Development of a Core Outcome Set for Infant Gastroesophageal Reflux Disease

*Maartje M.J. Singendonk, *Robyn Rexwinkel, *Nina F. Steutel, †Frederic Gottrand, ‡Lisa McCall, §Danielle K. Orsagh-Yentis, ||Rachel Rosen, ¶Caterina Strisciuglio, #Nikhil Thapar, **Yvan Vandenplas, *Marc A. Benninga, and *Merit M. Tabbers

ABSTRACT

Objective: In therapeutic trials for infant gastroesophageal reflux disease (GERD), ways to define GERD and measure and report study outcomes vary widely. The aim of this study was to develop a core outcome set (COS) for infant GERD.

Methods: The COS was developed using the Delphi technique, adhering to the Outcome Measures in Rheumatology Initiative 2.0 recommendations. Healthcare professionals (HCPs) (predominantly pediatric gastroenterologists and general pediatricians) and parents of infants (age 0–12 months) with GERD, listed up to 5 primary goals of therapy from their perspective and up to 5 persistent signs or symptoms that would signify inadequate treatment. Outcomes mentioned by >10% of participants were included in 2 shortlists. Next, HCPs and parents rated and prioritized outcomes on these shortlists. Outcomes with the highest rank formed the draft COS. The final COS was created after 2 consensus meetings between an expert panel and patient representatives.

Results: In total, 125 of 165 HCPs (76%) and 139 of 143 parents (97%) of infants with GERD completed the first phase. The second phase was completed by 83 of 139 HCPs (60%) and 127 of 142 different parents (89%). Outcomes of these phases were discussed during the consensus meetings and a 9-item COS was formed: ''Adequate Growth,'' ''Adequate Relief,'' ''Adverse events,'', ''Crying,'' ''Evidence of Esophagitis,'' ''Feeding Difficulties,'' ''Hematemesis,'' ''No Escalation of Therapy,'' and ''Sleep Problems.''

Conclusions: We developed a COS for infant GERD consisting of 9 items that should minimally be measured in future therapeutic trials to decrease study heterogeneity and ease comparability of results.

Key Words: core outcome set, gastroesophageal reflux disease, infants

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What Is Known

- Definitions, outcome measures, and measuring instruments used in randomized controlled trials on infant gastroesophageal reflux disease vary widely.
- Core outcome sets ensure reporting consistency regardless of the primary purpose of a trial.

What Is New

- We developed a core outcome set for infant gastroesophageal reflux disease through an international Delphi study.
- This 9-item core outcome set consists of patient-reported outcomes, clinical outcomes, and adverse events and may have the potential to decrease study heterogeneity and ease comparability of results of future trials.

Gastroesophageal reflux (GER) is the (in)voluntary backflow of stomach contents into the esophagus and occurs physiologically on a daily basis in all infants (1). Gastroesophageal reflux disease (GERD) is defined as GER causing bothersome symptoms and/or complications (2,3).

Despite the importance of symptoms in the definition of GERD, therapeutic trials of medications and surgery for GERD fail

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From the *Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Gastroenterology, Amsterdam, The Netherlands, the †Division of Pediatric Gastroenterology, Hepatology and Nutrition, CHU Lille, University Lille, France., the ‡Gastroenterology Unit, Women's and Children's Health Network, School of Medicine, North Adelaide, Australia, the §Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH, the ||Division of Gastroenterology, Aerodigestive Center, Children's Hospital Boston, Boston, MA, the ¶Department of Woman, Child and General and Specialistic Surgery, University of Campania ''Luigi Vanvitelli,'' Naples, Italy, the #Great Ormond Street Hospital for Children, London, UK, and the **KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium.

Address correspondence and reprint requests to Merit M. Tabbers, MD, PhD, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, H7-228, PO Box 22700, 1100 DD Amsterdam, The Netherlands (e-mail: m.m.tabbers@amc.nl).

Maartje M.J. Singendonk and Robyn Rexwinkel: Indicates shared first authorship.

