ECFS Neonatal Screening Working Group (NSWG)

Report for the Board, May 2020

In June 2019, the coordination for the ECFS NSWG was handed over from Prof Kevin Southern to Prof Jürg Barben at the European CF Conference in Liverpool. Since then, the NSWG committee has had two telephone conferences in 2019 and one face-to-face meeting at the NACFC in Nashville in October 2019. In addition, a "Core Group Working Meeting" has taken place in Paris in January 2020 (Anne Munck, Kevin Southern, Carlo Castellani, Jürg Barben), followed by two video conferences, as face-to-face meeting were not possible since the outbreak of the Covid-19 epidemic in March 2020.

The focus of the current work is

- To set up key outcomes for CF newborn screening (NBS) programmes
- To define the follow-up and monitoring of Children with CFSPID
- To summarize the current knowledge and challenges about NBS for CF in different review articles by members of the ECFS NSWG

Original aims of the Working Group

1. To support the implementation of newborn screening (NBS) for CF
2. To monitor performance and compare protocols to optimise effectiveness, whilst reducing negative impact
3. To encourage enrolment of all infants identified through NBS in clinical trials
4. To determine the optimal management of infants with an inconclusive diagnosis following newborn screening
5. Improving the processing of positive newborn screening results

The focus of work stream 5 will be on communication, establishing best practice for the different protocols that exist and disseminating this good practice. The work stream will also examine mechanisms for processing results, information for parent/carers and factors that impact on timeliness.

Additional objectives for the NSWG from 2018 onwards

To determine key outcome measures to evaluate the performance of CF NBS

6. To establish guidance and quality ranking on the collection of NBS outcome data
7. To assess knowledge of CFSPID in Europe
8. To provide resources to improve the evaluation and management of infants with CFSPID
9. To work with the ECFS Registry group to clarify definition and recording of CFSPID outcomes

Broader objectives

1. To continue to work in an open and inclusive manner
2. To encourage membership of the ECFS
3. To encourage participation from countries outside the EU

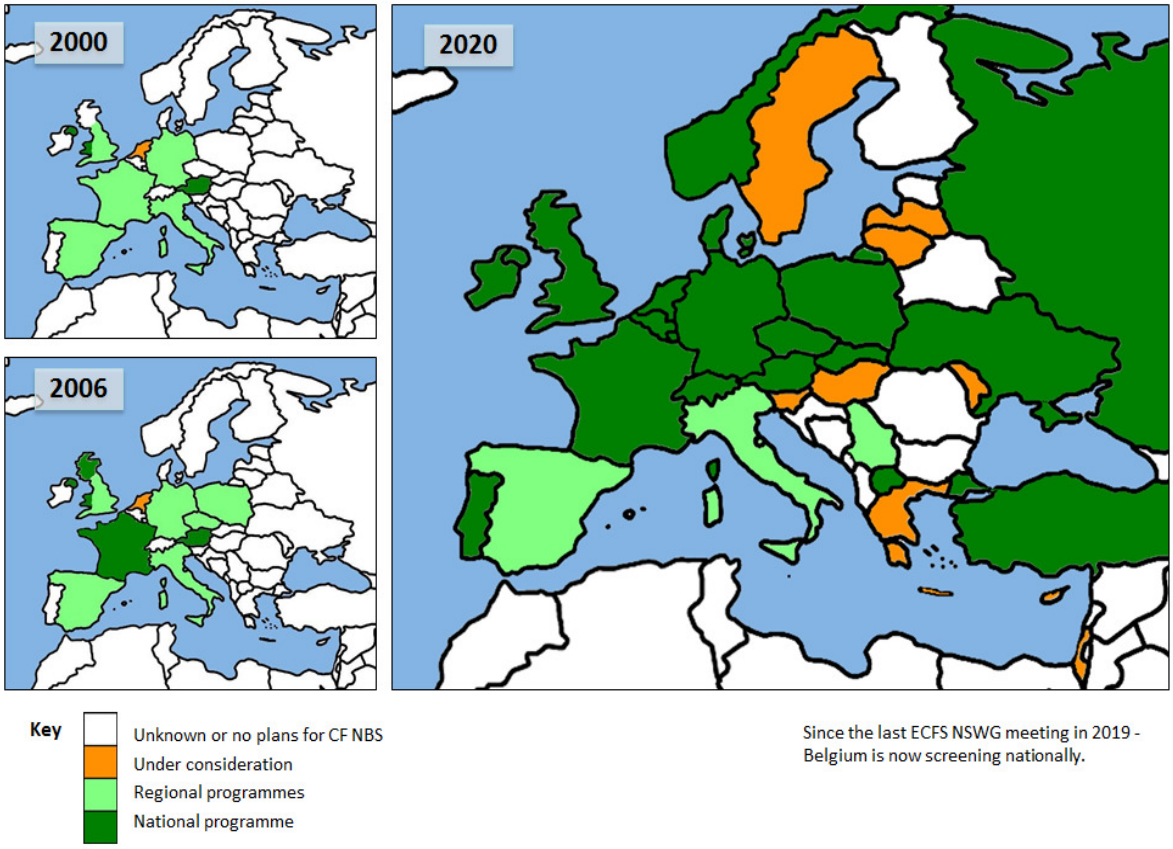
Summary of completed aims and objectives to date:

