CF Trust and CF Foundation registries

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**01/09/2021**

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| **Short title:** (CFTR MAGIC) | CFTR Modulators and Gastrointestinal Complications |
| **Acronym:** | CFTR MAGIC |
| **IRAS Project ID:** | N/A. |
| **Funding Source:** | NIHR Programme Development Grant. Reference number PDG NIHR202952 |

## REGISTRY PERSONNEL AND CONTACT DETAILS

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**Registry database Coordinating Centre:** University of Nottingham

## SYNOPSIS

| | |
|---|---|
| Title | CFTR Modulators and Gastrointestinal Complications (CFTR MAGIC): a registry study |
| Short title | CFTR MAGIC |
| Chief Investigator | Professor Alan Smyth |
| Objectives | **AIM: To elucidate the similarities and distinctions in non-pulmonary manifestations of CF including distal intestinal obstructive syndrome (DIOS) incidence and Pancreatic enzyme replacement therapy (PERT) usage between US and UK populations with cystic fibrosis (CF) in a parallel study. To assess how CFTR modulators impact upon recorded incidence and use.**<br>OBJECTIVES<br>• Describe DIOS events and PERT usage in UK and US registries 2007-2017<br>• Determine the effect of CFTR modulators on the incidence of DIOS and use of PERT: population time series<br>• Determine the effect of CFTR modulators on the incidence of DIOS and use of PERT: patient-level time series |
| Registry database Configuration | Parallel study |
| Setting | All people with CF included on the US or UK CF registries |
| Number of participants | All patients with CF who are registered on the UK or US CF registries from 2007-2017 will be included. |
| Eligibility criteria | All CF patients of any genotype who are registered on the UK or US CF registries from 2007-2017 will be included. |
| Description of interventions | Registry study. No individual patient interaction. |
| Duration of registry database | 24 months (1st October 2021 – 30th September 2023) |

## ABBREVIATIONS

CI Chief Investigator overall

CRF Case Report Form

GCP Good Clinical Practice

NHS National Health Service

PI Principal Investigator at a local centre

REC Research Ethics Committee

R&D Research and Development department

UoN University of Nottingham

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## REGISTRY BACKGROUND INFORMATION AND RATIONALE

## BACKGROUND

Cystic fibrosis (CF) is an autosomal recessive disorder, caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) gene encoding for the CFTR protein. CF affects around 10,000 people in the UK with a life expectancy of 49 years in 2019.[1] Although CF is a multi-system disorder, its impact on the respiratory track and gastrointestinal (GI) system are of particular clinical importance.[2] In the gut, CFTR mutations result in pancreatic exocrine insufficiency in around 85% infants resulting in maldigestion and impaired nutrition,[3] with adequate nutrition in CF linked to life expectancy.[4] Due to the success of the newborn screening programme in the UK most people with CF (pwCF) are now identified within the first few weeks of life and commenced on pancreatic enzyme replacement therapy (PERT). Cystic fibrosis has a high associated treatment burden, with PERT in particular contributing to this, with patients often have to take 25-30 capsules per day.[5] However, despite this almost all pwCF experience GI symptoms including abdominal pain, flatulence, constipation and bloating,[6] with two thirds missing work or school because of this.[7] This is why "How can we relieve gastro-intestinal symptoms, such as stomach pain, bloating and nausea in people with Cystic Fibrosis?' was identified as one of the top 10 research priorities in a James Lind Alliance Priority Setting Partnership (JLA PSP) in CF conducted by our group.[8]

In addition, other GI manifestations affecting pwCF include distal intestinal obstructive syndrome (DIOS), CF related liver disease (CFRD) and pancreatitis. DIOS is a severe GI complication in CF defined as a complete intestinal obstruction with an ileo-caecal mass and abdominal distension, thought to result from the accumulation of faecal material at the ileo-caecal valve.[9] It affected 5.7% pwCF in the UK (2.5% in <16 years and 7.7% in adults)[1] and 2.1% in the US (<18 years 1.7%, adult 2.4%)[10] in 2019. However, the pathology underlying DIOS and GI symptoms are currently not well understood.