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to use a common set of outcomes to assess improvement in GERD symptoms (4). Furthermore, bothersome symptoms may differ depending on if the symptoms are assessed by health care providers, patients, or patient's parents (5). Because of this lack of standardization of outcomes, comparisons of therapeutic trials are difficult and the quality of evidence supporting therapeutic interventions is weak (6,7).

To inform clinical practice, future trials that aim to determine benefits and risks of interventions should measure outcomes that are considered to be important to patients and parents and useful to healthcare professionals (HCPs). A way to achieve this is by developing a ''core outcome set'' (COS) for clinical trials, which represents the agreed minimum set of outcomes that should be measured and reported in trials in a certain area (8). These COS have already been used successfully in other healthcare areas, such as the Outcome Measures in Rheumatology Initiative (OMERACT) (9,10). Patient-reported outcomes (PROs) are increasingly measured in current research. However, only 16% of the currently available COS involved patients and representatives during the COS development process, limiting any value PROs may add to a COS (10).

Currently, no such standardized set of outcome measures including PROs is available for infants with GERD. The aim of our study therefore was to develop a COS for infant GERD by adhering to the OMERACT recommendations and ensuring active involvement of both HCPs and patients and their representatives throughout the whole process. This COS has the potential to improve quality and comparability in future outcome trials on infant GERD, thereby advancing the usefulness of research to inform clinical practice and enhancing patient care.

METHODS

A COS for infant GERD was developed by adhering to the stepwise approach as advised by the OMERACT 2.0 filter (6,7,9,10,12). The following steps were conducted: collecting important treatment outcomes (step 1) and creating the COS (step 2).

Step 1—Collecting Important Treatment Outcomes

HCPs visiting the 2016 European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) annual meeting in Athens, Greece, were invited to participate in the survey. No restrictions were applied as to age, level of expertise of setting of care. HCPs from Australia and the United States of America were invited separately by e-mail to ensure a global representation of HCPs (12,13). Our aim was to include at least 100 HCPs, similar to earlier studies (Supplemental Fig. 1, Supplemental Digital Content, *http://links.lww.com/MPG/B544*) (12,14). An English-written questionnaire was handed out on paper and participants were asked to list up to 5 primary goals of therapy from their perspective and up to 5 persistent signs or symptoms that would signify inadequate treatment. Answers were processed anonymously. All HCPs were invited to indicate whether they would like to be involved in the further phases of the development of the COS. For further information, the original questionnaires are available from the corresponding author.

Next, parents/caregivers (further referred to as ''parents'') from infants with GERD from Europe (Belgium, France, Italy, The Netherlands, and the United Kingdom), Australia, and the USA (n = 20 per country) were invited to participate in the survey. Diagnosis of GERD was made by the infant's treating physician, based on the definition as proposed by ESPGHAN/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines. Only infants who were otherwise healthy were included. Our aim was to include at least 140 parents, similar to earlier studies (Supplemental Fig. 1, Supplemental Digital Content, *http://links.lww.com/MPG/B544*) (12,14). An English-written questionnaire was provided by the infant's treating physician at the inpatient or outpatient clinic or by an independent researcher of our group by telephone after verbal informed consent. The original questionnaire was developed in English and presented to respondents in their native language. Parents were asked to list up 5 aspects of the treatment for GERD that would made them feel their child was being treated adequately/inadequately or that would made them feel comfortable/uncomfortable. Answers were translated back to English by the researchers that questioned the participants and were processed anonymously.

Step 2—Creating the Core Outcome Set

Step 2a—Creating a Short List

The second step in the development of a COS for infant GERD consisted of 4 phases. Listed outcomes by HCPs and parents were classified in predefined domains and grouped in core areas according to the OMERACT conceptual framework (10). To identify responses that were open to interpretation and to make categorization more accurate, responses were independently judged by 2 reviewers (M.M.J.S. and R.R.) and disagreements were adjudicated by discussion and consensus with a third-party arbiter (M.M.T.). When necessary, domains were added according to the outcomes reported by the HCPs and parents.

