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Report on Cystic Fibrosis Registries - Workshop 14 June 2017

Patient Registries Initiative

1. Executive summary

The EMA [Initiative for Patient Registries](#) aims to optimise and facilitate the use of patient registries for benefit-risk evaluations of medicinal products in the European Economic Area. Following a workshop in October 2016 that explored barriers and challenges to collaboration between stakeholders including registry owners, patients, regulators, reimbursement bodies, marketing authorisation holders and health technology assessment (HTA) bodies, the EMA hosted a workshop on cystic fibrosis (CF) registries in June 2017.

This explored in detail the factors to be addressed by an already well-organised Europe-wide collaborative registry in order to optimally support CF treatment benefit-risk evaluations of appropriate quality and representativeness for informing regulatory decisions. The outcome of the workshop was agreement by the stakeholders on implementable recommendations that will advance this objective. The factors discussed included registry governance, patient consents, data sharing, data quality, registry interoperability, and core common data elements needed by stakeholders.

Participants comprised representatives from the European CF Society Patient Registry (ECFSPR), national CF registries, marketing authorisation holders (MAHs), HTAs, national competent authorities (NCAs), and the European Medicines Agency (EMA). Prior to the workshop, participants considered questions relating to the factors to be discussed and provided information that formed the basis of the workshop discussions. This report includes participant observations on the current situation at national and European level in respect of the factors discussed, and in each case, makes recommendations for advancing the systematic use of registries to support regulatory evaluations.

The CF patient registry landscape in Europe is already well-established as evidenced by existing agreement on a core dataset collected by all registries, standard terminologies and definitions, existence of a shared registry platform with supporting software, the production of annual Europe-wide reports, and participation in post-authorisation studies of new treatments. For regulators, the geographical spread of the registry network is a key factor for understanding treatment practices and outcomes across the EU and data need to be of appropriate quality.



To ensure CF registries contribute optimally to regulatory evaluations throughout product lifecycles, the immediate priorities are to establish robust measures to assure the quality of registry data including the verification of source data uploaded to the national registries, to improve communications between registry holders, regulators, MAHs and marketing authorisation applicants (MAAs), and to create a centralised data application process with a fixed template research protocol to expedite evaluations. Table 1 summarises the main recommendations made by workshop participants and the agreed actions to be implemented to ensure the objectives are achieved.

Table 1: Summary of the main recommendations

Topic	Participants' Recommendations	Agreed Actions	Owners
Governance	Communicate to the public the benefits and uses of patient registry data	Improve registry holder, MAH and regulator communications so that registry holders understand the nature and quality of data needed for regulatory purposes and MAHs and regulators understand what information may feasibly be collected	ECFSRP
	Regulators and MAHs/MAAs to be aware of the data that can feasibly be collected by registries and to inform registries in advance on their data needs		Regulators MAHs / MAAs HTAs
	Registry holders should establish centralised data application process with a standard template for data requests	Set up a standard process for MAHs and regulatory requests for registry data	Reimbursement bodies
Informed consents, data protection and data sharing	Ensure all registry patients have provided informed consent	Registries to undertake audits of patient consents at appropriate intervals ensuring they are current and that any restrictions on data use and consent withdrawals are recorded	ECFSRP Registry Task Force
	Review whether the current consent is broad enough for possible future situations taking into account EU General Data Protection Regulation		
	Develop a policy on sharing summary, pseudo-anonymised, and individual patient data	Draft a policy on data-sharing with stakeholders	
Data Quality	Develop an agreed set of data quality indicators to be applied to all national registries.	Data quality to be audited regularly in national registries and the ECFSRP.	ECFSRP Regulators Registry Task Force ECFSR Data Quality Group
	Include source data verification procedures	Audit Results to be reported in the ECFSRP annual report	
	Agree on EU data quality standards to apply to the indicators	Propose EU standards for data quality indicators and for formal accreditation of registries for supporting regulatory evaluations (e.g., a regulatory qualification)	
Processes for Data upload	Explore options to minimise the number of (manual) steps and duplications in data entry	Map and review the current processes at national level to determine if steps could be removed or simplified	ECFSRP
Data elements	Existing ECFSRP common data elements are a suitable basis for regulatory evaluations	Allow targeted expanded data collection on a time-limited basis for specific evaluations	ECFSRP Patients
	Include patient reported outcome (PRO) measures	Agree on relevant PROs to be included for selected evaluations	HTAs Reimbursement bodies

Table 2 summarises the actions required from each of the stakeholder groups to deliver the workshop recommendations.

