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Which outcomes should be used in future bronchiolitis trials? Developing a bronchiolitis core outcome set using a systematic review, Delphi survey and a consensus workshop

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ABSTRACT

Objectives The objective of this study was to develop a core outcome set (COS) for use in future clinical trials in bronchiolitis. We wanted to find out which outcomes are important to healthcare professionals (HCPs) and to parents and which outcomes should be prioritised for use in future clinical trials.

Design and setting The study used a systematic review, workshops and interviews, a Delphi survey and a final consensus workshop.

Results Thirteen parents and 45 HCPs took part in 5 workshops; 15 other parents were also separately interviewed. Fifty-six items were identified from the systematic review, workshops and interviews. Rounds one and two of the Delphi survey involved 299 and 194 participants, respectively. Sixteen outcomes met the criteria for inclusion within the COS. The consensus meeting was attended by 10 participants, with representation from all three stakeholder groups. Nine outcomes were added, totalling 25 outcomes to be included in the COS.

Conclusion We have developed the first parent and HCP consensus on a COS for bronchiolitis in a hospital setting. The use of this COS will ensure outcomes in future bronchiolitis trials are important and relevant, and will enable the trial results to be compared and combined.

Trial registration number ISRCTN75766048.

Strengths and limitations of this study

- With stakeholder input from medically qualified staff, nurses and other clinical staff, and parents of children with bronchiolitis, we have developed a preliminary core outcome set (COS) for paediatric bronchiolitis trials.
- A mixed-method approach was used to determine which outcomes would be included in the COS.
- This COS can be considered when designing paediatric bronchiolitis trials as a minimum for outcomes to be collected and reported.
- While we followed guidance within the COMET (Core Outcome Measures in Effectiveness Trials) handbook in regards to Delphi processes and face-to-face consensus meeting format, one could argue that parental input during the consensus meeting had a relatively large effect on which items were included in the final COS.

INTRODUCTION

Background and objectives

Bronchiolitis, an acute viral lower respiratory tract infection which predominantly affects infants, is a major cause of morbidity and mortality worldwide.[1] Typical clinical features include a coryzal prodrome lasting approximately 3 days, persistent cough, increased respiratory rate, chest recession and wheeze or crackles on auscultation.[2] While most children with bronchiolitis have mild symptoms and can be managed at home,[3] in the UK and USA approximately 3% are hospitalised, most commonly between 3–6 months of age.[1 4]

Although multiple therapeutic interventions for bronchiolitis have been assessed in clinical trials, treatment remains supportive.[2] Oxygen therapy and the use of oximetry are the only interventions that have significantly impacted survival over the last 40 years, contributing to a reduction in mortality from approximately 20% in some studies to <1%.[5 6] Interventional clinical trials in bronchiolitis have increased in number over the past decade, investigating novel ways of administering oxygen nasally and non-invasively with varying levels of positive airway pressure or flow,[7–9] and novel antiviral medications against respiratory syncytial virus, the

principal viral cause of bronchiolitis.[10 11] More interventions are in the therapeutic pipeline.[12]

Randomised controlled trials (RCTs) are regarded as the gold standard for evaluating healthcare interventions.[13] Although they produce high quality evidence that inform clinical care through practice guidelines, their clinical impact is often diminished by variations in outcome measurement and reporting. Systematic reviews in many different branches of medicine have consistently demonstrated the large number and heterogeneity of outcome reporting in trials and other research studies.[14–16] This makes clinically relevant comparisons between trials and pooling of results in meta-analyses difficult. Furthermore, multiplicity of outcome measurement can lead to the selective reporting of significant findings, referred to as outcome reporting bias.[17]

A proposed solution is to develop and use a 'Core Outcome Set' (COS).[18] This consists of a minimum set of outcomes that key stakeholders agree are important, the measurement of which should be considered for all trials in a particular field.[18] This has the potential to improve the efficiency with which research can answer clinical questions. The benefits of COS have been embraced internationally by funding bodies,[18] regulatory bodies[19 20] and journal editors,[21] all of which recommend their use where available. As a result, the development of COS is increasingly common. The COMET (Core Outcome Measures in Effectiveness Trials) initiative has recorded approximately 700 published or ongoing studies into COS in many branches of medicine. Until now there has been no COS for trials of children with bronchiolitis although the need for one has previously been identified.[22]

The aim of this study was to obtain consensus from key stakeholders on which outcomes should be included in a COS for use in future bronchiolitis trials and other studies. This study formed part of a larger research project (Non-Invasive Ventilation for the Management of Children with Bronchiolitis: a feasibility study (NOVEMBR)).[23]

METHODS

The COS was developed in three phases using methods recommended by COMET and COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments).[18] The aim of the first phase was to generate a list of initial outcomes for consideration within the COS; this comprised a systematic review, stakeholder workshops and interviews. The second phase was a two-round Delphi survey, and the third phase, a face-to-face consensus meeting where results from the Delphi were presented.

COS-STAR (Core Outcome Set-STAndards for Reporting) guidelines for reporting were followed.[24]

Patient and public involvement

Parents were involved in writing the original study protocol, information sheets and Delphi questionnaires. Discussion regarding non-invasive ventilation (NIV) modalities was part of a separate exercise designing a protocol of NIV for infants with bronchiolitis. A parent was also a member of the trial management group.

Phase I: systematic review of the literature and stakeholder perspectives

Lists of outcomes were generated separately by both systematic review of the literature and stakeholder workshops/interviews.

The systematic review identified outcomes to assess efficacy and safety of interventions (pharmacological and non-pharmacological) used to treat children with acute bronchiolitis in published clinical trials since 2000 (search strategy provided in online supplemental appendix A). Details of this systematic review are not contained within this publication and will be published at a later date.

Parents or guardians were eligible to participate in a workshop or interview if their child had been admitted to hospital with bronchiolitis within the previous year. Eligible parents were invited to participate by research nurses at seven study sites (Alder Hey Children's NHS Foundation Trust (Liverpool); Wirral University Teaching NHS Foundation Trust; Countess of Chester NHS Foundation Trust; Derby Teaching Hospital NHS Foundation Trust; Darlington Memorial Hospital; Cambridge University Hospitals NHS Trust and Royal Alexandra Hospital, Brighton. The lead centre will be Alder Hey Children's NHS Foundation Trust (Liverpool)), through advertisements on social media. Healthcare professionals (HCPs) were eligible to participate in a workshop or interview if they had at least 6 months experience in managing children with bronchiolitis. Study sites emailed invitations to eligible HCPs to register interest in a workshop. Parent and HCP selection aimed to ensure variance (eg, child's age 0–24 months, gender and severity of illness and HCP role and hospital geographical location).

For both HCP and parent workshops, interview topic guides exploring aspects of trial design were developed based on previous research.[25–27] To identify prioritised outcomes, participants were first asked to reflect on their personal experiences including what they would consider as a sign that a child was getting better. To inform discussion, they were then shown a list of 34 outcomes (online supplemental appendix B) extracted from Cochrane Systematic Reviews and National Institute for Health and Care Excellence (NICE) guidance on bronchiolitis,[28] asked to consider which were important to them, and identify outcomes not included on the list. This process was adapted for parent interviews (eg, list of outcomes emailed to interview participants).

A professional transcription company (Voicescript, Bristol, UK) transcribed verbatim digital audio recordings. Transcripts were anonymised and checked for accuracy. NVivo V.10 software (QSR International, Melbourne, Australia) was used to assist in the organisation and coding of outcomes identified both through responses to direct questioning, and referred to by participants during interview and workshop discussions.

A conceptual outcomes framework was developed based on previous exploratory work in which domains and subdomains were defined and outcomes categorised accordingly.[29 30] Similar outcomes identified by systematic literature review and workshops/interviews were collapsed together—following discussions between study management group members.

Phase II: Delphi process and outcome scoring

Participants

Key stakeholders who participated in the Delphi survey included parents/legal representatives of children hospitalised with bronchiolitis defined as per UK NICE Bronchiolitis Guidelines (2015).[28] These were identified through Phase I workshops and interviews, and by the seven study sites by research nurses on the wards and asked whether they would like to participate, they were then contacted at a later date. Parents of children who had died during their hospital admission were not approached. Non-English speakers were not eligible to participate.

Also included in the Delphi survey were HCPs (and nurses/other clinical staff) with experience of caring for children with bronchiolitis. These were identified via emails sent to professional organisations, and distributed via global email address lists or associated social media sites. HCPs who had previously completed the NOVEMBR National Survey of Current Practice were also approached if they had expressed an interest in participating.[31] Participants were also invited to pass on details of the study to any of their own contacts who met eligibility requirements. The Delphi process was conducted and managed by DelphiManager software (www.comet-initiative.org/delphimanager). Access to the Delphi survey was via a hyperlink distributed by email. In round one, participants confirm their eligibility, and assigned a score (using a Likert scale of 1–9) to each of 56 outcomes, listed alphabetically, based on their opinion of its importance in the management of children with bronchiolitis. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines scale was used for scoring: scores of 1–3 indicated that the outcome was 'of low importance', 4–6 indicated 'equivocal—important but not critical for decision making' and 7–9 indicated 'critical for decision-making'.[32] Participants were also given the option to respond, 'do not know'. Lastly, there was the opportunity to suggest any additional outcomes along with a score for importance. All additional outcomes were reviewed by the Study Management Group (SMG) (which contained clinicians, research nurses, trials unit representatives and parents) and where applicable carried forward to round two.

Those who completed round one were invited to participate in round two. In round two participants were shown the distribution of scores given by each stakeholder group and then asked to review and re-score each outcome. At the end of the first-round participants were shown their own scores for and asked to re-score based on the same question as the first round.

Table 1 Definition of consensus

Consensus classification	Description	Definition
Consensus in	Consensus that outcome should be included in the core outcome set	70% or more participants scoring as 7–9 AND <15% participants scoring as 1–3 in each group
Consensus out	Consensus that outcome should not be included in the core outcomes set	≤50% of participants scoring as 7–9 in each group
No consensus	Uncertainty about importance of outcome	Anything else

Data were presented as counts and percentages for categorical data and mean and SD for continuous data.

Consensus for inclusion of an outcome in the COS was achieved if 70% or more participants gave the outcome a score of 7–9 and less than 15% gave a score of 1–3 in each stakeholder group for round two of the survey (table 1) in all three stakeholder groups. The rationale for these levels of agreement was based guidance in the published literature.[30 33] Consensus for exclusion of an outcome followed if 50% or fewer participants scored 7–9 in all of the three stakeholder groups. Any other outcome was classified as 'no consensus'. Reminder emails were sent to participants to encourage completion. Participants who completed both Delphi survey rounds received a certificate of completion and were entered into a prize draw to win an iPad. Completion of the surveys was deemed as consent to participate.

Phase III: consensus meeting

The results from each round of the Delphi survey were presented at a face-to-face consensus meeting involving a representative group of stakeholders; members of this group were those who participated in the survey or workshops and expressed an interest in attending the consensus meeting. Participants were not specifically invited based on their views in the survey and were not required to have completed the Delphi survey in order to participate. An independent medical professional, with expertise in COS development and not a member of the SMG, chaired the meeting. Meeting attendees were asked to review the full list of outcomes and were given the opportunity to discuss whether they agreed with the outcome consensus classifications from the Delphi process in Phase II. They were then asked to discuss the outcomes classified as 'no consensus' from the Delphi process. The Chair ensured that all participants had equal opportunity to give their views on each of the outcomes prior to voting taking place. Voting was carried out with the same 9-point Likert scale

used in the Delphi (described in Phase II) and conducted anonymously using TurningPoint software and handsets (Turning Technologies LLC, Youngstown, USA). At the end of the meeting the outcomes that met the criteria for 'consensus in' were presented to the stakeholders.

Registration

The study protocol was registered retrospectively with the COMET initiative and is available online,[23] and on the ISRCTN Registry (18 December 2017).

RESULTS

Phase I: literature review and stakeholder perspectives

The systematic review identified 154 studies for inclusion (online supplemental figure 1). Within these studies, 923 individual outcome measures were identified. These outcomes were grouped and tabulated under appropriate outcome domains using a predefined conceptual framework as described previously.[29 30] This work is being written up as a separate manuscript.

Between April 2016 and March 2017, 13 parents and 45 practitioners took part in five workshops (three for HCPs and two for parents); 15 other parents were also interviewed by telephone. No outcomes were identified during these workshops and interviews that had also not been identified as part of the systematic review.

All outcomes identified from the systematic review, workshops and interviews were reviewed by for similarity. Outcomes considered sufficiently similar with regards to what they measured were collapsed and merged together. Furthermore, this process was discussed and reviewed with the SMG to agree the final list of 56 outcomes to be included into the Delphi survey (online supplemental table 1).

Phase II: Delphi process

Round one of the survey was conducted between 19 February 2018 and 23 March 2018. Round two was conducted between 29 March 2018 and 13 April 2018.

Online supplemental table 2 shows the breakdown of stakeholder group and their participation in both rounds. In total, 299 participants (from the UK) registered on the online system and 286 (96%) scored at least one outcome in round one. Sixty-eight per cent (194/286) were medically qualified, 28% (81/286) were nurses and other clinical staff, and the remaining 4% (11/286) were parents. Participants were invited to round two if they had scored at least one outcome in round one. Sixty-eight per cent (194/286) participated in round two by scoring at least one outcome. Mean round one scores for those who participated in both rounds and those who participated in round one only were similar (online supplemental table 3).

Following round one, one item was added to the list of outcomes for consideration in round two: length of time spent on oxygen.

Table 2 Final outcomes to be included in a core outcome set from the Delphi process

Domain (subdomain)	Outcome
Physiological and clinical (general symptoms)	Appearance
	Level of consciousness
	Non-respiratory physiological parameters/vital signs
	Worsening illness
Physiological and clinical (feeding; nutrition and hydration)	Feeding
	Need for feeding tube
	Inhalation (breathing in) of milk; fluids or solids
Physiological and clinical (respiratory distress)	Apnoea
	Oxygen saturation
	Cyanosis
	Effort of breathing
	Paediatric Early Warning score
Physiological and clinical (respiratory interventions and support)	Need for respiratory support
Resource use (hospital related short term)	Critical care admission
Death	Death
Adverse events	Serious adverse events

Online supplemental table 4 shows the results from round two. Sixteen outcomes met the criteria for 'consensus in' for inclusion in the COS, 8 outcomes met the criteria for 'consensus out' and 32 outcomes were classified as 'no consensus'.

The final set of 16 outcomes that were included from the Delphi process are included in table 2.

Phase III: consensus meeting

The consensus meeting took place on the 14 June 2018 and was attended by 10 participants: 4 were medically qualified staff, 3 were parents and the remaining 3 were nurses and other clinical staff.