Advances in CF care has seen the development and introduction of CFTR modulator drugs, capable of targeting the basic defect of CF rather than the consequences of CFTR failure. Ivacaftor was first introduced in 2012 suitable for patients with gating mutations. Since then, a number of CFTR modulators have been developed the most recent being the CFTR modulator Ivacaftor/Tezacaftor/Elexacaftor: Kaftrio™ (UK) or Trikafta™ (US). This is indicated for 508del homozygote patients and patients with one copy of 508del combined with a minimal function mutation which comprises 90% of the UK CF population. Kaftrio was induced in the UK in 2020. CFTR modulators have already demonstrated dramatic improvements in respiratory outcome measures in CF,[11] however the impact of other aspects of the disease, such as within the gut are less well understood. A registry study in 2014 using US and UK data showed a lower prevalence of GI complications in patients receiving Ivacaftor although this was not significant. However, the average length of ivacaftor exposure in this study was short (2 years US, 1.3 year UK).[12]

Although our JLA PSP demonstrated that reducing GI symptoms was a research priority[7] there is currently a disconnect between this and ongoing clinical trials, with only three ongoing trials investigating GI symptoms.[13] In addition, there is no agreed,

validated outcome measures such as biomarkers or patient reported outcome measures in CF for GI symptoms that can be used as a primary end point[14] or agreed core outcome sets for trials. Finally, we do not yet know the impact of CFTR modulators on GI burden of the disease such as GI symptoms, PERT usage and the development of severe complications such as DIOS.

## RATIONALE

The overall study name is "A Comprehensive Approach To Relief Of Digestive Symptoms In Cystic Fibrosis: CARDS-CF". This will consist of 3 workstreams. We will complete a systematic review of the literature for outcomes and endpoints for studies of interventions to relieve GI symptoms in CF (workstream 3). This will help guide the development of the initial conceptual framework as part of the PROM development (workstream 1). A registry study will compare the trends in PERT usage and DIOS in the US and UK and will investigate the effects of the introduction of CFTR modulator drugs on PERT usage and the development of DIOS (workstream 2). This protocol relates specifically to workstream 2; CFTR MAGIC study.

## OBJECTIVES AND PURPOSE

### PURPOSE

To elucidate the similarities and distinctions in non-pulmonary manifestations of CF including DIOS incidence and PERT usage between US and UK populations with cystic fibrosis in a parallel study. To assess how CFTR modulators impact upon recorded incidence and use.

### PRIMARY OBJECTIVE

1. Describe DIOS events and PERT usage in UK and US registries 2007-2017
2. Determine the effect of CFTR modulators on the incidence of DIOS and use of PERT: population time series
3. Determine the effect of CFTR modulators on the incidence of DIOS and use of PERT: patient-level time series

### SECONDARY OBJECTIVES

To use objectives 1 to 3 above to generate a hypothesis regarding the effect of the newer CFTR modulators such as Symdeko/Symkevi and Tricaftor/Kaftrio of PERT usage and DIOS incidence in CF registry data post 2018. This will form the basis of future studies.

## DESIGN

### REGISTRY CONFIGURATION

STUDY DESIGN

This is a parallel data registry study using data from the UK and US CF registries. Application for data from the CF Foundation registry and UK CF Trust has been approved. Data will be obtained for 2007-2017 in both cohorts to allow for a minimum of 4 years of annualised data prior to the introduction of the first CFTR modulator drug, Ivacaftor, in 2012.

