Developing a core outcome set for children with protracted bacterial bronchitis

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ABSTRACT

Background: Protracted bacterial bronchitis (PBB) is a chronic endobrochial infection and a leading cause of chronic wet cough in children. There is an urgent need for a randomised controlled trial to investigate the optimal treatment but there is no core outcome set (COS) to inform choice of outcomes. A COS is a standardised set of outcomes representing the minimum that should be measured and reported in clinical trials of a specific condition. We have developed a COS for PBB.

Methods: Potential core outcomes were collated from a systematic review, interviews with parents and a clinician survey. A two-round Delphi survey of healthcare professionals identified which outcomes had consensus for inclusion. The final COS was agreed at a consensus meeting of parent representatives and clinicians.

Results: 20 outcomes were identified for the Delphi survey. After two rounds, 10 reached consensus. These were combined and edited at the consensus meeting into the final six: 1) Resolution of cough assessed using a cough score/diary recorded daily by parent(s) during treatment; 2) relapse of chronic wet cough and/or cumulative antibiotic treatment during ≥12 months follow-up; 3) change in child’s quality of life (parent-proxy reporting for young children); 4) emergence of antibiotic resistance; 5) development of bronchiectasis diagnosed on clinically indicated computed tomography scans; and 6) microbiological clearance of identified respiratory pathogen if samples readily available.

Conclusions: We have developed a COS for PBB which will reduce the outcome heterogeneity and bias of future clinical trials, as well as promoting comparison between studies.

Cite this article as: Gilchrist FJ, Ali I, Brodlie M, et al. Developing a core outcome set for children with protracted bacterial bronchitis. ERJ Open Res 2020; 6: 00344-2019 [https://doi.org/10.1183/23120541.00344-2019].
Background
Protracted bacterial bronchitis (PBB) is a leading cause of chronic wet cough in young children and is responsible for ~40% of those referred to secondary care with this problem [1, 2]. It is caused by chronic endobronchial infection with organisms such as Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis and Staphylococcus aureus [3]. The diagnostic criteria are: 1) chronic wet cough, 2) cough resolution following 2 weeks of oral antibiotics and 3) absence of symptoms or signs suggestive of another cause of wet cough [4]. Although response to antibiotics is part of the diagnostic criteria there is a paucity of evidence to inform the optimal duration of treatment. This has resulted in variation in practice [5, 6]. The incidence of chronic cough relapse in PBB has been reported as high as 76% [6]. It is not known if these relapses reflect incomplete treatment of the original infection or acquisition of a new infection. Recurrent PBB (>3 episodes per year) is associated with a future diagnosis of bronchiectasis [7, 8].

Core outcome sets (COS) are standardised groups of outcomes representing the minimum that should be measured and reported in all clinical trials of a specific condition. They aim to reduce outcome heterogeneity, reduce bias, improve the accuracy of data interpretation and allow meaningful comparisons between studies facilitating meta-analysis [9]. Although COS have been developed for use in interventional studies in children with causes of chronic dry cough (particularly asthma), no COS has been developed for children with PBB [10]. In PBB, the high rates of relapse and the significant long-term consequences mean there are a wide range of potential outcomes that clinical trials could report. As research in this area increases, a relevant COS is vital.

Aims and objectives
Aims
The aim of this study was to develop a COS for clinical and cost-effectiveness studies assessing the treatment of PBB in children. This has been undertaken in accordance with the Core Outcome Sets – Standards for Development document [11].

Objectives
The objectives of the study were 1) to collate a “long-list” of potential core outcomes from the following sources: a systematic review of previously published clinical studies of children with PBB, semi-structured interviews with parents of children with PBB and a survey of paediatric respiratory clinicians; 2) to conduct a Delphi survey (two rounds) to generate a “short-list” of outcomes about which relevant healthcare professionals have consensus for inclusion; and 3) to hold a consensus meeting where the final COS is agreed and prioritised by parent representatives and clinicians.

Methods
The protocol for the development of this COS was registered a priori on the Core Outcome Measures in Effectiveness Trials website (www.comet-initiative.org).

Systematic review
A systematic review was conducted searching the Cochrane, PubMed, World Health Organization Clinical Trials and MEDLINE (EBSCO) databases to identify prospective studies assessing response to treatment in children with chronic wet cough. The search terms can be seen in appendix 1. The abstracts of identified studies were screened independently by two reviewers (BK and JW) using the inclusion/exclusion criteria shown in appendix 1. Full-text versions were obtained when there was conflict over inclusion and when necessary, a third reviewer (FG) made a final decision. Full-text versions of the included papers were then obtained and the outcomes extracted.