1. *To support the implementation of NBS for CF*.

This is the primary aim of the NSWG and is being addressed by the following:

a) We are continuing to improve on our information network through the NSWG database. We have now over 50 **key workers** in 45 countries.

Figure 1: CF Newborn Screening programmes across Europe from 2000 until 2020 (April)



b) Support at international and national meetings.

Meetings since June 2019 have included:

- ECFS NSWG Annual meeting, Liverpool, UK, June 2019
- NSWG Core Group meeting at the NACFC, Nashville, USA, October 2019
- DNWG meeting in Utrecht, February 2020 (KS)
- Core Group working meeting in Paris 2020 (AM, KS, CC, JB)
- Tele and video conferences every 2 months (last in May 2020) of the Core Committee to discuss the management of projects and future directions

2. To monitor performance and compare protocols

We have addressed this specific aim through the following strategies since 2018. Since 2019, a core group (Anne Munck, Kevin Southern, Carlo Castellani and Jürg Barben) have been working on a project on how to measure the top key outcomes of CF NBS in Europe and the quality of the data collected in each country. A final draft of the main eight key outcomes has now been finalised and includes among others the following points:

Number of births /years; number of infants screened/year; number of infants with positive IRT or IRT/PAP /year; number of infants with inadequate dried blood sampling/year; number of infants referred for diagnosis assessment (sweat testing); number of infants NBS+ with a CF diagnosis/year; number of infants NBS+ with a CRMS/CFSPID diagnosis/year; number of infants who did not completed the NBS algorithm/year; number of cases diagnosed CF based on symptoms, family history and with and without MI, born in the previous year; number of infants diagnosed CF during these years (True+ and False-); mean age (median, min and max) in days, when family is first assessed by a CF specialist team (may be before age at sweat test).

It is planned to use they key outcome measures for future surveys. Kevin, Jürg and Anne plan to organise another survey this year, which is now delayed by the current Covid-19 epidemic.

3. To encourage enrolment of all infants identified in clinical trials

This aim is being addressed by the following activities (ongoing from last year):

a. Establishing close links with emerging Registries (liaison person: Lutz Naehrlich, in future: Andreas Jung). Provide database information for the purpose of encouraging recruitment to clinical trials, working closely with the ECFS Clinical Trials Network.

b. CF START – A UK trial to examine routine use of anti-staphylococcal antibiotic prophylaxis (£1.4 million HTA award). This trial lead by Kevin Southern will utilise NBS and the UK registry in an innovative manner, setting the template for future comparative effectiveness studies (see http://www.cfstart.org.uk/).

c. Dorota Sands, as member of the ECFS Clinical Trials Network, keeps the NSWG aware if any trials coming up and we can email out information to the NSWG without delay. It was also noted that one of the NSWG objectives is to enrolled newly diagnosed children onto trials but there are currently no trials to enrol onto.

