential in improving quality of care. Although age and developmental considerations remain a challenge in developing and using pediatric PROMs, their positive impact on improving health-related quality of life and quality of care has been reported (2). The relevance and applicability of these instruments will be enhanced by greater engagement of children and families in this process, from selection of the most important outcomes to development of an accurate PROM, and/or even in selecting the most suitable existing PROM.

Patient-driven MIDs help increase patient satisfaction and adherence to treatment advice (3). We obtained family and clinician views on probiotics as an example of a therapy which is accessible without prescription and asked what threshold they recognize as meaningful for the prevention of pediatric AAD. Interestingly, we found high levels of familiarity with probiotics and positive perceptions about their safety and effectiveness. There was also good agreement between parents and clinicians regarding MID of probiotics for this clinical condition.

6.5 Future directions

Based on the results of this doctoral thesis, the next steps are recommended:

- Higher levels of engagement of children and parents at all stages of pediatric PROM development, from study design to interpretation and dissemination of its findings.
- Reporting in more detail on positive and negative effects of child/family engagement on developing PROMs and determining MID and investigating how these factors impact the engagement and the quality of resulted PROM and MID.

- Developing mixed method studies and finding the best method to reconcile the distribution, anchor and qualitative data that results in a narrow range of MIDs for specific interventions and outcomes.
- Using the estimated MID derived from parent and clinician opinions in calculating sample size and interpreting the data of future RCTs on probiotics for prevention of pediatric AAD
- Conducting larger studies with children who are more severely affected to test the reliability of PAAD instrument and to measure the impact of AAD severity on family life.

6.6 Conclusion

This doctoral dissertation focused on patient engagement in the development of pediatric PROMs and MID determination. Our review studies showed that existing evidence regarding children/families' engagement in these areas is sparse and at a preliminary stage. Potential directions for future research were suggested in this thesis. We chose pediatric AAD and probiotics as our clinical conditions to implement patient-centered approaches in determining MID and developing an instrument to measure the incidence and severity of pediatric AAD. Parent and clinician opinions were obtained regarding MID of probiotics for preventing pediatric AAD and good agreement was found. The estimated MID will help in sample size calculation and interpretation of results of future RCTs. Lastly, the PAAD instrument was developed, and validity tested to measure pediatric AAD, with parents and children as members of our advisory council. Limitations of this study along with suggestions for future studies were discussed.

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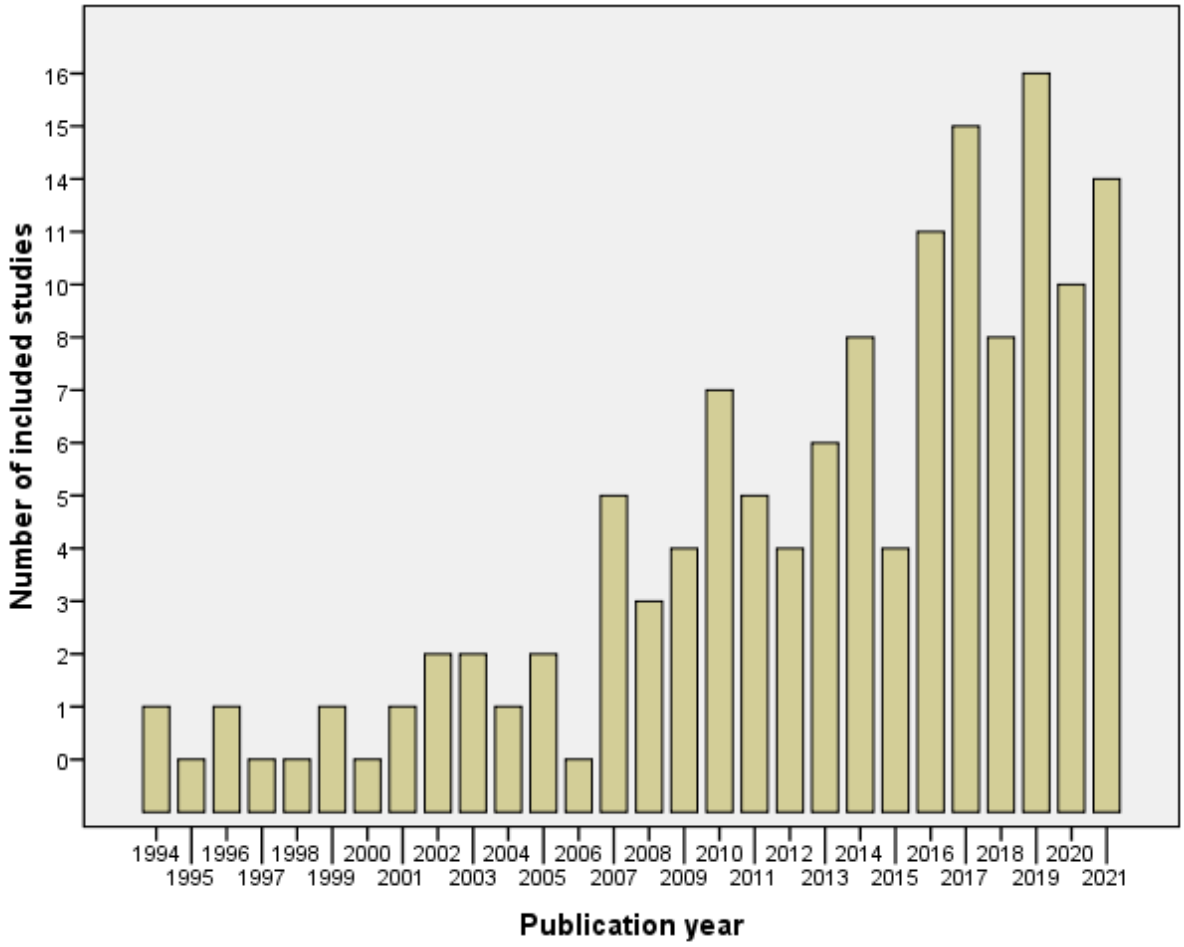
Appendices