Reported outcomes were then combined when considered appropriate (by M.M.J.S., M.M.T., and R.R.). Grouped outcomes that were mentioned by >10% of the participants were selected to create 3 different shortlists: 2 based on the answers of HCPs in the inpatient and outpatient settings, respectively, and 1 based on the answers of the parents, regardless of setting (9,11).

Step 2b—Rating Outcomes on the Shortlist

HCPs that had previously agreed to participate in further development of the COS, and members of The Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT) Working Group; the ESPGHAN; Neurogastroenterology Motility and Functional Gastrointestinal Disorders Working Group; the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; and Australian HCPs with a special interest in pediatric gastroenterology, were invited via e-mail to participate in the second phase and fill out an online questionnaire. We aimed to have at least 50% of the HCPs involved in the first step of the study also involved in the second step. HCPs were asked to rate each outcome for the inpatient and outpatient setting separately on a scale ranging from 1 to 9 (1–3 signifying an outcome of limited importance, 4–6 being important but not critical, and 7–9 being critical) (8,15,16). Consensus to whether an outcome should be included in the COS was defined as 70% or more of the HCPs rating it as 7 to 9 and fewer than 15% rating it as 1 to 3. Consensus that an outcome should not be included in the COS was defined as 70% or more rating it as 1 to 3 and fewer than 15% rating it as 7 to 9 (8,15,16).

A new cohort of 140 parents of infants with GERD (countries similar to those in the first phase of the development process, n = 20 per country) was invited to participate (methods for recruiting and questionnaire-taking as above). Parents were asked to rank the outcomes on the shortlist on a scale of 0 to 4 (0 = ''does not make me feel comfortable,'' 4 = ''makes me feel very comfortable'') and to prioritize these outcomes by selecting the 5 outcomes that made them feel the most comfortable (17).

Step 2c—Creating Top 5 Outcomes for HCPs and Parents

In this phase, the preliminary parental COS was created using the 5 outcomes with the highest rank. Methods for creating the HCPs preliminary COS were as described above. The 2 preliminary COS for parents and HCPs were then combined into 1. Last, following the OMERACT approach, adverse events were put forward to the preliminary COS.

Step 2d—Creating Final Set

In the first consensus meeting, the preliminary COS was discussed between the HCPs with expertise in the field of infant GERD and representatives of pediatric patients with GERD during the 8th European Pediatric Motility Conference in London, March 2018. The final COS was presented to the Neurogastroenterology Motility and Functional Gastrointestinal Disorders Working Group at the 51st ESPGHAN annual meeting in Geneva, May 2018. Consensus was defined as a unanimous decision from the expert panel.

RESULTS

Step 1—Identifying Important Treatment Outcomes

Healthcare Professionals

In total, 125 out of 165 HCPs (76%) from 33 different countries of origin completed the first questionnaire. Illegible outcomes were excluded (inpatient, n = 1; outpatient, n = 3). The listed outcomes ''diagnostics'' (outpatient setting, n = 2; inpatient setting, n = 3), ''follow-up'' (outpatient setting, n = 1) and ''observation'' (inpatient setting, n = 6) were also excluded as they were not considered to be appropriate parameters corresponding with measurable effects of therapeutic interventions for GERD. After exclusion, 59 different outcomes were reported for the outpatient setting and 57 for the inpatient setting (Supplemental Tables 1 and 2, Supplemental Digital Content, *http://links.lww.com/MPG/B544*).

Parents

Altogether, 139 out of 143 (97%) parents (66% mothers) from 7 different countries responded to the first questionnaire. Illegible outcomes (n = 3) were excluded and the listed outcomes ''diagnostics'' (n = 18), ''follow-up'' (n = 21), and ''observation'' (n = 7) for the same reason as described above. Listed outcomes were redirected into 1 direction (''adequately treated''). In total, 50 different treatment outcomes were reported (Supplemental Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B544*).

