Study Protocol

UK Cystic Fibrosis Registry
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Study Chief Investigator & data custodian	Dr Siobhán Carr Consultant Respiratory Paediatrician Royal Brompton Hospital Sydney Street London SW3 6NP
Study sponsor, data controller and data processor	Rebecca Cosgriff UK CF Registry Lead Cystic Fibrosis Trust 1 Aldgate London EC3N 1RE
Co-applicants	Dr Iolo Doull Consultant Respiratory Paediatrician Children's Hospital for Wales Dr Caroline Elston Consultant Adult Cystic Fibrosis Physician Kings College Hospital Dr Martin Wildman Consultant Adult Cystic Fibrosis Physician Northern General Hospital
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1. Introduction

The UK CF Registry is well established and used by all Cystic Fibrosis centres in the UK. The original CF database established at the University of Dundee has been fully incorporated into this current registry. This protocol serves to update the original research protocol to ensure it is line with current research registry practice.

1.1 Cystic Fibrosis

Cystic Fibrosis (CF) is the commonest life threatening genetically inherited disease in Caucasian people. Despite discovery of the gene in 1989, and much research aimed at correcting the gene defect and its cellular consequences, the therapies remain as yet focused on treatment of the major downstream effects of the disease, i.e. pulmonary infection and pancreatic insufficiency. The complex multisystem nature of the disease coupled with its life shortening effects has led to the development of centers designed to deliver specialist care with the aim of improving survival. The CF specialist centers provide a multidisciplinary team consisting of doctors, clinical nurse specialist, dieticians, physiotherapist social workers and psychologists and clerical staff all led and coordinated by a specialist physician.

1.2 Purpose

The purpose of this study is to maintain the UK CF Registry, to standardize patient care while facilitating local, regional and national audit as well as cross-sectional and longitudinal research.

2. Methods

The database has been designed to collate information about various aspects of CF from CF centres all over the UK. Information on the UK CF Registry can also be compared with information collected in other countries (see 4.4 below).

2.1 Two levels of operation of the UK CF Registry

- The national database consists of data merged from all the centres. As trends in the disease are tracked over time longitudinal data are held.

- Use of data in the national database is subject to approval from the Cystic Fibrosis Trust's Registry Steering Committee (see **Error! Reference source not found.**). Subsequent research projects will require relevant approvals from a Research Ethics Committee.

2.2 Patient anonymity

Patient anonymity is paramount within the structure of the database. This is achieved by the application of software to create a unique alpha-numeric PIN number. The PIN identifies the patient within the database and remains with him or her for life. A great advantage of this technique is that the same number is generated in each hospital where the patient is seen without the need for an expensive central number-generating authority. Since the identical PIN number is generated should the patient transfer to another CF clinic, this feature facilitates anonymous longitudinal patient tracking. The mechanism also ensures that patient names are known only to their immediate carers and authorised Cystic Fibrosis Trust Employees with direct responsibility for the UK CF Registry. When data are provided to external researchers as part of the data request process, a second randomized number is generated by the Registry team. The dataset provided to the external researcher includes this random number only, not the in-system PIN number. This two-stage anonymization process means that only the Registry team hold the 'key' to relating data back to the PIN, and then on to the individual patient's identifiable information.

2.3 Compliance with data protection legislation

The database is fully compliant with Data Protection legislation.

2.4 Gathering Clinical information

Routine clinical data will be collected in accordance with local protocol and entered in the patients' hospital notes. Data will then be transferred to the database.

2.5 Data accuracy

Data accuracy and completeness is considered central to the database protocol. Range and accuracy checks are available as standard reports within each CF centre. The software provides extensive reporting of data completeness for key parameters.

2.6 Access to data

Access to the entire database is regulated by the CF Registry Steering Committee, which meets quarterly to consider requests.

Authorised personnel at the Cystic Fibrosis Trust have access to the database for data verification purposes.

Authorised personnel at each CF centre will be able to review data entered on the centre's patients. Retrospective data from each patient will be available in a graphical format that will enable local clinicians to review individual trends and facilitate the planning of the patient's clinical management. Personnel will be only able to review data from their own centre; they will not be able to view data from other centres. Access to the database is password protected according to industry and NHS best practice standards.

3. Monitoring and Audit

Monitoring and audit will be conducted in accordance with the Cystic Fibrosis Trust's Standard Operating Procedures (SOPs).

Data validation visits will be undertaken by the central UK Registry team according to the Data Validation Standard Operating Procedure. Any amendments to the SOP are approved by the Registry Steering Committee.

4. Publication policy

The publication policy will be discussed and agreed with the Cystic Fibrosis Trust Registry Steering committee (RSC).

4.1 Annual data reports

Annual data reports will be produced by the Cystic Fibrosis Trust in conjunction with the RSC and published on www.cysticfibrosis.org.uk/registryreports.

4.2 Register of research projects

A publicly accessible register of research projects using data from the database are published at www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/apply-for-data-from-the-cf-registry, updated on a monthly basis.

4.3 Annual progress reports

Annual reports, a list of all projects for which access to data has been given, and a summary of developments in the management of the Registry will be submitted to the Research Ethics Committee on an annual basis.

4.4 Types of research to be supported

Data sharing will be conducted in accordance with the Standard Operating Procedures of the Cystic Fibrosis Trust. The data request process, and application form, is openly available on the Cystic Fibrosis Trust website (www.cysticfibrosis.org.uk/registry. The data request process is overseen by the Registry Research Committee, a sub-group of the UK CF Registry Steering Committee, with an out-of-meeting process for approving Requests. Membership of the Registry

Steering Committee is published on the Cystic Fibrosis Trust website. Types of research to be supported include but are not limited to those outlined below.