Appendix A-Search strategy (Medline) for child and parent engagement in developing pediatric patient-reported outcome measures systematic review

1	(Child* or adolescent* or teen* or paediatric or pediatric* or infant* or youth).ti,ab.
2	(father* or guardian* or mother* or parent* or care-giver* or caregiver).ti,ab.
3	exp Child/
4	exp Adolescent/
5	infant/
6	Pediatrics/
7	Caregivers/
8	or/1-7
9	patient reported outcome measures/
10	patient outcome assessment/
11	Patient reported outcome?.ti,ab.
12	(child-centric or child centric).ti,ab.
13	Patient reported measures.ti,ab.
14	or/9-13
15	scoring system development.ti,ab.
16	scale development.ti,ab.
17	instrument development.ti,ab.
18	index development.ti,ab.
19	measurement tool.ti,ab.
20	measurement instrument.ti,ab.
21	"Surveys and Questionnaires"/mt [Methods]
22	(questionnaire? or interview? or scale? or survey? or score?).ti,ab.
23	engage*.ti,ab.
24	consult*.ti,ab.
25	develop*.ti,ab.
26	involv*.ti,ab.
27	participat*.ti,ab.
28	perspective.ti,ab.
29	feedback.ti,ab.
30	Patient Participation/
31	Focus Groups/
32	or/15-31
33	"Quality of Life"/
34	32 or 33
36	8 and 14 and 34 [with QoL]
37	remove duplicates from 36

Appendix B- Number of included studies per year from 1994-2021



Appendix C-Search strategy (MEDLINE) for patient involvement in determining minimal important difference scoping review

1 mcid.ti,ab.
2 target difference?.ti,ab.
3 change score.ti,ab.
4 change point.ti,ab.
5 minimal clinically important difference/
6 (minim* meaningful adj1 (difference? or change? or effect?)).ti,ab.
7 (clinical* important adj1 (difference? or change? or effect?)).ti,ab.
8 (minim* important adj1 (difference? or change? or effect?)).ti,ab.
9 (clinical* meaningful adj1 (difference? or change? or improvement? or effect?)).ti,ab.
10 (smallest meaningful adj1 (difference? or change? or effect?)).ti,ab.
11 (minim* significant adj1 (difference? or change? or improvement? or effect?)).ti,ab.
12 (smallest significant adj1 (difference? or change? or improvement? or effect?)).ti,ab.
13 (sufficient* important adj1 (difference? or change? or improvement? or effect?)).ti,ab.
14 (sufficient* meaningful adj1 (difference? or change? or improvement? or effect?)).ti,ab.
15 (minim* clinical* adj1 (important or meaningful)).ti,ab.
16 ((calculat* or determin* or comput*) adj1 meaningful).ti,ab.
17 ((calculat* or determin* or comput*) adj1 important adj1 (difference? or change? or improvement? or effect?)).ti,ab.
18 ((calculat* or determin* or comput*) adj1 meaningful adj1 (difference? or change? or improvement? or effect?)).ti,ab.
19 (definition* adj1 (difference? or change? or improvement?)).ti,ab.
20 (smallest worthwhile adj1 (difference? or change? or improvement? or effect?)).ti,ab.
21 *sample size/
22 smallest real difference*.ti,ab.
23 exp Patient Participation/
24 exp Patient Preference/
25 Patient? preference?.ti,ab.
26 *Decision making/
27 decision-making.ti,ab.
28 patient? view?.ti,ab.
29 patient? opinion?.ti,ab.
30 patient? perspective.ti,ab.
31 patient involvement.ti,ab.
32 patient expectations.ti,ab.
33 exp Health Care Surveys/
34 interview/
35 "Surveys and Questionnaires"/
36 benefit harm tradeoff.ti,ab.
37 benefit-harm trade-off.ti,ab.
38 or/1-22
39 or/23-37
40 38 and 39
41 limit 40 to yr="1989 -Current"
42 remove duplicates from 41

Appendix D- Survey of parents/guardians' opinion on probiotic therapy for antibiotic-associated diarrhea in children

Probiotics definition: [Please read before responding questions]

Healthy intestines are home to trillions of good bacteria. Good bacteria help the whole body stay healthy. Probiotics are one kind of good bacteria. They can be found in fermented foods (e.g., yogurts) or taken as supplements in a powder or capsule form. Probiotics are thought to improve health in some situations by creating the right balance of intestinal bacteria.

Antibiotic-associated diarrhea definition:

Antibiotics are medicines that help the body fight bacterial infections. However, antibiotics can kill good intestinal bacteria as well, which can lead to diarrhea.

Considering the definitions above, please answer the following questions:

1) Before doing this survey, did you know what probiotics were?

