

ECFS Exercise Working Group

Report for the ECFS meeting in Lisbon 2013

Activities of the Exercise Working Group and achieved milestones 6/2012- 5/2013:

- 1) A 5-hour meeting of the group took place at the 35th ECFS conference in Dublin/Ireland on June 6, 2012 with 22 attendees from around the world. During that meeting, the group consented on some controversial issues around contraindications of an exercise test, reasons to stop a test and measurements taken during an exercise test. Furthermore, the group discussed the next steps in preparing the documents on physical activity assessment and exercise counselling.
- 2) Between June 2012 and October 2012, the document on exercise testing was circulated three more times with fine-tuning of the wording of the recommendations.
- 3) Prior to the North American CF conference in Orlando/Florida, a semi-final version of the Clinical Practice Guideline on Exercise Testing in CF was submitted to the ECFS board.
- 4) At the North American CF conference in Orlando/Florida a 2-hour meeting was held with 14 Participants and the Clinical Practice Guideline on Exercise Testing in CF was approved by all attending experts. Subsequently, further experts agreed to the document via email.
- 5) After feedback from the ECFS President Stuart Elborn on the Clinical Practice Guideline on Exercise Testing in CF was received, the authors of the Clinical Practice Guideline on Exercise Testing in CF had intense and continuing discussions on the next steps. These will be continued at the Lisbon meeting (see 7) below).
- 6) The group in Belfast headed by Judy Bradley (and with significant contributions from Lisa Kent and Brenda O'Neill) along with the group in Utrecht headed by Erik Hulzebos have to date summarised the physical activity assessment methodology in CF and have prepared a first draft of the Position Stand on Physical Activity Assessment in CF.
- 7) A 5-hour meeting of the ECFS Working Group with 23 expected participants will take place in conjunction with the ECFS annual meeting in Lisbon on June 12, 2013. At that meeting, the progress in all projects of the Exercise group will be presented and discussed.



ECFS – Diagnostic Network Working Group (DNWG) Annual report, May 2013

Aims:

The European CF Society Diagnostic Network Working Group (ECFS DNWG) was set up 10 years ago to evaluate new diagnostic techniques and to standardize procedures throughout Europe. The goal of this Network is to achieve pan-European cooperation on the definitions of disease, standardization of electrophysiological and genetic techniques and the exchange of information, difficult cases and the development of new diagnostic technologies. The goals of the ECFS DNWG are also closely related to application of the diagnostic techniques for drug development and clinical trials in CF, in cooperation with the ECFS Clinical Trials Network.

Meetings & Membership:

The ECFS DNWG meets at least twice a year usually at the ECFS conference and at a separate weekend during the year. All members of the ECFS with an interest in diagnostic topics in CF are welcome to participate in the work of ECFS DNWG. The DNWG has presently 65 members from 18 countries.

News and Activities:

Projects

A variety of DNWG projects from different areas of CF diagnosis and CFTR Biomarker are ongoing and under development:

- *DNWG CF Diagnosis Registry project (K. De Boeck):*
Aim: To unambiguously define the population characteristics for inclusion and/or analysis in CF registries, especially when registry data are used for ‘benchmarking’ of centers or countries. Workpackage 1: Determine the scope of the problem: who is reported in national CF registries?
- *ECFS ICM SOP diagnostic validation (N. Derichs)*
- *ECFS NPD SOP diagnostic validation (I. Sermet)*
- *Implementation of CFTR biomarker into clinical trials (in collaboration with ECFS CTN)*
- *CFTR3: New European database on rare CFTR mutations (N. Derichs)*
- *Diagnostic Webforum (I. Bronsveld)*
- *Update of CF Diagnostic Guideline/Algorithm (planned)*

Publications

De Boeck K, Kent L, Davies J, Derichs N, Amaral M, Rowe S, Middleton P, de Jonge H, Bronsveld I, Wilschanski M, Melotti P, Danner-Boucher I, Boerner S, Fajac I, Southern K, de Nooijer R, Bot A, de Rijke Y, de Wachter E, Leal T, Vermeulen F, J Hug M, Rault G, Nguyen-Khoa T, Barreto C, Proesmans M, Sermet-Gaudelus I; On behalf of the European Cystic Fibrosis Society Clinical Trial Network Standardisation Committee. CFTR biomarkers: time for promotion to surrogate endpoint? *Eur Respir J.* 2013 Jan;41(1):203-16.