Table 2: Summary of actions for the main stakeholder groups

Group	Actions
Regulators	<ul style="list-style-type: none"> Promote the potential value of data from patient registries to relevant stakeholders Facilitate communications between registry holders and MAHs/MAAs Support registry holders to establish robust measures for data quality assurance and provide guidance on mechanisms for accreditation of registries using existing platforms, e.g, a qualification procedure Include patient registry data where appropriate in regulatory processes throughout product lifecycles Engage with relevant initiatives that are also exploring the potential of registry data for healthcare evaluations, e.g., the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3
Registry Holders	<ul style="list-style-type: none"> Ensure harmonised processes for quality assurance of data, including source data verification, are applied systematically across CF registries Obtain accreditation for data quality and registry standards Develop a policy on sharing summary, pseudo-anonymised, and individual patient data Develop a standard process for handling MAH/MAA and regulatory requests for registry data Inform patients on the benefits and uses of registry data including appropriate data sharing with relevant stakeholders. Inform MAHs/MAAs and regulators of the type and detail of data that may feasibly be collected by registries and shared within consent and governance parameters
MAHs / MAAs	<ul style="list-style-type: none"> Understand the regulatory data requests that are likely to arise in the event of a successful application, especially for post marketing surveillance Consider early in new product development if appropriate registry data would have a place in the regulatory evaluations Identify if a suitable patient registry exists Develop a preliminary study protocol and explore with the registry holder/s and the regulator if the registry could fulfil the data needs
Patient Representatives	<ul style="list-style-type: none"> Engage with registry holders in order to understand and communicate to patients the potential uses and associated benefits and risks of sharing patient registry data to assist in medicines evaluations Advise on patient reported outcomes that might feasibly be collected in registries.
HTAs and Reimbursement Bodies	<ul style="list-style-type: none"> Learn about the nature and purpose of the data collected in patient registries Engage with registry holders to adapt registry data collection where feasible to support information needs Continue engagement with stakeholders through current initiatives, e.g., EUnetHTA Joint Action 3

In the next step, the CF stakeholder groups need to develop implementation plans. They will be facilitated in this by the EMA Registries Task Force.

2. Background

The EMA is exploring the use of real world data in supporting medicines authorisation. Its [Initiative for Patient Registries](#), launched in September 2015, aims to optimise and facilitate the use of existing patient registries for the benefit-risk monitoring of medicinal products throughout their lifecycles. Regulators and marketing authorisation holders face multiple challenges currently in using registry information to support benefit-risk evaluations of new treatments. These include poor coordination between ongoing initiatives at national and international level, absence of harmonised protocols, scientific methods and data structures for undertaking registry-based studies, limited transparency and capacity for data sharing and in some cases, doubtful sustainability of the registries.

At a Patient Registries Workshop in October 2016, stakeholders including registry holders, patient groups, MAHs, regulators and HTA and reimbursement representatives made recommendations on optimising the use of registry data – [Report of the Registries Workshop](#). The EMA undertook to deliver on a number of the activities arising, including bringing together stakeholders in certain disease areas to discuss particular recommendations and to act as exemplars for later recommendations generalizable to registries more broadly. The Cystic Fibrosis (CF) Registries Workshop was the first of these. It aimed to come to agreements on implementable recommendations that will help to assure the quality and interoperability of CF registry data for supporting regulatory evaluations while ensuring also that appropriate governance arrangements are in place.

The CF landscape is already quite mature from a registries perspective. The well-established European CF Society Patient Registry (ECFSR) is a common platform onto which data from thirteen national registries are uploaded annually and eighteen countries input data annually directly onto the platform. With an agreed core common data set of CF parameters and governance already in place, national registries collaborate, contributing data to undertake Europe-wide studies of CF care and treatment outcomes (<https://www.ecfs.eu/ecfspr>).

3. Workshop objectives, participants and methodology

3.1. Objectives

The primary objectives of the workshop were to agree on:

- ❖ Implementable recommendations on core data elements to be collected in CF registries, common procedures, consents, governance, data quality, and registry interoperability
- ❖ Actions to be taken for the further development and finalisation of recommendations.

3.2. Participants

All of the workshop participants had involvement with CF from a scientific, clinical or regulatory perspective. They included national registry and ECFSPR representatives, national competent authority

(NCA) CF medicines assessors, EMA assessors, a HTA representative, marketing authorisation applicants (MAAs) with CF products in development and MAHs with CF products on the European market. A patient representative had to withdraw and no reimbursement agency representative was available. The Workshop Agenda and Participant List are available in Appendix 1.

3.3. Methods

Participants selected one of three topics for group work:

- Group 1 – Common data elements needed by all stakeholders; Data validation
- Group 2 – Informed consents, governance, data protection, individual data v aggregated data; Ownership of data
- Group 3 – Common procedures, registry interoperability, quality assurance to support regulatory evaluations and data analysis.

Each group included participants representing registry holders, regulatory assessors, and MAAs/MAHs. Five weeks before the workshop, participants were sent a group-specific pre-work package that sought their views, experiences, and needs in relation to their group topic (Available in Appendix 2). The EMA Patient Registries Initiative team collated the responses and provided these as background information for each group during the week prior to the workshop. The intention was that participants had a good understanding of each other's perspectives in advance of the workshop in order to facilitate productive group work on the day.

At the workshop, following introductions, each group worked together with two moderators to discuss their topic, agree their recommendations, and then present these to the whole group who further discussed and refined them and agreed on the main recommendations and next steps. Throughout the discussions, the moderators made detailed notes of participants' observations in order to provide context for the final report and to explain factors that facilitated or limited the scope of the recommendations.