Step 2—Creating the Core Outcome Set

Step 2a–c—Creating and Rating Shortlists

Based on the outcomes mentioned by >10% of the HCPs, 2 shortlists (inpatient and outpatient setting) consisting of 9 and 7 outcome measures, respectively, were created (Table 1). These shortlists were rated and prioritized by 83 of the 139 approached HCPs (60%) from primary, secondary, and tertiary care centers originating from 29 different countries.

In total, 127 parents completed the second questionnaire and rated the outcomes on the shortlist. The shortlist resulting from the outcomes mentioned by >10% of parents is displayed in Table 2 and consists of 13 outcome measures. The 5 outcome measures on this shortlist with the highest rank were put forward to the parental preliminary COS.

TABLE 1. Shortlist of outcome measures from healthcare professionals (rated and prioritized)

Rank	Outcome measure	Average rating	Percentage (%)	
Outpatient setting			1–3	7–9
1	Failure to thrive	**7.70**	**3.6**	**88.0**
2	Hematemesis	**7.36**	**6.0**	**79.5**
3	Feeding problems*	6.51	3.6	53.0
4	Weight gain	6.30	8.4	55.4
5	General symptom improvement	5.52	10.8	26.5
6	Irritability of infant	4.93	24.1	15.6
7	Parental stress/anxiety	4.53	33.7	15.6
Inpatient setting				
1	Evidence of esophagitis	**7.39**	**2.4**	**78.3**
2	Hematemesis	**7.35**	**2.4**	**81.9**
3	GERD-related complications†	6.69	8.4	69.9
4	Feeding problems	6.35	3.6	68.7
5	Weight gain	6.06	10.8	45.8
6	Respiratory symptoms	5.88	10.8	43.4
7	General symptom improvement	5.29	12.0	26.6
8	Any use of antireflux medication‡	5.24	14.5	27.7
9	Vomiting in general	4.75	22.9	32.5

Outcomes that were scored by >70% of the respondents rating it as 7 to 9 and by <15% rating it as 1 to 3 and were thus put forward to the preliminary core outcome set are highlighted in bold.

GERD = gastroesophageal reflux disease.

*Including aversion, intake, pattern, volume, and milk tolerance.

†Including complications (outcome not further specified) (6), infections (4), Sandifer syndrome (1), associated disease (1), malformation in intestine (1), sepsis (1), *Helicobacter pylori* (1), skin eczema (1), dysphagia (1), perforation stomach (1), nasogastric tube trauma (1), esophageal strictures (1), surgery side effects (1), improved vital signs (1), abnormal upper gastrointestinal series suggestive of medical issues (1), ulcer (1), chest problems (1).

‡Including PPI, H2RA, and prokinetics.

TABLE 2. Shortlist of outcome measures from parents (rated and prioritized)

Rank	Outcome measure	Average rating	Percentage (%)
1	Education by healthcare professional	**3.31**	**47**
2	General symptom improvement	**3.15**	**57**
3	Parental reassurance	**3.07**	**39**
4	Parental satisfaction	**3.06**	**38**
5	Weight gain	**2.93**	**44**
6	Child comfort	2.85	62
7	Quality and/or quantity of sleep	2.60	43
8	Any use of antireflux medication*	2.50	28
9	Feeding problems†	2.34	24
10	Crying duration	2.21	29
11	Respiratory symptoms‡	2.15	24
12	Vomiting in general	1.96	10
13	Regurgitation in general	1.83	13

Outcomes that were put forward to the preliminary core outcome set are highlighted in bold.
*Including proton-pump inhibitors, histamine-2 receptor antagonists, antacids, and prokinetics.
†Including food aversion, food intake, feeding pattern, volume of feeds, pain, and milk tolerance.
‡Including coughing and wheezing.

Step 2d—Creating Final Core Outcome Set

The outcomes listed on the preliminary COS for the HCPs and parents were combined into 1 (Fig. 1—step 1). Figure 1 (steps 1 and 2 a–c) describes the creation of the final COS during the first consensus meeting in London, based on the preliminary COS for the HCPs and parents. Eventually, the final COS consisted of 9 items and was presented during the consensus meeting in Geneva, which consisted of general pediatricians, neonatologists, and mostly pediatric gastroenterologists from European countries, and the USA and Australia (Fig. 1—step 3).