☐Yes

☐No

2) Have you ever given your child/children probiotics, either in their food or as supplements?

☐Yes

☐ No (If No, Please Skip to question number 4)

3) If yes, what type of probiotics have you given your child/children? (Please check all that apply)

☐Foods containing naturally occurring probiotics (e.g., regular yogurt, Kimchi, Sauerkraut)

☐Foods containing supplemental probiotics (e.g., DanActive ®, Activia ®)

☐Probiotic supplements (e.g., Culturelle ®, Flora BABY®, Florastor®, VSL #3®, BioGaia®, Proxiflor®, UltraFlora ®Children's)

☐ Other: (Please specify) _____

4) What form of probiotic supplements do you think that your child would take? (Please check all that apply)

☐Powders/ Sachet [They can be used directly, or be sprinkled into food/drinks]

☐Capsules [They can be swallowed whole, or the capsule contents can be sprinkled into food/drinks]

☐Chewable pills

☐ Drops/liquid

☐ None of the above

5) Have any of your children ever experienced diarrhea from being on antibiotics (antibiotic-associated diarrhea)?

☐Yes

☐ No

☐ Do not know

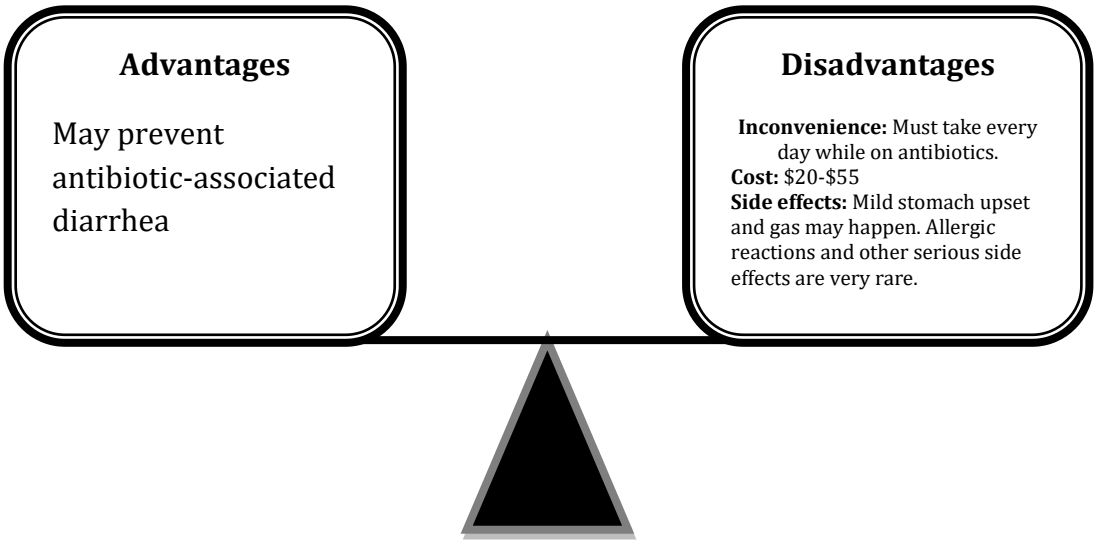
6) When considering probiotics given at the same time as antibiotics to **prevent** antibiotic-associated diarrhea in children, do you think:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Do not know
Probiotics are EFFECTIVE	☐	☐	☐	☐	☐	☐
Probiotics are SAFE	☐	☐	☐	☐	☐	☐

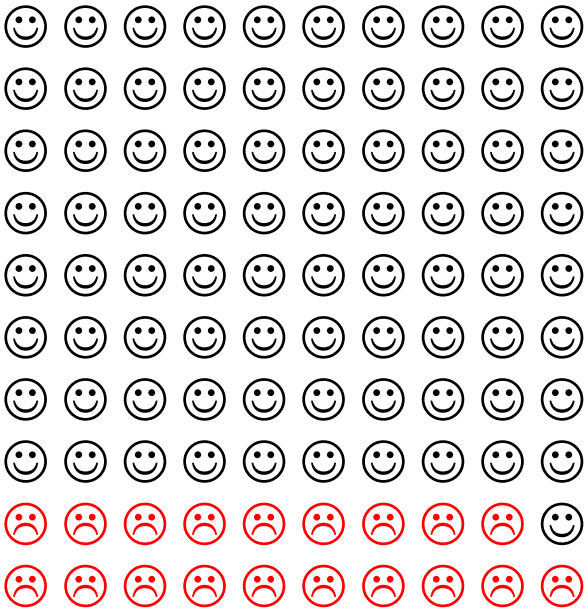
7) When considering probiotics to **treat** antibiotic-associated diarrhea in children, do you think:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Do not know
Probiotics are EFFECTIVE	☐	☐	☐	☐	☐	☐
Probiotics are SAFE	☐	☐	☐	☐	☐	☐

8) Please consider the information provided below:
Taking probiotics for prevention of antibiotic-associated diarrhea in children has:



Without probiotics, **19 out of 100 children** will develop diarrhea from antibiotics. The other 81 will not get diarrhea. It is unknown which child will or will not get diarrhea after taking antibiotics.



