Procedure No.: EMEA/H/SAB/080/1/QA/2017
EMA/CHMP/SAWP/802259/2017
Product Development and Scientific Support Department

Qualification Opinion

The European Cystic Fibrosis Society Patient Registry (ECFSPR)

Draft for consultation

On 13 March 2017 the Applicant European Cystic Fibrosis (CF) Society Patient Registry requested qualification of their patient Registry pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council. This procedure was undertaken as a multi-stakeholder procedure in parallel with Health Technology Assessment Bodies. This document represents the regulatory view. HTA views are given to the Applicant in accordance with HTA procedures.

The European Cystic Fibrosis Society Patient Registry (ECFSPR) is an established disease specific patient registry that collects CF clinical data. The ECFSPR consortium requested qualification of its registry as suitable for performing pharmacoepidemiological studies for regulatory purposes concerning medicines intended for the treatment of cystic fibrosis. The Applicant provided the Agency with the questions concerning the context of use for which they seek qualification, together with the supportive documentation.

Dr Peter Mol and Ms Blanca García-Ochoa Martín were appointed as coordinators. The Regulators' Qualification Team comprised of Dr Ferran Torres, Dr Caroline Auriche-Benichou, Dr Maria Jesús Fernández Cortizo, Dr Hanneke Van der Woude. The EMA Scientific Officer for the procedure was Dr Jane Moseley. The questions were also referred to PDCO, PRAC, and the Clinical Trial Facilitation Group

The procedure started during the SAWP meeting held on 2 – 5 May 2017. The first Regulators' Qualification team meeting took place on 06 June 2017. At its meeting on 06 – 09 June 2017, the SAWP adopted a list of issues to be addressed by the Applicant during the discussion meeting. The discussion meeting with the Applicant took place on 03 July 2017. The second Regulators' Qualification Team meeting took place on 29 August 2017. The third Regulators' Qualification Team meeting took place on 25 September 2017. The fourth Regulators' Qualification Team meeting took place on 23 October 2017. During its meeting held on 08 - 11 January 2018, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 22 –25 January 2018, the CHMP adopted the draft opinion to be given to the Applicant for public consultation. This CHMP draft opinion is annexed to this letter. The opinion and responses given by the CHMP are based on the questions and supporting documentation submitted by the Applicant, considered in the light of the current state of the art in the relevant scientific fields.

London, 25 January 2018

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Reader's Guidance

Please provide any comments in accordance with EMA public consultation process
Form for submission of comments
Specific privacy statement for public consultations

The European Cystic Fibrosis Society Patient Registry (ECFSPR) is an established disease specific patient registry that collects CF clinical data from 31 participating countries on ~ 42,000 patients. The ECFSPR consortium requested qualification of its registry as suitable for performing pharmacoepidemiological studies; i.e. post-authorisation safety surveillance (PASS) and efficacy (PAES) studies to support regulatory decision making in medicines for the treatment of Cystic Fibrosis. This procedure was undertaken in parallel with Health Technology Assessment bodies.

Six questions were posed by the Consortium to SAWP and HTAs in their request together with supporting documentation:

1. The Consortium considers that the target population for post-approval CF Registry Pharmacoepidemiology/Pharmacoeconomic studies for new CF medicines will be initially limited to countries with similar CF outcomes. Variables collected will be those that are routinely collected in CF clinical trials and routine clinical practice. Additional variables can be added in specific cases depending on EMA/HTA/Industry Requirements. Does EMA/HTA authorities agree?
2. The Consortium considers that current safety measures collected by the CF patient registries include complications/co-morbidities reported by patients with CF are sufficient for post-approval CF pharmacovigilance studies of new CF medicines. Registries can be adapted to collect specific additional drug related adverse events depending on EMA/Industry requirements. Is this acceptable to EMA?
3. The Consortium considers that, for post-authorisation pharmacoepidemiology / pharmacoeconomic studies of new CF medicines, efficacy and safety data should be collected and submitted to Industry/EMA/HTA annually. Is this acceptable to EMA and HTA authorities?
4. The Consortium believes that summary data rather than patient level raw-data is sufficient for robust post-authorisation pharmacoepidemiology and pharmacoeconomic studies of new CF medications. Does EMA & HTA authorities agree?
5. The Consortium considers that the existing data quality control mechanisms established and implemented by the European CF registries are sufficient for post-approval European pharmacoepidemiology and pharmacoeconomic studies of new CF treatments. Does EMA and HTA authorities agree?
6. The Consortium Considers that applying existing clinical trial methodology as well as propensity scoring mechanisms will be a robust way of analysing post approval pharmacoepidemiology studies of new CF medicines. Does EMA and HTA authorities agree?

Interactions with Regulators
A multi-disciplinary qualification team of regulators was constituted with representatives from PDCO, CHMP, PRAC, the Clinical Trial Facilitation Group and the SAWP. Patient representatives were invited.

Specific issues were raised by SAWP for discussion within the qualification procedure and discussed with ECFSPR on 03 July and 25 September 2017.

A public workshop with ECFSPR representatives, regulatory participants and other stakeholders also took place at the EMA premises on 14 June 2017.

Content of report
This report provides a final agreed draft Context of Use (p4) for public consultation describing where ECFSPR is deemed by CHMP as an appropriate data source for post-authorisation studies to support regulatory decision making on medicines for the treatment of cystic fibrosis, together with CHMP's response to the questions posed by the Consortium (p4-16).

Draft Qualification Opinion

Study aims

On the basis of the initial briefing document and additional information submitted during the procedure, CHMP considers that the current status of the ECFSPR (coverage, core dataset, governance, quality assurance approaches, and completeness of core variables), may allow its use as a data source for regulatory purposes in the context of the following studies concerning medicines authorised for the treatment of cystic fibrosis:

- Drug utilisation studies for total recorded population and by subgroup such as CF complications, age, gender, FEV1 status, genotype, etc.
- Drug efficacy/effectiveness studies
  Data from the ECFSPR could be used:
  - For concurrent assessment of post authorisation efficacy/effectiveness using annual best FEV1, mortality, pulmonary exacerbations using the ECFSPR working definition, or CF complications;
  - As a source of historical control data that could be used for contextualization, e.g. for comparative purposes in the context of non-randomized clinical trials (i.e. when this would be the only reasonable option).
- Drug safety evaluation
  The ECFSPR could be used as a tool to collect safety data with a particular focus on important identified and potential risks. In this context, not only assessment of cumulative annual incidence of potential or identified risks (adverse events) (i.e. currently recorded as CF complications or mortality) may be possible but also comparative assessment of new solicited safety data (adverse events of special interest) provided an appropriate control cohort can be constructed, i.e. if patients not exposed to the drug of interest are also monitored for the AE of interest.

Individual study considerations

- Individual studies for regulatory purposes using the ECFSPR should be conducted under a study protocol agreed before study start with regulatory authorities. Appropriate methods for observational studies to control for bias, chance and confounding factors should be considered.
- Early tripartite interaction - preferably at the stage of clinical development - with ECFSPR, regulators and Applicants is encouraged. Depending on the concrete study objectives and design/methodology, single or multi-country studies can be conducted.
- In certain cases to allow for wider data collection e.g. to address a particular research question an expanded (renewed) consent may be needed if data are to be collected, which are considered outside routine CF practice .

Further recommendations for enhancement

- Addition of an adverse event module using MedDRA coding for unbiased collection of adverse events across all CF centres.
- Continue the roll out of start and stop date recording for CF medications, including specific dosing information, when possible, and reasons for discontinuation.
- Continued liaison with patient groups.
- Pregnancy follow-up. For women of child-bearing age a 'Pregnancy since last review' field (yes/no) should be available. Further, the possibility to document the pregnancy outcome, when applicable, by including a drop-down list for outcome information (e.g. in line with teratology coding) should also be considered.
- Transplant patients: patients who underwent organ transplantation are not well covered in the ECFSPR as they are usually monitored in transplant centres most of which do not submit data to the ECFSPR. An effort should be done to increase the coverage of transplanted patients in the ECFSPR although it is acknowledged that this may be challenging.
- Linkage with prescription data for further assessment of safety and effectiveness issues.
- Other potential uses of the ECFSPR may include generating data to support validation of relevant biomarkers/surrogate endpoints. This is, however, currently out of the scope of this procedure.

Questions and background information posed by the Applicant

Background information as submitted by the Applicant[i]

European legislation requires post-authorisation safety (PASS) and efficacy surveillance (PAES) studies for new drugs. For drugs targeting rare diseases such as CF, the CF Community and the European Medicines Agency (EMA) are in favour of pharmaceutical companies working with existing CF patient registries to collect data on new medicines from real-life clinical use throughout Europe.

There are already well established CF patient registries across Europe. The European Cystic Fibrosis Society Patient Registry (ECFSPR) is an established disease specific patient registry with its own software platform, ECFSTracker, used for the collection of CF data from the participating countries in Europe. Data is collected once a year. ECFSPR is currently upgrading ECFSTracker to a version 2.0 that includes an audit function and is GCP compliant for clinical trials. It is anticipated that ECFS Tracker 2.0 will roll out in early 2019. ECFSTracker is a web-based program that can be maintained remotely. It is modular with the ability to easily add in new variables and new modules for pharmaco-epidemiology that can be restricted to countries and centres if required.