DISCUSSION

In this study, we developed a 9-item COS for infant GERD by identifying outcomes of importance from HCPs' and patients' perspectives worldwide. This COS consisted of a combination of PROs (3 items), clinical outcomes (5 items), and adverse events. Although vomiting and regurgitation could be predominant GERD symptoms, they were not included in the final COS. Reasons for this may be that both HCPs and parents are more concerned about the consequences of GERD, such as impaired growth or reduced intake, instead of GERD-related symptoms as vomiting. Several outcomes included in the current COS, such as crying and adverse events, overlap with outcomes included in recently developed pediatric COS (6,12,13). This may imply that similar aspects of treatment are considered important to parents, regardless of their child's underlying condition. There may thus be room for development of a general COS applicable to all pediatric functional gastrointestinal (GI) conditions that can be expanded with smaller disease-specific outcomes.

Although final agreement on these outcome measures was reached through consensus meetings, individual steps of the process revealed great heterogeneity in outcomes considered to be important by HCPs or parents and patient representatives. In general, parents and representatives considered outcomes associated with quality of life, like reassurance, education, and symptom relief as critical, whereas HCPs gave greater importance to objective clinical outcomes such as weight gain, endoscopic healing, and patient survival. A likely explanation may be that HCPs perceive objective improvement in signs of disease and prevention of complications of disease as their primary roles in the management of infant GERD. Because quality of life-related PROs are more intangible and may be nonspecific for GERD, HCPs place less importance on them. Despite those factors, this COS clearly indicates the importance of these measures to parents, yet none of the currently available randomized controlled trials on the management of infant GERD included PROs such as quality of life or parental satisfaction as outcomes of interest. Second, the OMERACT initiative recommends early involvement of parents, patients, and representatives throughout the COS development to ensure that these PROs truly reflect the patient's perspective (10,18,19). Patients and representatives were, however, involved during the development process of only 16% of the currently available COS (10). This provides implications for future research in this area (2,4). This COS may also be of use in clinical practice to facilitate shared decision making, because the COS is a reflection of outcome measures of greatest importance to HCPs and parents of infants with GERD. Clearly, there is a need for HCPs to provide better education and reassurance tools (20–22). Family-centered services may help define and address the specific goals and expectations of the parents, while simultaneously ensuring optimal clinical care of the infant.

Determining how to *measure* the outcomes included in this COS will be challenging. Several instruments have already been used in other intervention studies (2). For instance, endoscopy is a validated instrument to measure ''Esophagitis,'' and the Infant Gastroesophageal Reflux Questionnaire Revised is a reliable instrument to assess GERD symptoms in infants over time and report on treatment outcomes (2,23–26). However, for outcome measures such as ''Adequate Relief'' and ''Sleep Problems,'' where more than 1 instrument can be used, it may be difficult to find appropriate validated measurement tools. The Consensus-based Standards for the selection of health Measurement Instruments–COMET guideline, may help to find the most appropriate instruments (27). The adjustment of well-validated measurement tools in other healthcare areas may be a solution. For example, randomized controlled trials on functional GI disorders have shown that a simple dichotomous question (''yes''/''no'') can reliably measure ''Adequate Relief,'' and validated questionnaires can be used to assess patients' and parental quality of life (28–31). The first step, however, will be a detailed systematic review on the instruments that can be used to measure each of the agreed outcomes.