Interviews with parents
The outcome measures important to parents were identified using semi-structured interviews. As the average age for children with PBB is ~3 years [3], interviews with affected children were not deemed appropriate. Parents of children with PBB attending the paediatric respiratory clinic at Royal Stoke University Hospital (Stoke on Trent, UK) in November and December 2018 were invited to participate. The interviews were undertaken by a single researcher (IA) after obtaining informed consent. A series of open-ended questions were used to evaluate the parent’s experience of the impact of PBB and the outcomes they viewed as most important. These questions are listed in appendix 2. Each interview was recorded and transcribed. The transcripts were analysed according to published guidance [12]. In keeping with this guideline, we estimated that a sample size of 20 was needed, but recruitment stopped when analysis showed saturation had been reached with no new outcomes being identified [13, 14].

https://doi.org/10.1183/23120541.00344-2019
Clinician survey
A questionnaire was developed to identify the outcomes deemed important by clinicians for clinical trials of PBB. An electronic link to this questionnaire was sent to all the paediatric respiratory consultants working at Alder Hey Children’s Hospital (Liverpool, UK), the Great North Children’s Hospital (Newcastle upon Tyne, UK) and Royal Stoke University Hospital. The questionnaire can be seen in appendix 3.

Prioritisation of outcomes by stakeholders
The long-list of outcomes generated using the three sources detailed earlier was used in a two-stage, web-based, anonymised Delphi survey of relevant healthcare professionals [15]. Electronic invitations were sent out via the British Respiratory Paediatric Society (BPRS). The BPRS is a multidisciplinary organisation which exists to promote the respiratory health of all children and to improve the health of children with respiratory disease. Membership of the Society is open to healthcare professionals who are active in the field of paediatric respiratory medicine. The Delphi survey participants scored each outcome using the system developed by the Grading Recommendations Assessment Development and Evaluation (GRADE) working group. This uses scores of 1–9 (1–3: not relevant, 4–6: important but not critical, 7–9: extremely relevant). Participants had the opportunity to suggest additional outcomes that were not listed. Consensus for inclusion of an outcome in the short-list was based on >70% participants grading it “extremely relevant” (score of 7–9) and <15% as not relevant (score of 1–3). An outcome was excluded if >70% graded it “not relevant” (score of 1–3) and <15% as extremely relevant (score of 7–9). A minimum of 40 complete responses was agreed.

Stage 2 of the Delphi survey was only open to respondents who completed stage 1. Participants were informed of the outcomes for which consensus had been reached for inclusion or exclusion in round 1. They were then asked to re-score the remaining outcomes after reviewing their scores and those of all respondents from round 1. The criteria for consensus on inclusion and exclusion were the same as for round 1.

Consensus meeting
The short-list of outcomes which reached consensus for inclusion in the Delphi survey were discussed at a consensus meeting with parent representatives and clinicians. The short-list was sent to the participants in advance so they had time to review them. Each outcome was then discussed with the help of the meeting chair (IS). Outcomes were retained, edited or removed on the basis of the consensus between parents and clinicians and then prioritised. Items were only included in the final COS if there was universal agreement among all participants.

Ethics statement
We sought the advice of the National Research Ethics Service about whether this study required ethical review by a National Health Service research ethics committee. They advised that the project was not research, and so no formal application for ethical approval was made. No identifiable details about patients or families were collected.

Results
Systematic review
The initial search identified 227 studies (369 minus 142 duplicates). Full-text versions of 60 articles were obtained and five met the inclusion and exclusion criteria [4, 16–19]. A summary of these studies and the reported outcomes is shown in table 1.

Interviews with parents
After 16 interviews data saturation was reached as no new outcomes were being identified. All parents reported cough as the main symptom. This affected the child by disrupting sleep (15 out of 16), reducing appetite (eight out of 16) and reducing ability to exercise/play (five out of 16). The commonest negative effects on the parent(s) were disrupted sleep (16 out of 16), anxiety/worry (10 out of 16), the need to take time off work (five out of 16) and the need for multiple hospital appointments (five out of 16). Eight parents had concerns regarding prolonged courses of antibiotics causing side-effects or antibiotic resistance. When asked how long their child needed to be cough-free to view a treatment as a success, five reported <2 weeks, four reported 2–4 weeks, three reported 1–3 months, three reported 3–6 months and one reported 6–12 months. The most commonly suggested outcomes for future clinical trials in PBB were change in cough frequency/cough resolution and relapse of chronic cough. The other suggested outcomes matched the negative effects and worries listed.
Clinician survey