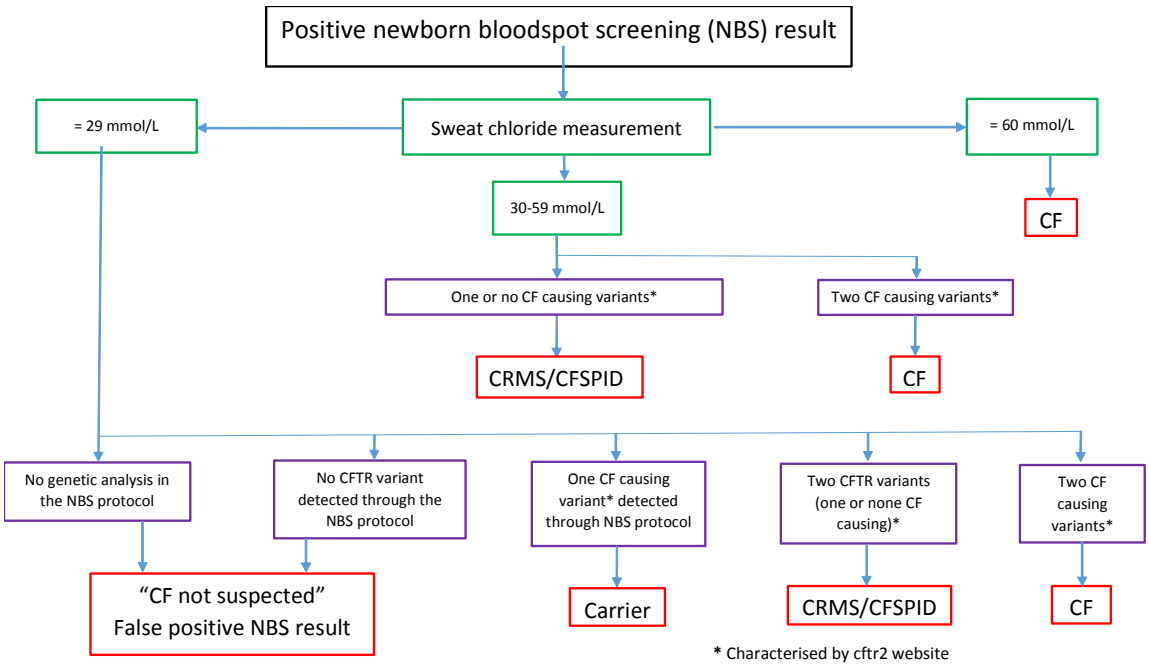
4. To determine the optimal management of infants with an inconclusive diagnosis following newborn screening

Last year, Silvia Gartner and the Core Committee have put together a web survey with the assistance of Jared Murphy (University of Liverpool at Alder Hey) to gather information on the understanding of CFSPID across Europe's respiratory and CF specialist clinicians as it would be useful to see the understanding of CFSPID and see what knowledge is out there already. This has been presented at the last ECFC in Liverpool. Silvia Gartner is in the process of summarizing and publishing this data.

Quickly following on from this, a combined European and American collaboration, headed by Kevin Southern, has clarified and harmonised the international definition of inconclusive diagnosis after

NBS. This work was finally published in the *Journal of Cystic Fibrosis* with the title «Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clarification of the harmonised international definition» (J of Cystic Fibros 2019;18:778–780):

Figure 2: *Outcomes after NBS for CF*



5. *To summarize the current knowledge in review article in cooperation with the International Journal of Newborn Screening*

Last year we were asked as a group to write and publish a series of review articles on NBS for CF in collaboration with the *International Journal of Newborn Screening* (IJNS). After consultation with the *Journal of Cystic Fibrosis*, who assured us that such a series of review articles would not fit into the current publication programme of the Journal, we started to collaborate with the IJNS and were able to attract well-known authors for this project (most members of the ECFS NSWG). Meanwhile eight articles have already been completed and published, another three are still pending. As a conclusion, the publication of a book is planned, which should have been presented at the annual NSWG Meeting at the ECFC in Lyon, but which will not take place because of the Covid-19 epidemic.