When round two classifications of 'consensus in' outcomes were reviewed, the inclusion of Paediatric Early Warning (PEW) score was discussed as not every hospital uses it and even in those that do, the composite measures can vary. However, participants agreed it should remain in the COS as a standardised, widely used objective PEW score has the potential to be a quick indicator of changing health and healthcare needs. No further comments were provided on 'consensus in' outcomes. Discussion around 'consensus out' outcomes was centred on the economic cost outcome; one participant believed it should be included since it impacts on whether the intervention is adopted by some healthcare funders. After some discussion, it was agreed that other core outcomes can be used

Table 3 Outcomes that were added to the core outcome set during the consensus meeting

Domain (subdomain)	Outcome
Physiological and clinical (general symptoms)	Pain and discomfort
	Parent report of symptoms and/or resolution of illness
Physiological and clinical (feeding; nutrition and hydration)	Reduced urine output
Physiological and clinical (respiratory interventions and support)	Length of time spent on oxygen
Life impact (health-related quality of life)	Quality of life
Resource use (hospital related short term)	Hospital length of stay
	Time until ready for discharge from hospital
Adverse events	Adverse events
	Long-term effects of illness or treatment interventions

for a health economic evaluation, without the need for a separate outcome.

Following discussion and re-vote, nine outcomes were added to the 'consensus in' list (table 3). The final COS contains 25 outcomes across eight domains (tables 2 and 3). In the Delphi, need for fluids given through a drip (intravenously) was scored 7–9 by 80%, 85% and 67% of medically qualified staff, nurses and parents, respectively. However, in the consensus meeting only 20% of meeting attendants scored it 7–9; discussions at the time centred on the relative subjectivity of the assessment of need for fluids through a drip and that it was not a critical outcome. Likewise, bronchiolitis severity score and additional chest infections/pneumonia were close to being included as 'consensus in' in the Delphi but were voted 'consensus out' during the consensus meeting. There were differing views in the room on whether or not a disease specific score should be included in the COS but after discussion, only 60% voted 7–9. Although all agreed additional chest infection/pneumonia was important, it was decided that it was not critical. A full report from the consensus meeting detailing discussion behind each outcome has been included in online supplemental appendix C. At the close of the meeting the final COS was agreed by all the participants.

Protocol changes

The definition of 'Consensus Out' was changed from '70% or more participants scoring 1–3 and <15% of participants scoring 7–9 in each group' to '≤50% of participants scoring 7–9 in each group'. This change was made for practical reasons only, in order to refine and reduce the list of outcomes to be discussed at the consensus meeting. Meeting attendees were also given the opportunity to comment on and discuss any of the 'consensus out' outcomes.

DISCUSSION

We have developed a COS of 25 outcomes of importance to medically qualified staff, nurses and other clinical staff, and parents of children with bronchiolitis, for use in RCTs of interventions for children with a clinical diagnosis of bronchiolitis in a hospital setting.

On the COMET database, 10% of the approximate 700 listed published and ongoing COS are in child health with most being for chronic paediatric diseases. Those for acute conditions include sepsis, infantile colic, appendicitis, head injury, acute diarrhoea and asthma. Two other studies on the COMET database mention bronchiolitis, one a systematic review of outcome measures and measurement instruments used in bronchiolitis RCTs,[34] and the other a European Respiratory Society guideline on 'Endpoints in respiratory diseases' based solely on expert views of HCPs and published in 2010.[35] This is the only COS developed for use in for bronchiolitis, one of the most common acute causes of childhood admission to hospital, developed using recommended consensus based methods.[18]

One of the strengths of this study was the involvement of both parent and HCPs in each phase and the necessity for agreement by each stakeholder group before consensus could be reached; this ensured all views were incorporated throughout. For example, at the final consensus meeting, discussions were carefully 'managed' by an independent chair who ensured all participants could voice their opinions and have their opinions heard. The use of 'anonymous' TurningPoint software also allowed peer/social pressures to be minimised when it came to voting. This enabled the views of all participants to be heard, and particularly those of parents who might otherwise have been reluctant to contribute when surrounded by experienced HCPs. As a result, parental 'championing' of four 'no consensus' items led directly to their inclusion in the COS (pain and discomfort, parent report of symptoms and/or resolution of illness, quality of life and reduced urine output). Three of these are relatively subjective measures. For changes in urine output, parents argued that this provided a tangible way for them to know whether a treatment or intervention was working and their child was 'on the mend'.

There were a number of limitations to this study. Since the Delphi survey was disseminated via mailing lists, it was not possible to ascertain the total number of individuals approached and therefore the proportion who took part. Also, although reminders for completion were circulated, not all participants who took part in round one also took part in round two. However, comparing scores for round one for those who completed both rounds with scores for those who completed round one only, did not highlight any attrition bias. Indeed, the overall number of participants who took part in both rounds of this study (194)

was above the median of 111 from a recent review of 31 published and ongoing studies that used a Delphi to develop a COS.[35] In our study, having fewer outcomes to assess may have increased the response rate from round one to round two.[36]

We would have liked to include a larger number of parents in the Delphi survey. Parents were approached during their child's admission to hospital with bronchiolitis and many agreed to take part in the study and gave their contact details. However, only 11 of these subsequently completed the two surveys. We speculate that by the time parents of otherwise healthy infants and young children were contacted some months after the acute bronchiolitis episode, time pressures perhaps meant that their priorities lay elsewhere. Of note, 30% of attendees at the consensus meeting were parents, which ensured their voice was heard at this crucial part of the process and that the consensus meeting comprised a representative group of stakeholders.

Responders were primarily UK based which raises the question of whether the COS would be applicable to trials overseas. An extension of this work would be to repeat the process including international participants, to determine whether the choice of outcomes changes depending on location. It is likely that this would indeed be so, given that respiratory support or nasogastric feeding are not universally available in all settings. Future work on the COS could also include pharmaceutical representatives and regulators.

Burden of measurement should also be taken into consideration when developing a COS. Although the COS we have developed contains 25 outcomes, it can be seen that several of the outcomes are related, for example, adverse events and serious adverse events would both be captured when measuring safety. Similarly, feeding and need for feeding tube, hospital length of stay and time until ready for discharge from hospital are related and would require minimal time to capture these data.

We believe the COS should be used by future trialists as the minimum set of outcomes that should be collected in a bronchiolitis trial. Importantly, this COS provides an essential step towards increasing and improving much-needed evidence synthesis in this disease area.[22 37] There was some discussion during the consensus meeting on how potential outcomes would be measured, for example appearance, however the chair reminded participants that the aim of the meeting was to agree on 'what' should be measured rather than 'how' to be measured. Now that we have established which outcomes should be reported, there is a need for future research to ascertain the best methods to operationalise these outcomes, particularly some of the more subjective ones such as pain and discomfort, parent report of symptoms and inhalation of milk/feeds.

CONCLUSIONS

This was an important study identifying the outcomes of importance to key stakeholder groups which will provide guidance to future trialists in paediatric bronchiolitis. This is particularly pertinent with anti-viral treatments in the therapeutic pipeline, and the need to clearly define how some existing interventions (such as high flow nasal cannula oxygen) are best used in clinical practice. We recommend researchers designing bronchiolitis trials consider this preliminary COS as a minimum for outcomes collected and reported in trials. Future work is now needed to test the validity and generalisability of the COS and ongoing work should include routine updating of the COS.

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Patient consent for publication Not applicable.

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Supplementary Appendix A

Novembr Study
Systematic Review Search Strategy: Bronchiolitis Core Outcome Set
Search Summary 17th November 2015

Database	Date searched	Number Retrieved	After duplicate removal
Medline (RCTS) 1946-17/11/15	17/11/15	1419	1373 (46)
Embase (RCTs) 1974-17/11/15	17/11/15	2516	2485 (31)
Central	17/11/15	420	417 (3)
Scopus 1982-present	17/11/15	199	197 (2)
Approximate number following de-duplicate of individual database			4,472
Number following de-duplicate between databases			3,042

Database: Medline via OvidSP <1946 to November 2015 Week 2 2012>

Search Title: Bronchiolitis Core Outcome Set |Medline -- 20 March 2012

Search Date: 20 April 2012

Results: 787; 771 after Ovid duplicate removal function

MeSH and text words for Bronchiolitis and Post-Bronchiolitis: 1. exp BRONCHIOLITIS/ 2. (bronchiolitis or wheez*).mp. 3. exp Respiratory Syncytial Viruses/ or exp Respiratory Syncytial Virus Infections/ 4. Respiratory Syncytial Virus$.mp. 5. (post adj3 (bronchiolit* or RSV or "respiratory syncytial")).mp. 6. (recurrent adj2 (cough* or wheez* or bronchiolitis)).mp.
7. or/1-6 [MeSH and keyword terms related bronchiolitis + post bronchiolitis] (29,498)
Mesh and text words for Infants: 8. exp Infant/ 9. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. 10. exp CHILD/ 11. (child* or preschool* or toddler* or kid? or kindergar* or boy? or girl?).ti,ab,jw,nw.
12. or/8-11 [combination of infant MeSH and keyword terms] (271,0191)
Study Design Filter for Randomized Controlled Trials: 13. randomized controlled trial.pt. 14. controlled clinical trial.pt. 15. randomized.ab. 16. placebo.ab. 17. clinical trials as topic.sh. 18. randomly.ab. 19. trial.ti.

Novembr Study
Systematic Review for Bronchiolitis Core Outcome Set: Search Strategy
Date 17th November 2015

20. or/11-17 21. exp animals/ not humans.sh.
22. 20 not 21 [Cochrane RCT filter for Medline; max sensitivity/specificity] (869,719)
21. and/7,10,20 [combination of terms for bronchiolitis, infants, RCTs] (1419)
22. remove duplicates from (1373) (46)

Database: Embase via Ovid <1980 to 2012 week 12>

Search Title: Bronchiolitis Core Outcome Set | Embase -- 3 April 2012 -- AM

Search Date: 17 November 2015

Results: 2515; after duplicate removal

Index and text words for Bronchiolitis and Post-Bronchiolitis: 1. exp BRONCHIOLITIS/ 2. (bronchiolitis or wheez*).mp. 3. exp Respiratory Syncytial Pneumovirus/ 4. Respiratory Syncytial Virus$.mp. 5. (post adj3 (bronchiolit* or RSV or "respiratory syncytial")).mp. 6. (recurrent adj2 (cough* or wheez* or bronchiolitis)).mp.
7. or/1-6 [bronchiolitis + post bronchiolitis terms] (41,544)
Index and text words for Infants: 8. exp Infant/ 9. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. 10. exp CHILD/ 11. (child* or preschool* or toddler* or kid? or kindergar* or boy? or girl?).ti,ab,jx.
12. or/8-11 (306,5267)
Study Design Filter for Randomized Controlled Trials: 13. random*.tw. 14. placebo*.mp. 15. double-blind*.tw.
16. or/13-15 [Embase RCT filter, J Med Libr Assoc 2006;94(1):41-47] (126,7053)
17. and/7,12,16 [combination of bronchiolitis, infant and RCT terms] (2516)
16. remove duplicates from 31 (2485)

Database: CENTRAL via Cochrane Library <November 2015>

Search Title: Bronchiolitis Core Outcome Set | CENTRAL – 17 November15

Search Date: 17 November15

Results: 420; after duplicate removal 417 (3)

Central

Index and text words for Bronchiolitis and Post-Bronchiolitis: 1. exp BRONCHIOLITIS/ 2. (bronchiolitis or wheez*).mp. 3. exp Respiratory Syncytial Viruses/ or exp exp Respiratory Syncytial Virus Infections/

Novembr Study

Systematic Review for Bronchiolitis Core Outcome Set: Search Strategy

Date 17th November 2015

4. Respiratory Syncytial Virus$.mp. 5. (post adj3 (bronchiolit* or RSV or "respiratory syncytial")).mp. 6. (recurrent adj2 (cough* or wheez* or bronchiolitis)).mp.
7. or/1-6 (974)
Index and text words for Infants: 8. exp Infant/ 9. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. 10. exp Child/ 11. (preschool* or toddler* or kid? or kindergar* or boy? or girl?)
12. or/8-11 (78,257)
13. and/7,12 [combination of bronchiolitis terms and infant terms] (688)
14. limit 13 to medline records (420)
15. remove duplicates from 3 (417)

Database: Scopus via SciVal <1982 to present>
Search Date: 17 November 2015
Results: 199

((TITLE(bronchiolitis OR wheez*)) AND (TITLE-ABS-KEY("Clinical Trial" OR "Clinical Trials" OR "Randomized Controlled Trial*" OR "Random Allocation" OR "double-blind method" OR "single-blind method" OR placebos OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective)) AND (TITLE-ABS-KEY(infan* OR newborn* OR neonat* OR baby OR babies OR Child* OR preschool* or toddler* or kid? or kindergar* or boy? or girl?)))

Clinical Trials Registries
Search Date: 26.11.5

Registry	Search Terms	Results
Clinical Trials (www.clinicaltrials.gov/)	**Bronchiolitis Respiratory syncytial Virus**	**224**
ISRCTN registry (www.controlled-trials.com	**Bronchiolitis Respiratory syncytial Virus**	**18**
International Clinical Trials Registry Platform Search Portal	**Bronchiolitis Respiratory syncytial Virus**	**623 records for 546**
UK Clinical Research Network Portfolio Database (www.portal.nihr.ac.uk/Pages/Portfolio.aspx).	**Bronchiolitis Respiratory syncytial Virus**	**0**

Novembr Study
Systematic Review for Bronchiolitis Core Outcome Set: Search Strategy
Date 17th November 2015

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Systematic Review for Bronchiolitis Core Outcome Set: Search Strategy

Date 17th November 2015

Supplementary Appendix B

Parent Interview OUTCOMES LIST

THIS INFORMATION WILL BE EXPLAINED TO YOU FULLY DURING THE INTERVIEW

- An outcome measure refers to **'what'** should be measured in a research study to find out whether a treatment is effective (whether the treatment helps to make children better).

- Studies often have a number of outcome measures to determine whether a treatment is effective – some are measured during a child's stay in hospital, whilst others are measured either at the end of their hospital stay or when they have left hospital.

- Researchers or doctors often suggest what outcomes should be measured in a research study. However, they do not always fully understand what it's like either to be a sick child or to be the parent/guardian of a sick child. That is why it's important we ask parents/guardians what outcomes they think a research study should measure to determine whether a treatment is effective.

- For the NOVEMBR study, we have reviewed lots of previous research studies on very ill children, including those that had a severe infection.

- Below is a list of outcomes that might be useful to measure. During the interview, we will ask you what you think about the outcome measures on this list.

- It's not a test! We just want to make sure we include outcomes that are important to parents/guardians and to children.