Countries such as the UK, Germany, France and others have their own national registries with their own software platforms for data collection. These registries collect data on an annual basis and upload annual data to the ECFSPR using ECFSTracker. ECFSPR and most of the national registries also have an option within their software platform to collect data at each patient encounter although few registries are using this type of data collection. The main limitation to the use of encounter based data collection is that most registries have a small budget with limited or no resources for data entry. Data collection is performed by already busy CF care-givers in their own time and at their own expense. Any requirement for encounter based data collection will require considerable additional financial support. It has been proposed that data for the purposes of pharmaco-epidemiology studies will need to be collected and reported to the EMA/Industry in a timely fashion. The mechanism of data reporting has yet to be determined and will be based on EMA's requirements and the ability of registries to provide this information under their current structures and within the requirements stipulated by research and ethics committees approving registry data collection and existing data protection legislation.

To date, the UK CF registry has the most experience in Europe with EMA pharmacoepidemiology studies. There are currently 5 active studies, initiated between 2012-2017. These are either PASS or PAES studies with study protocols* and report formats compliant with EMA guidelines. The positions of the ECFSPR and National Registries' outlined below are consistent with these studies.

* Study numbers for UK/EMA Pharmacoepidemiology studies: EMEA/H/C/001252, EU PAS 4270, EMEA/H/C/001225, EU/1/14/973/001 Horizon, EMEA/H/C/002494

Based on the coordinators' reports the CHMP gave the following answers:

Question 1

Target population and variables for collection

The Consortium considers that the target population for post-approval CF Registry Pharmacoepidemiology / Pharmacoeconomic studies for new CF medicines will be initially limited to countries with similar CF outcomes. Variables collected will be those that are routinely collected in CF clinical trials and routine clinical practice. Additional variables can be added in specific cases depending on EMA / HTA / Industry Requirements. Does EMA / HTA authorities agree?

Consortium's position

Target patient population

The target patient population for CF pharmacoepidemiology studies will include all European patients with cystic fibrosis. Clinical trials in patients with CF tend to exclude patient with very mild (lung function > 70% of predicted FEV_1 ($ppFEV_1$) in adults and >90% $ppFEV_1$ in paediatrics) or very severe disease (lung function <40% $ppFEV_1$ in both adults and paediatrics) as well as patients with significant CF co-morbidities including advanced renal/liver disease and pulmonary infections associated with more rapid decline in lung function (e.g. *Mycobacterium abscessus/Burkholderia cenocepacia*). The target population of this proposal will be all-comers with CF who are receiving newly approved treatments, including patients that would have been excluded from clinical trials.

Some variation in outcomes is seen across Europe but recent survival studies have shown identical survival for countries in the top 2 tertiles of income levels based on Gross National Income in USD as determined by World Bank (http://wdi.worldbank.org/table). Smaller, predominantly Eastern European countries have lower survival rates. As these countries also have the most incomplete coverage, initial pharmacoepidemiology studies will be best limited to countries in the top 2 tertiles of income, (see appendix 2 for countries with estimated coverage and survival curves for countries stratified by World Bank Income). This can be expanded as coverage of Eastern European countries improves. The ECFS is currently working on understanding why these survival differences exist. Irrespective of the survival outcomes, countries with good coverage should be included, even if outcomes differ, as long as sufficient patient numbers are recruited.

Outcomes of interest

There is consensus among the CF community as to which outcome measures should be used for drug efficacy clinical trials. Most of these are routinely collected by CF registries annually and could potentially be collected at regular intervals. If required, most CF registry software platforms can be modified to collect some additional outcome measures.

i) Patients demographics/Predictors of outcomes:
   a) Gender
   b) CFTR genotype
   c) sweat test
   d) Age
   e) Country of origin
   f) Pancreatic sufficiency status: This is usually determined by the need for pancreatic enzyme supplementation. Dosage of pancreatic enzymes is not collected as it varies from day to day depending on the fat content of the patient's meals. As over 90% of CF patients are pancreatic insufficient from birth, a start date is not routinely collected.

ii) CF Clinical trial outcome measures currently being collected by registries:
   a) Lung function (FEV1, FVC);
   b) Nutritional measures (Height, weight, BMI);
   c) Exacerbation frequency (No. of days of IV/oral antibiotics/hospitalization) as used in clinical trials *(currently exacerbation data is not collected by ECFSPR but is collected by many national registries)*
   d) CF Microbiology (Presence/Absence of common CF bacterial infections);
   e) Concomitant medications.
      Information on concomitant medications are collected by all CF registries. The level of detail does vary and can range from whether a patient is on a chronic therapy (yes/no) to more detailed information including start/stop date, dosage and reason for stopping. In most registries, this is limited to CF-specific medications. If recommended by EMA, concomitant medications section of each registry can be adapted to collect additional information on both CF-specific medications and all other medications.

For completeness of these variables: please see Question 5 on data quality.

iii) CF Clinical trial outcome measures not routinely being collected by registries or used routinely in clinical practice (NB It is possible to adapt registry software to collect most of this information):
   a) Lung function (LCI);
   b) CFTR Physiology (NPD, ICM, organoids);
   c) Patient reported outcomes (Quality of life assessments).
   d) Imaging studies (raw data or radiology reports) are not currently collected in registries. There is the potential to link registry IDs to radiology tests but this would have to be done at a centre level with additional Ethics approval and consent in place. Currently a defined format for use of imaging in clinical trials is not agreed but is in development.

iv) Pregnancy:
   a) Some registries collect information on pregnancy. This relates to outcomes reported by the mother. More detailed information on the child would require additional consent. Registries can be easily adapted to collect this information for new drugs if recommenced by EMA.
   b) Examples of data collected related to pregnancy:
      i. Spontaneous or medically assisted pregnancy
      ii. Mother weight at the end of pregnancy
      iii. Pregnancy outcome : birth Delivery, Spontaneous abortion, Therapeutic interruption,

Voluntary termination
iv. Delivery: natural or C-section
v. Premature birth
vi. Child: Date of birth, vital status, gender, birth weight and height, Child with CF

All data in i) and ii) are routinely collected at each clinic visit and all this information is collected as part of routine assessment of a CF patient's well-being.

Additional variables can be added and should be identified early. As variable selection will be dependent on the type of study drug under investigation, early dialogue between registries and pharmaceutical companies (around time of Phase II/III trial design) is essential to using registries for post-approval studies.

CHMP answer

Disease-based registry

Post-authorisation studies that are performed in patient registries wherein patients are recruited based on a disease (i.e., disease registry) rather than based on a specific drug exposure can be a useful tool to address uncertainties at the time of marketing authorisation (MA). These disease registries may prove of particular relevance in the case of orphan serious/life-threatening diseases such as cystic fibrosis (CF) where the clinical trials supporting MA could be of limited size and duration of treatment. Also, in certain populations, efficacy data may have some residual uncertainties stemming from the limited populations and feasibility reasons at the time of initial approval.

The European Cystic Fibrosis Patient Registry (ECFSPR) is an established disease specific patient registry that collects data from patients with CF in a large number of countries in Europe. The ECFSPR Consortium aims at qualifying the existing registry for the purpose of performing pharmaco-epidemiology studies.

The ECFSPR Consortium has presented a general overview of the data collected in the ECFSPR and across the represented countries. CHMP cannot provide a single answer if the target population and the collection of the data are universally sufficient. This will ultimately depend on the specific post-authorisation research question. Therefore, we recommend that companies submit a study protocol that discusses the relevance and validity of the ECFSPR data (including population) before a post authorisation study is initiated. Ideally, this is done before a MA Application (MAA) procedure is finalised, or perhaps already preplanned before a MAA is filed.

Some more specific comments on the Consortium's proposal are as follows:

Target population

Survival studies demonstrated that differences exist among the European countries in the ECFSPR in terms of patient outcomes. Therefore, the ECFSPR Consortium proposes that initially pharmaco-epidemiology studies will be limited to countries with the best survival rates, i.e. those in the top 2 tertiles of income (see appendix 1b). With a few exceptions, these countries are also those with the best coverage of the patient population (see appendix 1a). This proposal is understandable given the different baseline risks and can be endorsed as a starting point. It may limit, however, the generalisation/interpretability of the results of studies performed (see also question 2 in relation to safety aspects). It is, nevertheless, valuable that data are also available from countries with lesser Gross National Income levels. The proposed research into the apparent disparity in terms of survival outcome is welcomed.

During the discussion meeting an update on the participating countries/registries (as of June 2017) was presented. According to those data, the European CF population is broadly covered even if in some countries, with coverage <85%, not all centres in the country are participating. The ECFSPR has an active programme to increase coverage and to recruit the remaining non-participating countries/ centres which is endorsed.