If your child was on antibiotics, you would consider giving her/him probiotics if the chance of getting diarrhea decreased from 19 to: (Please choose one item)

☐12 in 100
☐9 in 100
☐7 in 100
☐I would not give probiotics to my child for prevention of diarrhea

9) Giving probiotics to children who are taking antibiotics may decrease the severity of diarrhea if it happens. Imagine a situation in which your child is on antibiotics. In deciding whether or not to give

them probiotics, which of the following possible effects could influence your decision? On a scale of 1-9, please rate the importance of each effect.

1= Not important at all
9= Extremely important

	1	2	3	4	5	6	7	8	9
It will decrease the number of bowel movements per day.	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will create less watery poop.	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will make the diarrhea go away sooner.	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will prevent my child from becoming dehydrated (dry)	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will allow my child to go back to day care or school sooner.	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will allow me to go back to work sooner.	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will allow my child to go back to his/her normal daily activities sooner (e.g. eating, sleeping, playing)	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will prevent me from having to take my child to the doctor or emergency department.	☐	☐	☐	☐	☐	☐	☐	☐	☐
It will prevent my child from being hospitalized.	☐	☐	☐	☐	☐	☐	☐	☐	☐

Some questions about you and your child being seen today:

10) Please indicate your child's age: _____days/weeks/months/years old (Please circle)

11) Please indicate your child's gender:

☐Female ☐Male

12) Please indicate your age:

☐20 or younger
☐21-25
☐26-30
☐31-35
☐36-40
☐41-45
☐46-50
☐ Over 50

13) Please indicate your gender:

☐Female ☐Male

14) Please indicate your ethnicity: (please check all that apply)

☐ White/ European/ Caucasian
☐ Black (e.g. African, African American, African Canadian, Caribbean)
☐ East Asian (e.g. Chinese, Japanese, Korean)
☐ South Asian (e.g. Indian, Pakistani, Seri Lankan, Bangladeshi)
☐ Southeast Asian (e.g. Burmese, Cambodian, Filipino, Laotian, Malaysian, Thai, Vietnamese)
☐ West central Asian and middle eastern (e.g. Arabian, Armenian, Iranian, Afghan, Israeli, Lebanese, Palestinian, Syrian, Turkish)
☐ Latin American (e.g. Mexican, indigenous Central and South American)
☐ North American aboriginals (e.g. North American Indian, Inuit, Metis)
☐ Pacific Islander
☐ Other: (please specify)_____
☐ Prefer not to answer

15) Please indicate your highest education level:

☐Did not finish high school
☐High school diploma
☐Post-secondary education without a bachelor's degree
☐Bachelor's degree or higher

Appendix E- Survey of physicians' opinion on probiotic therapy for antibiotic-associated diarrhea in children

Probiotics (definition):
Probiotics are live microorganisms intended to benefit the host when ingested in sufficient numbers. They are believed to promote healthy balance of gut microbiota through various mechanisms, including reducing colonization of pathogenic organisms through competitive inhibition of epithelial and mucosal adhesion. They are available in fermented foods (e.g., yogurts, drinks) and as supplements (e.g., capsule, powder).

Antibiotic associated diarrhea (definition):
Antibiotic associated diarrhea (AAD) is a condition in which diarrhea occurs after administration of antibiotics from initiation of therapy up to 8 weeks. C. difficile causes a small percentage of AAD. The published incidence of AAD in children ranges from 11% to 40%.

With regard to the definitions above, please answer the following questions:

1) If parents ask about use of probiotics, how do you respond?

☐I do not know enough about probiotics to make any recommendations

☐I only recommend probiotics for specific indications

☐I refer parents to other specialists or resources (please specify) _____

☐I do not recommend probiotics

☐ Other (please specify) _____

2) Without parents asking, have you ever recommended probiotics for your patients?

☐Yes

☐No (If no, please skip to question number 5)

3) For what indications have you recommended probiotics?

☐Prevention of antibiotic-associated diarrhea

☐Prevention of non-specific diarrhea
☐Treatment of antibiotic-associated diarrhea

☐Treatment of non-specific diarrhea

☐Prevention of viral respiratory tract infections

☐Other (please specify) _____

4) What type of probiotics have you recommended? (Please check all that apply)

☐Foods containing naturally occurring probiotics (e.g., regular yogurt, Kimchi, Sauerkraut)

☐Foods containing supplemental probiotics (e.g., DanActive ®, Activia ®)

☐Probiotic supplements (e.g., Culturelle ®, Flora BABY®, Florastor®, VSL #3®, BioGaia®, Proxiflor®, UltraFlora ®Children's)

☐I have advised probiotics but not recommended any specific product

- Please specify the indications in which you have recommended these types of probiotics:
_____