Rosala-Hallas A, *et al. BMJ Open* 2022; 12:e052943. doi: 10.1136/bmjopen-2021-052943

Outcomes that are measured during a child's stay in hospital

Outcomes related to breathing			
	Outcome	**Description of outcome**	**Description of how outcome is measured** **Short term (ST) outcomes are measured during the bronchiolitis illness** **Long term (LT) outcomes are measure at intervals following the child's recovery from the illness.**
1.	Additional chest infections	Children may develop other chest infections caused by different viruses or bacteria in addition to bronchiolitis.	Number of children who develop other chest infections **(ST)**
2.	Apnoea	Apnoea is a pause in breathing lasting greater than 10 seconds. Sometimes the baby may need stimulation to get them to take a breath. Apnoea usually occurs in young babies (less than six weeks old) or those babies who are born prematurely.	Number of children who have apnoeas **(ST)** Number of hours or days apnoea occurs **(ST)**
3.	Breathing difficulties	Children with bronchiolitis may have a number of breathing difficulties (fast breathing; chest muscles sucking in; noisy breathing; nostrils flaring; head nodding; using stomach to breathe).	Number of children with breathing difficulties. **(ST)** Number of hours or days it takes for the child's breathing difficulties to improve. **(ST)**
4.	Central Cyanosis	Children with breathing difficulties may not get enough oxygen in the blood turning the skin around the mouth and tongue blue.	Number of children with central cyanosis. **(ST)**
5.	Cough	Some children with bronchiolitis will have a cough	Number of children with a cough. **(ST)** The number of hours or days it takes for the child's cough to improve. **(ST & LT)**

6.	Respiratory rate	Respiratory rate is the number of breaths taken over a minute. The result will show whether the child's respiratory rate is normal or abnormal.	Number of children with abnormal respiratory rate. **(ST)** Number of hours or days the child has an abnormal respiratory rate. **(ST)**
7.	Respiratory/cardiac arrest	In some children who are very poorly they might stop breathing and their heart may stop beating. The children will need emergency treatment to try and restart their breathing and heart.	Number of children who have cardiac/respiratory arrest. **(ST)**
8.	Wheeze or crackles	Some children with bronchiolitis may develop a wheeze and/or crackles when they breathe.	Number of children with wheeze and/or crackles. **(ST)** Number hours or days the child has wheeze and/or crackles **(ST & LT)**
9.	Recurrent wheeze or development of asthma	Following a bronchiolitis infection some children may experience a wheeze on a number of occasions or go on to develop asthma.	Number of occasions child becomes wheezy following bronchiolitis infection **(LT)** Diagnosis of asthma. **(LT)**
Outcomes related to other aspects of child's health			
10.	Death	Although very rare some children may die following a bronchiolitis infection or as a result of treatment received.	Number of children who have died. **(ST)**
11.	Fever	A fever is when a child has a temperature measurement which is greater than 37.5°C (99.5°F).	Number of children with a fever. **(ST)** Number of hours or days a child has a fever. **(ST)**

12.	Heart rate	Heart rate is the number of beats over a minute. The result will show whether the child's heart rate is normal or abnormal.	Number of children with abnormal heart rate. **(ST)** Number of hours or days a child has an abnormal heart rate. **(ST)**
13.	Looks seriously unwell	As the child's illness worsens they can look seriously unwell (e.g. change in colour; change in behaviour; floppy; sleepy; irritable).	Number of children who look seriously unwell. **(ST)** Maybe assessed by either a parent or health care professional (may use a scoring tool)
14.	Poor feeding	The number of children who are unable to take usual amount of food or fluids. These children may need help with feeding. They may need to be given fluids either by a tube inserted into the child's tummy via their nose or mouth or a drip placed into a vein in their arm.	Number of children with poor feeding. **(ST)** Number of children who require feeding support (tube feeding or a drip). **(ST)** Number of hours or days the child required feeding support or has poor feeding. **(ST)**
15.	Quality of life	What impact has bronchiolitis had on the child and/or family?	Measured through completing a questionnaire or diary. **(ST & LT)**
16.	Sleeping	Bronchiolitis may affect children's usually sleeping pattern (eg waking more frequently or more sleepy).	Number of hours or days it takes for child to return to normal sleeping routine. **(ST)**
17.	Urine output	Some children with bronchiolitis can become dehydrated and do not produce a normal amount of urine.	Number of children who have a reduced amount of wet nappies/ urine volume. **(ST)** Number of hours or days the child has reduced wet nappies / urine volume. **(ST)**
Outcomes related to health care provision			
18.	Emergency department stay	Some children with bronchiolitis will be assessed in the emergency department.	Number of hours the child spends in the emergency department prior to hospital admission or discharge home. **(ST)**

19.	Healthcare visits	Parents/carers may seek medical advice from health care professionals (emergency department or community (GPs or Walk-in Centres) on more than one occasion.	Number of healthcare visits. **(ST)**
20.	Hospital admission	Some children with bronchiolitis will need to be admitted to hospital (via the emergency department or outpatients) for observation or treatment.	Number of children who require hospital admission. **(ST)**
21.	Hospital stay	The length of time your child spent in hospital.	Number of hours or days the child spends in hospital from admission through to discharge home. **(ST)**
22.	Intensive care unit stay	Some children will need to be admitted to intensive care if their illness worsens	Number of admissions to intensive care unit **(ST)** Number of hours or days the child spends in the intensive care unit. **(ST)**
23.	Time until ready for discharge	Some children may improve and meet the discharge criteria. However their discharge may be delayed due to other circumstances.	Number of hours or days until a child meets the hospital or study discharge criteria. **(ST)**
24.	Adverse events/health complications	An adverse event/health complication a child is when the child's condition worsens or they may develop other medical complications as a result of their illness or treatment received. These adverse events may occur either immediately within a short time period or after a longer period of time.	Number of children who experience an adverse event/health complication. **(ST & LT)** Number of hours or days it takes for your child to recover from any health complications/adverse events. **(ST & LT)**

Outcomes related to tests or assessment			
25.	Arterial or capillary blood gas test	A blood test which looks at the oxygen and carbon dioxide levels in the blood. The test will show whether their levels are normal or abnormal.	Number of children with abnormal blood gas test results. **(ST)** Number of hours or days of abnormal blood gas test results
26.	Bronchiolitis severity Score	Bronchiolitis severity may be assessed using a symptom score. Low scores indicate less severe bronchiolitis whilst higher scores usually indicate more severe bronchiolitis.	Score changes over a period of time for example hospital admission.**(ST)** Score changes before and after treatment has been given. **(ST)**
27.	Chest xray	Changes on chest xray may show chest infections or other medical problems	Number of children who have changes on their chest xray. **(ST)**
28.	Lung function tests	These are a group of tests which measure how well the lungs work in terms of breathing and getting oxygen to the rest of the body.	Number of children with abnormal lung function tests. **(ST & LT)**
29.	Oxygen saturations	This test measures the oxygen saturation levels in the blood using a probe with a light placed on the hand or foot. The test will show whether the oxygen levels are normal or abnormal.	Number of children with abnormal oxygen saturation levels. **(ST)** Number of hours or days of abnormal oxygen saturation levels. **(ST)**

Outcomes related to treatment			
30.	Continuous positive airway pressure (CPAP)	Some children with worsening breathing difficulties need breathing support from CPAP.	Number of children who require CPAP **(ST)** Number of hours or days a child needs CPAP.**(ST)**
31.	Invasive ventilation	Some children with worsening breathing difficulties need breathing support from invasive ventilation.	Number of children who require invasive ventilation. **(ST)** Number of hours or days a child needs invasive ventilation. **(ST)**
32.	Oxygen treatment	Some children will require oxygen treatment to keep their blood oxygen levels at a normal level.	Number of children who require oxygen treatment. **(ST)** Number of hours or days a child needs oxygen treatment. **(ST)**
33.	Parents' impression of treatment benefit.	Parents are asked their opinion as to whether their child has improved or worsened.	Measured by either a questionnaire, diary or scoring tool. **(ST)**
34.	Treatment use	Some children may need to have additional treatments/medicines if their illness worsens.	Number of additional treatments/medicines needed. Number of hours or days additional treatments/medicines are needed. **(ST)**

Supplementary Appendix C

Non-Invasive Ventilation for the Management of Children with Bronchiolitis: a feasibility study

NOVEMBR Consensus Meeting Report

Meeting date: 14th June 2018

Location: The Foresight Centre, University of Liverpool

Contents

Summary

The long term aim of this research is to find out how to best provide respiratory support to children with bronchiolitis when they are admitted to hospital. Before an answer to this question can be provided, feasibility must be assessed and a 'core outcome set' (COS) for trials of management of children with bronchiolitis must be developed.

A meeting was held on the 14th June 2018 to review the results of the NOVEMBR Delphi survey and agree which outcomes should be included in a core outcomes set. The meeting has resulted in a preliminary core outcome set for trials in the management of children with bronchiolitis.

1. Background

A list of outcomes was identified from:

- Conducting a systematic review i.e. extracting outcomes used in published bronchiolitis studies
- Stakeholder consultation (parent/carer and health care professionals) to identify outcomes considered important through either focus groups or interviews.

The identified outcomes were collapsed and merged together. Fifty-six outcomes were categorised within a bronchiolitis conceptual framework. These fifty-six outcomes were included into an electronic, two round, Delphi survey. Round one: stakeholder respondents (parents/carers and health care professionals) were asked to rate the importance of each outcome using a Likert scale and suggest any missing outcomes. Round two: respondents were provided with the anonymised results of each stakeholder groups and their own for consideration. Respondents were invited to rescore each outcome in light of these results. Each outcome was classified as 'consensus in', 'consensus out' or 'no consensus'.

Consensus Classification	Description	Current Definition
Consensus in	Consensus that outcome should be included in the core outcome set	70% or more participants scoring as 7-9 AND <15% participants scoring as 1-3 *in each group*
Consensus out	Consensus that outcome should not be included in the core outcomes set	<=50% of participants scoring as 7-9 *in each group*
No consensus	Uncertainty about importance of outcome	Anything else

Note: A scale of 1-9 was used in the Delphi exercise with 1-3 labelled as 'Not important', 4-6 labelled as 'Important but not critical' and 7- 9 labelled as 'Critical'.

A representative group of stakeholders were invited to attend a consensus meeting with an independent 'Chair'. The results from the Delphi survey were presented by which outcomes achieved criteria for 'consensus in' and 'consensus out'. For those outcomes which did not achieve consensus they were individually discussed and voted upon by stakeholders using TurningPoint software and the same criteria for consensus as the Delphi.

2. Meeting Attendees

An invitation to attend the meeting was sent to:

Rosala-Hallas A, *et al. BMJ Open* 2022; 12:e052943. doi: 10.1136/bmjopen-2021-052943

- Health professionals who completed the online Delphi survey and expressed an interest in attending future meetings
- Parents/carers who participated with either a workshop, interview or Delphi survey and expressed an interest in attending future meetings

Table 1- Meeting Attendees

Attendee	Stakeholder group /role
Paul McNamara	Chief Investigator
Clare van Miert	Lead Investigator
Ian Sinha	Independent Chair
Redacted	Parent*
Redacted	Parent*
Redacted	Parent*
Redacted	Medically qualified*
Redacted	Medically qualified*
Redacted	Medically qualified*
Redacted	Medically qualified*
Redacted	Nurses & other clinical staff*
Redacted	Nurses & other clinical staff*
Redacted	Nurses & other clinical staff*
Heather Bagley	Patient and Public Involvement Co-ordinator
Kerry Woolfall	Qualitative Researcher
Emma Bedson	Meeting Coordinator
Helen Eccleson	Meeting Coordinator
Helen Hickey	Meeting Coordinator
Hannah Short	Meeting Coordinator

**Eligible to vote via Turning Point software*

3. Meeting Agenda

The meeting was structured according to the NOVEMBR Consensus meeting agenda version V2.0, 04/04/2018 (appendix 1).

Professor Paul McNamara provided an overview of the NOVEMBR study including aims and objectives, variation in current practice at hospitals nationwide and why a future clinical trial and bronchiolitis core outcome set is needed. Dr Clare van Miert explained what a core outcome set is and provided a summary of how the list of outcomes presented at the meeting had been obtained.

See appendix 2 for the full minutes of the meeting.

4. Voting, Discussion and Results

Dr Ian Sinha ran through the list of outcomes that reached consensus through the Delphi survey and gave the stakeholder group the opportunity to discuss.

The following outcomes were all 'consensus in':

Table 3: Consensus In	
Outcome Name	**Summary of Discussions**
Appearance	None
Level of consciousness	None
Non-respiratory physiological parameters/vital signs	None
Worsening illness	None
Feeding	None
Need for feeding tube	None
Inhalation (breathing in) of milk, fluids or solids	There can be difficulties feeding due to exhaustion and milk going down the wrong way; all agreed aspiration is a serious issue so it is important to measure this.
Apnoea	None
Oxygen saturation	None
Cyanosis	None
Effort of breathing	None
Paediatric Early Warning (PEW) score	PEWS are not widely used and the composite measurements can differ. However, it was agreed that some form of standardised objective score can be useful as a quick indicator of improving health for junior clinical staff and for parents.
Need for respiratory support	None
Critical care admission	None
Death	None
Serious adverse events	None

The following outcomes were all 'consensus out':

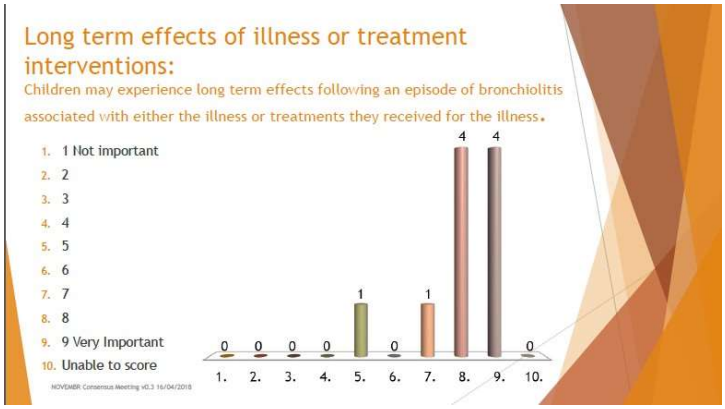
Table 4: Consensus Out	
Outcome Name	**Summary of Discussions**
Change to bowel habit	None
Recurrent wheeze	None
Fever	None
Cough	None
Need for medical tests	None
Behaviour change	None
Sleep	None

Economic costs	Economic cost influences whether or not the intervention is adopted by the NHS, it was agreed that knowledge of cost is important however not crucial. Data collected for other core outcomes can be used for a health economic evaluation, it does not have to be a separate outcome.