In addition, it was clarified that newborn screening is well established in Europe which is reassuring even if there are still some countries (mainly from Eastern Europe) where there seems to be no plans to implement such screening. As for important subgroups of patients that may not be included in the registry, the Consortium stated that the only CF patient group that may not be well represented is that of patients who have undergone lung transplantation. These transplant patients are usually monitored by transplant centres that do not submit data to the ECFSPR. Still, in many countries, transplant centres participate in the ECFSPR but not all.

Variables and outcomes of interest

A core set of patient demographics, predictors of outcomes, and common CF outcomes are routinely collected at each visit and are included in all CF registries. The proposed list of variables included in the initial request was considered rather comprehensive for disease-related features even if some clarifications/further description of the operational definition for each of the variables collected in the registry were considered needed.

The importance of maintaining a balance between the amount of information collected and the work required to enter the data that is done by local CF teams is acknowledged. The Consortium was open to the possibility to collect some additional variables. This would be useful to enhance the value of the registry as a potential tool/data source for the conduction of studies that should support regulatory decision-making.

Analysis of data beyond those variables routinely collected requires additional steps for example that an agreement is reached between registry holders and a study sponsor. According to the information provided, in the ECFSPR, certain patients' demographics/predictors of outcomes and certain outcome measures are collected in clinical practice and entered into the registry. Some outcome measures, however, that are used in clinical trials (e.g. lung clearance index (LCI), imaging, pregnancy outcome) are not routinely recorded, but the registry may be adapted for specific studies to record these data (see below). In cases where additional variables are felt to be needed (e.g. due to specific properties of the drug under study) this should be discussed with the holders of the registry at an early phase of drug development to facilitate timely start of studies post-authorisation.

During the discussion meeting, it was explained that entering and sending data to the ECFSPR is only possible when signed informed consent has been obtained. In order to collect additional (retrospective and/or prospective) data, re-consent will most likely be needed unless the additional variable is essential to understand the disease course of CF, in which case, the patient has already consented. It was also noted by the Consortium that re-consent requirements may be different among different countries represented in the ECFSPR.

Example of retrospective data worth collecting are baseline disease characteristics of the patient at the time of diagnosis of the disease i.e. not only at the time of his/her inclusion in the registry in cases where these dates are different. Moreover, additional baseline data may be needed e.g. at the start of a particular treatment, in the context of specific studies.

A concise set of variables is currently collected on an annual basis. The ECFSPR explained that they plan to extend the list to include data on e.g. LCI and nasal potential difference (NPD) measurements, exacerbations (including days of antibiotics IV use and hospitalizations), CF medication start and stop dates, reasons for stopping, dosages for therapies, etc. in the near future plans are also ongoing to align variables and their definitions to make data as comparable as possible on a global level (i.e. not only among Europe but also with US, Canada and Australia). The proposed strategy is overall supported. In addition, it is noted that there is the possibility that in ECFSTracker (the ECFSPR data-collection platform) certain centres/countries could include additional variables besides those reported at a European level which could be useful when conducting particular studies e.g. restricted to a certain setting/country.

The issue of completeness of data is considered critical and was also discussed with the Consortium. ECFSPR requires that centres and national registries complete the full data-set before submission. Once submitted, the ECFSPR statisticians check the data and ensure that the data are complete. Certain data may not be collected routinely, e.g. faecal elastase-1 and faecal fat, or in cases where the definition differs too much from the ECFSPR definition, data will be considered missing. As presented during the meeting, overall the completeness of data appears high with low percentage of missing information which strengthens the value of reported data. The relevance of incomplete or missing data will have to be addressed in the statistical analysis plan based on the goal(s) of a post-authorisation study performed on the ECFSPR data.

Some additional comments in relation to the currently collected or planned data are included below for consideration.

- Anthropometric data

Regarding the analysis of anthropometric outcomes (i.e., weight-, height-, and BMI-for-age z scores), the 2015 annual report indicates that the US population with reference values issued by the Centre for Disease Control (CDC) is being used as the population of reference. It is unclear why the World Health Organization (WHO) growth standards are not being used to compute z-scores.

- Exacerbations

Time to first pulmonary exacerbation and/or rate of pulmonary exacerbations is an important outcome in subjects with cystic fibrosis. In this respect planned ECFSPR work to enhance collection of data allowing the measurement of pulmonary exacerbation frequency is welcomed. The value of collecting use of IV antibiotics, duration of such treatment and hospitalizations is recognized since, in the absence of a universal definition of pulmonary exacerbation, these data regarding use of IV antibiotics in combination with certain symptoms and signs are commonly used as a marker of severe events. The inclusion of exacerbations by the need of additional oral or inhaled antibiotic is also welcomed.

Pulmonary exacerbations could be defined as an event of clinical deterioration in respiratory status that necessitates a change in antibiotic therapy (IV, inhaled, or oral). Therefore, (change in/addition of) antibiotic therapy could thus be used as a useful proxy for a CF exacerbation in the context of a post authorisation study. The operational definition of pulmonary exacerbations should be pre-specified in the frame of specific post-authorisation studies and whatever the definition used, the Consortium should be in the position of providing data on pulmonary exacerbations that require IV antibiotic therapy as this is considered a marker of severity.

- FEV1

The main outcome to assess lung function in subjects with CF who are able to perform spirometry (generally children aged 6 years and older subjects) is the absolute change in percent predicted FEV1. Within the registry only patients' best FEV1 of the year will be collected, which according to the Consortium accurately represents patient's lung function within the year and is a good indicator for trends over time. During the discussion meeting the Consortium also pointed out that in the UK, between the best of the year lung function and the lung function measured at annual review (i.e. the yearly check-up) there is a 4.6% margin. Even if the approach to collect only patients' best FEV1 of the year is understood, all available measurements may be required in the context of specific studies (e.g. for a concrete patient population) given that a 4.6% difference in percent predicted FEV1 is above what has been considered a clinically relevant difference in the context of clinical trials. Nevertheless, the ECFSPR recorded best FEV1 allows generation of longitudinal data on lung function over prolonged periods of time, i.e. years, that are unfeasible in a clinical trial setting. This may allow identifying modifications in the rate of decline of lung function in relation to specific treatments although with some delay (due to the single FEV1 measurement that will be reported per year) and even if these data would require cautious interpretation due to potential confounding factors.

- Concomitant medication

Medication data currently collected by the ECFSPR is on CF-specific medicines, i.e. those medicines used for the treatment of complications related to CFTR dysfunction. However, the recorded data do not include start and stop dates and the reasons for that. The Consortium was asked, further, whether it would be feasible to link external medical health/prescriptions records, e.g. for medication start and stop dates, to the ECFSPR data-collection software. This is not currently done by the ECFSPR but it could possibly be done in the future. The Consortium was particularly encouraged to explore possibilities in this respect.

Information on other medication to treat complications that are not directly related to CFTR dysfunction (i.e. non CF-specific medications such as those used for renal failure, depression, etc.) are not routinely collected. The possibility to record those data could be explored.

- LCI or other outcome measures

The Consortium also mentioned that they are working on a qualification structure in Europe to collect information on LCI even if it is still a research tool and not a standard procedure in most centres. This initiative is supported since, although there are some limitations to perform this test in younger children (e.g. below 4 years of age) who would require sedation, LCI is increasingly being used as a marker of early lung disease in children who cannot perform spirometry. There is indeed a need for new outcome measures for young children with CF who still have well-preserved lung function and who are less symptomatic than older subjects because current ones are based on reduction in symptoms. Furthermore, CFTR modulators may have the potential to slow disease progression and even reverse

damage which had previously been thought to be irreversible. With this in mind all efforts should be made to collect information on LCI even if high coverage in certain age groups may not be feasible. In addition to LCI, there are a number of measurements that could provide insight into early disease development including gastrointestinal biomarkers [Bodewes Frank AJA, Verkade HJ, Taminiau Jan AJM, et al. Cystic fibrosis and the role of gastrointestinal outcome measures in the new era of therapeutic CFTR modulation. Journal of Cystic Fibrosis 14 (2015) 169–177]. Taking all this into account, the Consortium was encouraged to (further) explore the possibility to use longitudinal data from the registry to support validation of relevant biomarkers/surrogate endpoints. This is, however, currently still out of the scope of this procedure.

- *Thoracic imaging* Thoracic imaging techniques such as computed tomography (CT) have been used in experimental studies using different scoring systems and may offer a novel supplemental endpoint for clinical trials of new CF therapies. Such techniques would also be of particular relevance for the assessment of CFTR modulators in young children since they may allow detecting structural lung disease (e.g. trapped air, mucous plugging, bronchial wall thickening, bronchiectasis) in these patients in whom other methods to assess lung disease may be relatively insensitive to mild disease. There are a number of issues that may hamper the use of CT scans for that purpose such as ionizing radiation and the need for general anaesthesia/sedation in younger children. Similarly, accurate longitudinal monitoring of CF lung disease progression and response to emerging therapies may require prolonged periods of time making this endpoint difficult to assess in short-term clinical trials. In this context, again, the ECFSPR seems the ideal setting to generate these data even if important issues such as which CT score will be used to quantify structural lung disease and its degree of validation would need to be considered.

