**To The Editor**

Journal of Cystic Fibrosis

Thank you for inviting a resubmission of this manuscript.

***Ms. Ref. No.: JCF-D-14-00327***

***Title: Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID); a new designation and management guideline for infants with an unclear diagnosis following newborn screening Journal of Cystic Fibrosis***

This is an important paper, reflecting a key output from the Neonatal Screening Working Group, together with important collaborations with the Diagnostic Network Working Group and the US NBS Quality Improvement Consortium.

This paper will impact on how these infants are managed globally, providing consistency of approach and designation.

This work has not been submitted for publication elsewhere and the revisions have been reviewed by all authors.

Finally, we would like to thank the reviewers for their detailed and reflective comments, which certainly have helped make this a better paper. It is our aim that this paper has a wide readership and we appreciate any suggestions that improve accessibility.

This document contains

1. Covering letter
2. Responses to reviewer comments
3. Revised manuscript (with changes highlighted in red)
4. Highlights (5 bullet points)

Yours, Kevin Southern (corresponding author)

**Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID); a new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening.**

**Response to reviewers’ comments**

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| **Comment Number** | **Section** | **Comment** | **Response** |
| **Reviewer #1:** |  |  |  |
| **Comment 1** | **Overview** | The care of infants identified by newborn screening who do not have a definitive diagnosis (as either having CF or as healthy carriers) is is an important topic. The guidelines developed in the United States do not carry strong weight in Europe, and so the development of European guidelines is appropriate. Experts throughout Europe were consulted. In the absence of data to guide management of these children, a Delhi consensus approach was appropriate. The paper aims to present the process followed to arrive at the consensus guidelines. **The paper is disorganised and hard to read, see specific comments.** | Our goal has been to write a paper that is accessible to a wide readership. Hopefully the responses and corrections below will improve readability, particularly for readers for whom English is not their first language.  We thank all the reviewers for taking the time to go over the paper in detail. |
| **Comment 2** | **Title** | I think it would be better to use the word inconclusive instead of unclear in the title. It may appear redundant but avoids the use of another term. | We agree with the reviewer that we do not want to add to what is already a confusing situation. We will therefore revert to using inconclusive instead of "unclear" in the title |
| **Comment 3** | **Introduction** | I would like to see a clearly stated aim of the paper. I believe that the aim is both to present these ECFS guidelines and the methodology to achieve consensus. | Sentence added to introduction. *This paper describes the method employed and the recommendations.* |
| **Comment 4** | **Methods** | Not all the list of participants is from Europe…a brief explanation of why/how others were included. | This project was co-ordinated by the ECFS Neonatal Screening Working Group but was an international process, not exclusively European. We have clarified this in the methods and have added the denominator asked for in comment 8 and response rate. |

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| **Comment 5** |  | The determination, a priori, of 80% agreement, seems fine, but surely there is a methodological reference or agreement on this figure from elsewhere (reference 4 is the same groups previous publication on this topic). Is there an original description of the Delphi method to reference? | We have added the Harold reference "The Delphi Method, techniques and applications" 2002 |
| **Comment 6** |  | Groups A and B need clear explanation/definition | We have added two bullet points to make this paragraph clearer. |
| **Comment 7** | **Results** | It is a great pity, in my mind, that the core group elected to have two statements for the CFSPID infants…this seems to generate confusion, complicate the recommendations and when there is no evidence for any of it, makes less sense. | The Core Group felt this to be a key outcome of this process, the distinction between these two cohorts was felt to be important and has resulted in good agreement on the two sets of statements. None of the 85 contributors to the Delphi process commented negatively on the decision to have two sets of statements. We have added a sentence in the discussion to clarify this. |
| **Comment 8** |  | No response rate is given (85 responses to round 1, but how many sent out? Same problem for round 2, I assume 85 sent out???)Report a % response rate. | Denominator and response rate added |
| **Comment 9** |  | It might be best to look at the figure now: Figure 1. The word equivocal should be removed and the correct term, CFSPID used (don't introduce another word!). | Yes sorry, this was a mistake, we have removed |
| **Comment 10** |  | Generally good flow diagram. |  |
| **Comment 11** |  | I can't really determine the difference between rewritten and modified. This could be better explained, this is a type of methodological issue. It would be OK to explain it more clearly in the text section round 2. | We agree this is quite confusing and hopefully will be clearer in the revised paper. We have clarified in the methods. Modified is when the statement is changed to improve clarity (some statements that achieved agreement were modified to improve readability). Rewritten is a fundamental change in the content, reflecting comments. We will clarify this throughout the paper and make the corrections highlighted. |