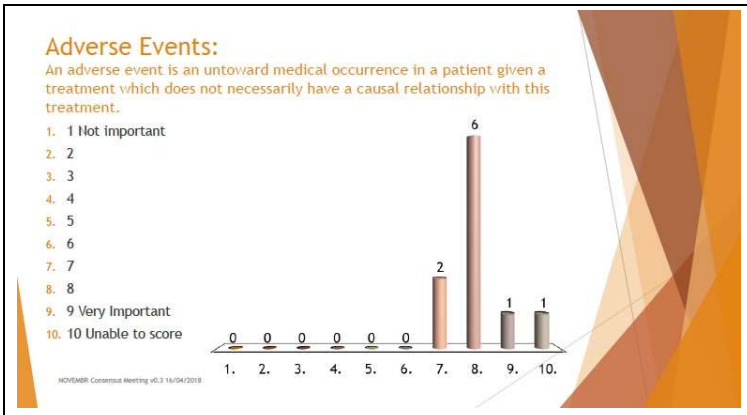
Dr Kerry Woolfall introduced the Turning Point software and conducted a test vote. Dr Ian Sinha then ran through each 'no consensus' outcome, allowing time for discussion prior to voting. Results as follows:

Table 5: Summary of stakeholder voting for each outcome which did not achieve consensus in Delphi

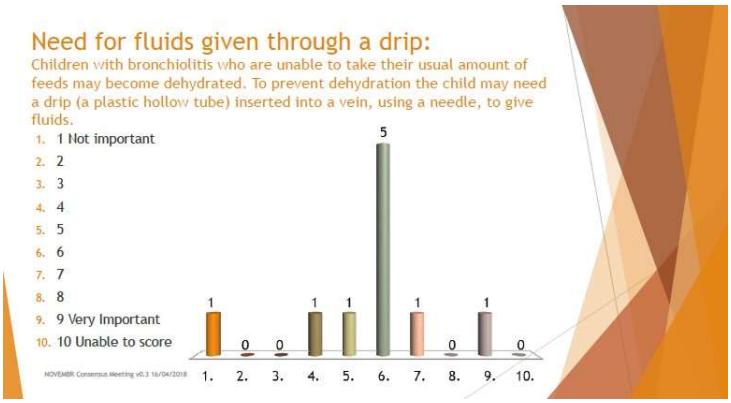
Outcome Name	**Long-term effects of illness or treatment interventions**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussed whether the long-term effects of a treatment would have an impact on the choice of treatment / intervention; all parents felt it was important.
Voting outcome:	**IN**



Outcome Name	**Adverse Events**
Number of participants scoring 1-9	**9**
Number of participants unable to score	**1**
Notes	Most members agreed measuring adverse events is important and had assumed they would have to be recorded for research.
Voting Outcome	**IN**

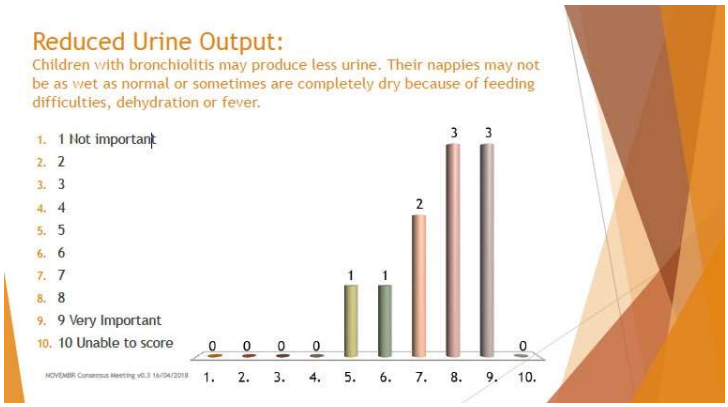


Outcome Name	Need for fluids given through a drip
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	It was agreed that this is a subjective measure and not crucial.
Voting outcome	OUT

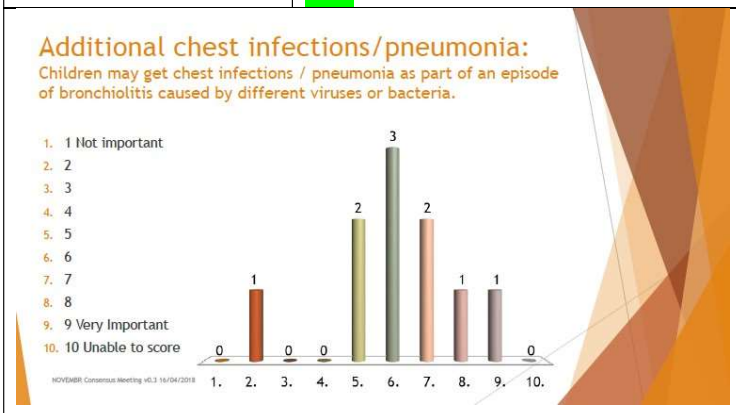


Outcome Name	Reduced urine output
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	It was agreed that it is a tangible way for parents to know that there is an issue and a nurse highlighted that it can indicate how well a treatment / intervention is working.

Voting outcome	**IN**

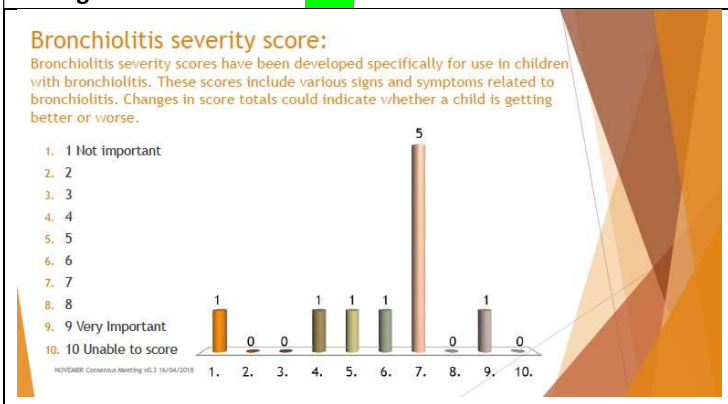


Outcome Name	**Additional chest infections / pneumonia**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	All agreed it is important because it could influence treatment / intervention choice but not critical.
Voting outcome	**OUT**

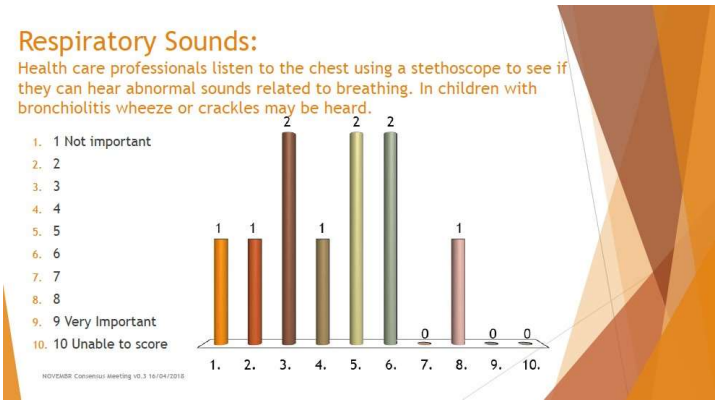


Outcome Name	**Bronchiolitis severity score**
Number of participants scoring 1-9	**10**

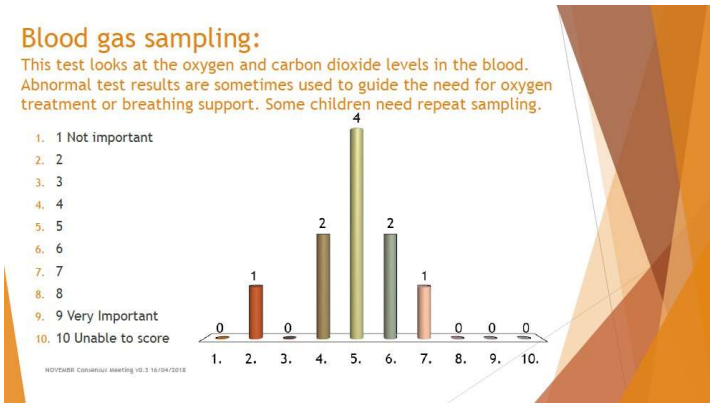
Number of participants unable to score	**0**
Notes	Discussions around whether or not a disease specific score would be useful when reviewing the results of a study revealed differing views within the room.
Voting outcome	**OUT**



Outcome Name	**Respiratory sounds**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted that any change in respiratory sounds would be due to another condition and not relevant to bronchiolitis.
Voting outcome	**OUT**

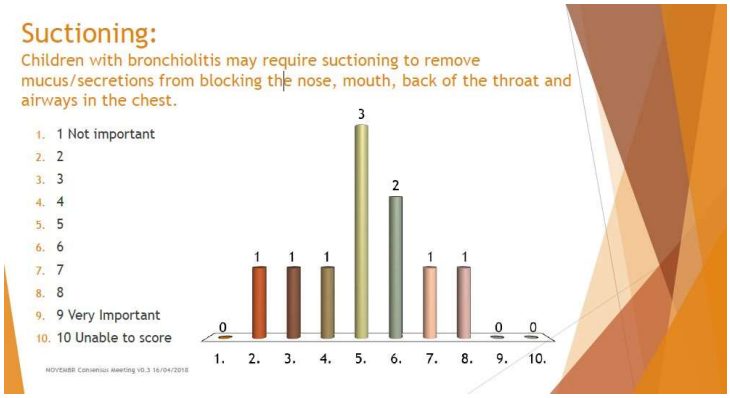


Outcome Name	Blood gas sampling
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted that it is not performed on every bronchiolitis patient and there are other indicators of treatment effect.
Voting outcome	OUT

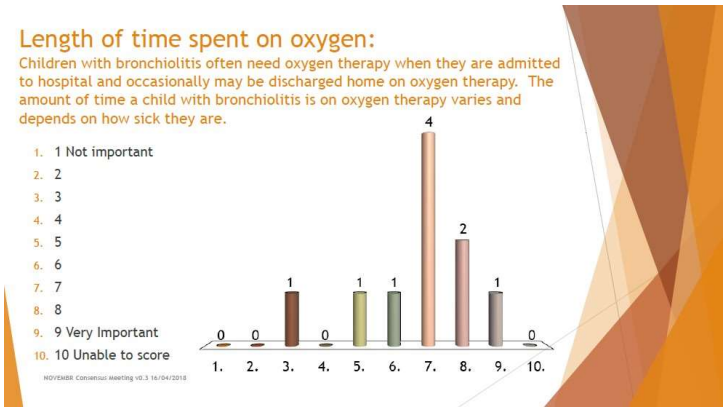


Outcome Name	Suctioning
Number of participants scoring 1-9	10

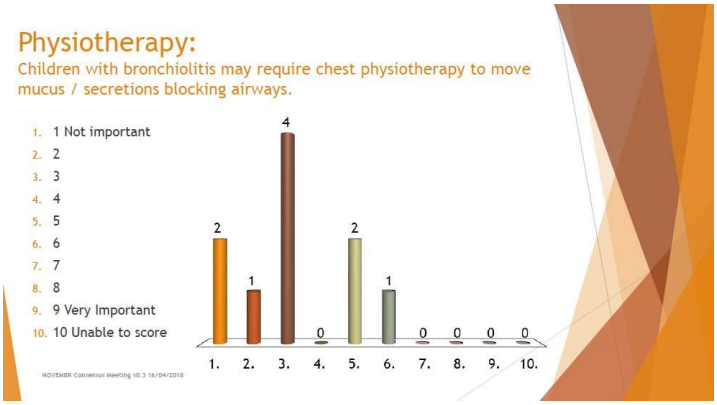
Number of participants unable to score	**0**
Notes	All agreed it could be useful for some types of bronchiolitis studies but not crucial for all.
Voting outcome	**OUT**



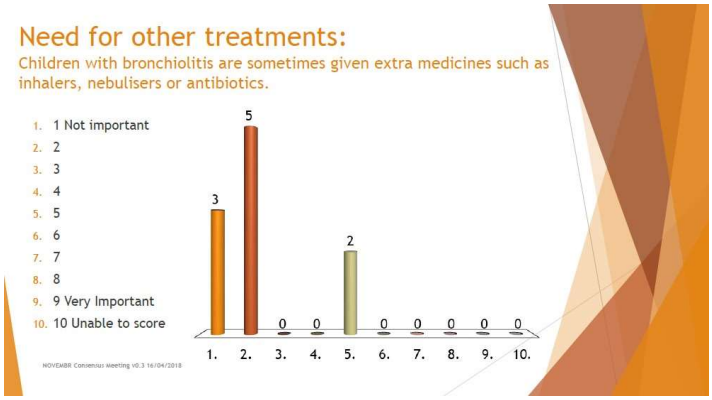
Outcome Name	**Length of time spent on oxygen**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Parents tend to score this higher because parents assume that if their child is still on oxygen that means they are not getting better. The impact on parents bonding with their child was also discussed.
Voting outcome	**IN**


Length of time spent on oxygen:
Children with bronchiolitis often need oxygen therapy when they are admitted to hospital and occasionally may be discharged home on oxygen therapy. The amount of time a child with bronchiolitis is on oxygen therapy varies and depends on how sick they are.
1. 1 Not important
2. 2
3. 3
4. 4
5. 5
6. 6
7. 7
8. 8
9. 9 Very Important
10. 10 Unable to score
0 0 1 0 1 1 4 2 1 0
1. 2. 3. 4. 5. 6. 7. 8. 9. 10.