De Boeck K, Derichs N, Fajac I, de Jonge HR, Bronsveld I, Sermet I, Vermeulen F, Sheppard DN, Cuppens H, Hug M, Melotti P, Middleton PG, Wilschanski M. ECFS Diagnostic Network Working Group. New clinical diagnostic procedures for cystic fibrosis in Europe. *J Cyst Fibros* 2011; 10 Suppl 2:S53-66.

Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, Sermet I, Schwarz M, Tzetis M, Wilschanski M, Bareil C, Bilton D, Castellani C, Cuppens H, Cutting GR, Drevinek P, Farrell P, Elborn JS, Jarvi K, Kerem B, Kerem E, Knowles M, Macek M Jr, Munck A, Radojkovic D, Seia M, Sheppard DN, Southern KW, Stuhmann M, Tullis E, Zielenski J, Pignatti PF, Ferec C. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros* 2011; 10 Suppl 2:S86-S102.

Meetings

During the last 12 months, we had 3 meetings to discuss work progress and present results to interested participants:

- Meeting at ECFC 2012 in Dublin
- Business meeting at NACFC 2012 in Orlando
- The Annual meeting of the Diagnostic Network took place in Jerusalem, Israel on 14-15 February 2013 hosted by Michael Wilschanski and was attended by 43 participants. The detailed meeting report is attached and available on the website.

Website

The DNWG website (http://www.ecfs.eu/ecfs_dnwg), located within the ECFS website, has been updated and advertised at different conferences and in communication with partners. Regular news, meeting programs, publications and contact details are communicated.

Networking

- New countries, new members
- Call for CF diagnostic cases at ECFC DNWG meeting (Dublin, Lisbon): Regular involvement of new local CF caregivers to DNWG

Young Investigators

We are actively promoting the involvement of Young Investigators to the DNWG group activities and presentations at meetings. For the Jerusalem meeting, we had presentations of 5 Young Investigators from Poland, Israel, Italy, Germany and The Netherlands.

New coordinator of DNWG

Since 2013, Nico Derichs (Berlin, Germany) is the new coordinator of the DNWG. The group thanked Michael Wilschanski (Jerusalem, Israel) for his successful leadership over the last years.

Perspectives:

Next meetings

- ECFC in Lisbon, Friday 14 June, 12:30 to 14:30, open to all participants at ECFC (Program at http://www.ecfs.eu/ecfs_dnwg).
- Business meeting at NACFC 2013 in Salt Lake City
- The next ECFS-DNWG Annual meeting will be held 13-15 February 2014 in Berlin (hosted by Nico Derichs).

Nico Derichs, Coordinator
28 May 2013

ECFS Gene Modifier Working Group

Major aim of the working group: To amalgamate EU-wide clinical and DNA data to identify genetic variants involved in CF disease severity.

The ECFS working group supports the emerging European Consortium to meet and to gather preliminary data for applying for a substantial European research grant.

Results obtained in 2012/2013

- **France:** the French project has been underway since 2007 with more than 4,100 French CF patients recruited (clinical data and DNA collected). A collaborative work with the North-American CF modifier genes consortium has been published last year in *Nature Genetics* (Sun et al., 2012) that provided evidence of association between meconium ileus and multiple genes encoding constituents apical plasma membrane where CFTR resides. The French grants are from the Agence Nationale de la Recherche (ANR), and the French CF Foundation "Vaincre la Mucoviscidose".

- **Italy:** in 2011, the Italians obtained a grant from the Italian CF Foundation "Fondazione per la Ricerca sulla Fibrosi Cistica". The inclusions started in the last trimester of 2012 and are on their way. The clinical data collected are similar to that of the French program, to easily combine them for further joined analyses.

- **UK:** a grant has been submitted to the Wellcome Trust (results expected in June 2013): the main goal of the project was to prospectively include neonatally CF-screened babies, to create a longitudinal cohort of up to 2000 CF children from five European countries.

- **Ireland:** In 2011-12, the Irish have included ~150 CF patients (clinical data and DNA collected). Irish local grants.

Meetings

- In December 2010: first meeting in Paris

- In 2011: meetings during the ECFS Basic Science Conference, the ECFS Conference Hamburg, and the NACFC.

- In 2012: meetings during the ECFS Basic Science Conference, and the ECFS Conference Dublin. In April 2012, 2 days of face to face meeting in Paris with the North-American consortium.

- In 2013: meetings during the ECFS Basic Science Conference, and the ECFS Conference Lisbon.

Next action that should be discussed within the group and paralleled with the issue of the Wellcome Trust application: applying for a European research grant to further support the scientific project.