With regards to the collection of LCI and imaging data one aspect of particular relevance, which would need to be specifically addressed/discussed, relates to whether similar e.g. methodology / techniques / equipment / reference values for interpretation are/will be used across centres.

- *CF complications*
Complications of CF are mentioned in relation to safety measures collected in the registry (see question 2) while it is felt that delaying complications may also be representative of changes in disease progression and, therefore, they could also be considered as efficacy endpoints. Hence, it would be useful if data from the registry could be used to document changes in disease progression including delaying the occurrence of CF complications such as cystic fibrosis-related diabetes (CFRD), cystic fibrosis-related liver disease (CFLD), distal intestinal obstruction syndrome (DIOS), lung or liver transplantation, allergic broncho-pulmonary aspergillosis, chronic *Burkholderia cepacia* complex, nontuberculous *mycobacteria*, chronic *Pseudomonas aeruginosa*, early *Pseudomonas aeruginosa* lung infection and chronic *S. aureus* lung infection. The ECFSPR is in the position to provide data on these complications except for DIOS.

- *Pregnancy*
As stated by the Consortium some national registries also collect information related to pregnancies on the basis of outcomes reported by the mother. Pregnancy follow-up is considered relevant information and it is therefore recommended that for women of child-bearing age a 'Pregnancy since last review' field (yes/no) should be available. Further, the possibility to document the pregnancy outcome, when applicable, by e.g. including a drop-down list for outcome information (in line with teratology coding) should be considered.

- *Quality of life*
The possibility to collect quality of life data by the ECFSPR was also discussed and it was agreed that the registry may be adapted to collect such information if required, e.g. in the context of a particular study, rather than routinely. Data on school and work absence could also be considered as these may reflect individual improvement in functioning and quality of life.

CHMP Conclusion
The Consortium presented the data that are collected within the ECFSPR. The population captured in the ECFSPR goes beyond the population included in clinical trials, representing in some, but not all, countries (nearly) all CF patients as based on new-born screening. Data on certain mutations that may define the course of the disease are captured. These 'real world' populations are also followed over extended periods of time (years).

The ECFSPR captures data on FEV1 and certain CF complications. Some outcome measures used in clinical trials, however, are not routinely collected (e.g. LCI and pulmonary exacerbations). Such data may be captured in the ECFSPR or its subsidiary registries for specific research / post-authorisation studies, but may be too limited to be conclusive in the overall ECFSPR study population. Efforts to collect these data more comprehensively in the registry are recommended.

The collection of pregnancy data and pregnancy follow up is limited. The addition of data regarding pregnancy follow up is recommended.

The ECFSPR thus collects a large amount of data that may serve as a basis for post authorisation studies for CF products (see context of use). The suitability of these data ultimately depends on the purpose of the study. Therefore, early interaction and careful planning between ECFSPR, industry and regulators/EMA is recommended.

For some initial studies, where it is appropriate, it is agreed that the target population should be limited to countries with similar CF outcomes, particularly as these countries provide homogenous data and the collection of data from these countries appear to be relatively comprehensive and robust. With respect to the currently collected variables, these are acknowledged to be important and relevant. However the adequacy of these will entirely depend on the planned study objectives and it is foreseeable that additional parameters will be needed for certain studies. Currently the logistics, feasibility and mechanisms for addition of new variables in a limited fashion to support a particular study are outlined and early interactions between the stake-holders will be necessary in order to support many other studies.

Question 2

Safety measures collection

The Consortium considers that current safety measures collected by the CF patient registries include complications/co-morbidities reported by patients with CF are sufficient for post-approval CF pharmacovigilance studies of new CF medicines. Registries can be adapted to collect specific additional drug related adverse events depending on EMA/Industry requirements. Is this acceptable to EMA?

Consortium's position

Registries can be adapted to collect some adverse effect data. Most countries in Europe have existing structures to collect adverse effects of new medications and the CF Registries will be considered an adjunct to this methodology. In some cases, CF registries could be linked to national systems for reporting adverse events,

Examples of safety monitoring and drug related adverse effects reporting that can be collected by European CF registries include:

i) Patient reported complications/comorbidities (e.g. haemoptysis) are currently collected by CF registries. See enclosed list of CF complications and comorbidities collected by ECFSPR and UK registries (Appendix 2);
ii) Additional drug related effects that that have been identified in clinical trials can be included;*
iii) Unexpected drug related adverse effects could be collected using open fields;*
iv) ECG abnormalities (QT prolongation);*
v) Laboratory abnormalities (liver function testing).*

* These elements will require modification of registry software. **As adverse events are often drug specific, it is essential that early dialogue takes place between industry and registries to select additional variables that are feasible and acceptable to the registries.**

CHMP answer

During the discussion, the Consortium clarified that ECFSPR investigators do not routinely collect all adverse events. The registry will thus not be suitable for identifying hitherto unknown safety signals of new adverse events as expedited reports. However, they may have a monitoring function for previously identified adverse events (e.g. in the frame of clinical trials).

In view of the initially submitted documentation, where reference to the UK registry was made as an example of what could be measured, some issues were put forward to the Consortium. These issues related to the definition of the variables, their availability in each of the registries, as well as to the definitions used and the terminology to code information. The identification of a core dataset of safety

variables ("need to know") to address key safety questions is considered critical. Therefore, at least the safety concerns addressed in the risk management plans of products indicated for the treatment of CF (i.e. important identified risks, important potential risks and missing information) should be considered in the core dataset of safety variables and in any case, for the risks associated with the product under study. These adverse events may include among others: ototoxicity, nephrotoxicity, emerging antibiotic resistance, harm to an unborn baby (foetal harm) and safety/efficacy of medication treatment in children under 6 years of age. Regarding liver disease, the possibility to collect patients' Child-Pugh score was also suggested for consideration, because this score is often used to classify the liver insufficiency and to provide recommendations if dose adjustments will be needed.

During the discussion meeting with the Consortium, it was agreed that a balance between quality and quantity of data, and clear definitions should be pursued. The Consortium also stated that in principle, extra variables can be included in the ECFSPR system either as a separate module or as additional variables to the standard case report form which is welcome (see additional discussion below). The related funding issues in this respect were acknowledged.

During the procedure, an important concern was raised on how to distinguish complications related to disease progression from those related to the medication used. During the discussion meeting, it was acknowledged that they are difficult to differentiate, but this question could be addressed by involving a matched control group not using the drug, to determine if the occurrence of the complication is different between the group of patients on the new drug and the control group. As currently set up, the ECFSPR will be able to report identified CF complications (e.g. haemoptysis, pneumothorax, etc.) on an annual basis. This approach is supported because assessment of cumulative annual incidence of potential or identified risks (adverse events) is possible, albeit currently limited to events recorded as CF complications or mortality. As for the collection of additional safety data the ECFSPR stated that this would only be possible if prospectively defined. In this context, as outlined above, it would be of particular relevance that a matched (unbiased) control group can be constructed (i.e. if patients not exposed to the drug of interest are also monitored for the AE of interest) to allow comparative assessment of new solicited safety data (e.g. adverse events of special interest). Thus, the principle role of the ECFSPR would be to evaluate and validate, rather than to identify, safety signals.

Since, as already mentioned, additional data might be required (due to a signal, the identification of a new safety concern or the launch of new products), the registry should be flexible enough to include new variables to the database which would enhance the potential use of this longitudinal data source for drug safety evaluation. As stated above, this option may well be possible and additional modules could be added. Other additional improvements that may be contemplated in relation to safety data collection would include the addition of a specific adverse event module using MedDRA coding for collection of adverse events across all CF centres. From a safety perspective the proposal to limit the conduction of initial pharmacoepidemiology studies to countries in the top 2 tertiles of income (see question 1) may not always be acceptable. In certain cases (e.g. to increase the size of the study population in relation to a certain rare event) it may useful to also consider data from those countries/centres, even if some adjustments may be required (e.g. to account for differences in particular baseline characteristics/risks).

CHMP Conclusion
The registry does not have a signalingg function regarding the occurrence of new adverse events, but could be used to monitor identified/potential adverse events. The current safety data set includes primarily known CF complications and comorbidities. In the future, and for specific studies, the safety data set could include any identified or potential risks of newly approved CF medications as described in their respective Risk Management Plans.

Question 3
Data collection timelines and submission to EMA
The Consortium considers that, for post-authorisation pharmacoepidemiology / pharmacoeconomic studies of new CF medicines, efficacy and safety data should be collected and submitted to Industry/EMA/HTA annually. Is this acceptable to EMA and HTA authorities?

Consortium's position
As most registries collect annual data, collecting and submitting data annually would be the most feasible way of assessing efficacy data. Specific safety data can be collected annually to complement

the already existing AE monitoring that exists in most European countries although registries would not be considered a substitute for other urgent safety reporting systems.

Reasons for use of annual data as opposed to more frequent reporting are

a) UK existing pharmacoepidemiology studies are using annual data upload. Only one UK study required six-monthly reports for five years and at our request the company concerned engaged with the EMA and changed to annual reporting
b) Annual review data may not be completed by some centres until the end of the calendar year, therefore, any analysis conducted mid-year may be disproportionate in study numbers and results may be misleading when comparing reports
c) More rapid reporting results in immediately starting one report just after delivery of the previous report which isn't feasible.