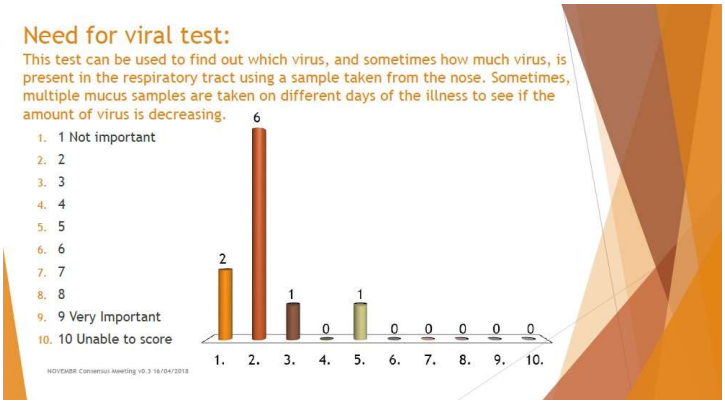
Outcome Name	Physiotherapy
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted that physiotherapy is not always appropriate for bronchiolitis.
Voting outcome	OUT



Outcome Name	Need for other treatments
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted that the Delphi responses were similar to physiotherapy.
Voting outcome	OUT

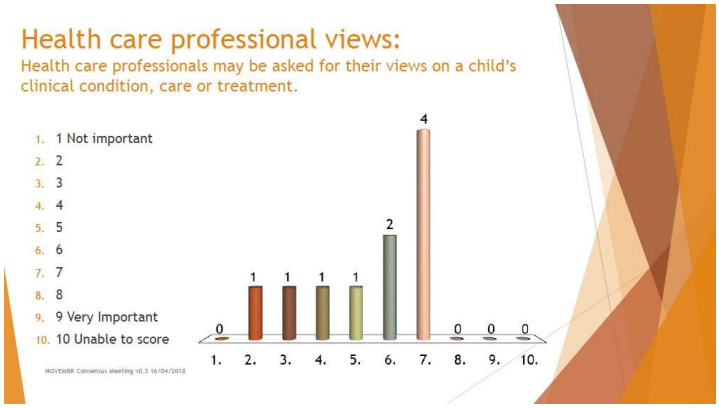


Outcome Name	**Need for viral test**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	All agreed it should be called “change of viral load”; a parent highlighted that in their experience it didn’t make a difference to their child’s treatment.
Voting outcome	**OUT**

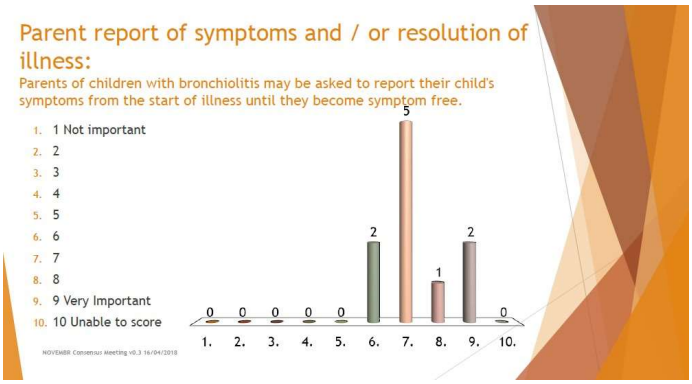


Outcome Name	**Heath care professional views**

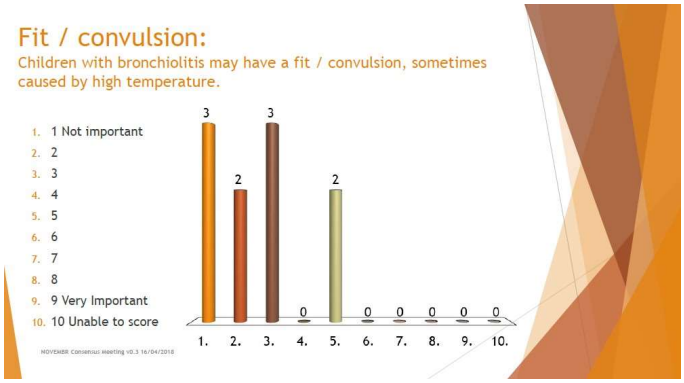
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	No significant discussion.
Voting outcome	**OUT**



Outcome Name	**Parent report of symptoms and / or resolution of illness**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted complete resolution of symptoms will usually be after hospital discharge.
Voting outcome	**IN**

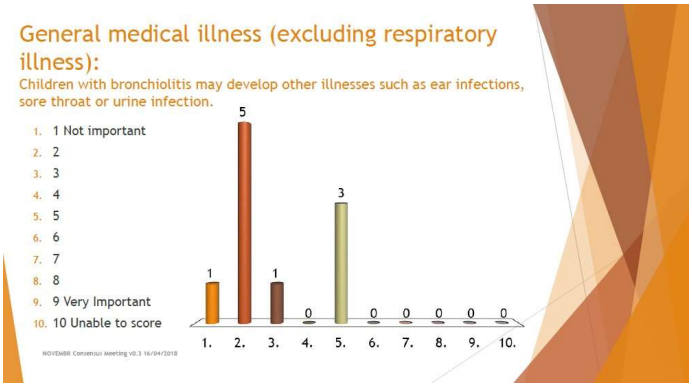


Outcome Name	Fit / convulsion
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted that whilst distressing they are not common and not directly linked to bronchiolitis.
Voting outcome	OUT

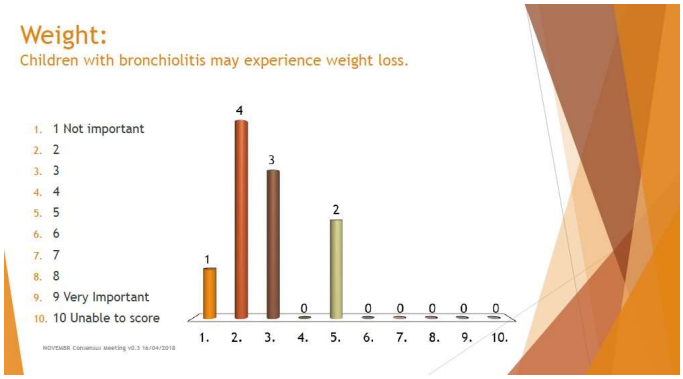


Outcome Name	General medical illness (excluding respiratory illness)
Number of participants scoring 1-9	10

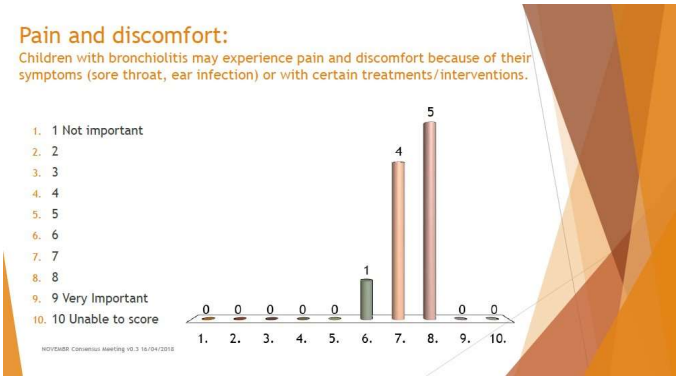
Number of participants unable to score	**0**
Notes	No issues raised.
Voting outcome	**OUT**



Outcome Name	**Weight**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted that parents scored weight higher than the other groups but also that weight will be put back on.
Voting outcome	**OUT**

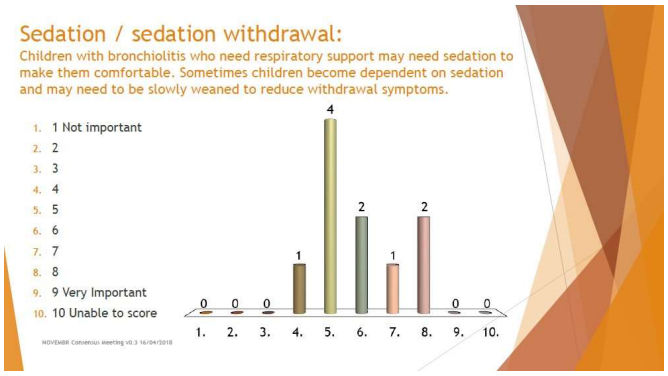


Outcome Name	**Pain and discomfort**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted that if parents could choose a treatment/intervention that would be less painful, they would. It was also highlighted that pain/discomfort could affect compliance.
Voting outcome	**IN**

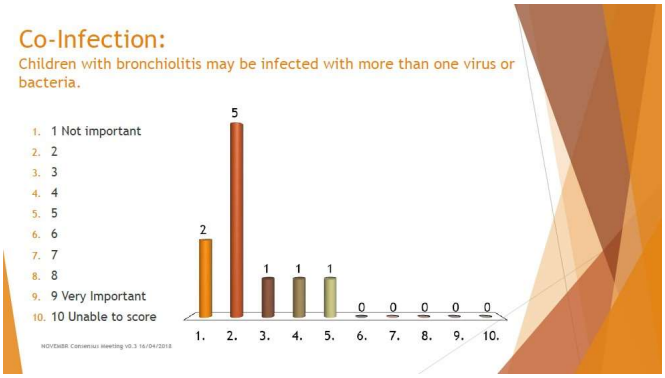


Outcome Name	**Sedation / sedation withdrawal**

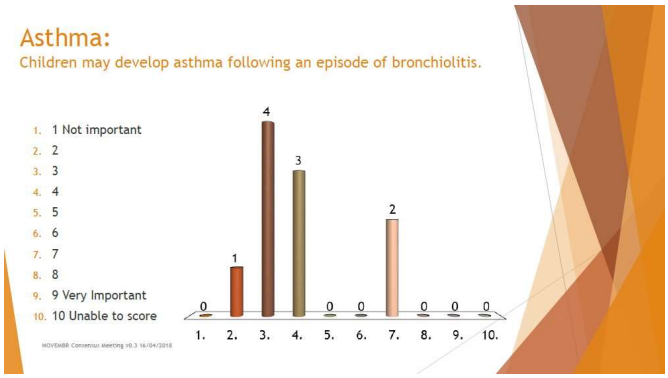
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted that sicker babies are sedated; voted on the "need for sedation".
Voting outcome	**OUT**



Outcome Name	**Co-Infection**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	All agreed this is similar to previously discussed "Additional chest infections / pneumonia".
Voting outcome	**OUT**

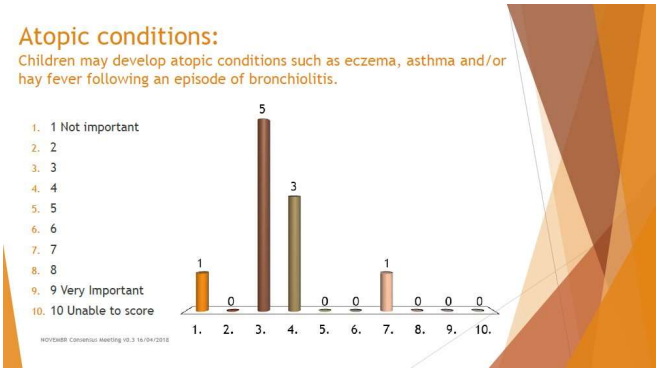


Outcome Name	Asthma
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	All agreed this is similar to the previously discussed “wheeze” and that it would be included under “long term effects of illness or treatment intervetions”.
Voting outcome	OUT

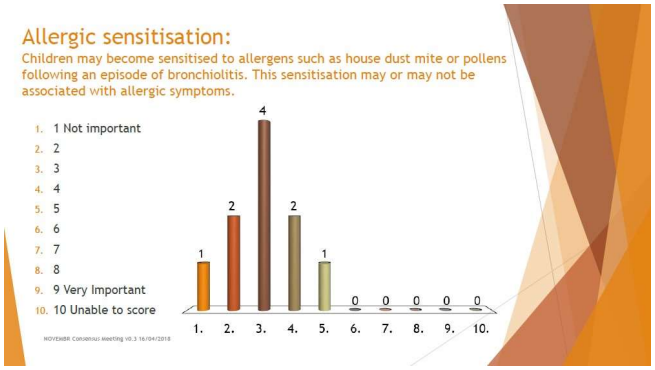


Outcome Name	Atopic condition
Number of participants scoring 1-9	10

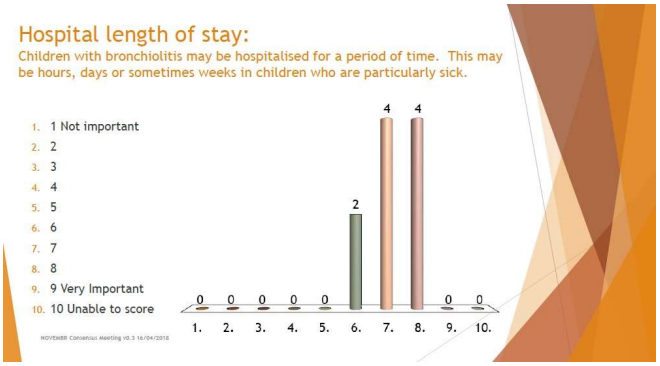
Number of participants unable to score	**0**
Notes	No issues discussed.
Voting outcome	**OUT**



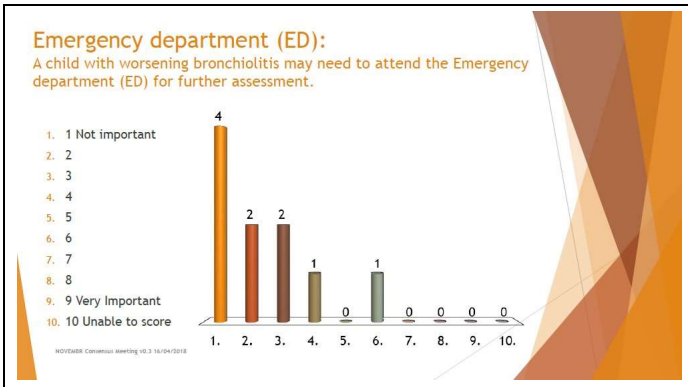
Outcome Name	**Allergic sensitisation**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	No issues discussed.
Voting outcome	**OUT**



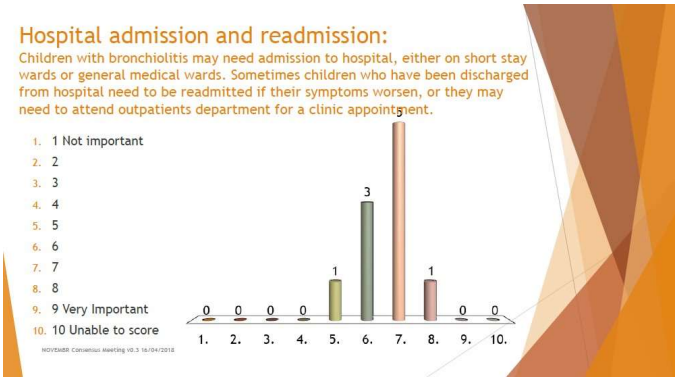
Outcome Name	Hospital length of stay
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted the impact length of stay can have on parents. They also highlighted that length of stay can vary due to parents feeling confident enough to care for their child, and regional differences e.g. access to community care. All agreed the child's recover date is more important.
Voting outcome	IN



Outcome Name	Emergency department (ED)
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted this would only be applicable to certain types of prevention trials.
Voting outcome	OUT

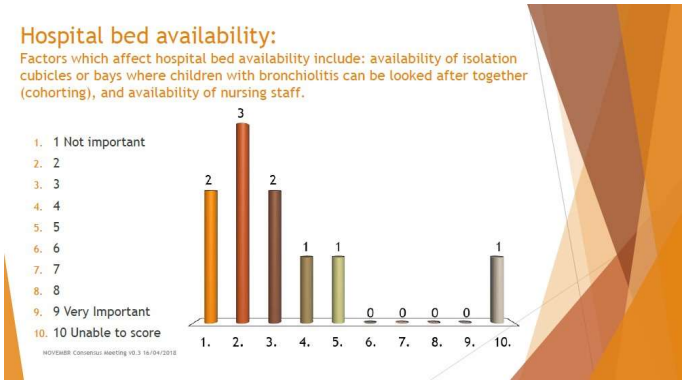


Outcome Name	Hospital admission and readmission
Number of participants scoring 1-9	10
Number of participants unable to score	0
Notes	Discussions highlighted re-admission would probably recorded as an adverse event. All agreed it is important but were unsure if it is crucial.
Voting outcome	OUT