4.4.1 Data linkage

The UK CF Registry dataset may be enhanced via linkage to National Health Service (NHS), Hospital Episode Statistics (HES), and/or Office of National Statistics (ONS) data, using a Trusted Third Party process to protect the identity of individuals and ensure the pseudonymisation of resulting linked datasets. Linkage may include health service utilization, diagnosis, and mortality data.

4.4.2 NHS Commissioning data

Data reports are provided to NHS Commissioners to facilitate the Payment by Results (PbR) process for Specialised Commissioning.

4.4.3 Collation with other databases to support meta-analysis (joint datasets)

The UK CF Registry seeks to establish collaborative relationships within the cystic fibrosis Registry network worldwide; principally by merging pseudonymised/anonymised datasets in order to make meaningful comparisons between countries. Proposals for new joint datasets will be considered by the Registry Research Committee.

European Cystic Fibrosis Patient Registry (ECFSPR)

The European Cystic Fibrosis Patient Registry is a Europe-wide Registry of anonymised, core data on people with cystic fibrosis. Whilst some countries submit data directly into the ECFSPR, those with existing National Registries, including the UK, submit an anonymised export on an annual basis. Those submitting data are automatically part of the ECFSPR Steering Committee, which is consulted on every data request. Countries have the right to opt out of their data being provided as part of any data request, and can request that applicants approach them directly. The data request process and Annual Data Reports from the ECFSPR can be found at www.ecfs.eu/ecfspr.

US/UK comparisons

The UK CF Registry and Cystic Fibrosis Foundation Patient Registry have a long-standing collaboration that has produced a cross sectional and longitudinal comparisons between the two countries using a comprehensive comparison methodology. Requests for access to the merged dataset must be approved by both Registries, and approached to a single Registry seeking to ultimately compare data should be referred to the existing merged dataset.

4.4.4 Industry requests

Requests from industry will be considered in-line with the process outlined above. Aggregated data only, not patient-level information, will be provided to Industry. Whilst requests to further the development, availability, or evaluation of new therapies for people with cystic fibrosis will be considered, those relating to marketing or promotion of products will not be granted.

PAES/PASS studies

The UK CF Registry has established a Programme of Post-authorisation efficacy studies (PAES) and Post authorization safety studies (PASS). These studies are conducted in-line with European Medicines Agency (EMA) guidelines and templates. The studies involve the production of aggregated data reports, produced by UK CF Registry statisticians and Principal Investigators, who are independent from the pharmaceutical company responsible for the production of the study therapy. No patient-level data is provided to pharmaceutical companies or the EMA as part of this process.

5. Amendments

All amendments must be submitted to and approved by REC, with R&D departments at participating sites notified according as instructed by REC.

Substantial amendments must be accompanied by a substantial amendment form for submission to the.

5.1 Study closure

The UK CF Registry is an ongoing study, with no foreseen end date. Renewal of REC approval, including a review of the study documentation set, will be undertaken in accordance with current REC Standard Operating Procedure v7.2 January 2017 (ref: 11.36).

6. Operation

6.1 Study population

6.1.1 Inclusion criteria

The study includes patients with a definitive diagnosis [1]of cystic fibrosis being cared for in the United Kingdom.

6.2 Informed consent

6.2.1 Patients aged 0-12 years

Patients aged 0-12 years old are consented by their parents after diagnosis prior to any data being added to the Registry.

6.2.2 Patients aged 13-15 years

Patients aged 13-15 years are to be provided with an assent/consent form to sign in addition to the consent form signed by a parent or guardian.

6.2.3 Patients aged 16 years and over

Patients aged 16 years and over are to be provided with an adult consent form.

6.3 Patient registration

Newly diagnosed patients are to be registered by creating a new demographic record on the UK CF Registry portal: https://cfregistry.org.uk.

6.4 Patient transfer and withdrawal

6.4.1 Patient transfer

When a patient's care transfers to a new cystic fibrosis centre, the patient will be re-consented at their new site, prior to the request for electronic transfer of their data being sent to the UK CF Registry team.

6.4.2 Patient withdrawal

Should a patient choose to withdraw from the UK CF Registry, they should be marked as 'consent withdrawn' on their electronic demographic Registry record. This will lock the record, preventing future data entry, and send an alert to the UK CF Registry team, who will remove identifiable data from the live Registry system.

7. Governance

Committee and Board Terms of Reference are approved, signed off and versioned in accordance with Cystic Fibrosis Trust SOPs. Meeting minutes are formally signed off at subsequent meetings and electronically stored at the Cystic Fibrosis Trust.

[1] Farrell et al., Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation, Journal of Paediatrics, 2017.

7.1 Cystic Fibrosis Trust Board of Trustees

As the body responsible for monitoring how the Cystic Fibrosis Trust, Data Controller, delivers its objectives, the Cystic Fibrosis Trust Board of Trustees is accountable for the governance of the UK CF Registry. Meets five times per annum.

7.2 Registry Steering Committee

The Registry Steering Committee is responsible for making recommendations to the Cystic Fibrosis Trust about the strategic direction of the UK Cystic Fibrosis Registry. Its membership includes representation of Adult and Paediatric Respiratory Physicians, Commissioners of CF care, People with CF, CF parents, and the Cystic Fibrosis Trust. Meets quarterly.

7.2.1 Registry Research Committee

A sub-committee of the Registry Steering Committee, the Registry Research Committee is responsible for evaluating applications for data from the UK CF Registry, and for devising the Registry Research Strategy. Meets quarterly

7.3 Registry Management Group

The Registry Management Group oversees the day to day management of the UK CF Registry, including the review of risks and issues. Membership includes the Chief Investigator/Chair of the Registry Steering Committee, Chair of the Research Committee and the Data Controller. Meets monthly.