The following topics are covered in these review articles:

- History of NBS for CF by *Georges Travert, Mary and Anthony Heeley (France)*
- The changing face of CF and the implications for screening by *Lutz Naehrlich (University of Giessen, Germany)*
- Monitoring and recording the performance of NBS for CF by *Dianne Webster & Natasha Heather (Auckland, NZ)*
- NBS for CF across the globe by *Philip M. Farrell (Wisconsin,* USA)
- A bio-ethical framework for NBS for CF by *Kevin Southern, Rachel Armstrong, Lucy Frith (Liverpool, UK)*

- Issues around measuring immuno-reactive trypsinogen (IRT) by *Ralph Fingerhut (Zürich, Switzerland)*
- The role of pancreatitis associated protein (PAP) in NBS for CF by *Olaf Sommerburg (Heidelberg, Germany)*
- The role of extended DNA analysis in NBS for CF by *Emmanuelle Girodon & Anne Bergougnoux (Paris, Montpellier, France)*
- Inconclusive diagnosis after newborn screening for CF by *Anne Munck (Paris, France)*
- Processing NBS results for CF by *Jürg Barben (St. Gallen, Switzerland)*
- Psychological impact of NBS for CF by *Jane Chudleigh (London, UK)*

Objectives still require to be achieved:

- The NSWG has provided a forum for quality improvement and the next five years will be critical in expanding these exercises across Europe.
- The experience of the NSWG is vast and this has been used in an inclusive manner to set the agenda for the objectives of the NSWG over the next five years.
- For our next European survey collecting international outcome data, we will use the developed key outcomes. This will enable us to collect international data in a more valid manner and produce a stronger evidence base for recommendations.
- Once established we may move to a quality ranking system, with guidance for all countries on the "best practice" with respect to data collection.
- Once we have established the requirements for QI, to develop and distribute resources to improve the evaluation and management of these infants.
- Implementation of a NBS for CF for all countries within Europe.

These sizeable projects will be undertaken in addition to all the standard activities of the Group

- Encouraging implementation of NBS
- Assessing performance
- Facilitating access to clinical trials
- Improving the processing of positive NBS results

Ongoing work

A quality exercise to compare outcome measures of CF NBS in Europe with a quality of data scoring system - this will be done via a questionnaire to each country screening in Europe. We will establish a core set of outcomes required to determine the performance of NBS for CF. We will also establish guidance on the standards expected for the collection of these data.

An important part of future work will be to better characterize the follow-up and monitoring of children with CFSPID and to publish recommendations of the NSWG in this regard.

In this context the question of a CFSPID registry also arises, which has to be clarified in cooperation with the Registry Group. In particular, there is a need to characterise the outcomes in children with CFSPID.

To organise the above activities, two separate sub-groups have been established:

1) Establishing core outcome set and standards for data collection
   Leads; Dr Anne Munck, Prof Jürg Barben, Professor Kevin Southern
2) Evaluating training needs for CFSPID
   Leads; Dr Silvia Gartner, Prof Kevin Southern, Dr Carlo Castellani

In addition, the NSWG will continue core activities of supporting developing programmes, organising meetings and producing newsletters.

On an annual basis, we will continue to organise the following meetings:

- At the NACFC – satellite meeting for core committee members of the NSWG
- Teleconference meetings (bi-annual) – core committee members
- ECFS NSWG Annual Meetings at the ECFS Conference (100 + participants)
- Contribute to the ECFS DNWG annual meeting

New members of the Core committee have been appointed and we are open to further applications.

Jürg Barben, May 2020

Addendum: Group photo of the NSWG at the ECFC in Liverpool, June 2019