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| **Comment 12** |  | Round 2…the numbers don't add up, Group A: in round 1 there were 15 statements, but after round two 15 (consensus) + 1 (no consensus)=16! Group B there were 17 statements in round 1, but after round 2, 16 (consensus) +???? | Thank you for highlighting this mistake, which we have corrected |
| **Comment 13** | **Back to the paper:** | Round 1: where does >60% approach consensus come from (this was not discussed a priori….may be best to just say seven statements had 60-79% consensus and leave the interpretation out! Also with "poor level of agreement" | This is a fair comment. We have removed this subjective assessment of the level of agreement. |
| **Comment 14** |  | The designation issue is really just one of the main statements and perhaps could be discussed after round 2. You don't report the level of consensus for the term CFSPID. While we are discussing the designation exercise, Figure 2 is very unclear...a figure should be self-explanatory...was this the question put to the group...round 1 or 2. Why do some responses have % figures, but others not? | We have taken on board these helpful comments. We have put all the designation exercise together in one section (we agree there was duplication before). We have clarified the Legend for Figure 2, including the% response for the two most popular options (now removed from Figure) |
| **Comment 15** | **Specific issues and Comments** | A brief explanation of why these statements were chosen for analysis would help. | See above |
| **Comment 16** |  | The cross infection statement (line 34-36) just appears after the follow-up section...what is it doing here, on its own..needs a title... | Thank you, we have added to title |
| **Comment 17** |  | Respiratory cultures...I see that A12 is taken out of recommendations...this leaves the recommendations for Group A with a missing number (this is the sort of thing that makes the whole paper/recommendations messy). However, the paragraph is finished with a recommendation anyway...but this is put at the end of Group B's recommendations in the statements list. | We have moved statement A12 and placed it under the A statements in the table. We agree with the reviewer that it was confusing before, but have not reordered the statements as we wanted to highlight that statement A12 did not reach consensus and for those infants, clinics should adopt local policy. We have clarified this in the discussion |
| **Comment 18** |  | The designation exercise gets a second billing! Now I see the % consensus! This disorganisation takes away from the paper. Have one section on Designation. | Thank you, see response to comment 14 |
| **Comment 19** |  | Sensitivity analysis..This is confusing...If 8 responses had a level of agreement below 80% when you looked back at round 1...6 of the round 1 statements had been revised or modified in response to comments, leaving 2 that were unchanged, but were now<80% at round 2....but these haven't been removed? So you are keeping them on the basis of round 1 responses, not round 2. Which round is correct? | The sensitivity analysis was a review of the process and has no bearing on the level of agreement. We have clarified this. |
| **Comment 20** |  | How about reporting the statements with the % agreement? | We are keen to keep this table simple, we can provide these statements and comments as an appendix or full list of comments etc if that is felt helpful. |
| **Comment 21** | **Discussion** | Paragraph 1..a poor start..this is mostly a rehash of the introduction. Come out and make a clear statement of important findings. | We agree with reviewer 3 about the term guideline and have changed throughout. |
| **Comment 22** |  | Paragraph 2 "in this guidance"...should read.."guideline" | Changed |
| **Comment 23** |  | Paragrapgh 7 "Alternatively clearer information may become available from the CFTR-2 database"...to do what? Exclude CF and let the children go? | We have added a comment that data from CFTR-2 may clarify if a mutation is disease causing. |
| **Comment 24** |  | Group A...how can this group have one or no mutations? Aren't they elevated IRT, two mutations (you might actually be better to think of them as CFTR sequence variations!) and normal sweat Cl?? Similarly...how can the sweat return to normal if it was normal to start with?....Perhaps there needs to be a clear definition of your two groups in the introduction (or method), ie where NBS can leave an infant. While we are on this topic, Group B in the consensus statement list includes infants with no mutations.. are these babies with very high IRT who had no mutations but still had a sweat test? | International advice is not to use "sequence variation" |

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| **Reviewer #2:** |  |  |  |
| **Comment 25** | **Major comments:** | This is a clearly written review of the process used to achieve consensus on the care of infants who have a positive newborn screen for CF but inconclusive diagnostic evaluation, and the new recommended terminology for describing such infants.There is one issue that is not adequately discussed in this paper: how the presence of CF-causing mutations versus mutations of variable significance might affect care. The US definition of CRMS includes indeterminate (or intermediate) sweat chloride with or without identification of two CFTR mutations, one or both of which are of unknown or variable significance. In this paper, the classification of groups A as normal sweat test with 2 CFTR mutations and group B as intermediate sweat with 0 or 1 CFTR mutations actually misses a fair number of infants with unclear diagnoses after newborn screening, including those with a severe mutation and the R117H mutation. I suspect that this was done for simplicity, and does account for most cases, but devoting a paragraph in the discussion to cases that may not be either group A or B and the need for additional clinical decision making in such cases is important. | Our previous work suggests that infants with 2 mutations and indeterminate sweat chloride values should be referred for standard CF care. We have added a sentence to clarify this. |
| **Comment 26** | **Minor comments:** | In figure 2, after "inconclusive diagnosis of CF" there is a (27%). This does not make sense in this context and should be removed. | Clarified as for comment 14 |
| **Reviewer #3** |  |  |  |
| **Comment 27** | **Overview** | This report summarizes the recommendations for the management of infants with a positive CF newborn screen (NBS) but inconclusive diagnostic testing. This was developed using the Delphi process involving the ECFS NWWG, a group of clinicians with a high degree of expertise and experience in CF NBS. While this document is useful and the Delphi method is an accepted approach to achieving consensus, I have some concerns that this document at times contradicts itself and presents a much stronger sense of rigor than is actually present. | We have tried to conduct an inclusive, open and robust process. We are not sure which component of the process the reviewer is referring to, although hopefully the changes we have made in response the detailed and helpful comments will make the manuscript clearer. |