Following the workshop, the Patient Registries Initiative team drafted the observations and recommendations made by each of the three groups and circulated these to the group members for review and amending (Summaries by Group available in Appendix 3). These were then collated into the eight sub-sections that are contained in Section 4 and are followed in Section 5 by an outline of the actions arising and their owners. The Patient Registries Taskforce will facilitate implementation of the recommendations by working with the owners in each case to establish task and finish work groups to deliver on the actions. The taskforce will also publish an implementation plan.

4. Workshop observations and recommendations

In this section, participants' detailed observations and recommendations relating to the use of CF patient registry data to support medicines evaluations are set out.

4.1. Utility of CF registries for regulators and marketing authorisation holders

Observations

- The availability of registry data in aggregate form to third parties such as regulators and MAHs would be of great value potentially for post-authorisation studies of safety and effectiveness.
- While registries may be useful for safety evaluation, they may be less useful for real time safety signal detection because data are not uploaded during each patient encounter and they do not routinely collect all of the information needed for pharmacovigilance purposes.
- Retrospective use of registry data for safety evaluations is considered as secondary use thereby falling under good vigilance practice (GVP) rules for safety data reporting (GVP Module VI: Management and reporting of adverse reactions to medicinal products).
- For MAHs, registries should fulfil the following criteria: availability of appropriate, verifiable data, adequate sample size, timeliness of response and of interactions between the MAH and registry holders.
- For regulators, the geographical spread of the registry network (i.e. wide range of EU countries) is a key factor for understanding treatment practices and outcomes across the EU and data need to be of appropriate quality.

Recommendations

- MAHs, regulators and registry holders, plus other stakeholders where relevant (for example, reimbursement bodies), should engage in discussions early during the regulatory processes for approval of new treatments to consider data needs and scientific / study protocols and to understand the range and nature of data that registries could provide, especially for post-authorisation studies.
- A centralised process with standard operating procedures (SOPs) for requesting registry data and would facilitate consistency in the information provided to registry holders by stakeholders requesting data.
- Standing agreements between MAHs and registry holders could facilitate provision of data for regulatory procedures, either routine (e.g., periodic safety update reports (PSURs), or exceptional (e.g., during a referral procedure).
- While acknowledged that registries are not the best source for identifying adverse events in real time, automated flagging of designated events may help identify certain serious events

and alert physicians to report them through normal routes but should not replace spontaneous reporting by physicians.

- For a specific post-authorisation study or adverse event signal validation, registries could participate in targeted, time-limited, monitoring following a protocol agreed with the requesting stakeholders. Studies should be registered into the EU PAS register.
- For a prospective post-authorisation safety study (PASS) to be set up within a registry, the study protocol should ensure that data collection is in accordance with GVP requirements (GVP Module VIII, PASS).

4.2. Governance and timelines for data requests from registries

Observations

- A key principle of registry governance is the protection of the patient (and site as necessary) anonymity.
- Current governance includes scientific board review and recommendations on requests for registry data. For urgent requests, the review process can be accelerated.
- Data analysis can be undertaken internally or through a third party (e.g. academic). The capacity for internal statistical analyses varies across registries. When results are shared with regulators or MAHs, independent third-party analyses are preferred by regulators if there is no adequate capacity to perform analyses internally, taking into account that potential conflicts of interest must be managed appropriately.
- Timeliness is important and providing recent data within short deadlines is currently a challenge for many registries.
- National registries holders have limited capacity to upload clinical information into the ECFSPR more frequently than once a year (usually at the beginning of the following calendar year).
- Funding may be obtained for services that registries provide to MAHs and (and in some cases) to regulators.

Recommendations

- Registry holders could establish a working group to agree on a common approach to the collection, reporting and sharing of data.
- Regulators should establish communications with both Registry holders and MAHs with the following objectives:
 - To be aware of the data that are collected or can be collected by registries when information or studies are requested by regulators from MAHs.
 - To support registry holders' understanding of regulators' requests to MAHs and of the data elements and the quality standards required.

- Regulators and registry holders should communicate to the patients and healthcare providers the benefits for public health and the potential uses of the data arising from patient participation in registries.
- Regulators and MAHs must understand the time schedule for data provision but given the time needed to upload data in the EU database, national registries could be approached if data are required very urgently.

4.3. Informed consents

Observations

- The current informed consent and governance framework permits provision of summary information from registries to external organisations such as regulators and MAHs. It may also allow provision of pseudo-anonymised data where justified by specific circumstances such as investigation of urgent safety or efficacy concerns.
- All registry based studies are conducted within the limits of the original consent obtained when joining the registry. Currently, the framework does not allow provision of individual patient data to MAHs.
- Patients are informed about the type of information that could be provided to external stakeholders (e.g., lung function, sputum culture data).
- For children included in the CF registries, a consent form is signed by the legal guardian/parent. Children need to provide their own consent once they reach the adult age of consent (16 or 18 years depending on the country).
- The impact of the new Generalised Data Protection Regulation ([GDPR regulation](#), to enter into force in May 2018) will be evaluated by registry holders. This is not expected to require important changes in the current framework of informed consent.
- Challenges of the current framework of informed consent are:
 - the need to ensure that national requirements are followed - this is a challenge for multinational registries.
 - consents are paper-based - electronic forms are not used, therefore tracking child to adult consents, restrictions, and withdrawals of consent is complex.