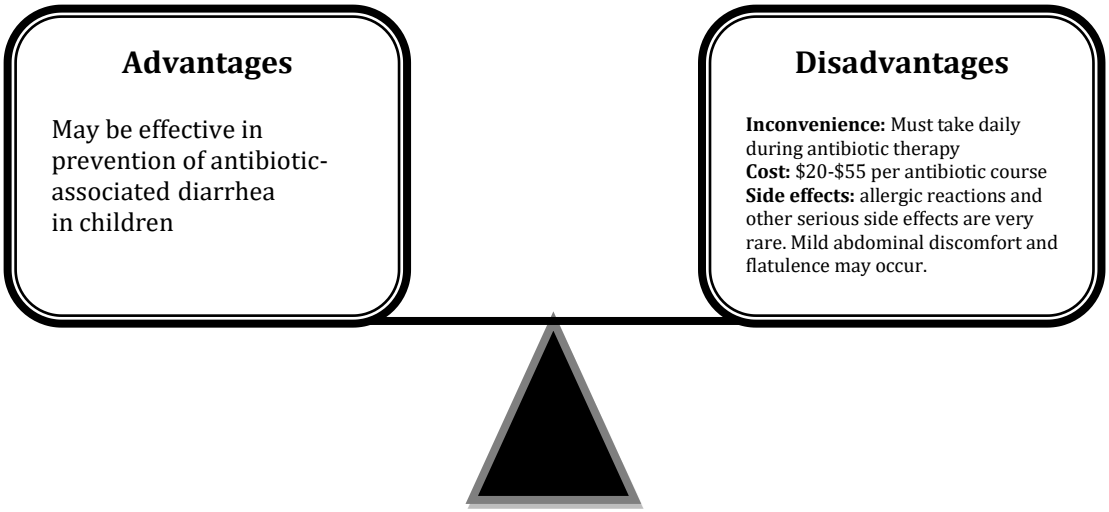
5) When considering probiotics to **prevent** antibiotic-associated diarrhea in children, do you think:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Do not know
Probiotics are EFFECTIVE	☐	☐	☐	☐	☐	☐
Probiotics are SAFE	☐	☐	☐	☐	☐	☐

6) When considering probiotics to **treat** antibiotic-associated diarrhea in children, do you think:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Do not know
Probiotics are EFFECTIVE	☐	☐	☐	☐	☐	☐
Probiotics are SAFE	☐	☐	☐	☐	☐	☐

7) Please consider the information presented below
Taking probiotics for antibiotic-associated diarrhea in children has:



According to a 2015 Cochrane systematic review, the incidence of antibiotic-associated diarrhea without probiotic therapy is 19%. I would consider probiotic prophylaxis if it would reduce the incidence rate from 19% to: (Please choose only one item)

NOTE:

- Number needed to treat (NNT) = Number of cases that need to be treated to prevent one case of antibiotic-associated diarrhea
- Options are based on 95% confidence interval of probiotics effectiveness in prevention of pediatric antibiotic-associated diarrhea

☐12% (NNT=13)

☐9% (NNT=10)

☐7 %(NNT=8)

☐I would not consider probiotic therapy for prevention of antibiotic-associated diarrhea

8) Currently, there is a huge heterogeneity in clinical trials of pediatric acute diarrhea in terms of diarrhea definition and outcomes measured. We, therefore, aim to develop and validate an instrument to measure antibiotic-associated diarrhea in children to be used in future clinical trials. We would like to identify the most important and relevant outcomes to include in the instrument based on your opinions.

On a scale of 1-9, please rate the importance of each potential beneficial outcome when considering probiotics for prevention of pediatric antibiotic-associated diarrhea:

1= Not important at all (you do not feel it needs to be measured in clinical trials)
9= Critically important (you strongly believe it is important to measure in clinical trials)

1 2 3 4 5 6 7 8 9

Stool frequency	☐	☐	☐	☐	☐	☐	☐	☐	☐
Stool consistency	☐	☐	☐	☐	☐	☐	☐	☐	☐
Duration of diarrhea	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dehydration (determined by a scoring system)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Effect on normal daily activities (e.g. eating, sleeping, playing)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Child absence from day care or school	☐	☐	☐	☐	☐	☐	☐	☐	☐
Parental absence from work	☐	☐	☐	☐	☐	☐	☐	☐	☐
Need for hospitalization	☐	☐	☐	☐	☐	☐	☐	☐	☐
Need for outpatient or emergency department visit	☐	☐	☐	☐	☐	☐	☐	☐	☐
Need for rehydration (intravenous or oral in a health care facility)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Some information about you and your practice:

9) Please indicate your gender:

☐Female

☐Male

10) Please check the category that defines your practice best:

☐General pediatrician

☐Subspecialty pediatrician (please specify):_____

11) Year of graduation (from specialty): _____

12) Average number of patients with suspected antibiotic-associated diarrhea that you see in a typical month: _____

Appendix F- Multinomial logistic regression of the effect of different factors on the choice of minimally important difference in responding parents

	MID choice of 12 vs. "I don't give probiotics"		**MID choice of 9 vs. "I don't give probiotics"**		**MID choice of 7 vs. "I don't give probiotics"**	
	Odd's ratio (95% CI)	*P value*	*Odd's ratio (95% CI)*	*P value*	*Odd's ratio (95% CI)*	*P value*
Familiarity with probiotics						
Yes	5.828 (0.459-73.943)	0.174	1.442 (0.083-24.951)	0.801	1.995 (0.167-23.764)	0.585
No	Reference		Reference		Reference	
Probiotic use						
Yes	0.186 (0.011-3.044)	0.238	0.236 (0.010-5.348)	0.364	0.340 (0.020-5.848)	0.457
No	Reference		Reference		Reference	
Child's previous experience of AAD						
Yes	5.211 (0.332-81.733)	0.240	1.925 (0.096-38.769)	0.669	2.847 (0.161-50.186)	0.475
No	0.809 (0.097-6.735)	0.845	0.513 (0.049-5.364)	0.577	1.594 (0.174-14.613)	0.680
I do not know	Reference		Reference		Reference	
Opinion regarding safety of probiotics for prevention of AAD						
Strongly disagree or disagree	-*		-*		-*	
Neutral	0.822 (0.093-7.292)	0.860	5.216 (0.255-106.565	0.283	0.324 (0.033-3.197)	0.335
Strongly agree or agree	2.565 (0.352-29.867)	0.299	7.552 (0.360-158.371)	0.193	2.393 (0.253-22.682)	0.447
I do not know	Reference		Reference		Reference	
Parent age						
<30 y/o	1.253 (0.101-15.548)	0.861	1.529 (0.088-26.654)	0.771	3.656 (0.285-46.828)	0.319
31-40 y/o	3.242 (0.252-9.427)	0.639	1.854 (0.227-15.165)	0.565	1.727 (0.248-12.006)	0.581
>41 y/o	Reference		Reference		Reference	
Parent ethnicity						
White/Caucasian	1.734 (0.303-9.914)	0.536	4.050 (0.449-36.506)	0.212	0.961 (0.161-5.728)	0.965