Data will be requested on the following patient-level variables;

- Year
- Current age/birth year
- Age at diagnosis
- Sex
- Ethnicity
- Height and weight or BMI
- Centre pseudoID
- Genotype
- CFTR modulator status (with date commenced and any treatment interruptions).
    - ivacaftor
    - lumacaftor/ivacaftor
    - tezacaftor/ivacaftor
    - elexacaftor/tezacaftor/ivacaftor
- DIOS events (with any date/encounter/timing variable available)
- Medication (with date commenced and any treatment interruptions).
    - Laxatives (including Movicol / Laxido)
    - PERT dosage/usage
    - Proton pump inhibitors
    - Azithromycin
- History of meconium ileus
- Disease status: $FEV_1$ (with any date/encounter/timing variable available)
- Comorbidities
    - CF related liver disease (including raised transaminases and cirrhosis).
    - CF related diabetes
    - Pseudomonas colonisation
- Gut complications (with any date/encounter/timing variable available)
    - Constipation
    - Intestinal obstruction
    - Acute pancreatitis

## REGISTRY DATA MANAGEMENT

A full data management plan is included separately. The Chief Investigator has overall responsibility for the registry data and shall oversee all data management. The data custodian will be the Chief Investigator.

## DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Registry database Duration: 24 months

Participant Duration: This is a registry study therefore no individual participant interaction. However, registry data from the US and UK CF registries will be used from 2007 to 2017.

### End of the registry study

Data will be destroyed in line with the UK and US CF registry requirements at the end of the study period. A detailed description of this is outlined in the data management plan. The end of the study will be 31/09/2023.

## SELECTION AND WITHDRAWAL OF PARTICIPANTS

### Recruitment

This is a registry study using data from 2007-2017 from the UK and US CF registries. As such no individual participants will be recruited to the study. PwCF have given explicit consent to their usual CF teams for their demographic, clinical care, and health outcomes data to be submitted to either the UK or US CF registries.

### Eligibility criteria

### Inclusion criteria

All CF patients of any genotype who are registered on the UK or US CF registries from 2007-2017 will be included.

### 4.2.2 Exclusion criteria

Patients whose CFTR modulator status is unknown or only have one year of CFTR data recorded on the registry will be excluded from the analysis of the effects of CFTR modulators. This is to account for the fact that DIOS data is annualised on the registry, therefore there is no certainty at what time of year DIOS was diagnosed in relation to commencing CFTR modulatory therapy.

### Expected duration of participant participation

No individual participant interaction. The CFTR MAGIC study will take place over 24 months, from 1/10/2021 to 30/9/2023.

### Participant Withdrawal

Not applicable – no individual participant involvement.

### Informed consent

PwCF have given explicit consent to their usual CF teams for their demographic, clinical care, and health outcomes data to be submitted to either the UK or US CF registries.[15, 16] Written consent is gained from pwCF or their parent/ legal guardian and as part of this they are made aware that the information may be used for research and to plan and improve the quality of clinical care. For the UK CF Trust the use of any data from the registry requires the approval of the Registry Steering Committee.[15] In the US, the request for registry data is reviewed and approved by the Patient Registry/Comparative Effectiveness Research Committee. The project has received approval from both the US and UK registries for patient data to be released to be used for this project. Data is released by the registries as anonymised forms of the data to maintain patient confidentiality. Additional patient specific consent for CFTR MAGIC is therefore not required.

## DATA COLLECTION REGIMEN

No new data collection will be necessary within this project. Existing data will be provided by the US and UK CF registries. Requests for the data was approved by the UK CF Trust Registry Steering Committee after reviewing the programme development grant aims, statistical analysis and plan for publication of results. In the US, the request for registry data was reviewed and approved by the Patient Registry/Comparative Effectiveness Research Committee and was subject to peer review. Data will be provided as anonymised data so the individuals cannot be identified and analysed using Stata software.

## ACCESS TO REGISTRY DATA

Data will be in the form of registry data provided from the US and UK CF registries from the period 2007-2017. These datasets will be provided as encrypted data via the registries preferred data sharing platform (Box.com or similar). Both registries have already reviewed and approved the sharing of their data for use within this project.