Recommendations

- The ECFS may wish to consider potential revision of the informed consent: 1), to cover all possible uses of registry data in line with the applicable legislation, 2), to apply to the range of situations where data might be shared in summary or (in rare circumstances) individual patient format, and 3), to accommodate patient requests that use of their data is limited to some organisations (such as regulatory authorities) or situations (such as to investigate a pharmacovigilance issue).

- Registry holders should assess the impact of the forthcoming GDPR regulation on circumstances where data sharing can be allowed (e.g. in the interest of public health – see Appendix 4).
- A policy on situations where sharing of summary, pseudo-anonymised data or individual patient data is permitted and acceptable should be developed to provide transparent guidance for potential requesters such as regulators and MAHs.

4.4. Data sharing

Observations

- Individual patient data are owned by the patients and/or CF centre. Tables generated from registry data and provided to a requester are owned by the requester and may be used only for the purpose defined in the request.
- Data collected for a sponsored clinical trial or post-authorisation study are owned by the sponsor and specified in contractual agreements between the sponsor and the registry holder.
- As noted (4.3. Informed Consents), the current framework does not permit sharing of individual patient data with MAHs.

Recommendations

- In cases where a MAH needs to provide registry data to regulators as part of a post-authorisation study, direct communications should take place between the registry holder, the MAH and the regulator to agree on the data that can be shared.
- Regulators need to consider how they could engage effectively with registry holders. EMA Scientific Advice could be an entry point for involving registry holders as well as MAHs in considerations of data needs for supporting regulatory evaluations.

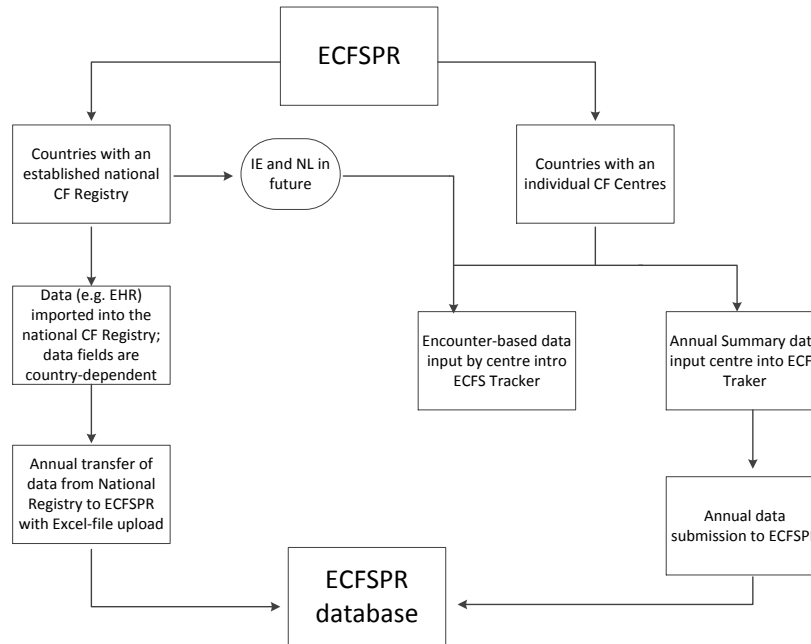
4.5. Processes for data upload into registries

Observations

- Registry holders from the Netherlands, France and the UK described their current data upload processes and future plans (Figure). Currently, data are uploaded manually from CF centre clinical records, including electronic health records, into the national CF registries. After data cleaning and management, data are uploaded annually into the ECFSPR.
- Following data upload to the ECFSPR from national registries, the data are cleaned, reviewed by the ECFSPR data analyst and discrepancies resolved directly with national registries. ECFSPR staff create an annual report that is usually published around 18-months following national uploads. For example, the annual report for 2016 will be available in Summer 2018.

- Validity checks are built into ECFS Tracker, the customised software program used for upload of CF data into the ECFSPR.
- In the future, some registries are planning to collect encounter-based clinical data using ECFS Tracker. This will reduce both duplication of effort in terms of manual data entry and risk of transcription errors.

Figure: Processes for data upload



IE=Ireland, NL=Netherlands, HER = electronic health record, ECFSPR= European CF Society Patient Registry

- Provision of data for products registries set up by MAHs: products registries are independent from the ECFSPR. Participating CF centres enter data into the products registries on an agreed frequency (e.g. every 3 months). These registries generally have inbuilt queries to assist with data cleaning and quality assurance. An interim analysis is performed following a data lock point. There is some duplication between the data collected in products registries and in the ECFSPR.
- Notwithstanding the lead time for publication of the ECFSPR annual report, data could be provided earlier upon request from regulators and in exceptional circumstances when access to individual patient data is required (e.g. urgent safety or efficacy issues/signals).
- There are currently five ongoing long-term EU pharmacovigilance studies utilising the UK CF Registry. Study update reports are published approximately 6-9 months following the end of the data entry year.