Other ethnicities	Reference	Reference	Reference
Parent education Bachelor's degree or higher Less than bachelor	1.994 (0.382-10.398) 0.413 Reference	1.355 (0.209-8.787) 0.750 Reference	2.392 (0.427-13.391) 0.321 Reference
Parent gender Female Male	0.177 (0.014-2.246) 0.182 Reference	0.211 (0.013-3.459) 0.276 Reference	0.325 (0.024-4.476) 0.401 Reference

*There were no enough data to provide values.
MID: Minimally important difference, AAD: Antibiotic-associated diarrhea, CI: Confidence interval

Appendix F- Multinomial logistic regression of the effect of different factors on the choice of minimally important difference in responding clinicians

	MID choice of 12 vs. 7		**MID choice of 9 vs. 7**	
	Odd's ratio (95% CI)	*P value*	*Odd's ratio (95% CI)*	*P value*
Physician gender Female Male	0.396 (0.039-4.012) Reference	0.433	0.273 (0.025-3.015) Reference	0.289
Specialty General pediatrician Sub-specialist pediatrician	0.409 (0.046-3.626) Reference	0.422	0.281 (0.028-2.773) Reference	0.277
Probiotic recommendation Yes No	7.279 (0.553-95.771) Reference	0.131	5.666 (0.356-90.097) Reference	0.219
Years since graduation	0.890 (0.744-1.065)	0.204	0.969 (0.799-1.175)	0.750
No of AAD patient visits	1.051 (0.802-1.377)	0.719	0.800 (0.564-1.136)	0.213

MID: Minimally important difference, AAD: Antibiotic-associated diarrhea, CI: Confidence interval

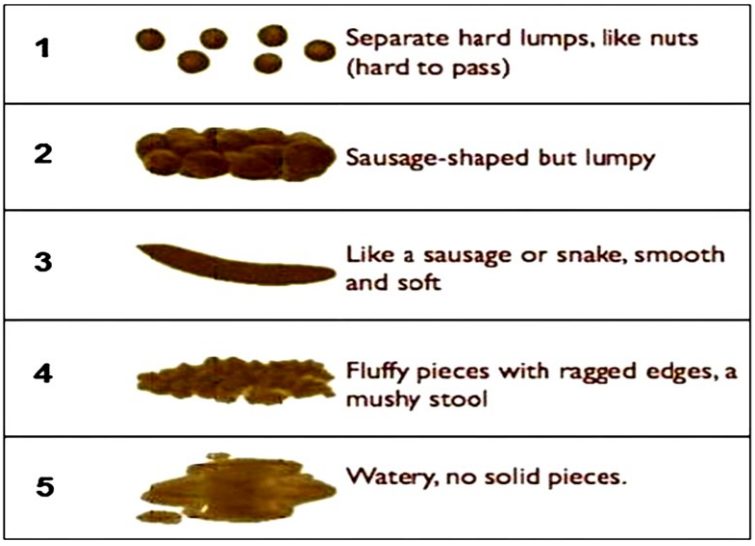
Appendix G- Numerical Rating Scale of bowel movement severity condition

"**This line shows how severe your child's condition was today**. In the **middle**, it shows your child had **normal** bowel movement. **Moving right** along the line shows more and more severe **diarrhea**. **The right end** shows very **severe diarrhea**. **Moving left** along the line shows more and more severe **constipation**. **The left end** shows very **severe constipation**. Mark the place that shows how much severe you think your child's condition was today.

Appendix H- Pediatric Antibiotic Associated Diarrhea Measurement Instrument-Outpatient

1) Stool consistency:

"Modified Bristol Stool Form Scale"



* Diarrheal stools (diagrams number 4 &5)

2) Maximum number of stools per 24-h period: _____ times
3) Diarrhea duration: _____days
4) Child's daily activities (e.g. eating, sleeping, playing):
   a. Normal b. Reduced, but still present c. Unable to participate
   d. Hospitalized due to diarrhea
5) Physician/nurse practitioner visits due to diarrhea:
   a. None b. Outpatient c. Emergency department visit d. Hospitalized due to diarrhea
6) Treatment:
   a. None b. Oral rehydration c. IV rehydration d. Hospitalization due to diarrhea

Appendix I- Baseline data collection form:

<table>
<tr><td>Participant Code:
_____</td><td>Participant's name (first/last):
_____
Initials: ___/____/___
F M L</td><td>Date: ___/____ /___
dd mm yyyy</td></tr>
<tr><td>Date of birth: ___/____ /___
dd mm yyyy</td><td>Age: _____ days/weeks/months/years old
(Please circle)</td><td>Gender:
☐Female ☐Male</td></tr>
<tr><td colspan="3">Ethnicity: (Please select all that apply)
☐ White/ European/ Caucasian
☐ Black (e.g. African, African American, African Canadian, Caribbean)
☐ East Asian (e.g. Chinese, Japanese, Korean)
☐ South Asian (e.g. Indian, Pakistani, Seri Lankan, Bangladeshi)
☐ Southeast Asian (e.g. Burmese, Cambodian, Filipino, Laotian, Malaysian, Thai, Vietnamese)
☐ West central Asian and middle eastern (e.g. Arabian, Armenian, Iranian, Afghan, Israeli, Lebanese, Palestinian, Syrian, Turkish)
☐ Latin American (e.g. Mexican, indigenous Central and South American)
☐ North American indigenous (e.g. North American Indian, Inuit, Metis)
☐ Pacific Islander
☐ Other: (please specify)_____
☐ Prefer not to answer</td></tr>
<tr><td colspan="3">Reason for current admission or visit:</td></tr>
<tr><td colspan="3">Primary diagnoses:</td></tr>
<tr><td colspan="3">Antibiotics prescribed: Name: _____
Dose/frequency: _____
Duration: _____</td></tr>
<tr><td>Final Decision:</td><td colspan="2">☐ Patient discharged
☐ Patient admitted to: _____Stollery Division
o Patient's medical record number: _____</td></tr>
</table>

Parent/Guardian Information		
Age: ☐20 or younger ☐21-25 ☐26-30 ☐31-35 ☐36-40 ☐41-45 ☐46-50 ☐ Over 50	Highest level of education: ☐Did not finish high school ☐High school diploma ☐Post-secondary education without a bachelor's degree ☐Bachelor's degree or higher	Gender: ☐Female ☐Male

The most convenient way for the follow up:

☐ Text (phone number):_____

☐ Telephone contact (phone number):_____

☐ Email (Email address): _____

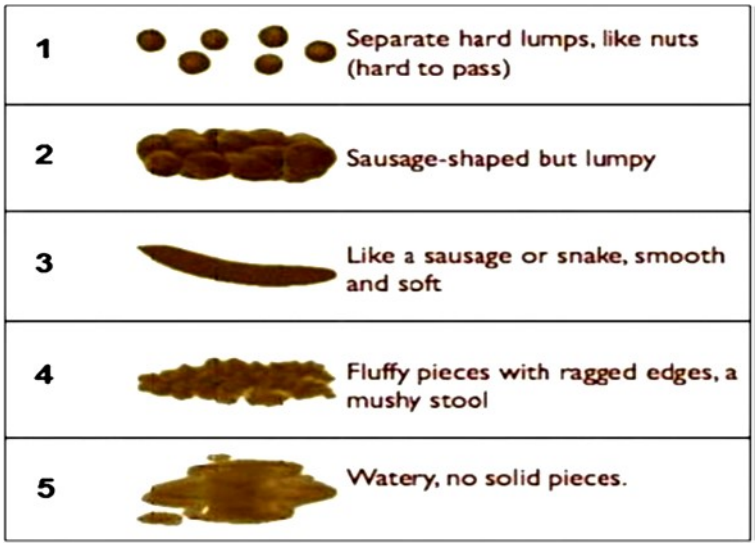
☐ Mail (Home or work address):_____

Appendix J-1- Daily collection form

Participant code: _____	**Initials:** ___/___/___ F M L	**Date:** ___/___/____ dd mm yyyy

<u>Most abnormal</u> stool appearance in the last 24 hours:

"Modified *Bristol S*tool Form Scale"



☐ No bowel movement

Number of bowel movements in the last 24 hours: _____ times

Did your child have vomiting in the last 24 hours?

☐Yes

☐No

If "**Yes**", How many times: _____

Did your child have fever in the last 24 hours?

☐Yes

☐No

If "**Yes**", What was the temperature: _____

Child's daily activities in the last 24 hours (e.g. eating, sleeping, playing):

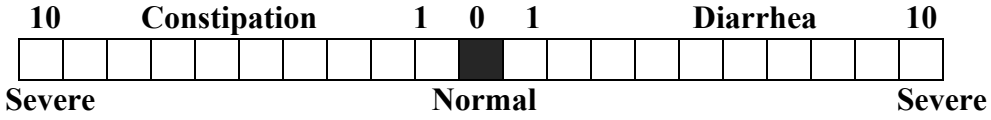
☐ Normal

☐ Reduced, but still present

☐ Not able to participate at all

☐ Hospitalized due to diarrhea

"**This line shows how severe your child's condition was today**. In the **middle**, it shows your child had **normal** bowel movement. **Moving right** along the line shows more and more severe **diarrhea**. **The right end** shows very **severe diarrhea**. **Moving left** along the line shows more and more severe **constipation**. **The left end** shows very **severe constipation**. Mark the place that shows how much severe you think your child's condition was today.