### Criteria for terminating the registry data

No data will be archived in a data repository following project completion due to the requirements of the CF Foundation and CF Trust registries. The CF foundation considers the project to be completed after 3 years. After this time data files and any copies of the files will be destroyed. The CF Foundation will be provided with written confirmation of destruction of the data and completion of the project or alternatively provided with a sufficient justification for continuation of the project if required. The CF Foundation maintains copies of all data sets sent to researchers and can provide the data again if required for auditing purposes. The CF Trust requires all data to be destroyed at the end of the project and that all data forms must be permanently destroyed within 12 months of the date of supply unless approval has been granted by the UK CF Registry Research Committee for an extension.

## STATISTICAL ANALYSIS

Data will be provided from the UK and US registries as an encrypted file and analysis will be performed using Stata software. Statistical analysis will be completed by members of the research team, led by Prof Iain Stewart. A full plan for statistical analysis is described below.

### Objective 1: Assess the rate of PERT use and the incidence of DIOS in UK and US registries 2007-2017

1. Descriptive analysis 2007-2017 to include:

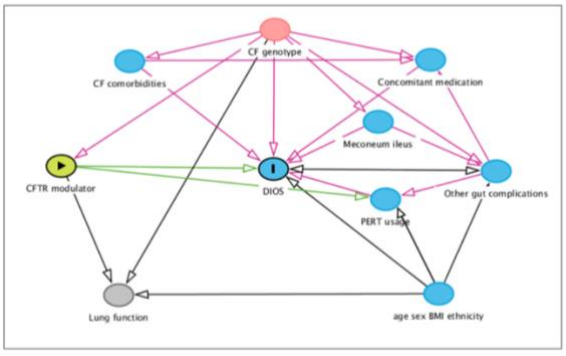
- Yearly cumulative incidence of DIOS and prevalence of PERT usage in the UK and US (2007-2017)
    - PERT use will be dichotomised (i.e use/no use)
    - Incidence of DIOS (event/no event)
    - Plotted by year, separated by registry
    - Stratification by age range (<6, 6-11, 12+)

- Patient demographics of DIOS and PERT reporting
    - The distribution of yearly reported incidence events and use prevalence (%) will be addressed according to age groups, sex, BMI, ethnicity, antibiotic use, comorbidities (including Pseudomonas colonisation, GI complication history, GI co-morbidities such as CFRD and CFRLD), $FEV_1$ lung function, centre (where available, pseudo ID).

Trends in the registries will be described, however no statistical tests will be used to directly similarities and differences between the registries over time due to the distinctions between the two registries.

2. The patient demographics lists above will be used for demographic propensity matched controls

- Patient-level data will be used to create registry-based control groups with similar demographic features to those taking CFTR modulators. Due to the restricted genotype eligibility criteria for the earliest CFTR modulator, Ivacaftor, the CFTR user group may have distinct features compared to the overall registry. In addition the restrictive indications for the use of Ivacaftor and limited number of DIOS events on the registry will therefore mean the number of events within exposed individuals may be low. Therefore propensity scores will be used to define a control group of non-eligible non-users that are otherwise representative at the year CFTR modulator exposure was commenced. See directed acyclic graph (DAG) below.
- Nearest neighbour matching, caliper 0.2 standard deviation, 3:1 ratio of unexposed to exposed will be used for propensity matching. Matching will be performed according to first year of exposure using all pre-exposure information in wide format. Standardised mean difference will be used to check covariate balance between matched and unmatched populations. Average treatment effect of treated will be used to assess matching specification with alternates.




Directed acyclic graph (DAG) for the potential relationship of CFTR modulator and DIOS

**Objective 2: Determine the effect of CFTR modulators on DIOS and PERT, using an population-level controlled interrupted time series**

Objective 2 will investigate the effect of CFTR modulator intervention on the rate on PERT use and DIOS incidence.