Recommendation

- Encounter-based data entry would minimise the number of (manual) steps and duplications currently needed to enter data into the national registries and from national registries to the ECFSPR.

4.6. Data quality

Observations

- Some data quality checks are already embedded in the national registries (FR, NL and UK) and in the ECFSPR through mandatory fields, visual prompts, and alerts to minimise errors (e.g. out-of-range data). In FR, software that recognises stable data fields has reduced manual data entry during the annual submission. The UK has a web-based platform that includes colour coding, text prompts and a user guide, all assisting in reducing errors and duplications.
- Potential barriers to data quality assurance were identified, including:
 - Lack of dedicated registry funding
 - Lack of national registry coordinators
 - Duplication of data entry
 - Timely data availability.

Recommendations

- Develop an agreed set of data quality indicators to be applied annually to each national registry
- Include national data quality information as a section in the ECFSPR annual report.
- Organise regular audits of the national registries and the ECFSPR to help guarantee data quality.
- Establish processes for source data verification.

4.7. Developing an agreed set of data quality indicators

Observations

- Table 3 includes suggestions from the group on how to define Data Quality (columns 'Elements' and 'Definition'), and how it could be measured using harmonised standard indicators of quality.

Table 3: Data quality elements

Elements	Definition	Indicators of quality	Solutions
Consistency	Uniformity of the data collected over time (e.g. same lab data entered annually)	Measure of number of fields filled over time (different standards on critical fields): e.g. 95%	<ul style="list-style-type: none"> Standard Terminology, Coding Standard Operating Procedures, User guides Menus, alerts, prompts Help screens/desk, training, newsletter
Accuracy	How well is the data entered? [eg, error frequency, out-of-range data, duplicates]	Changes in values of data filed creates alerts; Subset of variables tracked;	<ul style="list-style-type: none"> Validate against source data (e.g. 10% of registry data) Audits / Inspections Training, software checks
Completeness	How much data is missing?	Different for different indicators. Primary indicators strive for >90% completeness.	<ul style="list-style-type: none"> Audits / Inspections Mandatory fields to avoid missing data Trainings
Details	Lists of data variables	Between-registry consistency in variable definitions	<ul style="list-style-type: none"> Registry lists of data variable and their definitions
Representativeness	How well/accurately is the exposed population reflected by the registry data?	% of patients covered (compared to national social security systems)	<ul style="list-style-type: none"> Better linkage between systems Better communication to patients for enrolment

- Considering the observations above, enablers were identified that would help to operationalise data quality assurance measures:
 - Transparency of registries: e.g. provide feedback to clinicians or dashboards for healthcare professionals to view the evolution of their patients and understand the benefit of their contribution
 - Education of all stakeholders on assuring data quality
 - Agreement on indicators and standards of quality
 - Communication with regulators to understand regulatory data needs and acceptable standards
 - Funding or reimbursement based on completeness and quality of data
 - A process for registry audits and formal accreditation (e.g. by regulatory bodies) would increase trust in and empower registries.

Recommendations

- Agree on standards for data quality indicators, terminologies/coding and reporting requirements to apply to national registries and to the ECFSPR.
- Communicate the value of registries, their limitations, and the importance of consistent data quality to all participating healthcare professionals and to those using the data including MAHs, regulators, HTA and reimbursement bodies.

4.8. Common data elements

The ECFSRP has an agreed list of core common data elements with associated definitions, quality standards and inclusion criteria (Appendix 5). In the current initiative, there is no proposal to change the common data elements.

The observations and recommendations that follow below relate to the workshop discussions of challenges common to all CF registries, areas of difficulty in recording precise information, and considerations of whether and how these issues might feasibly be addressed.

4.8.1. Medication-related information

Observations

- Related to the information on the registry database, registry holders explained that generally, all information is entered manually by CF clinic staff and is mostly transcribed from the hospital/clinic record. For this reason, they include mainly CF-specific treatments.
- Recording the start and stop date of medication is problematic because while a clinical note might indicate a medication to be commenced, there is no straightforward means of knowing when it was dispensed and the patient actually commenced it. Similarly for the stop date for medications ceased or with a defined duration (e.g., a new antibiotic course). It was noted that this is less of a problem with new / expensive CF medicines than with older, more familiar, less expensive medicines.
- Dose changes over time are difficult to determine and to record. The start and stop dates for children's drugs are easier than for adults (who usually take more medications).
- Self-medication and variable doses are difficult to record. Short antibiotic courses are not comprehensively captured, especially for oral antibiotics prescribed in the community. IV medications for exacerbations are more completely captured. Medication adherence cannot be determined.
- As examples, the Swedish registry mentioned that co-medication is not very well recorded if the drug is not specific for CF. The UK registry can record the start and stop date for short term use of new CF drugs under investigation and the start date for long-term medications. The start/stop dates for 'month-on/month-off' antibiotics cannot be recorded.
- Regulators felt that at least all of the medications related to cystic fibrosis, and especially all inhaled/intravenous antibiotics, should be captured as indicators of both CF progression and numbers of exacerbations. Ideally, for regulators, medication for CF should indicate start/stop dates and dosing schedule.
- MAHs remarked that for safety / intolerance and to give some idea of effectiveness, it would be useful to know when and why a product was stopped.
- As a general wish, registry holders, supported strongly by the group, mentioned that linkages between registries and national health databases would assist in minimising duplicate data