Depending on EMA requirements, encounter based collection and regular (3 or 6 monthly) submission of efficacy and safety data could be accomplished but the transition to encounter based collection of efficacy and safety data would require increased funding of CF registries that is not currently available. In selected cases, if encounter based efficacy and safety data were essential, a restricted study limited to European registries that collect encounter-based data could be proposed.

CHMP answer

Data collection in the ECFSPR is usually performed on an annual basis but there is also an option where data can be entered in real-time at each patient's visit (encounter module in the ECFSTracker) that are collated in an annual summary at the end of the year and submitted to the ECFSPR. Even if this latter option may be able to provide data more frequently the encounter module in the ECFSTracker is not widely used across centres (mainly due to lack of financial support). At this stage, the CF population captured using this module is not fully representative of the European CF population.

The current proposal of the Consortium is to collect and submit data on an annual basis. This appears reasonable even if there may be exceptional cases (e.g. emerging urgent safety issues) where more frequent reports could be required. In case of specific post-authorisation studies, timelines may be different, where reporting may not necessarily be needed on an annual basis. In such studies a specific duration of follow-up may be specified after which a report is expected to be compiled.

An additional consideration regarding reporting relates to the time needed between when data is received at the central registry and when these data are cleaned and available for inclusion in the analyses. During the discussion meeting, the Consortium clarified that registries upload data in different ways to the central ECFSPR repository. Irrespective of how these data are uploaded, a report to the EMA may be produced approx. 6 to 9 months after the reporting calendar year which is welcome. Some further delays for data cleaning, interpretation and report writing result currently in ECFSPR annual reports becoming available approximately 18 months after the close of the calendar year. For national registries who use excel file-uploads (13 out of the 17 national registries), the publication of national reports would normally be possible between 6 to 9 months after the end of the previous year. For countries where data are included manually but directly, once a year, into the ECFSTracker software (85 centres from 19 countries) the time-frame to generate the annual report for the EMA would be similar, i.e. 6-9 months. It may be possible to make reports available earlier to the EMA for those centres using the encounter-based module. This may be useful in specific cases.

In relation to the inclusion of new variables the Consortium noted that, ideally, this should be done at the start of the calendar year. Again, for those registries using encounter-based software a shorter time frame may be possible. The limitations of adding a new variable later during the year were acknowledged, e.g. information of the previous months might be missed, and the need for early interaction and careful planning between the registries and industry/EMA was again highlighted.

CHMP conclusion

For certain study objectives like long-term efficacy/safety data, the CHMP could broadly agree with annual reporting with the comment that specific study milestones for study reporting should be refined and tied to individual scientific questions. However for some other studies, where for example the study objective is an early quantification or confirmation of a specific safety finding (which is added in to the registry), the collection and reporting frequency of data may need further justification.

Question 4
Type of data to be submitted to EMA
The Consortium believes that summary data rather than patient level raw-data is sufficient for robust post-authorisation pharmacoepidemiology and pharmacoeconomic studies of new CF medications. Does EMA & HTA authorities agree?

Consortium's position
There is no additional scientific value to using raw data versus summary data. Raw data collected by registries can be analysed by the registry statisticians and the results shared with industry for reporting to EMA. We would propose that these statisticians would be independent and be university based. In the rare cases where the statistical plan was unacceptable to industry, a trusted third party could be used for the analysis.

Also, within the current registries' ethical approval and consent, it is possible to share summary data with industry/ EMA at regular intervals and could be provided without additional informed consent. Sharing of patient-level raw data with pharmaceutical companies would require additional informed consent which could take years to collect. It is currently the policy of the ECFSPR and National Registries not to share raw data with industry.

CHMP answer
The restrictions regarding submission of patient level raw-data to the industry and/or regulatory agencies are understood. During the discussion meeting, the Consortium stressed the limitations of sharing raw data as it would require laborious re-consenting of patients. Even if this was understood and in fact submission of raw data will not generally be required, the possibility exists that under certain conditions, anonymized patient data may be needed, e.g. to support regulatory decision-making, and needs to be considered.

The Consortium's proposal that patient level raw data will be analysed by ECSFR-certified statisticians for reporting to EMA and national authorities seems acceptable for most situations. In addition, they suggested that if, in certain cases, an independent re-assessment of the data would be required this could be conducted by an independent academic institution with no link with the industry. This is considered reasonable and generally adequate for most situations.

Question 5
Data quality and completeness
The Consortium considers that the existing data quality control mechanisms established and implemented by the European CF registries are sufficient for post-approval European pharmacoepidemiology and pharmacoeconomic studies of new CF treatments. Does EMA and HTA authorities agree?

Consortium's position
The ECFSPR and National Registries have agreed to a standardised approach to how data is defined, collected and presented in CF registries. Examples of these are enclosed in the attached documents (Appendix 2). This is part of the global Harmonization project initiated by CF Registries from Europe, US, Canada and Australia.

Data Quality at the ECFSPR level
A list of variables collected by the ECFSPR and definitions has been defined by the national registries in 2007 and is available: https://www.ecfs.eu/sites/default/files/general-content-files/working-groups/ecfs-patient-registry/VariablesDefintions3.14.pdf

The countries participating to the ECFSPR agree to comply with those guidelines. If it is not possible, they declare the discrepancies in an annual conformity document.

The data quality group developed a list of data quality controls so that countries apply them when they collect national data as well as a final check-list before uploading data. In case of discrepancy, data are corrected in the national and European databases. The controls are built into the ECFSTracker software and any discrepancies are reviewed by the ECFSPR statistician following submission of the data to ECFSPR. Any perceived errors are communicated to each centre and corrected if required. ECFSPR SOP for data is shown in Appendix 3.

Data Quality at the National level

National registries apply the European guidelines to their national questionnaire. A few registries follow guidelines like GPPs (Good Pharmacoepidemiology Practices). Nevertheless, a recent survey on data entry showed a diversity in organization, SOPs, quality control and background of people involved in national registries. Following this study, the data quality group decided to help national registries developing quality controls and assurance with the objective within two years of more than 90% of the countries attaining a reasonable level of quality.

Both ECFSPR and the National Registry software also have built in business rules to ensure that the data entered into the registry are within certain physiologic limits to reduced accidental error.
In the future, it is anticipated that audit with source verification of a sample (10%) of files will be performed as part of registry quality control.

Completeness of each variables varies. Most countries with >80% coverage would report >90% of required data. Note: Some registries may not collect information on a specific variable routinely, or in cases where the definition differs too much from the ECFSPR definition, the information will be set to missing.
Examples of completeness include in ECFSPR Annual Report 2014:
i) Age, gender ~100%
ii) CFTR Genetics, Age diagnosis, *P. aeruginosa* infection status: >95%
iii) Lung function (FEV1) /Nutritional measures (BMI): >85%.

CHMP answer

Overall the Consortium has quality assurance activities to ensure the quality of data. However, even if the ECFSPR and national registries have agreed to a standardised approach to how data is defined, collected and presented in CF registries, no details were provided in the initial submission to understand what data, and their quality, are available in each country. During the discussion meeting the structure of the ECFSPR and the role of the different parties involved were explained. In relation to the differences in variables' definitions across countries/centres, the ECFSPR has an ongoing project intended to harmonize variables and their definitions on a worldwide level which is supported (see question 1). Other aspects of data collection and data-quality checks were also explained, e.g. that once the data is received by ECFSPR the statisticians perform a final check and contact the centre/national registry in case there are inconsistencies, to correct or validate, according to a standard operating procedure. After the annual data report is published no changes are allowed unless in very exceptional cases. It was also mentioned that the upgraded version of ECFSTracker will include an audit trail functionality which is supported.

The ECFSPR data quality project group is working with national registries to enhance the quality of data across countries/centres. The objective is that, in the next two years, standard operating procedures will be used by 90% of the national registries, all registries will use coding documents and that data entry check at centre level will be 100%. These proposed targeted improvements are obviously welcome. There is also the intention to perform an audit at 75% of the participating centres by 2019. The audit is planned to be based on key factors from the annual report and pharmacovigilance studies and will cover 10% of the data provided. This would provide reassurance about the quality of data and is therefore supported.

With regard to data completeness the ECFSPR requires that centres and national registries complete the full data-set before submission. Once submitted, the ECFSPR statisticians check the data and ensure that the data are complete. As already mentioned in the answer to question 1, some registries may not collect information on a specific variable routinely, e.g. faecal elastase and faecal fat, or in cases where the definition differs too much from the ECFSPR definition, the information will be set to missing. According to the data submitted/shown (from 2015) completeness rate is promising and the percentage of missing information is, on average, low. Efforts should in any case continue to further minimize missing data, which include either information not available or data entry errors.