Responses were received from 20 (80%) out of 25 paediatric respiratory consultants. All identified change in cough frequency/cough resolution as the most important outcome. Suggested methods of assessing this included parental report post-treatment, cough score recorded daily during treatment and 24-h ambulatory

BOX 1 Combined long-list of outcomes generated from systematic review, parent interviews and clinician survey

| Resolution of cough |
|---------------------|
| 1. Resolution of cough reported by parent after treatment |
| 2. Resolution of cough assessed using a cough score/diary recorded daily by parent during treatment |
| 3. Resolution of cough assessed using a 24-h ambulatory cough-meter worn during treatment |

| Other treatment-effect outcomes |
|---------------------------------|
| 1. Change in systemic symptoms (pyrexia/lethargy, etc.) reported by parents before and after treatment |
| 2. Change in examination findings before and after treatment |
| 3. Change in lung function before and after treatment |
| 4. Change in exercise capacity before and after treatment |
| 5. Change in chest radiography findings before and after treatment |
| 6. Change in child’s quality of life before and after treatment |
| 7. Change in parents’ quality of life before and after treatment |
| 8. Microbiological clearance of causative organism by end of treatment |
| 9. Side-effects of treatment |
| 10. Development of antibiotic resistance by end of treatment |

| Longer-term/follow-up outcomes |
|-------------------------------|
| 1. Frequency of chronic cough relapse during follow-up |
| 2. Healthcare utilisation during follow-up |
| 3. Antibiotic use during follow-up |
| 4. Development of antibiotic resistance during follow-up |
| 5. Development of bronchiectasis |
cough-meter worn during treatment. Other potential outcomes were child and parent quality of life (QoL), systemic symptoms such as temperature and lethargy, lung function, exercise capacity, chest radiograph changes, relapse of chronic cough during follow-up, healthcare utilisation, side-effects of medication, antibiotic resistance and the incidence of bronchiectasis.

**Delphi survey**

The list of outcomes from the systematic review, parent interviews and clinician survey that were put into the Delphi survey can be seen in box 1. Complete responses were received from 65 paediatric respiratory healthcare professionals (52 consultants, 10 trainees and three allied healthcare professionals) in round 1 and 51 in round 2 (44 consultants, six trainees and one allied healthcare professional). Consensus was reached in round 1 for

| TABLE 2 Results of Delphi survey |
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seven out of 18 of the outcomes to be put forward to the consensus meeting. Consensus was reached in round 2 for three out of 11 remaining outcomes (table 2). The suggested duration of follow-up is shown in table 3.

Consensus meeting

The consensus meeting was attended in person by three parent representatives and three paediatric respiratory consultants (FG, IS and WC). A fourth consultant participated via live video link (MB). Each of the 10 outcomes that reached consensus in the Delphi survey was discussed at length (box 2). It was agreed that a number of the outcomes could be combined or omitted. There was consensus that resolution of cough reported by parents after treatment (outcome 1) did not add anything if a cough score/diary was completed daily by the parent during treatment (outcome 2). With regards to outcomes 3 and 4 it was agreed that the key outcome should be the child’s QoL, but this could be reported by the parent if the child was too young to complete it. Outcome 5 generated the most discussion, as microbiological confirmation of a lower airway pathogen is no longer part of the diagnostic criteria for PBB and it was agreed that children should not undergo additional invasive sampling. Despite this, all the parent representatives strongly believed it was an important outcome and should be reported if samples were available or could be obtained non-invasively. All contributors thought that outcomes 6 and 7 could be combined. It was agreed that cumulative antibiotic use and frequency of chronic cough relapse were both ways of assessing relapse. Which outcome would be most appropriate for a clinical trial depends on the methodology, so the option to do either or both was included. With regards to outcome 10, it was universally agreed that bronchiectasis was an important outcome, but computed tomography scans should only be undertaken if clinically indicated. The six outcomes in the final COS were then prioritised (box 3).

Discussion

We have developed a COS for PBB following a robust methodology that was defined and registered a priori. This now represents the minimum to be measured and reported in future clinical trials of PBB. If researchers do this, it will reduce outcome heterogeneity and bias, allowing meaningful comparisons between studies, thereby facilitating meta-analysis.