Appendix J-2-End of the study form

Participant code: _____	**Initials:** ____/____/_____ F M L	**Date:** ____/____/_____ dd mm yyyy
Diarrhea duration: _____days		
Physician/nurse practitioner visits due to diarrhea: ☐ None ☐ Outpatient (please indicate date: _____) ☐ Emergency department visit (please indicate date: _____) ☐ Hospitalized due to diarrhea (please indicate date: _____)		
Treatment: ☐ None ☐ Rehydration (oral, nasogastric tube, intravenous- please circle) ☐ Hospitalized due to diarrhea ☐ Other (please specify:_____)		
Child's absence from school/day care due to diarrhea: ☐ Yes ☐ No ☐ Child does not attend school/day care If "**Yes**", How many days: _____		
Parents' absence from work due to child's diarrhea: ☐ Yes ☐ No ☐ Parent does not work outside the home If "**Yes**", How many days: _____		

Appendix K- Associations of participant characteristics with incidence of diarrhea according to four different definitions

	COMS		P value	NRS		P value	WHO		P value	Parent		P value
	AAD N=40	No AAD N=8		AAD N=37	No AAD N=11		AAD N=24	No AAD N=24		AAD N=13	No AAD N=26	
Age of child												
0-3 yr	24(96%)	1(4%)		24(96%)	1(4%)		17(68%)	8(32%)		4(22.2%)	14(77.8%)	
4-6 yr	8(61.5%)	5(38.5%)	**0.010**	5(38.5%)	8(61.5%)	**< 0.001**	2(15.4%)	11(84.6%)	**0.009**	3(25%)	9(75%)	0.07
>6	8(80%)	2(20%)		8(80%)	2(20%)		5(50%)	5(50%)		6(66.7%)	3(33.3%)	
Gender of child												
Female	20(87%)	3(13%)	0.7	19(82.6%)	4(17.4%)	0.5	11(47.8%)	12(52.2%)	0.7	4(21.1%)	15(78.9%)	0.1
Male	20(80%)	5(20%)		18(72%)	7(28%)		13 (52%)	12 (48%)		9(45%)	11(55%)	
Ethnicity of child												
White	21(84%)	4(16%)	1	21(84%)	4(16%)	0.3	15(60%)	10(40%)	0.1	7(35%)	13(65%)	0.8
Other	19(82.6%)	4(17.4%)		16(69.6%)	7(30.4%)		9 (39.1%)	14(60.9%)		6 (31.6%)	13(68.4%)	
Outpatient	32(80%)	8(20%)	0.3	29(72.5%)	11(27.5%)	0.2	17(42.5%)	23(57.5%)	**0.04**	10(31.2%)	22(68.8%)	0.6
Inpatient	8(100%)	0		8(100%)	0		7(87.5%)	1(12.5%)		3(42.9%)	4(57.1%)	
Antibiotic type												
Amoxicillin only or in combination	19(86.4%)	3(13.6%)	0.8	18(81.8%)	4(18.2%)	0.4	10(45.5%)	12(54.5%)	0.3	7(35%)	13(65%)	0.4
Cephalosporin only or in combination	18(81.8%)	4(18.2%)		17(77.3%)	5(22.7%)		13(40.6%)	19(59.4%)		4(25%)	12(75%)	
Other	3(75%)	1(25%)		2(50%)	2(50%)		1(25%)	3(75%)		2(66.7%)	1(33.3%)	
Antibiotic duration (days) Mean±SD	8.8±4.5	6.1±2.1	0.1	8.9±4.7	6.7±2	0.1	9.1±5.4	7.5±2.5	0.1	9.7±7	8.2±2.5	0.4

AAD: Antibiotic-associated diarrhea, COMS: Core Outcome Measurement Set; NRS: Numerical Rating Scale, WHO: World Health Organization

*Comparisons made using independent sample T test or Chi-square.

Appendix L- Cronbach's α of PAAD instrument severity score according to different definitions

	COMS	WHO	NRS	Parent
Cronbach's α	0.52	0.61	0.31	0.29

COMS: Core Outcome Measurement Set; NRS: Numerical Rating Scale, WHO: World Health Organization

Appendix M- Inter-item correlation matrix

	Diarrhea frequency	Daily activities	Physician/nurse practitioner visit	Dehydration treatment	Diarrhea duration			
					COMS	WHO	NRS	Parent
Diarrhea frequency	1	0.25	-	0.20	0.7	0.85	0.39	0.23
Daily activities		1	-	-0.093	0.15	0.06	0.11	0.14
Physician/ nurse practitioner visit			1	-	-	-	-	-
Dehydration treatment				1	0.09	0.03	0.16	0.03

Acceptable level of correlation: 0.2-0.5, more than 0.7, one could be deleted.
COMS: Core Outcome Measurement Set; NRS: Numerical Rating Scale, WHO: World Health Organization

Appendix N- Corrected item-total correlation for items of the severity scale according to different definitions

	Corrected item-total correlations			
	COMS	WHO	NRS	Parent
Diarrhea duration	0.67	0.78	0.39	0.24
Diarrhea frequency	0.72	0.87	0.41	0.26
Daily activities	0.19	0.14	0.16	0.2
Dehydration treatment	0.13	0.09	0.18	0.11

Acceptable level of correlation: >=0.3
"Physician/nurse practitioner visit" was removed as the score variance was zero.
COMS: Core Outcome Measurement Set; NRS: Numerical Rating Scale, WHO: World Health Organization