entry to a registry from other data sources. However, this was not anticipated to happen in the foreseeable future for most/all registries.

Recommendations

- All CF-related medication should be recorded with dose and start/stop dates as precisely as possible; if actual dates cannot be determined, the month of commencing / stopping and the duration of treatment are of value and should be recorded.
- For any CF treatments ceased, the date (as precisely as possible) and reason should be recorded.

4.8.2. Co-morbidities and associated medications

Observations

- Some registries include tick box lists of co-morbidities (the UK has a list of approximately 20 co-morbidity tick boxes). Information on all medications prescribed and their indications was considered necessary in order to have a record of co-morbidities and to be alert to drug interactions, e.g. concomitant use of anti-depressants, anxiolytics, hormonal contraceptives.

Recommendation

- Record patients' co-morbidities and associated medications with indication, current dose but not start/stop dates.

4.8.3. Medication-related adverse events

Observations

- Registry holders noted that registries are not suitable for identifying adverse events in real time. Medication-related complications are not systematically pro-actively sought or recorded. Participants did not consider that doing so was feasible. As uploads are annual, registries are also unsuitable for expedited adverse event reporting.
- Registries could be used to evaluate signals or new/potential safety issues on a targeted, time-limited, basis and would be willing to do so upon specific request and protocol from a MAH or regulator; patients exposed and not-exposed to a certain treatment could be monitored.

Recommendations

- It is not feasible for registries to seek and record medication-related adverse events or complications.
- For specific signal follow up, registries could participate in targeted, time-limited, monitoring following a protocol agreed with the requesting stakeholders.

4.8.4. Clinical trial participation and recording of trial medications, compassionate use (managed access), and off-label use of treatments

Observations

- Information on clinical trial participation is not consistently sought /recorded in all CF registries. Trial participation may be missed altogether due to short 6-month clinical trial treatment periods (typically) that may not be recorded in the annual review of patient histories when preparing the data to be uploaded into the registry.
- Participants considered it desirable to record if patients are enrolled in a clinical trial, for example, in the case where some CF drugs cannot be taken concomitantly with a trial medicine thereby explaining deviation from recommended practice. The UK registry remarked that all of its fields on clinical trial participation were not being filled & some are under consideration for removal.
- A separate consent is completed when patients participate in a clinical trial. Trial data are not recorded in or shared with the registry.
- If a patient is known to be participating in a clinical trial, it will be unknown while the trial is ongoing whether the patient is taking active or placebo medication.
- Both compassionate use and off-label use of medications are captured in national registries and the ECFSPR.

Recommendations

- Pro-actively ask about and record clinical trial participation.
- Include as fully as possible information on compassionate use and off-label use of medications.

4.8.5. CF Exacerbations

Observations

- There was a discussion on whether respiratory exacerbations are CF-related events or treatment/medication-related events. The consensus was that they are CF-related.
- MAH participants felt that exacerbations should be pre-defined (with standardised terms and values). This would be helpful for long-term observations and follow-up. Registry holders noted that this is not feasible as there is no specific definition of exacerbation and severity varies, both within & between patients. In general, exacerbations treated with oral antibiotics are likely to be less severe than those needing intravenous antibiotics and/or hospitalisation.
- While the current annual dataset does not capture all of the short-term antibiotic treatments, especially oral antibiotics, registry holders can record how many times the patient reported taking antibiotics for respiratory exacerbations. As a general observation, intravenous antibiotic treatments are recorded more accurately and completely than oral treatments (as preceding section).

Recommendations

- Respiratory exacerbations should be considered as CF-related events. In the CF clinical care setting, an exacerbation is a clinical diagnosis and a standardised definition is not possible.
- Record the number of days per year of intravenous antibiotic use and/or hospitalisation.

4.8.6. Severity of CF at commencement of a new treatment

Observation

- For patients starting a new therapy, regulators felt that the CF severity at that point should be clearly defined. This could help with outcomes / benefit follow-up. In practical terms, it is feasible to base judgement of severity on the most recent registry-recorded measures of FEV1, BMI, infection status, pancreatic enzyme use, and so on, but it is not possible to determine these measures again on the date of a new therapy commencement.

Recommendation

- For an indication of CF severity status at commencement of a new treatment, the most recently registry-recorded severity parameters may be used as measures.