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| **Comment 28** |  | 1. I am uncomfortable with calling these recommendations "guidelines". Over the last several years, the process of guideline development has become much more rigorous, and consensus opinion in the absence of actual evidence is considered the lowest grade of evidence. Most guideline systems, such as the U.S. Preventive Services Task Force or GRADE, will preface consensus based recommendations either as optional or very weak. It's OK to use consensus when there is an absence of evidence, but it's important to be transparent about the limitations of this approach as a clinical practice guideline. Would the authors consider changing the title to "recommendations" or results of a consensus conference? | We have changed guidelines to recommendations throughout |
| **Comment 29** |  | 2. Some of the consensus recommendations lack a clear rationale. For example, if no interventions are being recommended, why recommend that infants follow up at a CF specialty clinic? Primary care physicians are perfectly capable of weighing infants and asking about cough. Especially in the absence of evidence supporting these recommendations, there should be some explanation or rationale for why this is being recommended. | The opinion of the reviewer is shared by some, that primary care physicians are quite capable of following the progress of these infants, but the vast majority of respondents felt that a CF physician should be responsible (though many felt this did not need to be in a CF clinic and there were convincing arguments as to why review in a non-CF clinic may be appropriate). We can provide detail like this for every statement but we were keen not to present an overlong manuscript. We feel we have achieved that whilst highlighting the issues that were contentious. |
| **Comment 30** |  | 3. The recommendations differ between CFSPID infants with normal sweat Cl and those with intermediate sweat Cl, but the Discussion does not make that clear (p. 11/lines 45-51). What is the rationale for the difference in recommendations? Is the group concerned that these infants are at higher risk for developing features of CF disease? | We have clarified this in the methods and discussion. |
| **Comment 31** |  | 4. There seems to be a contradiction between their statement that CFSPID infants should not be over medicalised and their recommendation to do things like give antibiotics for a cough. | Only for infants in Group B, the recommendation was that these infants should have a lower threshold for oral AB's than the general population. It is important to remember that these statements reflect a consensus, we had more intensive and less intensive suggestions (but these were in the minority) |
| **Comment 32** |  | 5. Several groups around the world are looking at the outcomes of CFSPID, so we are likely in the near future to have some actual data that can inform clinicians. The authors should acknowledge that their recommendations are likely to require review and possible revision within the next few years. | We agree it is important these recommendations are reviewed as more evidence emerges with respect to the outcome of this large population. Final sentence added. |

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID); a new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening.

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**Abstract**

**Background**

Newborn screening (NBS) for cystic fibrosis (CF) results in the recognition of a number of infants with a positive NBS result, but an inconclusive diagnosis. Varied practice exists with respect the management of these infants.

**Methods**

A Delphi consensus approach was used to determine agreement on statements generated by a Core Group of Specialists. A designation (naming) exercise was required after Round 1 and further expert opinion was sought to guide that process. After Round 2, a sensitivity analysis was undertaken to assess the impact of attrition on subsequent agreement levels.

**Results**

Infants were divided into group A (normal sweat chloride and two CFTR mutations, at least one of which has unclear phenotypic consequences) and group B (intermediate sweat chloride and one or no CFTR mutations). 32 statements were produced for Round 1 and 24 achieved consensus. After Round 1, a designation exercise was undertaken and the term “CF Screen Positive, Inconclusive Diagnosis (CFSPID)” was suggested for Round 2. Agreement was achieved for this statement and for all other statements aside from the need for routine respiratory culture, on which there was divided opinion. The Core Group advocated local practice for this issue. A sensitivity analysis demonstrated that consensus for Round 2 was achieved by change in opinion rather than attrition.

**Conclusion**

We have generated a new designation and statements to guide the management of infants with CFSPID through a robust international Delphi process. These statements will be a valuable tool for CF teams and will improve the consistency of management of these infants.

**Introduction**

Newborn screening (NBS) for cystic fibrosis (CF) is a valid public health strategy for a population with a high incidence of the condition.([1](#_ENREF_1)) There has been rapid and considerable global expansion of this strategy over the past ten years with a wide variety of protocols employed.([2](#_ENREF_2)) All programmes rely on measurement of immuno-reactive trypsinogen (IRT) from a dried blood sample taken during the first week of life.([2](#_ENREF_2)) This is a sensitive screening test for CF, but a second tier test is needed to improve the specificity of the protocol. Second tier tests vary from programme to programme, and often include DNA analysis.([3](#_ENREF_3)) The diagnosis is confirmed by clinical assessment, DNA testing and measurement of chloride concentration in sweat (the sweat test).

In some cases the sweat chloride result may be intermediate or CFTR gene changes may be recognised, the phenotypic consequences of which are unclear. Previous work by this group produced a consensus guideline for the evaluation and early management of infants with an inconclusive or equivocal diagnosis following screening.([4](#_ENREF_4)) This work provided an algorithm for the investigation of these infants with a particular focus on communication with the families.

At the same time a consensus group in the US also considered this issue and developed guidelines with similar themes to the European guidelines.([5](#_ENREF_5)) The US group proposed a term for designation of these infants, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)-related metabolic syndrome (CRMS). This designation reflects the nomenclature stream under which CF is categorised in the US and the need for a diagnostic designation to comply with US funding arrangements. The European guidelines did not propose a designation, advocating clear communication of this interim situation to the family.

Despite these two guidelines, it has become apparent through published commentaries and surveys of European programmes that diverse practice exists with respect to the management of these infants, ranging from early discharge with little information to the family to full CF care in a CF centre.([6](#_ENREF_6), [7](#_ENREF_7)) There is limited data on the long-term outcomes, but it is clear from epidemiological studies that a significant number will have minimal or no phenotypic consequence.([8](#_ENREF_8), [9](#_ENREF_9)) We also know from case reports that a small number will develop significant CFTR related airway disease that has an impact on their well-being and potentially their survival.([10](#_ENREF_10))

In view of this lack of consensus and the limited evidence base on which to guide treatment, the ECFS Neonatal Screening Working Group (NSWG) organised a further Delphi process to determine consensus on the management of these infants. This paper describes the method employed and the recommendations.