Resolution of cough is part of the diagnostic criteria for PBB [4], so its inclusion as the most important outcome is unsurprising. Of the three ways to assess cough resolution, the use of a 24-h ambulatory cough-meter was the only method that did not achieve consensus in the Delphi survey (box 3). Despite this, a number of respondents graded this outcome as more important and relevant than the other two methods. Their comments suggested that this outcome was the only way to truly quantify a change in cough frequency, as it removed subjectivity. Those who did not rate it as important referenced a lack of familiarity with the equipment and a perceived lack of published evidence on its use in children. In clinical practice, success of treatment is usually assessed from the reports of parents after treatment, which explains the high rate of consensus for this outcome. It was agreed in the consensus meeting that this outcome would not add any additional information to that obtained from a cough score/diary being recorded daily by parent. This later outcome was therefore included in the final COS.

Relapse of PBB is common and recurrent PBB (>3 episodes per year) is associated with a subsequent diagnosis of bronchiectasis [7, 8]. Relapse of chronic cough and antibiotic use during follow-up both reached consensus in the Delphi survey. In the consensus meeting it was acknowledged that although related, these two outcomes may be different as children could be prescribed antibiotics for relapse of wet cough before the duration fulfils the criteria for chronic cough. Which of the two is most appropriate to be measured and reported in a trial will depend on how relapse of cough is assessed and treated. It was therefore agreed that either or both could be reported. Both QoL outcomes (parent and child) reached consensus for inclusion in the Delphi survey. At the consensus meeting it was agreed the outcome should be child QoL with

**BOX 2** Short-list of outcomes reaching consensus in Delphi survey

1. Resolution of cough reported by parent after treatment
2. Resolution of cough assessed using a cough score/diary recorded daily by parent during treatment
3. Change in child’s quality of life before and after treatment
4. Change in parents’ quality of life before and after treatment
5. Microbiological clearance of causative organism by end of treatment
6. Development of antibiotic resistance by end of treatment
7. Development of antibiotic resistance during follow-up
8. Frequency of chronic cough relapse during follow-up
9. Antibiotic use during follow-up
10. Development of bronchiectasis
parent-proxy reporting in young children. This reflects guidance for measuring QoL in children in other disease areas due to discrepancies between parent-proxy and child self-reporting [20, 21]. There are validated parent-proxy and self-reported QoL questionnaires for children with chronic cough [22, 23].

Antimicrobial resistance is an important issue for parents and clinicians, as highlighted in the parent interviews and the Delphi survey. It is also an initiative area for the Medical Research Council and the focus of a 5-year action plan and 20-year vision from the UK Government. As such, it is a key outcome for future clinical PBB trials which involve antibiotics. Although there is a clear association between PBB and bronchiectasis [7, 8], the exact relationship is complex, as the development of bronchiectasis manifests as a clinical continuum in which the early features are indistinguishable from PBB [24]. Given the morbidity associated with bronchiectasis, it is an important outcome in future clinical trials. But the radiation dose associated with chest CT means they should only be undertaken if clinically indicated. Microbiological clearance of identified lower airway pathogens achieved consensus in round 1 of the Delphi survey and all the parent representatives in the consensus meeting viewed it as important. However, microbiological confirmation is not part of PBB diagnostic criteria and the parent representatives agreed the taking of invasive samples should be minimised. It was therefore agreed that this outcome should be included but with the caveat of basing it on readily available samples. This highlights the need for a study to investigate the correlation between culture results obtained from bronchoalveolar lavage, induced sputum and cough swab samples.

We accept there are limitations to this COS. The parents and clinicians who contributed were all UK-based, so careful consideration needs to be made before applying the findings to other countries. This is particularly relevant in countries with higher rates of non-cystic fibrosis bronchiectasis or pulmonary tuberculosis. Before this COS is used in such countries we suggest that discussions are held with a group of parents and clinicians to check for missing outcomes and confirm clinical relevance. The clinician survey was limited to paediatric respiratory consultants working in three hospitals, which potentially introduced bias. This was addressed by giving those involved in the Delphi survey the opportunity to suggest additional outcomes if omissions were spotted.

Conclusions
In summary, we have developed a COS that can be used in future clinical trials involving children with PBB. The robust methodology has ensured the outcomes included in this COS were developed, edited and prioritised by a wide range of relevant healthcare professionals and parent representatives.

Acknowledgements: We would like to thank the parents of children with protracted bacterial bronchitis who were interviewed and the healthcare professionals who completed the Delphi survey. We would also like to thank the three parent representatives: Sarra Bickmore, Emily Hinton and Maria Pickford.

Conflict of interest: F.J. Gilchrist has nothing to disclose. I. Ali has nothing to disclose. M. Brodlie is supported by a Medical Research Council Clinician Scientist Fellowship (MR/M008797/1). W.D. Carroll has nothing to disclose. B. Kemball has nothing to disclose. J. Walker has nothing to disclose. I. Sinha has nothing to disclose.

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