4.8.7. Hospitalisation

Observations

- Registries record the total days of hospitalisation during the year.
- Only hospitalisations related to CF are captured.
- Emergency room visits are not captured.

Recommendation

- No new recommendation or query: days of hospitalisation annually are recorded (as are days of intravenous antibiotics which may exceed days of hospitalisation in situations when intravenous treatment can be provided in the community).

4.8.8. Microbiology

Observations

- It was noted that *'The ECFSPR collects data on chronic Staphylococcus aureus, chronic Burkholderia infection and at least a once-yearly detection of non-tuberculous mycobacteria and Stenotrophomonas maltophilia and will collect data on chronic Haemophilus influenzae and Aspergillus infection and at least one yearly detection of MRSA and Achromobacter in the near future. Some information is highly depend on the lab testing methods and specific requests especially non-tuberculous mycobacteria. Resistance testing is not well harmonized and the exact breakpoint for MIC is often not reported'*.

- Some participants thought it was not useful to look for resistance patterns other than for MRSA.
- An approach similar to that for ADR evaluation might be most practical: if there is a specific query in relation to a pathogen, registries could participate in targeted, time-limited, monitoring following a protocol agreed with the requesting stakeholders.

Recommendations

- Record the first time isolation of pseudomonas (already current practice).
- Record if there is chronic colonisation with pseudomonas (already current practice).
- Record if there is MRSA colonisation (already current practice).
- For specific pathogen-related question, registries could participate in targeted, time-limited, investigation following a protocol agreed with the requesting stakeholders.

4.8.9. Genotype

Observations

- Registries capture information related to the mutations in the two alleles of the gene. Intragenic modifications that may affect the phenotypic expression of the disease such as the poly-T status in case of the presence of an *R117H-CFTR* mutation are also captured and can be provided.
- It was suggested that information should be collected regarding mutations in the two alleles of the gene and intragenic modifications known or suspected to influence the phenotypic expression of the disease.

Recommendation

- Record information related to the mutations in the two alleles of the gene.

4.8.10. Transplantation

Observations

- When a patient is transplanted, s/he is moved from the CF registry to the transplant registry. Registry holders mentioned that it could be possible to have some information about the transplant on the registry.
- All agreed that despite transplantation, CF-specific care is still needed. In Sweden, transplant CF patients continue in the CF registry; In the UK, the NHS has a package that can be "moved" with patients to transplant registry.
- Transplantation was an acceptable endpoint for follow-up.

Recommendations

- CF patients transplanted in centres that also provide CF care could continue to be followed up through the CF registry.
- CF patients transplanted in non-CF centres should have the transplant & its outcome recorded by the CF registry recognising that ongoing follow-up is not generally possible.

4.8.11. Patient reported outcomes (PROs)

Observations

- It was agreed that would be of value to capture PROs in the registries. This is not currently done.
- Certain PRO information is of particular interest to HTA and reimbursement stakeholders.

Recommendation

- Patient, clinical, and registry groups to determine what is possible in relation to inclusion of PROs in registries and how these might be standardised and operationalised.

4.8.12. Pregnancy

Observations

- Most registries include a field for pregnancy information. More information about child development would need a different consent to what is obtained already and would not be feasible for all registries. The German registry noted that it is feasible to collect pregnancy-related information but agreed that for information on the child, a different consent would be needed. The Swedish registry agreed, but all three registries noted that the main problem would be the extra work needed to collect the information.
- Registries noted that as a first step, it could be possible to record if a patient was pregnant, dates from when to when, and record outcomes like continued pregnancy, spontaneous abortion, live birth, birth weight.

Recommendation

- For women of child-bearing age, include a 'Pregnancy since last review: Yes / No' field with a drop-down list of outcomes if the option 'Yes' is selected.

4.8.13. Differences between CF centres & patient moves from one centre to another

Observations

- Registry holders mentioned that the main data that is collected may vary somewhat between different CF centres but most collected many/most of the ECFSPR variables.

- Patients have to request if they wish to move from one CF centre to another, even in the same country. In Germany, if a patient moves to another centre, s/he retains the same ID, and the new centre can access data recorded by the previous centre. Clinic doctors cannot see the registry data of the patient, but they can see the clinical history / data.

Recommendation

- When a patient moves between CF centres and this also involves moving to another CF registry, the registries should also communicate so that the original registry information can be transferred.

4.9. Summary of the main recommendations

A summary of the main recommendation is presented in Table 1 in the Executive Summary section of the report.

5. Next steps and Actions

5.1. Role of the Patient Registries Task Force in guiding implementation of recommendations

The Patient Registries Task Force will work with CF stakeholders where possible to assist in developing plans to facilitate implementation of the Workshop recommendations. This will prioritise the recommendations for which actions were agreed (Table 1) and assist in ensuring that actions are completed by each owner to an agreed timeline (Table 2 and Appendix 3).