Harriet Corvol, Coordinator

Neonatal Screening Working Group (NSWG)

Board Report (April 2013)

It has been an exciting year for the NSWG after ratification as an official ECFS Working Group in September 2012. Since September the WG has had administrative support (temporary contract with the University of Liverpool for 3 years). This has provided great impetus to the group and has enabled the WG to address the specific aims listed below.

Group members

We now have over 350 members on the NSWG database. Members come from a number of backgrounds, including numerous physicians from across the globe. The group has been widely advertised through the WG newsletters and we have been actively seeking relevant CF NBS key contacts from around Europe and beyond. Membership is broad and includes scientists from screening laboratories that run newborn screening programmes. Two of the wider objectives of the WG are to encourage all members to join the ECFS and to broaden membership to professionals from outside of Europe, in particular countries from South America. We have already have contact with Uruguay but are now trying to make contact with Chile and Brazil.

Core Committee

The WG is co-ordinated by a Core Committee of volunteers

- Kevin Southern (Co-ordinator)
- Olaf Sommerburg (Germany)
- Juerg Barben (Switzerland)
- Jeannette Dankert-Roelse (Netherlands)
- Anne Munck (France)
- Sarah Mayell (UK)
- Carlo Castellani (Italy)
- Silvia Gartner (Spain)
- Barry Linnane (Eire)
- Dorota Sands (Poland)

Specific Aims of 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 equivocal diagnosis following newborn screening

Broader objectives

1. To work in an open and inclusive manner
2. To encourage membership of the ECFS
3. To encourage participation from countries outside the EU
4. To explore commercial use of information gathered by the WG (we will seek guidance from the ECFS on this)

Progress report for each specific aim

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

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

- A. We have now established a regular newsletter to discuss NBS and report on progress in specific countries. So far this has included Switzerland, Spain, Austria, Ireland, Norway, the Netherlands and France (newsletters attached). The next newsletter will include reports from Poland and Russia.
- B. Support at international and national meetings. Meetings within the past year have included;
 - i. Orlando, USA. Representation at US SIG meeting (10/10/12) – KS has reported on this within the second newsletter
 - ii. Budapest, Hungary. Presentation at the ISNS (5/11/12)
 - iii. Jerusalem, Israel, workshop at the DN meeting (14/2/13)
 - iv. Belek, Turkey, presentations at Turkish Respiratory Meeting (2-5/4/13)
 - v. Verona (ECFS Standards meeting), (12-13/4/13)

Future meetings;

- i. ECFS NSWG Annual Meeting, Lisbon, Portugal. A satellite meeting at ECFC (12/6/13)
- C. We are establishing an information network through the database. We now have 37 key country contacts, with the database now holding over 350 members which is constantly growing and being updated
- D. We have identified key workers in most countries without NBS and aim to maintain a separate database of progress in those countries (updated every 3 months)
- E. We have improved the information available on the NSWG webpage on the ECFS website, including a repository for newsletters
- F. We aim to produce a pack for countries with emerging programmes with all the necessary information (both hard copy and virtual)

2. To monitor performance and compare protocols

We will address this specific aim through the following strategies

- A. The database is constantly in use as a functional tool to interact with WG members
- B. Key workers in each country with NBS have been identified. We are now in the process of developing and maintaining a separate database of performance, updated annually.
- C. Three questionnaires were developed with support from the Core Committee. Form A is a survey of countries without NBS, collecting data on plans and obstacles to NBS. Forms B & C are to collect data from countries and regions that are currently screening.
- D. The forms were distributed in February 2013. Supplementary forms have been sent out to further contacts in March and April. Forms were also sent to the US and Canada, with support from the CFF.
- E. Forms have been returned from 45 contacts
 - 1. 16 from countries without NBS
 - 2. 15 from countries with national programmes
 - 3. 14 from countries with regional programmes
 - 4. At least 10 more forms expected from regions and countries with CF NBS
- F. Preliminary results will be presented at the NSWG meeting in Lisbon.

- G. Standards of Care for NBS have been developed. These were produced by a Delphi consensus methodology and reflect the comments of all members of the Core Committee. These standards were ratified in the Verona meeting (13/4/13) and are attached.

