Steering Group meeting
8 June 2018, Belgrade
Minutes

1. **Overview ECFSPR activities January-June 2018** (Lutz Naehrlich)
   a) Coverage and Participation:
   The number of countries participating in ECFSPR has increased to 36, the number of patients increased to over 44,719. The database contains longitudinal data from 2008 to 2016.
   - The following countries have joined ECFSPR between January and June:
     Armenia, Croatia, Cyprus and Poland
     - Yerevan State Medical University University “Muratsan Hospital", CF centre, Yerevan, Armenia;
     - University Hospital Centre Zagreb, paediatric CF centre and adult CF centre, Zagreb, Croatia;
     - Dziekanow Paediatric Hospital, CF centre, Warsaw, Poland.
   - The following centres joined:
     - University Hospital St. Marina-Varna, Second Paediatric Clinic, CF centre, Varna, Bulgaria;
     - Medical School, University of Cyprus, paediatric and adult CF centre, Nicosia, Cyprus;
     - Hospital of Lithuanian University of Health Sciences centre, Paediatric department, CF centre, Kaunas (LT);
     - Clinical Emergency Hospital for Children, CF centre, Brasov, Romania;
     - Mother and Child Health institute, CF centre, Bucharest, Romania;
     - National CF centre, Timisoara, Romania.
   - Countries in the pipeline: Estonia, Finland and Iceland.

   b) Business Plan:
   A Business Plan 2018 - 2020 has been drafted to outline ECFSPR’s strategic direction. It has been approved by the ECFS Board. The document will be distributed to the Steering Group members for review. Once the Business Plan has been approved and potentially edited, it will be published on the ECFSPR website.

   c) Annual Report:
   - The Annual Report 2016 has been published 18 months following the close of the 2016 calendar year. For the first time we have reached the primary objective, defined in the Business Plan, to publish the report within this timeline. It is a great achievement thanks to the hard work of all parties involved. A big congratulations and thank you to all the participating centres and national registries!
   - The Annual Report 2017:
     - Publication of the report is planned for beginning of June 2019, at the ECFS conference.
     - We will work on updating the structure and design of the report. A working group of 3-4 people from Steering Group members will be established and will meet in the autumn of this year. If you are interested please contact ecfs-pr@uzleuven.be.

   d) Scientific Committee:
   - The term of Abi Jackson (IE) and Nataliya Kashirskaya (RU) has ended. In order to meet the challenge to increase scientific output it was decided to extend the Scientific Committee with 4 Steering Group members, i.e. with 2 additional members. The newly formed Scientific Committee consists of: Siobhan Carr (UK), Elpis Hatziagorou (GR), Anders Lindblad (SE), Milan Macek (CZ), Angeliki Preftitsi (patient representative), Anna Zolin/Annalisa Orenti (statisticians) and Lutz Naehrlich (Executive Committee representative).
   - The Scientific Committee will meet in October to discuss the strategic direction.

e) Patient project:
   - Is in collaboration with CF Europe (CFE), the federation of patient organisations in Europe.
   - The Memorandum of Understanding (MoU) between CFE and ECFSPR will be prolonged for another 3 years. The patient organisations from Belgium, Italy, Luxembourg, Netherlands and Switzerland will fund the ECFSPR with a total amount of € 30,000/year for a period of 3 years. It will enable ECFSPR and CFE to continue working on the projects to bring data closer to people with CF and their families and make the Registry and what it can do for the CF community more visible. Current projects are: At-a-Glance reports, Posters, Interactive maps, and social media.

f) Benchmarking:
   The Benchmarking modules has been finalised and is integrated in the current version of ECFSTracker.
   - The functionality includes graphs, boxplots and tables on selected benchmarks, and allows comparison of:
     - a country to another country, or a group of countries;
     - a centre to another country, or a group of countries.
   - Centre to centre comparison in a country is possible provided all centres have agreed to share their centre's (anonymised) data with the other centres in their country. ECFSPR will provide a template that can be used to collect agreements from the centres.
     NB If a centre does not wish to share their data it is possible to exclude this centre from the centre-to-centre comparison.
   - The ECFSTracker users have been informed by ECFSPR about this module. Lutz Naehrlich invites the Steering Group members to promote the functionality in their country.
   - The Benchmarks will also be integrated in ECFSTracker 2, the updated version of the software.
   - It is strongly advised to follow a course in order to interpret the results correctly. A course will be shortly available on the ECFS Education Platform, www.ecfs.eu/education/courses.