5.2. Actions for Regulators

Regulators need to support CF stakeholders broadly by:

- Promoting the potential value of data from patient registries to MAHs, HTAs, reimbursement bodies and patient groups.
- Facilitating communications between registry holders and MAHs.
- Supporting registry holders to establish robust measures for assuring the quality of registry data and providing guidance on mechanisms for formal accreditation of registries.
- Including patient registry data where appropriate in regulatory processes.
- Engaging with relevant initiatives that are also exploring the potential of registry data to contribute to healthcare evaluations, for example, the work of EUnetHTA in its Joint Action 3 (Work package 5B) and the European Platform on Rare Diseases Registration.

5.3. Actions for Registry Holders

Registry holders need to prioritise measures to assure the quality of registry data and its reliability for supporting regulatory evaluations of new medicines by:

- Ensuring that processes for quality assurance of registry data, including source data verification, are harmonised and applied systematically across CF registries.
- Gaining certification of the data quality and the standards applying in the patient registry.
- Developing a policy on sharing summary, pseudo-anonymised, and individual patient data with stakeholders.
- Developing a standard process for MAH and regulatory requests for registry data.

In addition, Registry holders need to optimise communications with patients, MAHs, and regulators by:

- Informing patients on the benefits and uses of patient registry data including appropriate sharing with relevant stakeholders.
- Informing MAHs and regulators of the type and detail of registry data that may feasibly be shared within consent and governance parameters.

5.4. Actions for MAHs

Marketing Authorisation Holders and Applicants need to have discussions with regulators early in the clinical development of new medicines in order to:

- Understand the regulatory data requests that are likely to arise in the event of a successful application, especially for post marketing surveillance.
- Consider if appropriate registry data would have a place in the regulatory evaluations.
- Identify if a suitable patient registry exists.
- Develop a preliminary study protocol and explore with the registry holder/s and the regulator if the registry could fulfil the data needs.

5.5. Actions for patient groups

Patient representatives need to engage pro-actively with registry holders in order to:

- Ensure they understand and can communicate to patients the potential uses and associated benefits and risks of using patient registry data to assist in medicines evaluations, including appropriate sharing with relevant stakeholders.
- Provide insight on patient reported outcomes that might feasibly be collected in registries.

5.6. Actions for HTAs and reimbursement bodies

HTAs and reimbursement bodies need to develop their understanding of the possible roles for patient registries in supporting technology assessments and informing reimbursement decisions by:

- Learning about the nature and purpose of the data collected in patient registries.
- Engaging with registry holders to adapt or optimise data collection in order to support their information needs where feasible.

Ongoing work by the European Network for Health Technology Assessment in its Joint Action 3 (Work package 5B) is highly relevant in this respect bringing together multiple groups to focus on registries in health technology assessment.

5.7. Summary of the main actions

A summary of the main actions is presented in Table 2 in the Executive Summary section of the report.

6. Conclusions

The CF patient registry landscape in Europe is already collaborative and mature. There is willingness by all stakeholders to optimise the use of CF registry data for supporting regulatory evaluations. An early priority for ensuring this is to establish robust measures to confirm the quality of registry data. Ideally this would be accompanied by certification through existing platforms thereby helping to assure users that the data are of acceptable quality for regulatory purposes. A second priority is to improve communications between registry holders, regulators and MAHs/MAAs and to create a centralised process for requesting and obtaining data. The ultimate objective is that relevant data from registries will be incorporated in benefit-risk evaluations throughout medical product lifecycles.

7. Glossary

- Anonymised Data: Data 'rendered anonymous in such a way that the data subject is not or no longer identifiable' (Appendix 4, GDPR, Recital 26)
- ECFSPR: European CF Society Patient Registry
- Encounter-based data entry: patient data entered directly to the ECFSPR during the clinical encounter, for example, an out-patient visit
- EUnetHTA: European Network for Health Technology Assessment
- GDPR: Generalised Data Protection Regulation – Refer Appendix 4
- GVP: good vigilance practice
- HTA: Health Technology Assessment

- IPD: Individual patient data - Data separately recorded for each participant in a clinical study
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf
- Informed consent: The process by which a patient learns about and understands the purpose, benefits, and potential risks of a medical or surgical intervention, including clinical trials, and then agrees to receive the treatment or participate in the trial (medicinenet.com)
- MAA: marketing authorisation applicant
- MAH: marketing authorisation holder
- NCA: national competent authority
- Patient Registry: An organised system that uses observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp
- Pseudo-anonymised Data: data processed 'in such a way that the data can no longer be attributed to a specific data subject without the use of additional information.' (Article 4 (5), GDPR)
- SOP: Standard Operating Procedure.

8. Appendices

Appendix 1 - Workshop Agenda and Participant List

Appendix 2 – Pre-work for participants (slides)

Appendix 3 - Tables of topic recommendations made by each of the three work groups

Appendix 4 - Generalised Data Protection Regulation [GDPR regulation](#)

Appendix 5 - European CF Society Patient Registry agreed list of common data elements with definitions; list of participating countries, [ECFSPR Variables and Definitions](#)

Link to reach Appendices 1-3

[European Medicines Agency - News and Events - Cystic fibrosis workshop - Registries initiative](#)