We will test the hypotheses that;

a) Ivacaftor introduction (2012) in patients with gating mutations lowered the rate of PERT use and the incidence of DIOS in both registries, and that
b) The introduction of Orkambi (Ivacaftor/Lumacaftor) for those homozygous for F508del mutations in the US (2015) lowered the rate of PERT use and the incidence of DIOS. Specifically, we hypothesise a downward trend, no lag.

Hypothesis 2b will be explored in the US population only given that introduction of Orkambi was delayed in the UK until 2019.

ITS will explore proportion of DIOS events at population level in the CFTR modulator population and the propensity score defined comparator population. ITS will explore proportion of overall PERT usage (user/non user), and the proportion of individuals with a reduction in weight standardised PERT dose (decrease/no decrease)

- Sensitivity will include distributed lag of 1-3 (years) to account for the possibility that exposure time in the first year was not sufficient for a change in outcome, compared to non-lagged, and to explore PERT usage status change to non-user.
- Autoregression will be visually assessed and effects will also be compared with those from autoregressive model (Prais-Winsten).

Analysis will be performed overall and stratified by 1) Age group (<6, 6-11, 12+) to account for clinical distinctions in pre-schoolers, school age children and adults, 2) History of meconium ileus, as these individuals are at higher risk of DIOS events.

Analysis of hypothesis 2a: Controlled interrupted time series: ivacaftor analysis in G551D criteria

- Segmented regression (with and without lag term), and Prais-Winsten regression for serial correlation.
- Impact model: downward trend (no/minimal level change)
- Model includes: pre intervention, level change, post intervention: interaction with covariates (age, gender, disease status).
    - Pre intervention: no CFTR modulator (time control)
    - Post intervention: ivacaftor (minimum 6 months)
        - US 2007-2011:2012-2017
        - UK 2007-2011:2012-2017
- Propensity score matched controls (demographic control)

Analysis hypothesis 2b. Interrupted time series: lumacaftor/ivacaftor analysis in US F508del subgroup.

- Hypothesis, downward trend no lag.
- Pre intervention no CFTR modulator: (time control)
- Post intervention: lumacaftor/ivacaftor, minimum 6 months
    - US 2007-2014:2015-2017
- Propensity score matched controls (demographic control)

- Parallel plot of UK F508del homozygous subgroup (indirect genotype control)

**Objective 3: Determine the effect of CFTR modulators on DIOS and PERT: patient-level time series**

This will focus on patient level associations to complement the registry level findings. We will specify explore associations in the incidence of PERT usage and DIOS events between 2012 and 2017 in individuals with CFTR modulators, compared to propensity matched controls.

- UK 2012-2017 & US 2012-2017 separately
    - Exposure: ivacaftor (minimum 6 months) vs No modulator (matched)
        - Secondary comparator: ivacaftor alone and lumacaftor/ivacaftor (US only)
- DIOS events:
    - Outcome: Patient-level annualised DIOS event counts
    - Multilevel Poisson Regression model for count data (or negative binomial) by year
        - Incidence rate ratio (frequency of DIOS events)
        - Adjusted analysis for main covariates (DAG – Fig 2), also include history of DIOS as pre-exposure time will not be modelled.
    - Contingency table with $\chi^2$/fisher if insufficient events for modelling.
- PERT usage:
    - Outcome: Patient-level annualised PERT dosage standardised by weight
        - Secondary: decreased PERT usage vs continued/increased
    - Multilevel linear regression for continuous data
        - Secondary: multilevel logistic regression for dichotomised data
        - Adjusted for main covariates (DAG – Fig 2), also include history of DIOS as pre-exposure time will not be modelled.
- Sensitivity analyses
    - CFTR modulator start year excluded, finite distributed lag (1-3 years).
    - Long run propensity (cumulative 0-3 years), cumulative modulator exposure.