2. **ECFSTracker** (Jacqui van Rens)

- ECFSPR is working on an upgraded version of ECFSTracker, which is based on a more advanced technology. Benefits are: an enhanced user interface, improved tools for data and user management, an audit function, GCP compliant (which is useful for clinical trials), and the possibility to add a module to collect data for post-marketing purposes.
- In general, the structure will remain the same but there are some changes, such as:
  - New additional variables will be included in the Core data section, the Annual Summary section and the Encounter functionality. A list will be distributed to all contributing centres and national registries;
  - Enhanced checks and controls to decrease the number of errors;
  - Navigation and visualisation: a coloured flag system will indicate the completeness of various sections of the Patient Annual Summary.
- The upgrade will be developed in stages: we will primarily focus on delivering the Annual Summary functionality for direct data-entry and file-upload, followed by the Reports and Benchmarking functionalities, and the Encounter functionality.
- ECFSPR provided all necessary documentation and information to OpenApp, and currently the team is working on cleaning the database from duplicated patients and aligning the ECFSPR database with the country databases. Also, a standard operating procedure is in the pipeline on how to handle patients that need to be excluded from the Annual Summary for various sorts of reasons, e.g. withdrawal of consent, reversal of diagnosis, lost to follow-up.
- Planning: the software will be launched in January 2019 to enable the users to start entry of 2018 data.

- Online training will be provided in the form of webinars, organised during the last quartile of 2018, videos of the different steps will be online available, and during the ECFS conferences demo sessions, general and on specific topics, will be organised.

3. **Reports 2016 & 2017** (Annalisa Orenti)
   - 2016 report:
     - The reports contains information from 44,719 patients living in 31 countries.
     - Coverage has increased.
     - Percentage of missing data has been reduced.
     - National registries continue to align their variables with the ones used by ECFSPR. In this report, for the first time, all countries report "best FEV1 of the year".
   - 2017 report:
     - We will use a phased deadline, as we did with the 2016 report. The data-collection deadlines are: 1 July 2018 for direct data-entry, and 1 October for file-upload national registries.
     - Planning:

       Direct data-entry countries:
       - October 2018: error correction procedure;
       - December 2018: distribution country tables and review by countries;
       - April 2019: review annual report.

       National Registries:
       - November-December 2018: error correction procedure;
       - January 2019: distribution country tables and review by countries;
       - April 2019: review annual report.
   - During summer the ECFSPR statisticians will perform internal data quality checks on the longitudinal data of all countries. If any longitudinal inconsistencies and/or missing values the countries will be contacted with a list to review.

4. **Data Quality** (Lutz Naehrlich)

   Lut Naehrlich gives a brief summary of what has been discussed in the Data Quality meeting on 7 June 2018, which was attended by most Steering Group members:
   - The ECFSPR is planning to work on further enhancing the quality of data, which is essential for the annual reports, research and post-authorisation studies. The project is based on the work previously done by ECFSPR and the national registries, led by Vincent Gulmans.
   - In the proposed data quality project will focus primarily on the direct data-entry countries. Onsite validation visits will be performed from 2019 onwards in a selection of centres in the participating countries. In the autumn of this year ECFSPR will start with pilot validation visits in Austria, Portugal, Slovakia and Switzerland.
   - ECFSPR will provide a standard operating procedure (SOP) framework for all participating countries. National registries may use these SOPs to conduct their own data quality programme within their country.
   - ECFSPR will be collaborating with the Centre for Clinical Trials at the University of Mainz (IZKS), Germany, to establish and conduct the data quality programme.
   - The focus areas will be: data-completeness, -consistency, -uniqueness, -validity and -accuracy.
   - The data quality programme, including SOPs, accreditation key indicators, planning and approach, will be presented at the wintermeeting, January 2019.