**Methods**

A core group (AM, AS, JB, KWS and SM) produced preliminary statements through a series of face-to-face meetings, teleconferences and email discussions. The level of evidence to support each statement was recorded. Once finalised by the Core Group, the statements were circulated by email to all members of two ECFS working groups (the Diagnostic Network and the Neonatal Screening Working Group). Additional invitations were made to increase multidisciplinary input. In total, 391 invitations were sent. It was determined, *a priori*, that an agreement level of 80% would constitute consensus, consistent with previous exercises by this group and work in other fields.(4, 11)

For Round 1, participants were asked to rate the statements by either agreeing or disagreeing. Participants in disagreement were asked to provide an alternative statement. Participants were encouraged to include comments, which were all assessed by the Core Group and influenced the altered statements for Round 2.

Following Round 1, the core group revised statements not achieving consensus taking into account comments and suggestions. When the meaning of a statement was changed these statements were called rewritten. Some statements that achieved consensus were modified, if the comments were felt to improve or clarify a statement. Modified and rewritten Round 2 statements were circulated to all respondents to Round 1, together with the original statements and comments.

During the consensus process it became apparent that most participants considered there was a requirement for a diagnostic label to classify infants with inconclusive diagnosis. A separate designation exercise (described more fully in the Results) was therefore undertaken to determine consensus on a diagnostic term for these infants.

After Round 2, a sensitivity analysis was undertaken to determine if the result of Round 2 was a reflection of changing opinion or rather a consequence of attrition in the number of respondents. For participants that contributed to Round 2, we reassessed their responses to Round 1 to assess the impact on agreement. This analysis was to retrospectively assess the Delphi process and had no bearing on the final statements.

**Results**

The first outcome of the Core Group discussion was the decision that two sets of statements were necessary to reflect different degrees of clinical concern for infants with a normal sweat chloride value (<30 mmol L-1) compared to infants with an intermediate sweat chloride value (30-59 mmol L-1).(12)

* Group A, normal sweat chloride value (<30 mmol L-1)
* Group B, intermediate sweat chloride value (30-59 mmol L-1)

Infants in Group A have two *CFTR* mutations, at least one of which has unclear phenotypic consequence. Infants in Group B have one or no *CFTR* mutations. Infants with two *CFTR* mutations and an intermediate sweat chloride should be referred to a CF clinic, as per previous consensus agreement.(4)

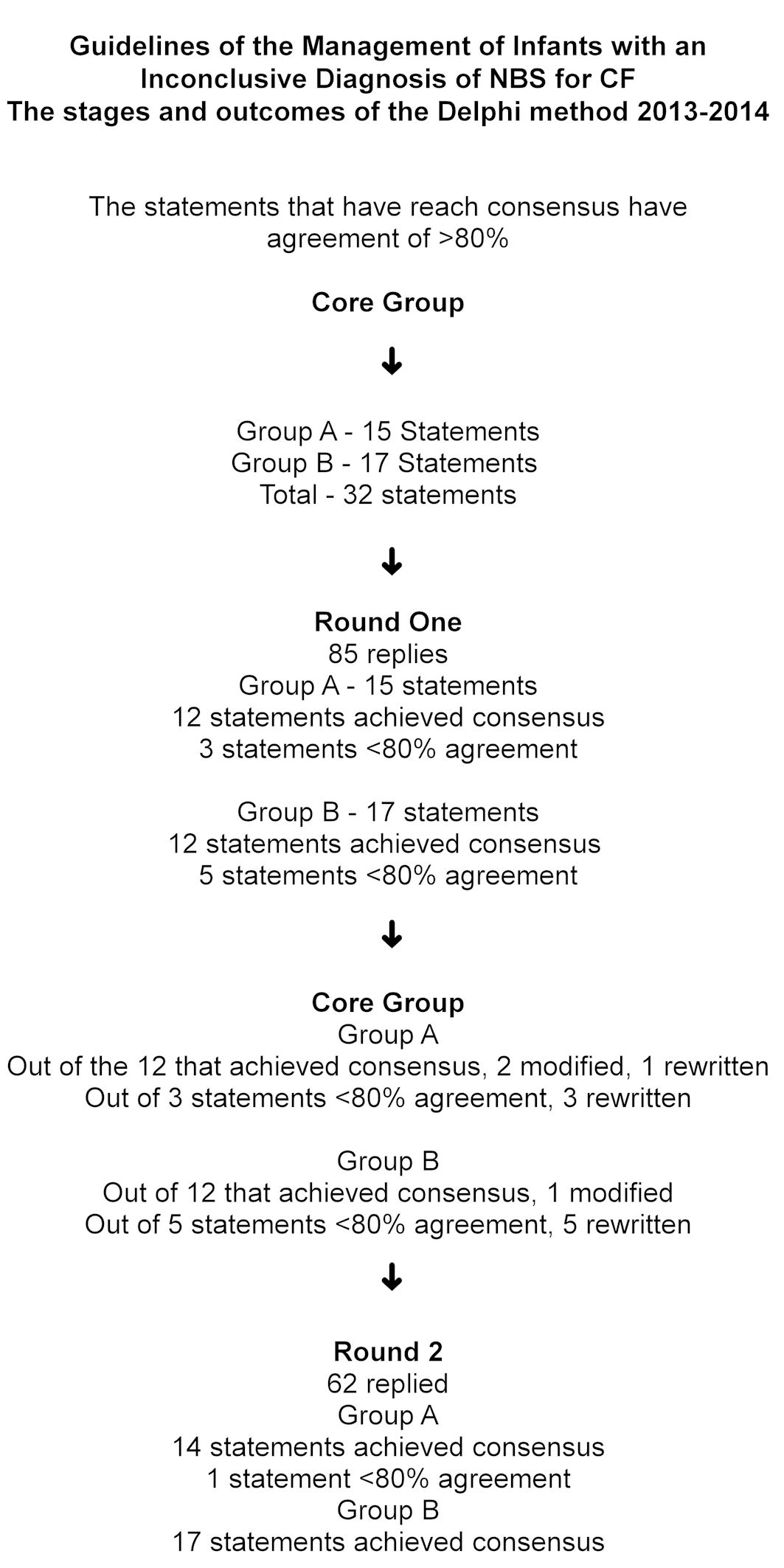
Statements for Group B were associated with more active interventions. The decision to establish this grouping was subjective, after much discussion, and not based on any current evidence that infants in Group A have a better course than infants in Group B.