**Sample size and justification**

N/A.- registry study

## ADVERSE EVENTS

This is a registry study therefore there is no individual participant interaction and as such no associated risk or burden for participants in the study. Patient's data will be provided as anonymised data and therefore patient confidentiality will be maintained.

## ETHICAL AND REGULATORY ASPECTS

## ETHICS COMMITTEE AND REGULATORY APPROVALS

Requests for the data required the approval of the UK CF Trust Registry Steering Committee after reviewing of the programme development grant aims, analysis and plan for publication of results. In the US, the request for registry data was reviewed and approved by the Patient Registry/Comparative Effectiveness Research Committee and was subject to peer review.

The data will be provided from the registries as anonymised data so the individuals cannot be identified. Specifically, the CF Foundation requires that no individually identifiable information from the CF Foundation Patient Registry shall be included in publications and other written products and data must be presented in the aggregate. Both US and UK registries require that all tables or presentation of the data generated from registry data should include a patient count of five or more in each cell and any values less than 5 should be represented as <5.

The registry study will not be initiated before the protocol, data management plan and application form have received approval / favourable opinion from the University of Nottingham ethics committee. Should a protocol amendment need to be made that requires ethical approval, the changes in the protocol will not be instituted until the amendment have been reviewed and received approval / favourable opinion from the REC. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

## INFORMED CONSENT AND PARTICIPANT INFORMATION

N/A – individual informed consent as part of the CFTR MAGIC study is not required. As described in detail in the Consent Section above PwCF have given explicit consent to their usual CF teams for their demographic, clinical care, and health outcomes data to be submitted to either the UK or US CF registries.[15, 16] Written consent is gained from pwCF or their parent/ legal guardian and as part of this they are made aware that the information may be used for research purposes.

## RECORDS

### Case Report Forms

N/A – this is a registry study therefore no individual participant involvement or requirement for CRFs.

### Source documents

No new data collection will be necessary within this project. Existing data will be provided by the US and UK CF registries. Data for the registry study will be provided by the CF Trust (UK) and CF Foundation (US). Requests for the data required the approval of the UK CF Trust Registry Steering Committee Patient

Registry/Comparative Effectiveness Research Committee in the US. Only research staff involved in the study shall have access to the registry data and analysis.

### Direct access to source data / documents

The study data and associated documents shall made be available at all times for review by the Chief Investigator and inspection by relevant regulatory authorities.

## DATA PROTECTION

All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the registry will be treated confidentially in the same way as all other confidential medical information. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

Access to data file locations on university servers is granted only by written request from a senior manager and limited to research staff and PhD students where required. Access to secure data file locations is managed by University of Nottingham IT services and accessed by university username and password. The Chief Investigator and researchers will be aware of their professional duty to maintain confidentiality at all times. All data stored on University Servers is backed up by University of Nottingham I.T. Services on a daily basis.

The University of Nottingham licences Microsoft OneDrive, an ISO 27001 information security management compliant service for storage of working data. We will use this for the storage and backing up of data. Both registries require the data to be stored on a secure encrypted network. OneDrive will allow for the secure and controlled sharing of data amongst relevant members of the research team. Any off site working with the data will be backed up and stored on the University of Nottingham OneDrive as soon as possible.

## QUALITY ASSURANCE & AUDIT

## INSURANCE AND INDEMNITY

N/A – registry study

## DATA CONDUCT

Procedures for the collection and analysis of data for the registry may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of registry staff and training received; local document control procedures; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria) and accountability of registry materials.

## REGISTRY DATA

The chief investigator, or where required, a nominated designee shall carry out monitoring of the data as an ongoing activity. Evidence of monitoring and systems audits will be made available for inspection by the REC as required.
Monitoring of registry data shall include source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local data and validation of data manipulation.

## RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the registry data. Specific requirements from both registries require that data be destroyed at the end of the study period and therefore will not be archived.