Pharmacovigilance (Ed McKone)

- New medicines are coming on the market regularly. These medicines need to be monitored in Post Authorisation Safety Studies (PASS) and Post Authorisation Efficacy (PAES) studies according the European Medicine Agency (EMA) regulations, to support regulatory decision making for medicines used in the treatment of CF.
- In 2016 the EMA organized a Registry Initiative and hosted an inaugural meeting in London in November 2016 to discuss using existing patient registries for PASS and PAES studies. The EMA expressed that they were in favour of using existing registries for these studies, and in particular using the ECFSPR as a model for a procedure to use by other rare diseases.
- Together with representatives from the national registries of DE, FR, IE, UK, ECFSPR established an academic consortium in 2017 to apply for a qualification advice (advice on how to improve in order to apply for an opinion) or an opinion (which is final and binding) from the EMA. A fee was involved to conduct this process, but EMA granted a waiver.
- A working group was formed, consisting of ECFSPR representatives, representatives of the national registries (France, Germany, UK), the ECFSPR data-controller, and a CTN representative.
- As part of the qualification procedure we were invited to the EMA office to clarify in two meetings our structure and what we can deliver; the limitations of the registries were clearly explained.
- The result of this procedure is an opinion qualification from EMA that the ECFSPR is an appropriate platform for the collection of CF data for pharmacovigilance to support regulatory decision making for medicines used in the treatment of CF. As a last step in the qualification process, a draft "Context of Use" document, describing the regulatory view, was made available for public consultation on the EMA website. People could respond with their comment to the EMA. Comments were received from several pharmaceutical companies. The working group has formulated a reply, which has been sent to EMA in mid-June. In October EMA informed that we have received a final opinion. The final Context of Use is available on the EMA website: www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development#qualification-opinion-on-the-european-cystic-fibrosis-society-patient-registry-(ecfspr)-and-cf-pharmaco-epidemiology-studies-section
- A report on the CF Registries workshop Initiative for Patients, organised by EMA in 2017, is also available on the EMA website: www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500236631.pdf.
- One of the EMA requirements is data of good quality. Lutz Naehrlich is leading the Data Quality project and activities are ongoing to further improve data- quality. For more information refer to point 4 – Data Quality.
- The main challenges as discussed with the EMA are:
  - Informed consent: we do not want to change the currently used informed consent forms and go through a re-consent process, therefore only aggregated data will be provided to the Industry/EMA, and no raw data.
  - The information submitted to ECFSPR is routinely collected in the clinic. In ECFSTracker new variables will be added to the existing variable set, which will meet many of the EMA requirements. In future we may need to collect information on quality of life and patient reported outcomes. These topics will be included in the Encounter functionality of ECFSTracker 2.
  - We agreed with the EMA that we will provide data which is collected on an annual basis, and this is sufficient.
  - Adverse events (AE) monitoring: it has been made clear to the EMA that registries can't be used for early recognition of AEs nor for monitoring AEs. Registries can collect information on a prospective basis and a variable, as a safety measure, can be added in the future data-collection.

- Reports will be generated by the statisticians from ECFSPR and national registries.
- Ed McKone refers to an article, which has been published recently by the UK CF Registry on "Use of a rare disease patient registry in long-term post-authorisation drug studies: a model for collaboration with industry", by Bilton D, Caine N, Cunningham S, Simmonds NJ, Cosgriff R, Carr SB, The Lancet 2018 July; 6(7): 495-496, DOI: 10.1016/S2213-2600(18)30192-9.

5. **Overview Scientific Activities** (Elpis Hatziagorou)
   - In the first two quarters of 2018 one data-application was received (in 2017 9 request in the same period). In general the number of requests from researchers, especially researcher from within the ECFS community, is increasing.
   - Manuscripts:
     In 2017, 3 manuscripts were published:
     - Effect of Allergic Bronchopulmonary Aspergillosis on FEV1 in Children and Adolescents with Cystic Fibrosis: A European Cystic Fibrosis Society Patient Registry Analysis. Kaditis AG, Miligkos M, Bossi A, Colombo C, Hatziagorou E, Kashirskaya N, Monestrol de I, Thomas M, Mei-Zahav M, Chrousos G, Zolin A. Arch Dis Child 2017; 102: 742-747 .
     - Epidemiology of CF: How registries can be used to advance our understanding of the CF population. Jackson AD, Goss CH J Cyst Fibros, 2017 Dec 21. pii: S1569-1993(17)30970-0. doi: 10.1016/j.jcf.2017.11.013. [Epub ahead of print]
     - Year to year change in FEV1 in patients with cystic fibrosis and different mutation classes. De Boeck K, Zolin A. J Cyst Fibros. 2017; 16: 239-245.