The extent of quality control mechanisms that are necessary to provide the requisite quality assurance will depend on the study objectives and the endpoints, particularly relating to the variability in the relevant parameter and accuracy of measurements that are deemed necessary. Therefore the quality/validity of the data will need to be justified at the time a study is performed also considering its objectives. Early interaction with all stakeholders, industry, regulators and ECFSPR is regarded relevant and should be considered at e.g. time of scientific advice. Depending on the specific study proposals and objectives, single or multi-country studies could be conducted. In case a single country

study is performed interactions with the particular country-based registry within the network, when possible, would appear adequate and the particular registry governance should be applied.

Question 6
Analysis plan of registry data
The Consortium considers that applying existing clinical trial methodology as well as propensity scoring mechanisms will be a robust way of analysing post approval pharmaco-epidemiology studies of new CF medicines. Does EMA and HTA authorities agree?

Consortium's position
Efficacy determination will be assessed using standard clinical trial statistical methodology. Changes in lung function and nutritional measures from baseline (pre-treatment) will be compared using mixed-effects models for repeated measures. Negative binomial regression models will be used to determine the number of pulmonary exacerbation events in pre- and post-therapy.

Registries also offer the opportunity to compare with patient groups that have not received therapy. For comparison of longitudinal changes in lung function (and other outcomes) to a registry control group (on no treatment), patients on treatment will be matched with up to five eligible control patients using a propensity scoring approach. This methodology has been used in previous studies using CF patients from the US CFF and UK CF registry. Candidate variables for propensity score matching will be based on identified risk factors related to CF lung function decline at baseline (spirometry measures, age, sex, nutrition measures, bacteriology, CF-related diabetes, and drugs). Annualized mean rate of change (slope) in $ppFEV_1$ will be estimated with all available FEV_1 measures and compared to controls using a mixed-effects regression models. This has been used successfully by the CFF and UK registries for post-approval registry studies. Refs below.

Safety analysis will be descriptive and will be presented as summary statistics. No formal statistical plan is envisioned for the safety analysis. We recommend that safety data be collected from a carefully selected control registry group for comparison.

Examples of post-authorisation propensity scoring studies in CF:

1. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, Huang X, Lubarsky B, Rubin J, Millar SJ, Pasta DJ, Mayer-Hamblett N, Goss CH, Morgan W, Sawicki GS. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017 Feb;5(2):107-118.
2. Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, Konstan MW. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med. 2015 Oct 1;192(7):836-42.
3. Bai Y, Higgins M, Volkova N, Bengtsson L, Tian S, Sewwal A, Nyangoma S, Elbert A, Bilton D. Real-world outcomes in patients (pts)with cystic fibrosis (CF)treated with ivacaftor (IVA): analysis of 2014 US and UKCF registries. Presented at ECFS 2016

CHMP answer
In principle, it is agreed that clinical trials statistical methodology may be applied, including the use of propensity scores that may be helpful to somehow compensate the allocation bias due to the lack of randomisation, for post-approval pharmacoepidemiology studies of new CF medicines. However, the most appropriate analysis method and the assessment of whether the propensity score approach is valid will depend on the research question, patient population, and outcomes for the specific study. It is anticipated that these considerations will be reflected in study-specific protocols and related statistical analysis plans.

It is important to consider that the potential set of variables required for the propensity score approach may vary among studies and will need to be available for the treatment and control groups. For example, as part of the propensity score analysis the registry data will first need to be reduced to the set of individuals who could have had the possibility of being in both the treatment and control group (e.g. those in the control group would have otherwise been eligible to receive treatment).It is noted that propensity scores can be used in several ways (i.e. matching, inverse probability of treatment weighting (IPTW), stratification and adjusting). While matching could generally be considered the preferred approach, the other methods may be more appropriate depending on the concrete study characteristics.

Also, a critical assumption for propensity score methods is that all confounders have been adequately measured and included in the propensity score model. While it may be difficult to anticipate the potential confounders in future studies, it is recommended that lists of confounders are generated for a range of anticipated studies to identify confounders that may not have already been considered for inclusion in the registry. The propensity to receive a treatment may also depend on clinic-level treatment policies (i.e. patients might be switched to a new treatment or receive supplemental treatment based on a broader policy rather than individual patient characteristics). In some situations sensitivity analyses based on instrumental variable analysis might be helpful to account for the potential bias of unknown confounders.

It is recommended that these considerations related to the anticipated use of propensity score analysis or other analysis methods to adjust for potential confounders are also extended to safety studies as this method can also be applied to safety-related outcomes.

Indeed there is no universal statistical solution to cover every situation. This applies to the methods described for the analysis. Negative binomial regression may be ideal to answer a particular scientific question and with better performance to the Poisson models; however, in other occasions extended Cox models accounting for recurrence and time-dependent covariates might be more adequate. Mixed Models for different type of variables might also be ideal but again not the best methods for some situations. The handling of missing data for intermediate time-points or to manage drop-outs might be completely out of the Missing At Random (MAR) assumption where those methods rely on. Thus, while in some cases even the assumption a Missing Completely At Random (MCAR) might be acceptable, in other cases the Missing Not At Random (MNAR) might be considered the only acceptable solution. It is described that the safety analysis will be only descriptive. Again, a different approach might be needed and a precise plan to manage different follow-up times and handling of missing data.

In summary, as discussed above, it is not possible to agree on a single statistical method for every situation. Therefore, the most appropriate statistical procedure would need to be selected/tailored on a case-by-case basis to specifically address the scientific question of interest and it would have to be predefined.

Other comments

As a general rule only in cases where a specific study protocol based on the registry requires making an intervention beyond clinical practice, such protocol should follow legal requirements for interventional trials. In this respect a distinction should be made between a disease registry itself, which is purely observational, and the specific studies, including pharmacoepidemiology studies or post-authorisation safety or efficacy studies (all based on specific protocols) that could be done within it, and which could be either observational or interventional depending on the data to be collected. In relation to this issue, which is not specifically addressed in the above report, the following recommendation/clarification has been issued by the Clinical Trial Facilitation Group and is included here for reference:

"The basic criteria defined in Directive 2001/20/EC for non-interventional clinical studies on safety and efficacy of medicinal products are that:

- the *medicinal product* is prescribed in accordance with the terms of marketing authorization, and the chosen therapeutic strategy is standard of care at a particular clinic and not decided in advance by a study protocol, and
- no additional *diagnostic* or *monitoring procedures* are applied to patients compared to normal practice at a particular clinic.

In situations of doubt whether a clinical study is an interventional clinical trial or not, the clinical trial unit of the national competent authority in the Member State where the research is planned should be contacted for advice.

In the future, similar criteria will apply as described above in the clinical trials regulation (EU) No 536/2014, which will apply after the Clinical Trial Portal and Database have reached full functionality (time point to be defined by EMA Management Board)."

965 **Appendix 1a**: ECFSPR Coverage by country*
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Table 1.1 Number of patients in year 2015, by country.

Country	Patients registered, not lost to follow-up	Patients seen	Estimated coverage 2015
Austria	733	704	90%
Bulgaria	134	134	66%
Czech Republic*	590	571	>95%
Denmark*	496	467	>95%
France*	6553	6553	90%
Germany*	5363	5363	>90%
Greece**	590	561	>95%
Hungary*	558	558	>90%
Ireland*	1263	1060	>90%
Israel**	665	550	95%
Italy*	5222	5206	95%
Latvia	38	37	>90%
Lithuania[1]	14	14	20%[1]
Luxembourg	26	26	>80%
Rep of Macedonia	114	105	>90%
Rep of Moldova*	54	45	68-76%
The Netherlands*	1401	1367	98%
Portugal**	338	300	>95%
Romania[2]	46	44	10%[2]
Russian Federation*	2883	2875	83%
Serbia	180	180	>90%
Slovak Republic**	256	213	>90%
Slovenia	96	94	>95%
Spain	1854	1772	62-66%
Sweden*	645	645	>95%
Switzerland**	878	852	>95%
Turkey	95	93	3%
Ukraine	159	122	15-18%
United Kingdom*	10810	9587	99%
Total	42054	40098	

* Countries with an established national CF registry.42054

** These countries have a national registry, but use the direct data-entry function of ECFSTracker.

[1] Coverage is 100% for adults and 0% for children.

[2] Coverage is 100% for children and 0% for adults.