*Round 1*

32 statements were generated for Round 1 (Figure 1).

Eighty-five responses from specialists in 25 countries (within and outside Europe) were received (22% response rate). Twenty-four of the 32 statements achieved a level of agreement over 80% (Figure 1).

**Figure 1**



**Designation exercise**

In Round 1, specialists were asked to consider the statement,

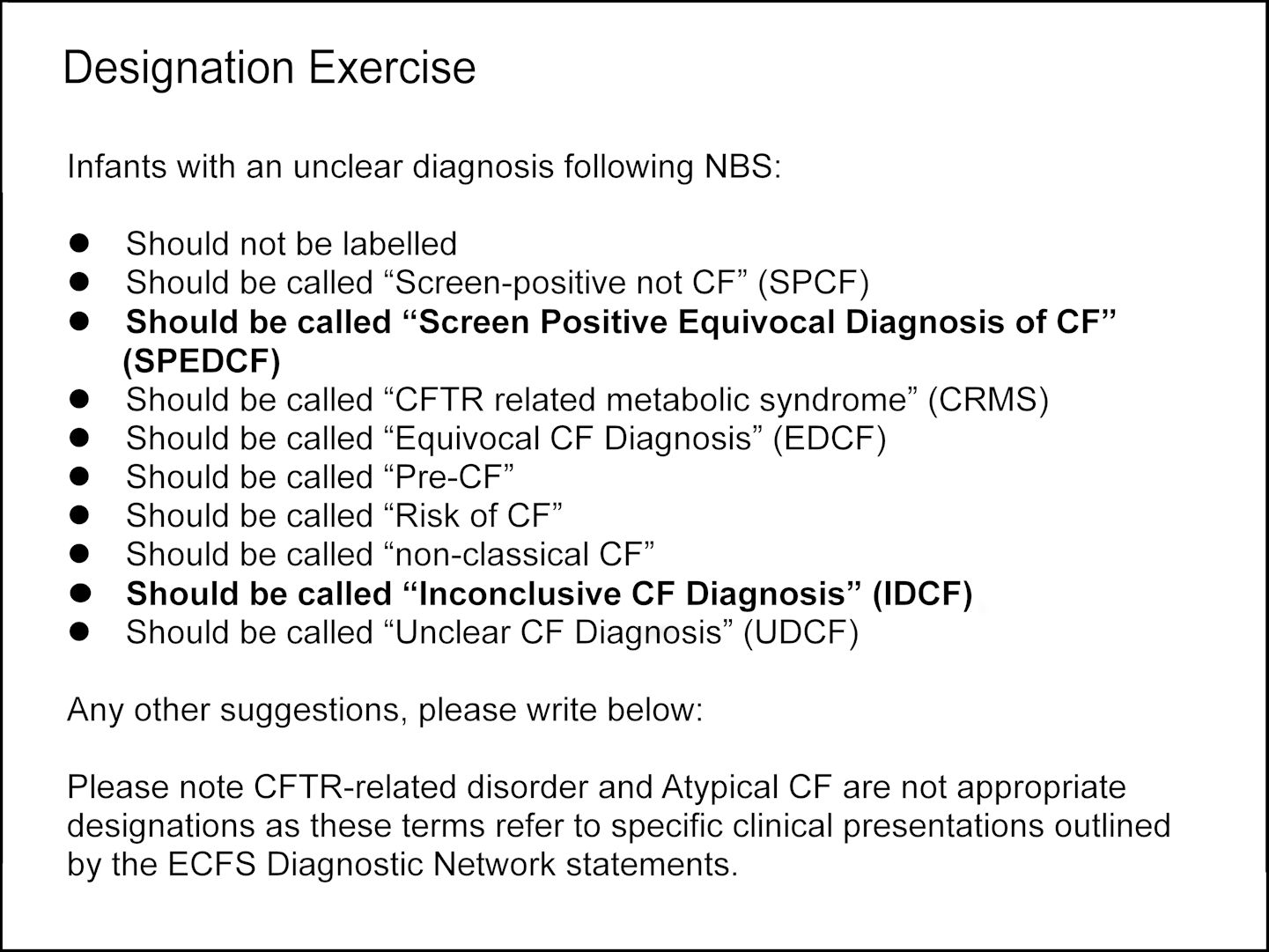
*“Physicians should avoid using terms such as CFTR-related metabolic syndrome (CRMS) to designate these infants, as this may lead to unnecessary medicalisation.”*

This achieved an 80% agreement for Group A and 76% for Group B. It was clear from the comments that the majority of respondents considered that a consistent designation for these infants would be helpful for data collection and communication with families, but did not agree with use of the term CRMS.

A list of 10 alternative designations (including “no label” option) was compiled by the Core Group from all the suggestions provided and circulated to the respondents from Round 1 as a separate Designation Exercise (Figure 2). Sixty-three replies were received to the designation exercise. Fifty-eight respondents (92%) agreed with the use of a label, and it was clear from comments that including “screen positive” was an important part of the designation.