This study has several strengths and some limitations. Currently, there is no consensus regarding the best methodology for the

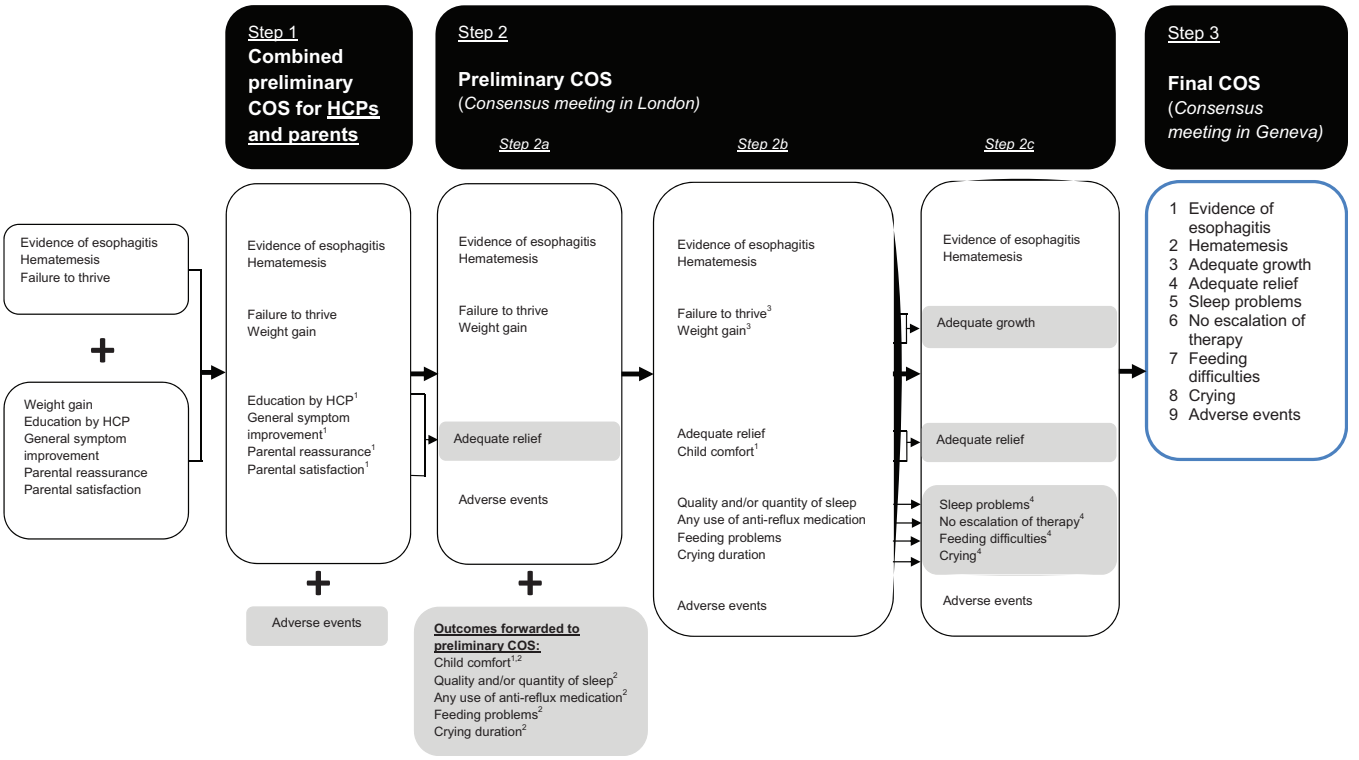

FIGURE 1. Preliminary and Final core outcome set for infant gastroesophageal reflux disease (GERD). Step 1: ''Adverse Events'' was added following the methodology. Step 2: Preliminary COS was presented and discussed during the first consensus meeting in London. A, Based on expert opinion, outcomes ''Education by Healthcare professional,'' ''General Symptom Improvement,'' ''Parental Reassurance'' and ''Parental Satisfaction'' on the parental preliminary COS were grouped together under the single outcome measure ''Adequate Relief.'' This resulted in a shift of the outcome ranks on the parental shortlist and consequently, of a shift of the outcomes that could be forwarded to the parental preliminary COS. All outcomes included in the preliminary COS for HCPs were considered relevant to the panel and no changes were made. B, C, ''Failure to Thrive'' and ''Adequate Growth'' were grouped together under one outcome measure: ''Adequate Growth,'' and also ''Child Comfort'' was grouped under ''Adequate Relief.'' Terminology to define the outcome measures was discussed and adjusted where deemed necessary. [1]Grouped under the single outcome measure: ''Adequate Relief.'' [2]Grouping of outcomes resulted of a shift in ranking on the parental shortlist and therefore additional outcomes could be put forward to the preliminary COS, which were included after discussion. [3]Grouped under the single outcome measure: ''Adequate Growth.'' [4]Redirection of terminology to describe the outcome measure. COS = core outcome set; HCP = healthcare professional.