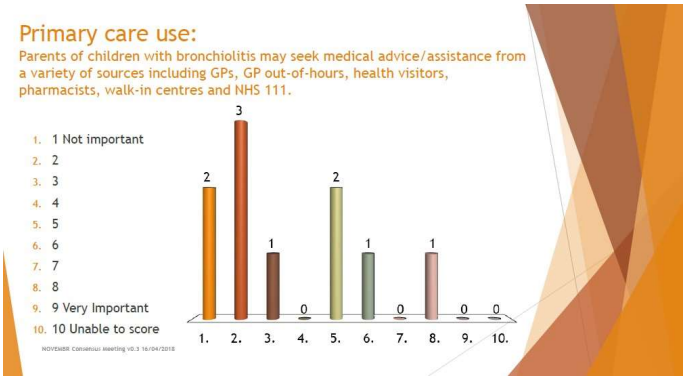


Outcome Name	Hospital bed availability
Number of participants scoring 1-9	9
Number of participants unable to score	1

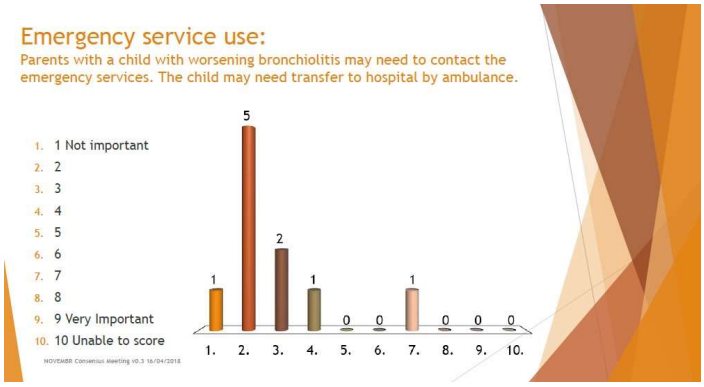
Notes	Discussions highlighted bed availability could influence the choice of treatment / intervention.
Voting outcome	**OUT**



Outcome Name	**Primary care use**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted this is similar to the previously discussed "emergency department".
Voting outcome	**OUT**

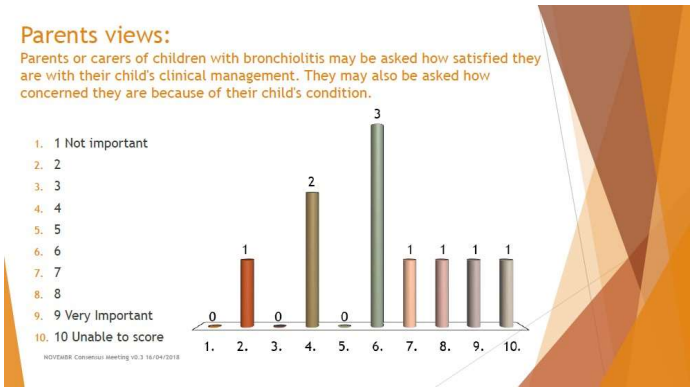


Outcome Name	Emergency service use
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted this is similar to the previously discussed “primary care use”.
Voting outcome	**OUT**



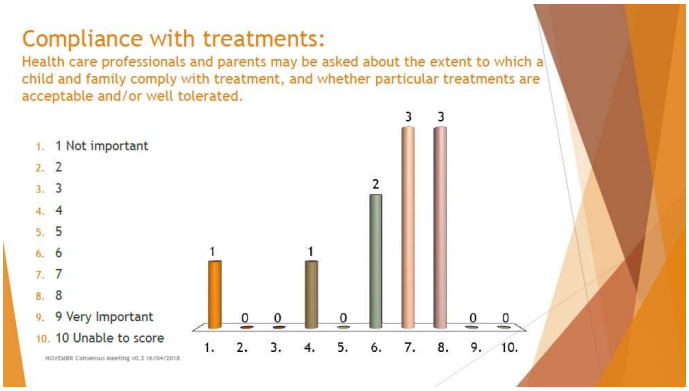
Outcome Name	Time until ready for discharge from hospital
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Parents felt it is more important and precise than “length of stay” which can be influenced by a number of different factors. Paul McNamara explained that length of stay would be used to assess cost.
Voting outcome	**IN**

Outcome Name	Parents views
Number of participants scoring 1-9	9
Number of participants unable to score	1
Notes	All agreed their felt the "parents views" outcome addresses whether or not parents have any specific concerns based on the intervention / treatment they may or may not be receiving.
Voting outcome	OUT

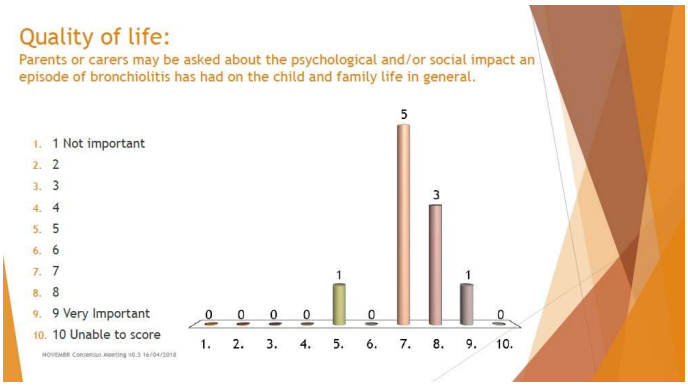


Outcome Name	Compliance with treatments
Number of participants scoring 1-9	10
Number of participants unable to score	0

Notes	Parents felt it was important as a child may have a treatment preference which could influence compliance.
Voting outcome	**OUT**



Outcome Name	**Quality of life**
Number of participants scoring 1-9	**10**
Number of participants unable to score	**0**
Notes	Discussions highlighted this is important to parents.
Voting outcome	**IN**



5. Meeting summary

Dr Ian Sinha provided a summary of the meeting (see Appendix 2 for full account) The following outcomes were agreed at the consensus meeting:

Table 9: Summary of outcomes discussed

Outcome	Percentage of meeting participants scoring 7-9	Percentage of meeting participants scoring 1-3	Consensus?
Long term effects of illness or treatment interventions	90.0%	0.0%	**In**
Adverse events	100.0%	0.0%	**In**
Need for fluids given through a drip	20.0%	10.0%	**Out**
Reduced urine output	80.0%	0.0%	**In**
Additional chest infections/pneumonia	40.0%	10.0%	**Out**
Bronchiolitis severity score	60.0%	10.0%	**Out**
Respiratory sounds	10.0%	40.0%	**Out**
Blood gas sampling	10.0%	10.0%	**Out**
Suctioning	20.0%	20.0%	**Out**
Length of time spent on oxygen	70.0%	10.0%	**In**
Physiotherapy	0.0%	70.0%	**Out**
Need for other treatments	0.0%	80.0%	**Out**
Need for viral test	0.0%	90.0%	**Out**
Health care professional views	40.0%	20.0%	**Out**
Parent report of symptoms and/or resolution of illness	80.0%	0.0%	**In**
Fit/convulsion	0.0%	80.0%	**Out**
General medical illness (excluding respiratory illness)	0.0%	70.0%	**Out**
Weight	0.0%	80.0%	**Out**
Pain and discomfort	90.0%	0.0%	**In**
Sedation/sedation withdrawal	30.0%	0.0%	**Out**
Co-infection	0.0%	80.0%	**Out**
Asthma	20.0%	50.0%	**Out**
Atopic conditions	10.0%	60.0%	**Out**
Allergic sensitisation	0.0%	70.0%	**Out**
Hospital length of stay	80.0%	0.0%	**In**
Emergency department (ED)	0.0%	80.0%	**Out**
Hospital admission and readmission	60.0%	0.0%	**Out**
Hospital bed availability	0.0%	77.8%	**Out**
Primary care use	10.0%	60.0%	**Out**

Emergency service use	10.0%	80.0%	**Out**
Time until ready for discharge from hospital	90.0%	10.0%	**In**
Parents views	33.3%	11.1%	**Out**
Compliance with treatments	60.0%	10.0%	**Out**
Quality of life	90.0%	0.0%	**In**

'How' to assess the outcomes was identified as a concern by the meeting attendees.
Any overlap across 'In' outcomes will be considered by the research team to ensure that there is no duplication in the final list of outcomes.

The next step for the research team is to review 'how' to measure each outcome.

Appendix 1

Non-invasive ventilation in the management of children with bronchiolitis

NOVEMBR Delphi Consensus Meeting
14th June 2018
9.30am
Venue: The Foresight Centre, University of Liverpool
Contact Details (The Foresight Centre): Tel: 0151 794 8060 Email: foresight@liv.ac.uk

Agenda	
9.30am	Arrival and registration Pre-meeting parent and health care professional briefing
10.00am	Introduction from chair: Housekeeping; ground rules for discussion
10.10am	Welcome & introduction to the NOVEMBR study • Introduction to core outcome sets • Introduction to the NOVEMBR Delphi survey / study methods • Outline of today's session
10.30am	'Consensus-in' & 'Consensus-out' items
11.00am	Break
11.15am	Introduction to turning point
11.30am	'No consensus' items
1.00pm	Lunch
1.30pm	'No consensus' items continued
2.45pm	Break
3:00pm	Meeting summary
3:15pm	What happens next?

NOVEMBR Consensus Meeting Agenda V2.0 04/04/2018

Appendix 2

	**NOVEMBR** **Delphi Consensus Meeting**
Thursday 14th June 2018, 09:30am – 3:30pm The Foresight Centre, University of Liverpool	
Time	Agenda item
09:30 am	**Arrival and registration** Pre-meeting parent and health care professional briefing
10:00 am	**Introduction from Chair: Housekeeping; ground rules for discussion**
	IS welcomed attendees. IS highlighted that attendees are a combination of doctors, nurses and parents and asked that this is considered throughout the day when discussions take place and that people respect each-others views and opinions.
10:10 am	**Welcome & introduction to the NOVEMBR study**

	PM provided an overview of study findings for the management of children with bronchiolitis to date. PM discussed that there is currently no evidence or guidance for which intervention works best. PM highlighted that the main aims of the NOVEMBR study are firstly to assess current practice at sites and whether they could support a research study into the management of children with bronchiolitis and secondly, to develop a core outcome set which can be used a basis for all future paediatric trials in bronchiolitis; this would mean that data across all of these types of trials is comparable. • **Introduction to core outcome sets** CvM provided the group with the COMET definition of what a core outcome set is. • **Introduction to the NOVEMBR Delphi survey / study methods** CvM discussed that as part of the NOVEMBR study, information collected from a systematic review, parent and healthcare professional workshops and parent interviews was collated to develop the initial list of 58 outcomes which could be used as a basis for all future research. As the list was too long, a Delphi survey was then circulated to reduce the number of outcome. The consensus meeting today is to help reduce the number of outcomes down further. A parent queried how many outcomes would be ideal. PM discussed that there is no exact figure and the list has already been significantly reduced from 110 to 58 outcomes. The session today will determine which of the outcomes that were borderline 'in' or 'out' should be included or not.

	Outline of today's session CvM went through the agenda for the day with the group.
10:30 am	**'Consensus-in' & 'Consensus-out' items**

	IS explained that the first group of outcomes that will be reviewed are the outcomes that reached consensus via the Delphi survey. The group will be given the opportunity to express any concerns/particularly strong feelings about any of the outcomes on the 'in' or 'out' lists. IS stressed to the group that he has had no prior involvement in the NOVEMBR study and this will be the first time he has viewed the results from the Delphi to try and ensure that he remains and independent member and does not introduce any bias to the session. The group had been sent the list of items that had reached consensus 'in' and 'out' prior to the session. They were also provided with an opportunity to review the list prior to discussion during the session. **Consensus-in** A medically qualified member of the group raised whether ''appearance'' is objective, discussions followed how this can be measured. IS stressed that the purpose of today's session is to look at 'what' should be measured, not 'how' this can be measured. A parent queried what PEWS is and whether this is covered by the measurements listed as other outcomes. A medically qualified member of the group confirmed that the PEWS is a number of measurements taken over a period of time and that it would be covered by measurements listed as other outcomes. The medically qualified member also suggested it should not be included in the list of outcomes because the measurements used can differ (throughout the different Trusts), it is not validated and it is not widely used so would not be comparable across studies. The need for some form of PEWS as an objective measurement/standard set of severity scores in a research study was discussed. A medically qualified member suggested junior doctors/less experienced nurses are more likely to find the score as a useful tool until they are able to monitor appearance etc. and make judgements based on their experience. There was general agreement that although PEWS may not be the most appropriate score to use, a method of measuring variables will be needed for measuring effects 'before' and 'after' study intervention. The importance to parents (100% scored as 7-9 in the Delphi survey) was discussed; a parent explained that the score can sometimes offer reassurance to them that their child is getting better. Due to time limitations IS advised that appearance and PEWS could be discussed further if needed later in the day. IS also explained that the majority of Delphi respondents have already voted in favour of their inclusion in the final list, so whilst any discussions would be noted the outcomes will not be removed from the 'In' list. A nurse highlighted that they were surprised ''inhalation of milk, fluids or solids'' was included as this can happen without bronchiolitis. IS explained that 100% parents and 95% nurses felt this is important, during subsequent discussion it was suggested that the slightly lower percentage of medically qualified Delphi

	participants who felt this is important may be due to doubts whether any bronchiolitis interventions would increase/reduce the risk of aspiration. Parent members of the group discussed that in their experience, feeding was very difficult due to exhaustion and the possibility of milk going down the wrong way. A medically qualified member highlighted that as aspiration is such a serious issue, it is important to measure this; no strong feelings against this were expressed. Discussions started regarding how to measure if an intervention influences aspiration. IS reminded the group that the session is not to discuss 'how' to measure outcomes, just 'what' outcomes need to be measured. IS also noted that the Delphi survey results for aspiration were voted highly across the board. All happy with rest of 'in' outcomes. **Consensus-out** A nurse member of the group expressed concerns that economic cost was not listed as an outcome as it impacts research and whether the intervention is adopted by the NIHR. It is important to demonstrate that the intervention is not only beneficial but is cost-effective. A medically qualified member provided an example: nasal high-flow costs £50 however standard oxygen costs pennies; even if it is not part of the core outcome set it could be added if required as part of a randomised control trial. Discussed that knowledge of cost is important but costs change over time so it is not crucial. All agreed that economic costs are important but not crucial. KW highlighted that the data collected for other core outcomes can be used for a health economic evaluation, it does not have to be a separate outcome. CvM queried whether recurrent wheeze was a concern to parents as a long term outcome; all present agreed that other outcomes, such as asthma, were more important.
11:00 am	**Break**
	Break commenced at 11:15am.
11:15 am	**Introduction to Turning Point**
	KW provided an introduction to the TurningPoint software. A test slide was completed all confirmed they were happy with the process and all voting buttons were working.
11:30 am	**'No consensus' items**
	The group were sent the list of 'no consensus' items prior to the meeting taking place. Before voting commenced, IS highlighted the following points to the group:- • All voting must consider whether the outcome is 'crucial' or not

	• We are not looking at 'how' to measure the outcome, just 'what' outcomes must be measured