The column "Patients registered, not lost to follow-up" shows the patients that attend centres, and includes patients that have not been seen during the year but are known to be alive that year. The column "patients seen" presents only the patients who have attended the clinic during the year. The column "Estimated coverage 2015" shows the estimated percentage of CF patients living in that country who are included in the national registry/national data collection as reported by the country. For some countries one individual centre may include almost all patients, e.g. Latvia and Serbia.
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Appendix 1b: Survival by Gross National Income across Europe

i) Classification of countries

country_long	gni_ca~t	gni_ca~a
Moldova	T1	2.24
Ukraine	T1	2.64
Macedonia	T1	5.14
Serbia	T1	5.54
Romania	T1	9.5
Russian Federation	T1	11.45
Hungary	T1	12.98
Lithuania	T1	14.94
Latvia	T2	14.98
Slovak Republic	T2	17.57
Czech Republic	T2	18.14
Greece	T2	20.32
Portugal	T2	20.53
Slovenia	T2	22.19
Spain	T2	28.53
Italy	T2	32.81
Israel	T2	35.77
France	T3	40.54
United Kingdom	T3	43.39
Belgium	T3	44.25
Germany	T3	45.94
Austria	T3	47.41
Netherlands	T3	48.86
Ireland	T3	52.58
Sweden	T3	57.92
Denmark	T3	58.55
Switzerland	T3	84.63

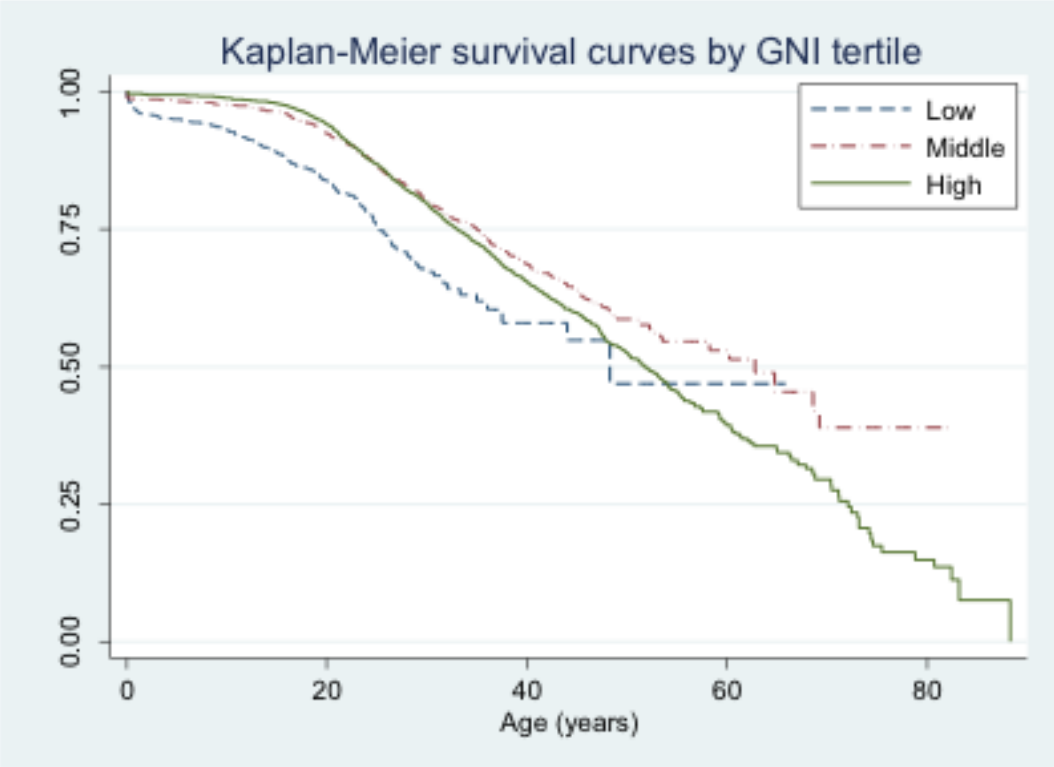
977 ii) Survival analysis by GNI Tertiles

Table 1: Summary statistics and results

GNI Tertile	Subjects	GNI range (per US$1,000)	Person years	Deaths	Median Survival Age (years) (95% CI)	Hazard Ratio (95% CI)*
Low	3,574	2.24 - 14.94	14359.9	155	48.3	1.80 (1.54 – 2.21)
Middle	10,187	14.98 - 35.77	43123.7	356	62.8	0.94 (0.83 – 1.06)
High	30,151	40.54 - 84.63	115361.8	1202	51.7 (50.1 – 53.8)	1.00 (ref)

GNI = gross national income; CI = confidence interval;* No confidence intervals were able to be calculated for the low and medium tertiles due to lack of data;** Hazard ratios and 95% confidence intervals calculated from a Cox regression adjusted for gender and F508 mutation class.

Figure 1: Survival Curves



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Appendix 2a: Examples of Variables (ECFSPR) and Complications (UK) collected in European CF Registries

Demographics	Therapy
CF centre code	Inhaled continuous hypertonic NaCl this year
Patient code	Inhaled continuous antibiotic this year
Year of follow-up	Inhaled continuous bronchodilators this year
Date of birth (year and month)	In Oxygen therapy this year
Gender	Use of rhDNase this year
Status of patient	Use of continuous azithromycin (or other macrolide) this year
Cause of death	Use of ursodeoxycholic acid this year
Date of death	Use of pancreatic enzymes this year

Diagnosis	Complications
Diagnosis confirmed	Allergic broncho-pulmonary aspergillosis this year
Age at diagnosis	Diabetes: daily insulin treated this year
Type of sweat test	Pneumothorax requiring chest drain this year
Electrolytes	Liver disease this year
Chloride value	Haemoptysis major over 250 ml this year
Meconium Ileus	Pancreatic status: faecal elastase
Neonatal screening	Pancreatic status: faecal fat
	Occurrence of malignancy this year

Genotype	Microbiology
First mutation	Chronic *Burkholderia cepacia complex*
Second mutation	*Nontuberculous mycobacteria* this year
	Chronic *Pseudomonas aeruginosa*
	Chronic *Staphylococcus aureus*
	Stenotrophomonas maltophilia this year

Follow-up	Transplant
Date of best FEV_1 recorded this year	Liver transplant
Value of best FEV_1 recorded this year	Year of latest liver transplant (if occurred before or during this year)
Value of best FVC recorded this year	Lung transplant
Height measured at date of best FEV_1 (or in case of no FEV_1 last height of the year)	Year of latest lung transplant (if occurred before or during this year)
Weight measured at date of best FEV_1 (or in case of no FEV_1 last height of the year)	

Appendix 2b: Example of complications collected by UK CF Registry

6.1.	Does patient have CFRD or impaired glucose tolerance?	○ Yes ○ No
	a. Impaired glucose tolerance	[ ] (mmol/l) ☐ Not known
	b. CFRD Diagnosis	○ CFRD with fasting hyperglycaemia ○ CFRD without fasting hyperglycaemia ○ Other glucose abnormality
	c. CFRD Complications	☐ None ☐ Diabetic Retinopathy ☐ Diabetic Microalbuminuria ☐ Other ☐ Not known
	i. If 'Other', please specify	[ ]
	d. Was patient prescribed treatment for CFRD?	○ Yes ○ No
	If 'Yes',	☐ Dietary change ☐ Oral hypoglycaemic agents ☐ Intermittent insulin ☐ Chronic insulin

Cancer

6.2.	Has patient been newly diagnosed with a cancer since last annual review?	○ Yes ○ No
	a. If 'Yes', Cancer type	[ ]
	i. If 'Other' please specify	[ ]

Septicaemia

6.3.	Septicaemia positive blood cultures since last encounter	○ Yes ○ No ○ Not known
	a. Septicaemia related to indwelling port catheter	○ Yes ○ No ○ Not known
6.4.	Septicaemia cultures identified	[ ]
	If 'Other' please specify	[ ]
	a. Septicaemia episode number	[▾]
	1st date	[ ] ☐ Not known
	2nd date	[ ] ☐ Not known
	3rd date	[ ] ☐ Not known
	4th date	[ ] ☐ Not known
	5th date	[ ] ☐ Not known

989 **Appendix 3:** ECFSPR SOP for data checking and uploading
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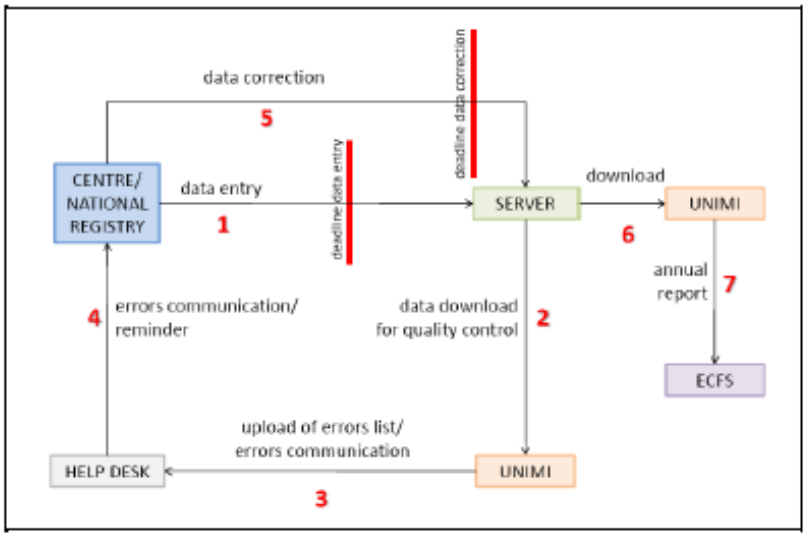
Standard operating procedure (SOP)
Error reporting and data correction

1. Purpose

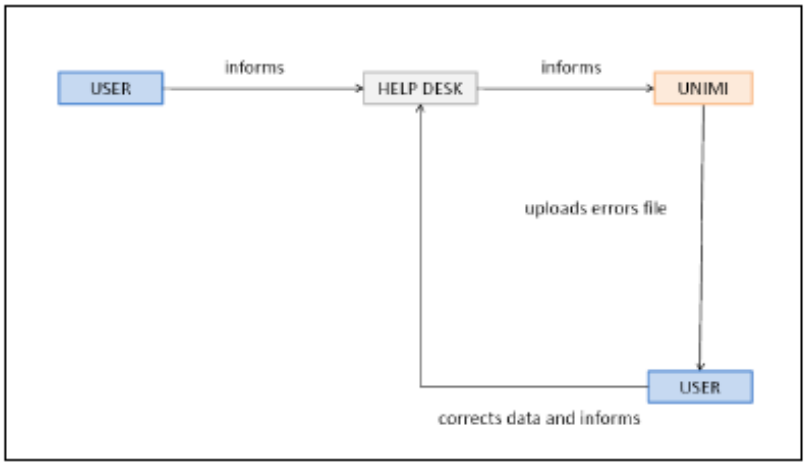
The purpose of this SOP is to describe a standardised approach for (1) reporting errors found in the ECFSPR database to data providers (centres/countries), for (2) reporting errors present in the database found by the users and for (3) correcting such errors. The overall procedure is outlined in figure 1.