     In 2018: 10 manuscripts are in the pipeline.
   - Ongoing projects in 2018:
     - The effect if DNase on longitudinal lung function in European patients with CF. Project lead: Ed McKone in collaboration with Roche. Aim is to submit abstract to NACFC 2018. Manuscript is in the pipeline;
     - Survival analysis: nonsense mutations and socio-economic status across Europe. Project lead: Ed McKone. Manuscript is in the pipeline;
     - CF Mortality in childhood. Project lead: Rita Padoan. Manuscript is ready and will be resubmitted.
     - Changing epidemiology of respiratory bacteriology. Project lead: Elpis Hatziagorou. Manuscript is in the pipeline.
     - Risk factors for decline in FEV1. Project lead: Elpis Hatziagorou. Preliminary results were presented in the Steering Group in Belgrade. The data-analysis will be finalized in July, and a manuscript will be prepared.

6. **Patient Project** (Andreas Jung)
   Specific projects have been developed to reach out to the patients and are still ongoing:
   - The At-a-glance report 2016, which contains key-information of the Annual Report, has been published together with the 2016 Annual Report.
   - The interactive map on the ECFSPR website has been introduced in 2017 and has been updated with 2016 data.
   - The country specific posters are being developed, many have been published and several are still in the pipeline. The posters with 2016 data will be finalized before the end of 2018.
   - Social media: a Twitter account is in the air and regularly used. An ECFSPR account on Facebook hasn't been launched, as we are looking into resources to maintain the account.
   - A communication plan will be developed in the next months.
   - In September a survey will be distributed amongst patient organisations and CF healthcare providers to explore how these projects are received and how we can improve. The results will be presented at the Steering Group meeting in January 2019.

7. **HIT-CF** (Kors van den Ent)
   - HIT-CF Europe is a research project, funded by the European Commission, to provide personalised treatment for people with CF with ultra-rare CFTR mutations. Kors van den Ent is the project coordinator.
   - The project is a consortium of ECFS, CFE, pharmaceutical companies and laboratories. Discussions are ongoing with additional pharmaceutical companies to join the project, and make additional medicines available to test.
   - Project objectives:
     - To give access to CFTR-modulating drugs to patients with rare CFTR-mutations;
     - To develop a personalized CF treatment using organoids;
     - To generate an accessible Biobank for future CF-research.
   - ECFSPR provided a table with information on patients wilt ultra-rare mutations by country in Europe for selection of countries to perform the study.
   - During the wintermeeting 2018 in Brussels the ECFS Clinical Trial Network was approached to perform a feasibility survey, which resulted in a selection of CTN sites in 10 countries. Centres outside the network may send eligible patients to one of the selected CTN sites; the centre should contact the preferred CTN centre. NB Bear in mind that follow-up is possible. CF Europe (CFE) is looking into the extra costs for travel.
   - 500 biopsies need to be collected from CF patients. The drugs from the 3 participating pharmaceutical companies will be tested on these organoids. Subsequently, the best responders per drug will be selected, and 3-double blinded placebo controlled cross-over clinical trials will be performed.
   - Standardisation and central reading is being worked at, and so far successful.
   - Work is being done on the preparation of bio-banking, which includes a lot of legal an ethical issues, and will be developed in different stages.
   - The group is currently in discussion with the Innovation Task Force of the European Medicine Agency.
   - The project has defined milestones, see slide.
     - Sept 2018: start drug screening on organoids;
     - End 2019: start clinical trials;
     - End date project: 2022.
   - CFE, as partner in this project, developed and launched a HIT-CF website, www.hitcf.org.

8. **Presentation country registries** (Hana Kayserova, Andreas Pfleger)

   The country representatives of Austria, Andreas Pfleger, and Slovakia, Hana Kayserova, presented their national registry of respectively Austria and Slovakia. For more information we refer you to the slides.