	• There are 10 voting members present (3 parents, 3 nurses and 4 medically qualified) which means that 7 or more members need to vote 7-9 for the outcome to be 'in' • There will be a 2-3 minute deadline for each outcome • The outcomes have been grouped and ranked from those that were almost 'in' to those that were almost 'out' **1. Long term effects of illness or treatment interventions** Discussed whether, from a clinical and parent perspective only, the longterm effects of a treatment would impact the choice of a treatment/intervention. A medically qualified member highlighted they were questioning whether it was important as a number of parents who completed the survey did not think that this was important. All parents present felt that this was important. Discussed that it is a difficult outcome to measure for most trials. ***Outcome: In*** **2. Adverse events** Discussed whether measuring adverse events would be beneficial; most members agreed they had assumed that adverse events had to be recorded in research. An example of this was provided where a patient is being transferred between wards and their oxygen saturation drops during the transfer due to a limitation of the equipment. Although this is not related to treatment, it could still be recorded as an adverse event. ***Outcome: In*** **3. Need for fluids given through a drip** Discussed that this is subjective as the thresholds for IV use vary. Enteral feeding via NGT preferred by medically qualified and nurses. Discussed whether it is crucial to measure whether a child ended up on a drip or not. Parents did not think it is crucial. ***Outcome: Out*** **4. Reduced urine output** Discussed that reduced urine output is a tangible way for parents to initially tell that there is an issue with their child and that they need to attend hospital (along with a fever). IS queried whether, from a treatment perspective, this could be used as a before and after measurement; received mixed responses. A nurse member of the group highlighted that this could also be an indicator of how well the child is feeding which may be due to the type of treatment/intervention they have received. ***Outcome: In*** **5. Additional chest infections/pneumonia** Discussed possible reasons for a lower percentage of medically qualified rating this as important during the Delphi; possible reason is that it is difficult to measure. All present in room agreed that it is important and could influence choice of treatment/intervention however there are uncertainties about whether it is a critical outcome. Nurses present agreed that they would consider the risk when picking a treatment however if the

	child had a chest infection/pneumonia they would come under another category of child than a bronchiolitis patient. ***Outcome: Out*** **6. Bronchiolitis severity score** Discussed that although both the bronchiolitis severity score and PEWS are used to indicate if a child is getting better or worse, the bronchiolitis severity score is disease specific whereas PEWS is a generic paediatric score. Discussed that similar to PEWS, not all hospitals use the bronchiolitis severity score as not everyone agrees it is a valid scoring system. IS asked the group to consider whether the group would find a score like this useful when reviewing the results of a study and not to base their vote on whether the scoring system is valid. IS highlighted that if a scoring system is deemed useful, it would be up to the research team to strive to find/create a suitable scoring system. Group discussed and there was disagreement as to whether people would find a score like this important when reviewing results of a study. Post vote, a medically qualified member of the group discussed that the emergency department use scoring systems a lot to assess the likelihood of a major event and whether it is likely that further review by a specialist is going to be required. ***Outcome: Out*** **7. Respiratory sounds** Clarification provided for the group as to what this means. Discussed that respiratory sounds would not affect treatment; once a child has been diagnosed with bronchiolitis, they are treated for bronchiolitis. Any changes in sound would be due to another condition and would not be relevant to bronchiolitis. Parents did not feel that this is an important outcome. ***Outcome: Out*** **8. Blood gas sampling** A parent queried what added value measuring blood gas has over measuring oxygen saturation. Discussed that sometimes an increased accumulation of carbon dioxide leads to acidosis which is not always obvious until later on in a child's admission which can then lead to HDU intervention. Discussed whether it is crucial as it is not performed on every bronchiolitis patient and there are other indicators of treatment effect. PM confirmed that the study is UK-specific so practice in other countries does not need to be considered. Group reminded to vote on whether they think it is crucial for this sampling to be performed on every baby taking part in bronchiolitis research. ***Outcome: Out*** **9. Suctioning** Discussed that suctioning is performed routinely in some areas but not others. Highlighted that the question is whether the need for suctioning should be measured by treatment/intervention group. All in agreement that it could be useful for certain types of bronchiolitis studies e.g. antiviral studies, but not crucial for all bronchiolitis studies. Parent member of the group discussed that it was unpleasant witnessing their child being suctioned however it did help with their symptoms. ***Outcome: Out***

10. Length of time spent on oxygen

Discussed that this was scored as important by a high percentage of parents during the survey. Parents highlighted that this is probably due to the fact that parents assume that if their child is still on oxygen then it means that they are not getting better. A medically qualified member discussed whether the length of time spent on oxygen can also have a negative impact on the parent's bonding experience with the baby. Discussed that length of hospital stay is more important to medically qualified members and nurses as some children can go home on oxygen. Discussed whether it is crucial that this is measured for all bronchiolitis research. ***Outcome: In***

11. Physiotherapy

Discussed that the results for this outcome were borderline; IS highlighted that the question is not whether people think physiotherapy for babies with bronchiolitis works or not, it is whether it is crucial to measure whether one treatment/intervention means that a child is less likely to need physiotherapy over another and whether that would influence your decision to choose one treatment/intervention over another. Discussed that physiotherapy is not always appropriate for bronchiolitis. ***Outcome: Out***

12. Need for other treatments

Discussed that there were similar responses to item 11 'need for other treatments' in terms of the group ratio. No additional discussion in the room. ***Outcome: Out***

13. Need for viral test

Discussed that the outcome should be labelled as ''change of viral load''. A parent member of the group discussed that in their experience, the results of the viral test did not make a difference to the treatment their child received.
Outcome: Out

14. Health care professional views

Clarified that this is looking at the clinician or nurses 'gut feeling' based on their experience. Highlighted that there were average responses to this in the Delphi survey, approximately half of parents thought this was important.
Outcome: Out

15. Parent report of symptoms and/or resolution of illness

Discussed that this is looking at the complete resolution of symptoms, the point where the parent reports that the child is back to their normal self. This could be weeks rather than days so will be after hospital discharge in a lot of cases. No one felt that this was totally unimportant. ***Outcome: In***

	16. Fit/convulsion Discussed that although important for the child and scary for the parent, fits/convulsions are rare and are not an outcome of bronchiolitis, they are linked to the child being unwell. ***Outcome: Out*** **17. General medical illness (excluding respiratory illness)** No issues discussed. ***Outcome: Out*** **18. Weight** Discussed that this was scored highly by parents and not so highly by nurses and clinicians. Discussed whether it is a crucial outcome as weight can be put back on. ***Outcome: Out***
1:00 pm	**Lunch**
1:30 pm	**'No consensus' items continued**

	IS provided a recap of the items voted in during the session so far. **19. Pain and discomfort** This was scored as important by a high percentage of parents, but the percentage of nurses and clinicians scoring it as important was lower. Parent members explained that they understand there will be some level of discomfort however if they could choose a treatment/intervention that would be less painful, they would. All in agreement. A medically qualified member of the group suggested that the lower scores from the nurses and clinicians in the Delphi may be due to the outcome being difficult to measure. IS highlighted that if it is important for this outcome to be measured then it will be up to the research team to find a way to measure it. Discussed that pain/discomfort could affect compliance. ***Outcome: In*** **20. Sedation/sedation withdrawal** Discussed that sicker babies are administered sedation as part of respiratory support. Voted as to whether the 'need for sedation' should be included in the core outcome set and measured across all trials in bronchiolitis. ***Outcome: Out*** **21. Co-infection** Members agreed this is similar to the previously discussed item 5 ''Additional chest infections/pneumonia''. ***Outcome: Out*** **22. Asthma** Members agreed this is similar to previously discussed consensus-out item ''wheeze'' and would also come under long-term conditions, along with the following items 23 & 24. Discussed whether the group felt that items 22, 23 & 24 need to be explicitly listed as separate outcomes. Discussed the

	definition of a wheeze and whether it differs from asthma; parent members discussed that asthma involves more management and care than a wheeze. ***Outcome: Out***
	23. Atopic conditions *Outcome: Out*
	24. Allergic sensitisation *Outcome: Out*
	25. Hospital length of stay Borderline result from Delphi for medically qualified and parents, even less so for nurses. Discussed the impact length of stay has on parents, especially when they have other dependent children. Nurses discussed that there are occasions when the child is medically ready for discharge however the parents may not feel confident enough to go home. The length of stay can differ by region due to access to facilities/community care etc. Discussed that the date of discharge is not the most important factor, the child's recovery date is more important i.e. when they were assessed as medically ready for discharge. ***Outcome: In***
	26. Emergency department (ED) Discussed whether this outcome would only be applicable to certain types of prevention trials rather than intervention trials, for example, whether a vaccination led to decreased levels of attendance at A&E. ***Outcome: Out***
	27. Hospital admission and readmission Discussed whether any readmissions to hospitals would be recorded as an adverse event and whether this needs to be listed as a separate outcome. Discussed with the parents what their thoughts would be about repeated admissions. All agreed that this is a good measurement however the group was unsure whether it would be crucial to measure for a randomised control trial. ***Outcome: Out***
	28. Hospital bed availability Discussed how relevant this is as an outcome of research as it would be more likely that bed availability would influence the treatment/intervention that can be provided. ***Outcome: Out***
	29. Primary care use Discussed that this is similar to previously discussed item 26 ''emergency department''. Discussed with parents in group whether they would access primary or secondary care resources if their child became unwell again. Mixed responses from parents, although mainly primary care e.g. walk-in centres. ***Outcome: Out***

30. Emergency service use

Members agreed this is similar to previously discussed item 26 ''emergency department'' and item 29 ''primary care use''.

Outcome: Out

31. Time until ready for discharge from hospital

Discussed that this could be combined with item 25 ''length of stay''. Parent members of the group discussed that in their opinion this outcome is more important and precise than length of stay in hospital as there are factors other than the child's well-being that can extend the length of stay. Only measuring the length of stay could make it look as though a treatment/intervention has not been successful whereas there could be other factors e.g. social factors/time of day etc. that are delaying the child's discharge. Discussed reasons why length of stay would be important and whether there can be an amended vote for length of stay/whether it is needed as well as time until ready for discharge; PM highlighted that it would be used to assess cost.

Outcome: In

32. Parents views

Highlighted that the help text covers 2 completely separate questions. Parents discussed whether this is addressing whether the parent has any specific concerns based on the treatment/intervention their child may or may not be receiving (for example if they had been randomised to the observational group). A medically qualified member discussed that they do not think the parent's opinions on their child's care are crucial to the child's outcome. Another medically qualified discussed that a 'perfect' study would include the parent's views alongside the clinical and scientific outcomes as they should be viewed as equally important. KW highlighted that there could be a qualitative element included in a quantitative study to measure these views if required.

Outcome: Out

33. Compliance with treatments

Discussed if two groups were included in a randomised control trial whether it would be critical to measure compliance to the intervention/treatment across both groups. Parents felt that this was important as a child may prefer certain treatments over others which means they would be more likely to comply with the treatment. Medically qualified members highlighted that ITT analysis is always considered. Results from vote were very close.

Outcome: Out

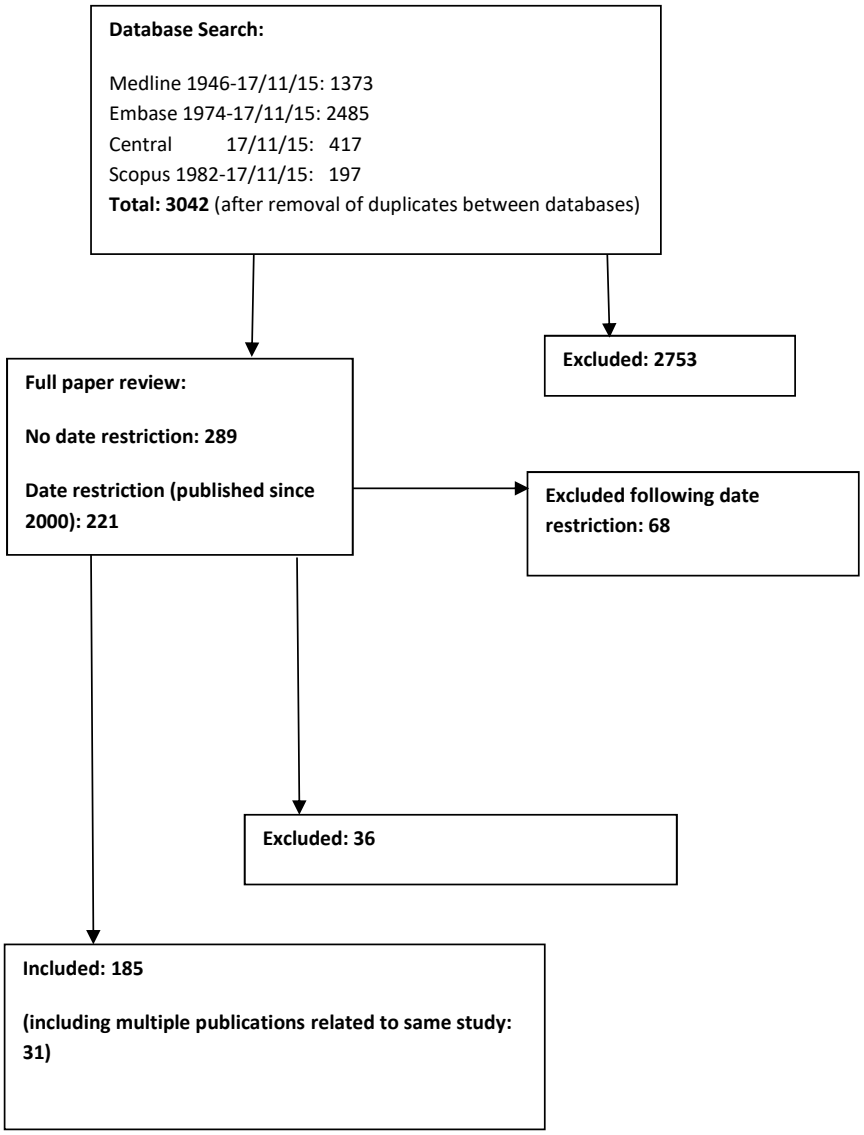
34. Quality of life

Parents discussed that this is important to them and as bronchiolitis affects a significant number of infants it is likely to be important to a number of other parents to. IS stressed that it is not important at the moment 'how' this will be measured, just whether it should be measured.

Outcome: In

2:45 pm	**Break**
3:00 pm	**Meeting summary**
	PM thanked the group for attending and for contributing to a very successful day. IS provided the following summary:- • 'How' to assess the outcomes has been raised as an issue/concern. • Feeding was raised as a clear concern. • The session highlighted the importance of parental views being included in a trial, especially when the child is discharged home. • Long-term effects of treatment, resources including length of stay and discharge date, adverse events and quality of life were all flagged as important outcomes. IS confirmed that any overlap across 'In' outcomes would be considered to ensure that there is no duplication in the final list of outcomes. IS also highlighted the importance of today's session and its impact on all future research into bronchiolitis and stressed that just by agreeing the list of outcomes, there has been a massive advance in bronchiolitis research and in changing the practice of managing bronchiolitis.
3:15 pm	**What happens next?**
	IS confirmed that the next step is for the research team to review 'how' to measure each outcome. PM highlighted that the findings from the NOVEMBR study will be published and a summary will be made available via the study website.