The results of this exercise were discussed by the core group and with representatives of the ECFS Diagnostic Network Working Group (ND) and the US Quality Improvement Consortium (RP). The designation exercise identified two clear favourites with respect to designation, “*Screen Positive Equivocal Diagnosis of CF”* and “*Inconclusive CF Diagnosis”* (Figure 2). The Core Group and invited experts felt that a term that combined these statements would be ideal, as equivocal is a challenging word for some non-English speakers and it was felt important to include CF Screen Positive. The Core Group decided on the term **Cystic Fibrosis Screen Positive, Inconclusive Diagnosis** (CFSPID) and a modified statement including this designation was circulated in Round 2. In Round 2, the statements (A7 and B7) advocating this term achieved 90% agreement for Group A and 92% for Group B.

Figure 2



*Round 2*

Eight statements did not achieve consensus in Round 1 and were all rewritten (3 from group A and 5 from Group B). Twenty-four statements (12 for each group) achieved agreement (>80%) in Round 1. Three of these (2 Group A, 1 Group B) were modified to improve clarity. One statement (on designation) was rewritten, despite achieving agreement for Group A. Three modified and nine rewritten statements were presented to the participants for Round 2 (Figure 1).

Sixty-two responses were received for Round 2 (27% attrition rate). A consensus of greater than 80% was achieved on all six statements relating to Group B, and 5 of the six statements for Group A, therefore following Round 2 consensus was achieved on 31 out of 32 statements (Table 1). The statement on respiratory cultures is discussed below.

**Specific issues and comments**

**Follow up arrangements and cross infection**

The round 1 statement suggested that children should be followed up in a specialist CF clinic “unless local circumstances enable reliable long-term follow-up”. Although this statement achieved consensus for Group A, it did not for Group B. Comments revealed that participants felt strongly that the care of these infants should be led by a CF specialist physician whether or not this was in a CF clinic because of the difficulty in determining outcomes for these infants. The statement was therefore rewritten for Round 2.

A statement relating to cross-infection achieved consensus in Round 1, but was modified for Round 2, because the Core Group felt comments improved the clarity of the statement.

**The CFTR-2 website (www.cftr2.org)**

The majority of respondents felt that CFTR-2 was an important source of information but that responsibility for reviewing this website should be with clinicians, not the parents. Whilst the website may be helpful for families, respondents commented that a number of rarer mutations are not currently included in the website and the resource is only available in English. The statement was therefore rewritten to state that clinicians should regularly review the website and discuss the findings with families. This achieved consensus for both Groups A and B.

**Influenza vaccine**

The round 1 statement suggested routine annual influenza vaccination and there were varied responses to this, reflecting the lack of evidence in this area. Agreement was achieved for Group B (intermediate sweat chloride), but not Group A. Many respondents felt this recommendation excessive for children who are likely to be healthy. A rewritten statement for Group A was circulated in round 2, removing routine influenza vaccination from the recommendations for this group and this achieved agreement.

**Respiratory Cultures**

Agreement was not achieved on statement 12 for Group A. This reflects divided opinion on this matter, ranging from respondents who felt undertaking a respiratory culture was an unnecessary and distressing investigation for an infant to those who felt strongly that cultures should be obtained at every patient encounter with the CF service. It was not possible to achieve consensus regardless of the direction of the statement. We have recommended local practice should be adopted for routine respiratory culture.

**Dietary salt intake**

In Round 1, it was suggested that children in Group B (intermediate sweat chloride) should be advised not to restrict their dietary salt intake, in contrast to the usual public health advice. This was felt to be excessive, as in the absence of confirmed CF the risk of salt loss was felt to be minimal under normal circumstances. The statement was rewritten to advise non-restriction of dietary salt intake only in periods of increased sweat loss and consensus was achieved.

**Sensitivity Analysis**

Sixty two participants responded to Round 2. When the Round 1 responses of these participants were analysed retrospectively, there were some different outcomes compared to the results for all the respondents. One statement that did not reach consensus in Round 1 did when only respondents to Round 2 were considered, but 8 statements that did reach consensus in Round 1 had a level of agreement below 80%. Overall this exercise demonstrates that the consensus achieved in round 2 was a result of changing opinion as opposed to attrition with only previously positive participants responding to Round 2.

The final statements are listed in Table 1. Consensus was not achieved for statement A12 concerning respiratory cultures, and we recommend that clinics continue to use local protocols, until more evidence is available to guide practice.

**Discussion**

The management of children with an inconclusive diagnosis following NBS for CF has been extremely variable between different countries, regions and even within the same clinic. Clear guidance to CF teams on this topic is required. We hope the production of these recommendations will lead to a more consistent experience for families in this position.

The recommendations have been developed through a robust and inclusive process, adopting a Delphi approach. The consensus statements reflect a general reluctance to engage these healthy infants in unnecessary medicalisation but also anxiety that some of these infants will eventually develop significant disease. Communication and education of the families has been a consistent theme and developments in the field, such as the CFTR-2 website, have been incorporated in this process.

The use of the new term **Cystic Fibrosis Screen Positive, Inconclusive Diagnosis** (CFSPID) is aimed at aiding communication between professionals and with families. It is a descriptive term rather than a diagnostic label, as these infants do not have a disease but have a number of risk factors for developing CF related issues in the future. Two other benefits of designation are 1) providing a “diagnostic” label, which is important in some healthcare systems to activate appropriate support and 2) providing a clear classification to support reliable data entry to facilitate long term analysis of outcomes. At present, data from these infants is either inappropriately stored on CF registries or not at all.