development of COS. In accordance to the vast majority of currently available COS, we followed the COMET Initiative guidelines for COS development and used a Delphi survey to obtain information from a global group of participants (8,11,32,33). Other methods include the nominal group technique, a consensus development conference and a semistructured group discussion (34–37). However, these all require face-to-face communication early in the process. The Delphi process avoids the logistical and economic challenges associated with face-to-face meetings (11,32,33). Moreover, it enables participants to vote anonymously; thereby, minimizing the risk of bias resulting from more dominant individuals affecting the opinions of the group (7). It may, however, be possible that an alternative method would have led to a different COS, as was seen in 4 COS in childhood asthma—all of which used a different methodology (6,38–40).

A major strength of this study is that we included participants from 5 different continents and >30 countries. We reached a response rate of 60%, which is similar to previous studies in this field (6,12,13). Second, we actively involved patient representatives during the consensus meeting, which has only been done by a slight minority of currently available COS (10). As we developed a COS for *therapeutic trials* on infant GER *disease*, we aimed to include HCPs directly involved in the management of infant GERD. We used fewer primary care and general pediatricians involved in the management of infant GER, because therapy is not needed for these infants. We therefore conducted the survey during the ESPGHAN annual meeting. We primarily included pediatric gastroenterologists and general pediatricians with a special interest in GI problems. It may be possible that there are differences in responses between pediatric gastroenterologists and pediatricians. However, since we included predominantly pediatric gastroenterologists and numbers in the other groups are small, no group-to-group comparison was performed. Last, we used both a 9-point- and 5-point Likert scale to rate the importance of the outcome measures noted in round 2 of the COS development. Reducing the risk of researchers' drawing conclusions based on their own beliefs, potentially causing bias, is a major advantage of the 9-point Likert scale, and was set for the HCPs in this COS process (8). The 5-point Likert scale creates a clear difference between categories, making it more comprehensible for people who are not experts in the field, and is a powerful scale for parents to rate the outcomes in this COS (41).

A limitation of our study may be that participants from developing countries were under-represented (13%), which could limit the external validity of this COS in a developing country

setting (ie, Gross National Income per capita as calculated by the World Bank Atlas method, 2016). Furthermore, there may be a bias for developed countries (42). The included outcome measures in this COS are, however, only the baseline minimum number to include in future studies, and stakeholders can include additional and specific items as required, as some outcome measures may be specific to their culture or their country's health organization. Second, the questionnaire was developed in English and presented to respondents in their native language. The answers were translated back into English by the researchers who had questioned the participants. It is possible that the answers may have been misinterpreted. It should also be noted that, despite our efforts and with the help of our colleagues, some illegible and listed outcomes reported by the participants were not included, which could have induced reporting bias.

In conclusion, we developed a COS for infant GERD consisting of 9 outcome measures that should, at minimum, be measured in future clinical research trials on infant GERD. This COS has the potential to increase comparability of future studies in the field of infant GERD and will therefore allow better evidence-based decision making. It is important to emphasize that this COS is dynamic and will require future review and adjustment. In addition, it will depend on the study population (ie, severity of disease), design of the study, and the intervention assessed which outcomes are appropriate to be included. Implementation of this COS will unavoidably require a clear consensus on how to define GERD in different age groups to obtain homogenous patient populations and facilitate comparison between studies (2,43). The next step will be to identify which measurement tools are required, and which tools are not adequately validated to allow successful implementation (27).

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