Figure 1 Outline of SOP for error reporting and correction

A: errors detected by statisticians team



B: errors detected by the user



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2. Definitions

SD

The service desk, in charge of providing assistance to data providers.

UNIMI

The University of Milan, in charge of data management and statistical analysis of ECFSPR data.

RC

The Registry Executive Coordinator; is the person who provides a central role for information exchange, project coordination, management of sensitive timelines and general administration in the ECFSPR.

USER

Anyone allowed to enter/upload the data to the ECFSPR.

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3.1 Procedure for correction of errors detected by the statisticians.

This procedure is carried out on an annual basis, in preparation for data freezing and creation of the annual data report.

Step	Action	Responsibility
1	The SD sends by e-mail a reminder 4 weeks before and again to the centres that haven't sent their data, 2 weeks before the deadline for data entry to data providers.	SD
2	The SD sends by email a reminder 3 days before the deadline for data entry to users that they will be blocked and may not enter data for current year after the deadline.	SD
3	The day following the data-entry deadline, UNIMI prevents ALL users from entering the data for current year and downloads the database.	UNIMI
4	UNIMI performs data quality controls.	UNIMI
5	If no errors are found in a centre/country UNIMI reports this to the SD. Go to 6. If errors are found, UNIMI reports the codes of the centres/countries for which there is the need to correct the data to the SD. Go to 7.	UNIMI
6	The SD thanks the centres/countries for which there is not the need to correct the data, verifies the number of patients and notifies them that they will receive the annual report. Go to 16.	SD
7	The SD notifies the centres/countries for which there is the need to correct the data, that they will receive the list of errors in their database. The e-mail includes: • a confirmation of the number of patients; • a reminder that patients without the confirmed diagnosis will not be included in the registry as CF-patients; • the instructions on how to correct the data (open the software, use the interface to correct the data, notify the SD when they have completed the data correction), and the deadline for data correction.	SD
8	UNIMI creates one excel file containing the errors found in the database, according to the agreed format.	UNIMI
9	UNIMI notifies the SD that the excel files containing the errors found in the database are ready. The SD will be able to access the list of errors through the ECFSPR's secured website, when the excel files will have been uploaded.	UNIMI
10	The SD notifies the registry coordinator and UNIMI that e-mails with instructions have been sent.	SD
11	UNIMI uploads the errors on ECFSTracker and checks that the correct number of records have been uploaded. NOTE: This action allows the users to correct the data relating only to the records for which errors are found. All other records are blocked, i.e. not modifiable.	UNIMI
12	The SD periodically checks through the website the process of data correction and, one week before the deadline for data correction, sends an e-mail reminding this deadline to data providers.	SD
13	After the deadline for data correction, UNIMI downloads the database with corrections.	UNIMI
14	UNIMI performs data quality controls to check if errors still exist.	UNIMI
15	If errors still exist, data are put to missing for analyses.	UNIMI
16	Data are frozen for the current year. Physical freezing: on a CD Rom. Logical freezing: sending a command to the server from an UNIMI workstation.	UNIMI
17	End.	

3.2 Procedure for correction of errors detected by users

This procedure is carried out on a need basis, should any of the following happen:

1) If the users detect any error in their database, not detected by the statisticians team, but they are not allowed to make corrections because the users have been blocked (i.e. after step 2 of the procedure outlined in section 3.1). These errors are therefore detected when the ECFSPR working year is still active.
2) If the users detect any error in their database, not detected by the statisticians team, but they are not allowed to make corrections because the data have been frozen. These errors are therefore detected for closed years (i.e. after the annual data report has been finalized).

This procedure is NOT carried out when the users detect any error in their database, relating to the active year of the ECFSPR (i.e. before step 2 of the procedure outlined in section 3.1). In that case the user can correct the error directly in their program and it will be corrected in the central database when sent.

Step	Action	Responsibility
1	The user reports the error to the SD, specifying the year of update in which the error is present and the patient ID.	USER
2	SD informs UNIMI.	SD
	UNIMI allows the centre/country to correct the data on the requested year.	UNIMI
3	UNIMI creates one excel file containing the errors found in the database, according to the agreed format.	UNIMI
4	UNIMI notifies the SD that the excel file containing the errors found in the database is ready.	UNIMI
5	The SD sends the user the instructions on how to correct the data (open the software, use the interface to correct the data, notify the SD when they have completed the data correction).	SD
6	The SD notifies UNIMI that e-mail with instructions has been sent.	SD
7	UNIMI uploads the excel file with errors on the server and checks that the correct number of records have been uploaded. NOTE: This action allows the users to correct the data relating only to the records for which errors have been reported. All other records are blocked, i.e. not modifiable.	UNIMI
8	UNIMI informs the SD that the file has been uploaded.	UNIMI
9	SD informs the centre/country that the file has been uploaded and corrections are now possible.	SD
10	The user informs SD that the correction has been made.	USER
11	SD informs UNIMI that the centre/country in question ended the data correction.	SD
12	If the corrections refer to the active year of the registry and the annual data report has not been finalised yet, UNIMI downloads the database with corrections and uses it for the annual data report. If the corrections refer to frozen years, no further actions will be necessary.	UNIMI
13	End.	

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[i] All annexes mentioned under the Applicant's position refer to the documentation submitted with the request.

Standard operating procedure (SOP)
Annual report

1. Purpose

The purpose of this SOP is to describe a standardised approach for creating the annual data report of the ECFS Patient Registry (ECFSPR).

2. Definitions

RD

The Registry Director; is the person appointed by the ECFS Board who assesses the project progress.

RC

The Registry Executive Coordinator; is the person who provides a central role for information exchange, project coordination, management of sensitive timelines and general administration in the ECFSPR.

EC

The Executive Committee; is in charge of monitoring the ECFSPR activities.

SD

The Service Desk; is in charge of providing assistance to data providers.

UNIMI

The University of Milan; is in charge of data management and statistical analysis of the ECFSPR data.

USERS

Anyone allowed to enter/upload the data to the ECFSPR.

3.1 Procedure for drafting the annual report.

This SOP is carried out on an annual basis, after the error reporting and data correction described in the SOP for error reporting and correction (version 3).

Prerequisite: final clened data are in the database.

Step	Action	Responsibility	No. of working days needed	Minimum no. of working days needed
1	UNIMI performs statistical analyses on the final cleaned database according to the agreed contents of the report and considering the information obtained from the ECFSPR Variables Conformity Survey (http://study.ecfs.eu/node/10)	UNIMI	20	15
2	UNIMI drafts tables/basic graphs by country and sends them to the registry director for revision	UNIMI	20	15
3	The registry director reviews the tables/basic graphs and sends comments/corrections to UNIMI	RD	5	5
4	UNIMI makes amendments, if needed, on the tables/basic graphs according to registry director's comments/corrections and sends to SD (and to the registry coordinator for cc) the tables/basic graphs	UNIMI	10	5
5	SD sends to the users the tables/graphs for checking the numbers	SD	1	1
6	The users send comments/corrections on the tables/basic graphs to UNIMI through a webbased questionnaire specifically created to collect comments/corrections on the annual report	USERS	15	10
7	UNIMI makes amendments, if needed, to tables/basic graphs according to the feedback received from the users	UNIMI	15	10
8	UNIMI creates the annual report and sends it to the Executive Committee for comments	UNIMI	15	10
9	The Executice Committee sends comments on the annual report to UNIMI through the questionnaire	EC	5	5
10	UNIMI makes amendments, if needed, finalises the annual report and sends the annual report to the registry coordinator	UNIMI	10	5
11	The registry coordinator sends the annual report to the users	RC	1	1
12	The users send comments on the annual report to UNIMI through the webbased questionnaire	USERS	10	5
13	UNIMI makes amendments, if needed, and sends the annual report to the registry coordinator	UNIMI	15	10
14	The registry coordinator sends the approved report for printing, uploading to the website and to the Steering Group	RC	1	1
15	End			