Specific requirements are as follows;
**The CF foundation requirements;**
The CT Foundation considers the project to be complete after 3 years. After this time data files and any copies of the files must be destroyed and the CF foundation provided with written confirmation of destruction of the data and completion of the project or provide sufficient justification for continuation of the project. The CF Foundation maintains copies of all data sets sent to researchers, and can provide the data again if required for auditing purposes. The US registries requires the following statement to be included when submitting a manuscript to a journal.

*Data are available upon request through the Cystic Fibrosis Foundation Patient Registry/ Comparative Effectiveness Research Committee. You can contact the committee at datarequests@cff.org. Restrictions on access to data are to ensure patient privacy for all persons in the CF Foundation Patient Registry.*

The CF Trust requires all data to be destroyed at the end of the project and that all data forms must be permanently deleted/destroyed within 12 months of the date of supply unless approval has been granted by the UK CF Registry Research Committee.

## DISCONTINUATION OF THE DATABASE BY THE SPONSOR

N/A

## STATEMENT OF CONFIDENTIALITY

There is no individual participant recruitment or involvement in this study and as such the risk of participant identification if low. Both US and UK registries require that all tables or presentation of the data generated from registry data should include a patient count of five or more in each cell and any values less than 5 should be represented as <5 to prevent patients being identified through the data. The data custodian is the Chief

Investigator. Data will not be shared outside the research team without prior approval from the US and UK registries.

## PUBLICATION AND DISSEMINATION POLICY

On completion of the study, the data will be analysed, tabulated and a Final Study Report prepared. Funders will be acknowledged within the publications but do not have any rights for review or approval of data for publication. As research data will be provided by the UK and US CF registries, these will be cited in any future publications as directed by the registries as follows;

**CF Trust specific requirements;**
The CF Trust will be acknowledged in publications using the following *citation "UK CF Registry. Cystic Fibrosis Trust, 2019"* and a copy of the publication also shared with them. On completion of the study we will provide outputs of the study to the CF Trust.

**CF foundation requirements;**
The CF foundation require annual updates on the project until completion and encourages dissemination of the work at professional conferences. Prior to the submission of abstracts, poster presentations, and manuscripts, a copy will be sent to datarequests@cff.org for review and approval by the CF Foundation and/or members of the Patient Registry/CER Committee. Seven days for review of abstracts or poster presentations, and 30 days to review manuscripts is required. In addition, once the manuscript is accepted by a scientific organisation, a copy of the paper shall be forwarded to datarequests@cff.org on notice of such acceptance, along with the name of the publication. When abstracts, exhibits, invited papers, or manuscripts are prepared using CFFPR data, the work must include the following acknowledgment:

*The authors would like to thank the Cystic Fibrosis Foundation for the use of CF Foundation Patient Registry data to conduct this study. Additionally, we would like to thank the patients, care providers, and clinic coordinators at CF centres throughout the United States for their contributions to the CF Foundation Patient Registry.*

At the end of the study we will also hold an online dissemination event for pwCF in addition to preparing a lay summary of outcomes and also disseminating the results via social media accounts.

## USER AND PUBLIC INVOLVEMENT

This study is in response to a James Lind Alliance Priority Setting Partnership for CF.[8] "How can we relieve gastrointestinal symptoms, such as stomach pain, bloating and nausea in people with Cystic Fibrosis" was ranked the 2nd most important research priority amongst pwCF, their families and healthcare professionals. CARDS-CF has had patient and public involvement throughout its design process. A co-applicant central in the development of CARDS-CF is a person with CF. She will have continued involvement and will sit on the management group for CFTR MAGIC as well as workstream 1.

## REGISTRY FINANCES

### Funding source

This study was funded by the NIHR programme development grant. Reference number PDG NIHR202952

### Participant stipends and payments

n/a – registry study

**SIGNATURE PAGES**

Signatories to Protocol:

**Chief Investigator:** (name) Prof Alan Smyth

Signature:

Date: 1/9/21

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