Supplementary Figure 1 – Systematic Review Flow Diagram



Supplementary Table 1 – Outcomes presented at Round 1

Domain (subdomain)	Outcome
Physiological and clinical (general symptoms)	Appearance
	Change to bowel habit
	General medical illness (excluding respiratory illness)
	Fever
	Fit/convulsion
	Weight
	Level of consciousness
	Pain and discomfort
	Sedation/sedation withdrawal
	Non-respiratory physiological parameters/vital signs
	Parent report of symptoms and/or resolution of illness
	Worsening illness
Physiological and clinical (feeding; nutrition and hydration)	Feeding
	Need for fluids given through a drip
	Need for feeding tube
	Inhalation (breathing in) of milk; fluids or solids
	Reduced urine output
Physiological and clinical (Respiratory distress)	Apnoea
	Blood gas sampling
	Oxygen saturation
	Bronchiolitis severity score
	Cyanosis
	Respiratory sounds
	Effort of breathing
	Paediatric Early Warning (PEW) score
Physiological and clinical (short term symptoms)	Cough
Physiological and clinical (respiratory infections and complications)	Additional chest infections/pneumonia
Physiological and clinical (respiratory interventions and support)	Need for respiratory support
	Physiotherapy
	Suctioning
	Need for other treatments
	Need for viral test
	Need for medical tests
Physiological or clinical (long term conditions)	Recurrent wheeze
	Asthma
Physiological and clinical (blood and immune)	Atopic conditions
	Allergic sensitisation
	Co-infection
Physiological and clinical (other)	Health care professional views
Life impact (functioning)	Behaviour change
	Sleep
Life impact (health related quality of life)	Quality of life
Life impact (tolerability/acceptability)	Compliance with treatments
Life impact (carer satisfaction/delivery of care)	Parents views
Resource use (hospital related short term)	Emergency service use
	Hospital bed availability
	Emergency department (ED)
	Hospital admission and readmission
	Critical care admission
	Hospital length of stay
	Time until ready for discharge from hospital
Resource use (community related short term)	Primary care use
Resources use (economic)	Economic costs
Death	Death

Domain (subdomain)	Outcome
Adverse events	Adverse events
	Serious adverse events
	Long term effects of illness or treatment interventions

Supplementary Table 2: Number of responders for each round by stakeholder group

Stakeholder group	Registered (% of Total) [a]	Graded at least one outcome in round one (% of [a]) [b]	Graded all outcomes in round one[1] (% of [a])	Graded at least one outcome in round two (% of [b])	Graded all outcomes in round two[1] (% of [b])
Medically qualified	205 (69%)	194 (95%)	150 (73%)	145 (75%)	115 (59%)
Nurses and other clinical staff	82 (27%)	81 (99%)	54 (66%)	42 (52%)	33 (41%)
Parents	12 (4%)	11 (92%)	7 (58%)	7 (64%)	4 (36%)
Total	**299 (100%)**	**286 (96%)**	**211 (71%)**	**194 (68%)**	**152 (53%)**

Supplementary Table 3: Comparing round 1 scores of those who responded to both rounds and those who responded to round 1 only

Domain	Outcome	Mean round 1 scores of those who responded to both rounds		Mean round 1 scores of those who responded to round 1 only	
		N	*Mean (SD)*	*N*	*Mean (SD)*
Adverse events	Adverse events	187	7.15 (1.54)	74	7.24 (1.62)
	Long term effects of illness or treatment interventions	186	7.27 (1.45)	75	7.33 (1.73)
	Serious adverse events	186	7.59 (1.44)	75	7.73 (1.58)
Death	Death	185	8.04 (1.40)	75	7.87 (1.70)
Life impact (carer satisfaction/delivery of care)	Parents views	192	6.65 (1.34)	76	6.63 (1.50)
Life impact (functioning)	Behaviour change	191	5.62 (1.42)	76	5.80 (1.88)
	Sleep	191	5.60 (1.42)	76	5.58 (1.78)
Life impact (health related quality of life)	Quality of life	190	5.99 (1.55)	74	6.05 (1.66)
Life impact (tolerability/acceptability)	Compliance with treatments	192	5.88 (1.75)	74	6.34 (1.77)
Physiological and clinical (blood and immune)	Allergic sensitisation	191	5.27 (1.63)	78	5.46 (1.77)
	Atopic conditions	191	5.42 (1.60)	78	5.55 (1.80)
	Co-infection	192	5.96 (1.57)	77	5.92 (1.74)
Physiological and clinical (Respiratory distress)	Apnoea	194	8.23 (1.10)	83	8.19 (1.09)
	Blood gas sampling	193	6.45 (1.68)	83	6.82 (1.51)
	Bronchiolitis severity score	189	6.68 (1.77)	77	6.92 (1.73)
	Cyanosis	192	7.68 (1.47)	84	7.89 (1.23)
	Effort of breathing	194	7.76 (1.19)	84	8.01 (1.10)
	Oxygen saturation	194	7.77 (1.21)	83	7.92 (1.21)
	Paediatric Early Warning (PEW) score	193	6.99 (1.68)	82	7.30 (1.33)
	Respiratory sounds	194	6.21 (1.80)	84	6.65 (1.78)
Physiological and clinical (feeding; nutrition and hydration)	Feeding	194	7.25 (1.31)	84	7.45 (1.40)
	Inhalation (breathing in) of milk; fluids or solids	190	6.98 (1.43)	82	7.02 (1.63)
	Need for feeding tube	192	7.14 (1.18)	84	7.21 (1.48)
	Need for fluids given through a drip	192	7.07 (1.36)	85	7.22 (1.31)
	Reduced urine output	193	6.61 (1.49)	84	6.94 (1.56)
Physiological and clinical (other)	Health care professional views	192	6.24 (1.36)	75	6.35 (1.57)

Domain	Outcome	Mean round 1 scores of those who responded to both rounds		Mean round 1 scores of those who responded to round 1 only	
		N	*Mean (SD)*	*N*	*Mean (SD)*
Physiological and clinical (respiratory infections and complications)	Additional chest infections/pneumonia	192	6.71 (1.21)	79	6.77 (1.29)
Physiological and clinical (respiratory interventions and support)	Need for respiratory support	193	8.07 (1.07)	78	8.09 (1.02)
	Need for medical tests	192	5.50 (1.75)	77	5.42 (1.75)
	Need for other treatments	191	6.18 (1.56)	78	6.06 (1.65)
	Need for viral test	192	5.42 (1.85)	75	5.60 (1.71)
	Physiotherapy	190	5.77 (1.64)	76	5.86 (1.69)
	Suctioning	191	6.20 (1.53)	76	6.55 (1.56)
Physiological and clinical (short term symptoms)	Cough	193	5.13 (1.61)	79	5.27 (1.72)
Physiological or clinical (general symptoms)	Appearance	194	6.69 (2.01)	92	7.10 (1.83)
	Change to bowel habit	194	3.09 (1.50)	92	3.20 (1.59)
	Fever	194	5.79 (1.55)	92	5.95 (1.69)
	Fit/convulsion	193	5.98 (2.02)	92	5.85 (2.03)
	General medical illness (excluding respiratory illness)	194	5.85 (1.63)	92	6.17 (1.64)
	Level of consciousness	194	7.52 (1.79)	92	7.65 (1.64)
	Non-respiratory physiological parameters/vital signs	194	7.11 (1.35)	92	7.23 (1.40)
	Pain and discomfort	193	6.15 (1.56)	92	6.05 (1.62)
	Parent report of symptoms and/or resolution of illness	191	6.63 (1.33)	92	6.75 (1.58)
	Sedation/sedation withdrawal	173	5.69 (1.99)	87	5.70 (2.11)
	Weight	194	5.46 (1.65)	92	5.65 (1.81)
	Worsening illness	194	7.75 (1.08)	92	7.68 (1.25)
Physiological or clinical (long term conditions)	Asthma	191	6.24 (1.52)	79	6.06 (1.86)
	Recurrent wheeze	192	6.30 (1.44)	78	6.22 (1.59)
Resource use (community related short term)	Primary care use	186	6.33 (1.55)	73	5.99 (1.74)
Resource use (hospital related short term)	Critical care admission	192	7.69 (1.17)	75	7.56 (1.33)
	Emergency department (ED)	190	6.95 (1.46)	76	6.92 (1.74)
	Emergency service use	189	6.84 (1.45)	76	6.82 (1.69)
	Hospital admission and readmission	192	7.14 (1.32)	75	7.17 (1.23)
	Hospital bed availability	188	6.52 (1.86)	76	6.34 (2.10)

Domain	Outcome	Mean round 1 scores of those who responded to both rounds		Mean round 1 scores of those who responded to round 1 only	
		N	***Mean (SD)***	***N***	***Mean (SD)***
	Hospital length of stay	192	7.28 (1.35)	76	6.82 (1.65)
	Time until ready for discharge from hospital	192	7.17 (1.33)	76	6.79 (1.71)
Resources use (economic)	Economic costs	185	6.26 (1.66)	74	5.77 (2.01)

Supplementary Table 4: Results from Delphi Survey Round 2

Domain	Outcome[1]	Consensus	Percentage (%) of responders who scored 7-9			Percentage (%) of responders who scored 1-3		
			Medical	Nurses	Parents	Medical	Nurses	Parents
Physiological or clinical (general symptoms)	Appearance	In	72	86	71	1	2	14
	Change to bowel habit	Out	1	0	14	83	71	14
	General medical illness (excluding respiratory illness)	No consensus	36	45	71	2	5	0
	Fever	Out	18	38	29	5	0	0
	Fit/convulsion	No consensus	34	55	100	9	2	0
	Weight	No consensus	20	21	71	8	10	14
	Level of consciousness	In	90	88	100	1	0	0
	Pain and discomfort	No consensus	28	36	86	2	0	0
	Sedation/sedation withdrawal	No consensus	27	46	71	9	11	14
	Non-respiratory physiological parameters/vital signs	In	86	90	100	1	0	0
	Parent report of symptoms and/or resolution of illness	No consensus	63	64	71	0	0	0
	Worsening illness	In	94	98	100	0	0	0
Physiological and clinical (feeding; nutrition and hydration)	Feeding	In	84	83	100	1	2	0
	Need for fluids given through a drip	No consensus	80	85	67	1	2	0
	Need for feeding tube	In	81	88	83	1	2	0
	Inhalation (breathing in) of milk; fluids or solids	In	76	95	100	1	0	0
	Reduced urine output	No consensus	61	79	83	1	2	0
Physiological and clinical (Respiratory distress)	Apnoea	In	97	98	100	0	0	0
	Blood gas sampling	No consensus	41	45	86	3	2	0
	Oxygen saturation	In	94	98	86	0	0	0
	Bronchiolitis severity score	No consensus	60	68	100	3	2	0
Physiological and clinical (Respiratory distress) cont.	Cyanosis	In	90	95	100	1	0	0
	Respiratory sounds	No consensus	34	76	86	6	2	0
	Effort of breathing	In	92	98	100	0	0	0
	Paediatric Early Warning (PEW) score	In	72	88	100	5	0	0
Physiological and clinical (short term symptoms)	Cough	Out	7	14	33	17	10	0

Domain	Outcome[1]	Consensus	Percentage (%) of responders who scored 7-9			Percentage (%) of responders who scored 1-3		
			Medical	Nurses	Parents	Medical	Nurses	Parents
Physiological and clinical (respiratory infections and complications)	Additional chest infections/pneumonia	No consensus	66	83	100	1	0	0
Physiological and clinical (respiratory interventions and support)	Need for respiratory support	In	98	98	100	0	0	0
	Length of time spent on oxygen	No consensus	25	39	100	4	5	0
	Physiotherapy	No consensus	24	39	67	10	5	0
	Suctioning	No consensus	38	71	83	4	0	0
	Need for other treatments	No consensus	32	46	83	4	0	0
	Need for viral test	No consensus	16	17	67	14	10	0
	Need for medical tests	No consensus	15	24	83	10	2	0
Physiological or clinical (long term conditions)	Recurrent wheeze	Out	36	24	40	3	0	0
	Asthma	No consensus	35	17	60	2	2	0
Physiological and clinical (blood and immune)	Atopic conditions	No consensus	14	12	60	10	5	0
	Allergic sensitisation	No consensus	10	10	60	12	7	0
	Co-infection	No consensus	35	31	80	3	0	0
Physiological and clinical (other)	Health care professional views	No consensus	41	74	50	1	0	0
Life impact (functioning)	Behaviour change	Out	17	10	17	4	2	0
	Sleep	Out	16	19	17	6	5	0
Life impact (health related quality of life)	Quality of life	No consensus	41	21	80	1	0	0
Life impact (tolerability/acceptability)	Compliance with treatments	No consensus	37	62	67	6	0	0
Life impact (carer satisfaction/delivery of care)	Parents views	No consensus	55	64	67	1	0	0
Resource use (hospital related short term)	Emergency service use	No consensus	59	27	50	2	0	0
	Hospital bed availability	No consensus	55	59	67	6	2	0
	Emergency department (ED)	No consensus	69	54	83	2	2	0

Domain	Outcome[1]	Consensus	Percentage (%) of responders who scored 7-9			Percentage (%) of responders who scored 1-3		
			Medical	Nurses	Parents	Medical	Nurses	Parents
	Hospital admission and readmission	No consensus	76	43	67	0	0	0
	Critical care admission	**In**	95	90	100	1	0	0
	Hospital length of stay	No consensus	79	55	67	1	0	0
	Time until ready for discharge from hospital	No consensus	77	55	17	1	0	0
Resource use (community related short term)	Primary care use	**Out**	36	27	50	3	2	0
Resources use (economic)	Economic costs	**Out**	36	18	17	3	3	17
Death	Death	**In**	95	98	100	1	0	0
Adverse events	Adverse events	No consensus	87	67	83	0	0	0
	Serious adverse events	**In**	94	83	100	0	0	0
	Long term effects of illness or treatment interventions	No consensus	87	86	67	0	0	0

A preliminary analysis was undertaken by a separate statistician prior to the consensus meeting. The results above are those from the final analysis which identified 2 minor errors from the preliminary analysis: '*Need for medical tests'* was originally classified as '*consensus out'* but should have been '*no consensus'; 'Primary care use'* was originally classified as *'no consensus'* but should have been *'consensus out'*. During the face-to-face consensus meeting **all outcomes** were discussed and there was specific time set apart to discuss '*no consensus'* and *'consensus out'* outcomes, therefore it was decided the discrepancies from the preliminary analysis had negligible impact on the final results.