Another key outcome of this process was the division of these infants into those with a normal sweat chloride (Group A) and those with an intermediate sweat chloride (Group B). Statements for Group B reflected a higher level of clinical concern for these infants.

Thirty two statements were produced to guide CF physicians and multi-disciplinary teams in managing these infants consistently. The nature of follow up and investigations was one of the most debated issues by participants but we have managed to attain consensus from a wide range of experts and views. It was considered important these children are managed by a clinician with experience in CF, though not necessarily in a CF clinic since they do not have CF and do not require input from the multidisciplinary team. One of the key themes in the consensus is that these children should not be “over-medicalised”. Other than a repeat sweat test at 6-12 months of age, no routine investigations are advised at diagnosis for these children.

At annual review, no routine investigations are advised. We could not achieve a consensus on the matter of routine respiratory cultures in asymptomatic children, reflecting the strength of feeling on this issue. Overall, it was agreed that investigations should be guided by clinical symptoms and signs. Clear information should be provided to both families and the primary care physician regarding recognising and acting on significant symptoms.

The importance of communication with families is highlighted throughout the guideline and participants felt very strongly that this was one of the main issues, although at the moment it was felt that accessing the CFTR-2 website should be the primary responsibility of the physician rather than the parents.

Duration of follow up has not been discussed, as this will be dependent on individual progress. Infants may move from a designation of CFSPID to CF if clinical features of CF become apparent or if the sweat test moves from an intermediate to a CF-confirmatory result. Infants with CFSPID have a positive newborn screen for cystic fibrosis representing some degree of lifetime risk for the development of CFTR-related disorder which families should be aware of.(13) Infants in Group B who have one or no mutations whose sweat test subsequently returns to normal range could be considered as having a significantly lower lifetime risk. Future work will determine more clear recommendations on length of follow-up.

Management of infants with an inconclusive diagnosis after NBS for CF is challenging. The production of these recommendations will hopefully result in a more consistent approach for families in this situation and a firmer foundation on which to assess the outlook for these infants. These recommendations will be reviewed as more evidence on the outcome of infants with CFSPID becomes available.

**Table 1**

|  |  |
| --- | --- |
| **Group A, normal sweat chloride value (<30 mmol L-1) and two *CFTR* mutations, at least one of which has unclear phenotypic consequences** | |
| **A1** | Infants should be followed up in specialist CF clinic. If they are seen in a non-CF clinic they should be reviewed by a CF physician (or a physician with an interest in CF). |
| **A2** | For infants attending a specialist CF clinic, policies should ensure that the infant is not exposed to any increased risk of cross infection. |
| **A3** | Infants should undergo a repeat sweat test aged 6-12 months. Depending on genotype, a further sweat test may be considered in the second year of life. |
| **A4** | Infants should be reviewed in clinic between 6 and 12 months of age, and thereafter annually (or more frequently, as indicated by clinical concerns or family anxieties). |
| **A5** | Annual review should clinically assess growth, weight gain and respiratory condition. Biochemical or radiological investigations should only be undertaken if clinically indicated. |
| **A6** | Families should be fully informed regarding their child’s genetic and biochemical results. They should understand that their child does not have a definitive diagnosis of cystic fibrosis and that this will be reviewed annually. |
| **A7** | Reflecting the absence of a clear diagnosis, the term “Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)” should be used to describe these infants. |
| **A8** | Clinicians should review the CFTR-2 website at the annual review for new information regarding the infant’s genotype and discuss these findings with the family. |
| **A9** | Families and the primary care physician should be given clear information as to how to contact the CF team in the following situations; failure to gain weight adequately, persistent loose stools or persistent respiratory symptoms (more than 2 weeks). |
| **A10** | Children should receive routine childhood immunizations. |
| **A11** | Children should not be exposed to cigarette smoke. |
|  |  |
| **A13** | Children and their families should be encouraged to adopt a healthy lifestyle consistent with national guidance on exercise, nutrition and other aspects of public health policy. |
| **A14** | Families should be offered a referral for genetic counselling. |
| **A15** | Details of infants in this group should be kept on an appropriate national database. |
|  |  |
| **A12** | *Did not reach consensus (79% agreement). Respiratory cultures should be taken routinely at annual review and when clinically indicated.* |

|  |  |
| --- | --- |
| **Group B, intermediate sweat chloride value (30-59 mmol L-1) and one or no *CFTR* mutations** | |
| **B1** | Infants should be followed up in specialist CF clinic. If they are seen in a non-CF clinic they should be reviewed by a CF physician (or a physician with an interest in CF). |
| **B2** | For infants attending a specialist CF clinic, policies should ensure that the infant is not exposed to any increased risk of cross infection. |
| **B3** | Infants should undergo a repeat sweat test aged 6-12 months. |
| **B4** | Clinic follow-up may be 3-monthly, or less frequently depending on clinical assessment. The frequency of follow-up appointments may lessen with time, but children should be followed up annually as a minimum standard. |
| **B5** | Annual review should clinically assess growth, weight gain and respiratory condition. Biochemical or radiological investigations should only be undertaken if clinically indicated. |
| **B6** | Families should be fully informed regarding their child’s genetic and biochemical results. They should understand that their child does not have a definitive diagnosis of cystic fibrosis and that this will be reviewed annually. |
| **B7** | Reflecting the absence of a clear diagnosis, the term “Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)” should be used to describe these infants. |
| **B8** | Clinicians should review the CFTR-2 website at the annual review for new information regarding the infant’s genotype and discuss these findings with the family. |
| **B9** | Families and the primary care physician should be given clear information as to how to contact the CF team in the following situations; failure to gain weight adequately, persistent loose stools or persistent respiratory symptoms (more than 2 weeks). |
| **B10** | Oral antibiotics should be provided when the infant has a cough (lower threshold than for the general population). The Primary care physician should be provided with clear guidance to this effect. If the cough persists for more than 2 weeks, the infant should be reviewed by the CF team, respiratory cultures taken and further investigation considered. |
| **B11** | Children should receive annual influenza vaccine in addition to all routine childhood immunisations. |
| **B12** | Children should not be exposed to cigarette smoke. |
| **B13** | Respiratory cultures should be taken routinely at annual review and when clinically indicated. |
| **B14** | Children and their families should be encouraged to adopt a healthy lifestyle consistent with national guidance on exercise, nutrition and other aspects of public health policy. |
| **B15** | Parents should be informed of the sweat test result and advised that during periods of high sweat loss\*, dietary salt intake should not be restricted. (\* hot weather, increased physical activity, fever etc.). |
| **B16** | Families should be offered a referral for genetic counselling. |
| **B17** | Details of all children in this group should be kept on an appropriate database. |