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

This specific aim is being addressed by the following

- A. Establish close links with emerging registries. Provide database information for the purpose of encouraging recruitment to clinical trials, working closely with the ECFS Clinical Trials Network.
- B. Lobbying organisations to highlight the issue of clinical trials in CF, in particular on the large number of infants recognised through NBS
- C. To support the design and implementation of pragmatic clinical trials. A proposal has been submitted to the UK HTA (funding agency) for a large pragmatic trial examining anti-staphylococcal antibiotic prophylaxis (CF-START)

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

This aim is being addressed by the following

- A. The survey of current practice in established NBS programmes (covered by the 2013 Survey and including US sites via the SIG), audited by the standards published in 2009
- B. We will present the preliminary findings in Lisbon
- C. Core statements are being produced to initiate a Delphi consensus process to establish clear guidance on the management of these infants (Shawcross, Southern and Mayell).
- D. We are working with the CFF Special Interest Group (NBS) to form a global consensus on terminology and management of these infants. Dr Parad has been invited to speak in Lisbon and will be a key contributor to this Delphi methodology and we will be reporting the initial results of our consensus project in Salt Lake City.
- E. A statement on equivocal diagnosis is included in the ECFS Standards of Care document (attached).

Challenges achieved

1. An information network for members of the NSWG has been achieved
2. In countries without NBS, we have identified a key worker
3. In countries with NBS, we have identified a key worker
4. Populating the WG webpage with up-to-date information
5. Regular WG newsletter

Challenges on-going

1. In countries without NBS, monitor progress (3 monthly to record plans for implementation)
2. In countries with NBS, supply annual progress reports for a database
3. To record the protocol undertaken in each country (2013 Survey)
4. To record performance as determined by population screened and results (information being gathered by the 2013 Survey), including
 - a. Number of infants diagnosed with CF through NBS
 - b. Number of infants with an equivocal diagnosis following NBS
 - c. Number of assessments/sweat tests (and results when available)
 - d. Number of false negative NBS tests (true, meconium ileus or equivocal)
 - e. Incidence of CF

5. Key workers will be encouraged to join the ECFS and become members of the Core Group
6. To liaise with national and European Registry Groups to collect longer term outcome data (some crossover with the Diagnostic Network on this project)
7. To survey practice with respect to management of infants with an equivocal diagnosis (consensus process)
8. To develop and maintain resources to support implementation
9. To support a further consensus project to achieve Specific Aim 4

ECFS Non Tuberculosis Mycobacteria Working Group Report May 2013

The working party has three main aims:

- a. Develop NTM management guidelines.
- b. Develop NTM-specific fields for the ECFS patient registry.
- c. Facilitate in the development of a greater evidence base for the management of NTM infection in CF.

a) Development of Management Guidelines

Following discussions between Stuart Elborn and Bruce Marshall, it was agreed to develop joint ECFS / NACFF Management Guidelines. The guidelines committee is co-chaired by Charles Haworth (Papworth Hospital, Cambridge, UK) and Andres Floto (Cambridge University, Cambridge, UK). The working party is split into five sub groups which are outlined below:

- Epidemiology and Risk Factors
- Screening
- Microbiology
- Treatment
- Transplantation

Experts from Europe and North America (Ken Olivier, Kevin Winthrop, Isabelle Sermet, Jerry Nick, Ron Gibson, Karsten Kotz, Jean-Louis Herrmann, Richard Wallace, Jakko Van Ingen, Andres Floto, Charles Daley, Lisa Saiman, Alan Smyth, Charles Haworth, Diana Bilton, Peadar Noone and Paul Corris) are collaborating on the project.

The guidelines group has participated in numerous email exchanges, conference calls and two face-to-face meetings (San Francisco May 2012 + Orlando October 2012) to develop the consensus statements and this process will be complete at the end of this calendar year.

b) NTM Specific Registry Fields for the ECFS database

We have developed NTM specific registry fields in collaboration with Hanne Olesen and hope to incorporate them into the ECFS Registry (and possibly some national registries). This would enable:

- a) The collection of novel information about the epidemiology of NTM infection in CF.
- b) The evaluation of outcomes following implementation of the new clinical management guidelines (compared to historical data sets).
- c) Identification of NTM-infected patients that may be willing to participate in clinical trials of novel therapeutic agents

We are collaborating with Laura Viviani to interrogate the current ECFS registry data set on NTM - we reviewed the initial analysis earlier this year and have requested a multivariate analysis to identify potential risk factors for NTM disease.

c) Development of evidence base for the management of NTM infection in CF Clinical Trials

The CFF are funding a research programme in Denver to evaluate the treatment algorithms developed during the ECFS / CFF NTM guidelines process.

Charles Haworth

Andres Floto