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**Legends**

**Figure 1**

An illustration of the phases of the Delphi process. The contributions at each phase are recorded. Statements that required a change in content were called rewritten. Some statements were modified (minor changes) to improve clarity, but with no change in meaning. Group A (normal sweat chloride value (<30 mmol L-1) and two *CFTR* gene mutations, at least one of which has unclear phenotypic consequence) and Group B (intermediate sweat chloride value (30-59 mmol L-1) and one or no *CFTR* mutations). Consensus was achieved if agreement was > 80%.

**Figure 2**

From the responses to Round 1, the Core Group produced these 10 options, which were circulated for the designation exercise. Respondents were asked to select their preferred option. The two most popular options were “Screen Positive Equivocal Diagnosis of CF” (33%) and “Inconclusive CF Diagnosis” (27%).

**Table 1**

The 31 statements that achieved consensus. These recommendations guide management of infants in Group A (normal sweat chloride value (<30 mmol L-1) and two *CFTR* gene mutations, at least one of which has unclear phenotypic consequence) and Group B (intermediate sweat chloride value (30-59 mmol L-1) and one or no *CFTR* mutations). One statement (A12) did not achieve satisfactory agreement.

**References**

1. Farrell PM. Is newborn screening for cystic fibrosis a basic human right? *J Cyst Fibros* 2008;7:262-5.

2. Castellani C, Southern KW, Brownlee K, Dankert Roelse J, Duff A, Farrell M, et al. European best practice guidelines for cystic fibrosis neonatal screening. *J Cyst Fibros* 2009;8:153-73.

3. Southern KW, Munck A, Pollitt R, Travert G, Zanolla L, Dankert-Roelse J, et al. A survey of newborn screening for cystic fibrosis in Europe. *J Cyst Fibros* 2007;6:57-65.

4. Mayell SJ, Munck A, Craig JV, Sermet I, Brownlee KG, Schwarz MJ, et al. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. *J Cyst Fibros* 2009;8:71-8.

5. Borowitz D, Parad RB, Sharp JK, Sabadosa KA, Robinson KA, Rock MJ, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr* 2009;155:S106-16.

6. Nelson MR, Adamski CR, Tluczek A. Clinical practices for intermediate sweat tests following abnormal cystic fibrosis newborn screens. *J Cyst Fibros* 2011;10:460-5.

7. Ren CL, Desai H, Platt M, Dixon M. Clinical outcomes in infants with cystic fibrosis transmembrane conductance regulator (CFTR) related metabolic syndrome. *Pediatr Pulmonol* 2011;46:1079-84.

8. Scotet V, Audrezet MP, Roussey M, Rault G, Dirou-Prigent A, Journel H, et al. Immunoreactive trypsin/DNA newborn screening for cystic fibrosis: should the R117H variant be included in CFTR mutation panels? *Pediatrics* 2006;118:e1523-9.

9. Thauvin-Robinet C, Munck A, Huet F, Genin E, Bellis G, Gautier E, et al. The very low penetrance of cystic fibrosis for the R117H mutation: a reappraisal for genetic counselling and newborn screening. *J Med Genet* 2009;46(11):752-8.

10. Peckham D, Conway SP, Morton A, Jones A, Webb K. Delayed diagnosis of cystic fibrosis associated with R117H on a background of 7T polythymidine tract at intron 8. *J Cyst Fibros* 2006;5:63-5.

11. Harold A. The Delphi Method, Techniques and applications. New Jersey Institute of Technology: Linstone & Murray Turoff; 2002

12. Goubau C, Wilschanski M, Skalická V, Lebecque P, Southern KW, Sermet I et al. [Phenotypic characterisation of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis.](http://www.ncbi.nlm.nih.gov/pubmed/19318346) *Thorax*. 2009 Aug;64(8):683-91

13. Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E et al. [Recommendations for the classification of diseases as CFTR-related disorders.](http://www.ncbi.nlm.nih.gov/pubmed/21658649) *J Cyst Fibros*. 2011 Jun;10 Suppl 2:S86-102.

**Highlights**

* Some infants have an inconclusive diagnosis of CF following newborn screening
* A Delphi consensus was undertaken to guide the management of these infants
* These infants should be called “CF Screen Positive, Inconclusive Diagnosis (CFSPID)”
* Overall, the recommendations suggest limited intervention, but careful monitoring
* Interventions for infants with an intermediate sweat chloride were more pro-active.