FULL/LONG TITLE OF THE STUDY

A Comprehensive Approach To Relief Of Digestive Symptoms In Cystic Fibrosis: CARDS-CF

SHORT STUDY TITLE / ACRONYM: CARDS-CF

RESEARCH REFERENCE NUMBERS

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- **This protocol has been designed to ensure regard for the HRA guidance**

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Date: 21/12/21

Signature:

Name: (please print):

Prof Alan Smyth

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STUDY SUMMARY

Study Title	A Comprehensive Approach To Relief Of Digestive Symptoms In Cystic Fibrosis: CARDS-CF
Internal ref. no. (or short title)	CARDS-CF
Study Design	CARDS-CF consists of 3 workstreams **Workstream 1:** A series of focus groups, semi-structured interviews and a survey to develop a patient reported outcome measure (PROM) for daily measurement of gastrointestinal symptom burden in Cystic Fibrosis (CF). This PROM will be trialled daily, for two weeks, on a app. **Workstream 2:** Study using registry data from the US and UK CF registries to compare trends of pancreatic enzyme use and rates of distal intestinal obstruction syndrome over a 10 year period. **Workstream 3:** Systematic review of the literature of outcomes and endpoints use in studies investigating interventions to relieve GI symptoms in CF. **<u>This protocol relates to Workstream 1 only.</u>**
Study Participants	People with Cystic Fibrosis aged 12 years and over.
Planned Size of Sample (if applicable)	Approximately 20 participants for focus groups and semi-structured interviews, with approximately 180 participants for survey completion and up to 150 participants to achieve 100 adequate completed responses from participants for trialling of the PROM in the smartphone app.
Follow up duration (if applicable)	The total time involved will be dependent on the extent of the participant's involvement in the study. PROM development is expected to take 24 months from start date to project completion. Participants may be involved for a maximum of 18 months. A breakdown of their involvement is as follows: - Focus group: 1 day - Interview: 1 day - Survey: 1 day - App completion: 2 weeks
Planned Study Period	24 months from project start date to completion.

Research Question/Aim(s)	Through this study, we aim to develop a PROM for GI symptom burden in CF.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	DETAILS OF FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
NIHR Programme Development Grant. Reference number: PDG NIHR202952	Funding for using the app provided by uMotif®, data analysis, participant expenses, ancillary costs and dissemination costs.

ROLE OF STUDY SPONSOR AND FUNDER

The sponsor and funder have supported the research after review of the proposed study design. All aspects of the design have been conceived and developed by the investigators. The study sponsor will monitor the study conduct against applicable regulatory standards. The study sponsor and funder will have no role in the conduct, analysis, or interpretation of the study. The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The Lead Investigator and co-investigators will act as a study steering group. This will entail regular meetings either face to face or conducted online via MS Teams as well as telephone and electronic written communication.

ROLE OF PATIENTS AND THE PUBLIC IN DEVELOPMENT OF THE STUDY

The study has had patient and public involvement throughout its design process. The study is based on a recent James Lind Alliance Priority Setting Partnership for CF.[1] People with Cystic Fibrosis (pwCF), their families and healthcare professionals identified "how can we relieve gastro-intestinal (GI) symptoms, such as stomach pain, bloating and nausea in people with Cystic Fibrosis" as one of the top 10 research priorities in CF. Our work will address this research question. In addition, a co-investigator on this study is a person with CF. She will have ongoing input throughout the study and will sit on the management group for workstreams 1 and 2. She will advise on PROM development, recruitment, and retention of participants. Along with members of a young person's advisor group, she has advised on content within the participant information sheet and consent development. Finally, focus groups and interviews involving pwCF are essential for completion of this study.

Key Words:

Cystic Fibrosis
Gastrointestinal function
Gastrointestinal symptoms
Symptom burden
Patient Reported Outcome Measure

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STUDY FLOW CHART

This project consists of 3 workstreams. The Gantt chart in Figure 1 outlines the proposed timeline for completion of the different workstreams within the project. Workstreams 1 and 2 will run in parallel and are expected to take 2 years from start to completion of the final analysis and write up. This protocol relates to workstream 1 only and the flow chart in Figure 2 displays the expected pathway for this study.

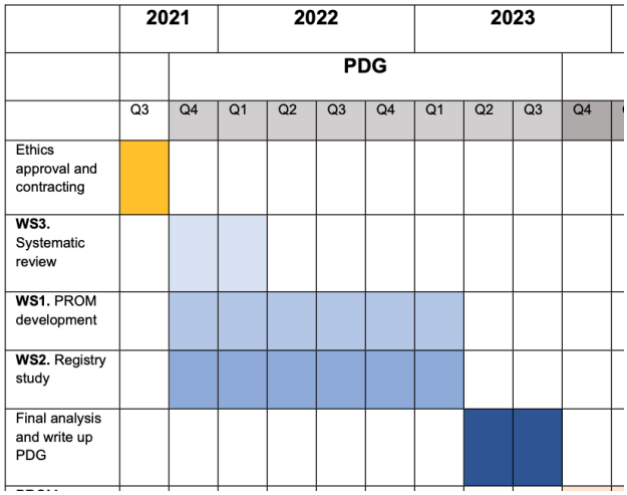

Figure 1: Gantt chart for the proposed timeline for CARDS-CF

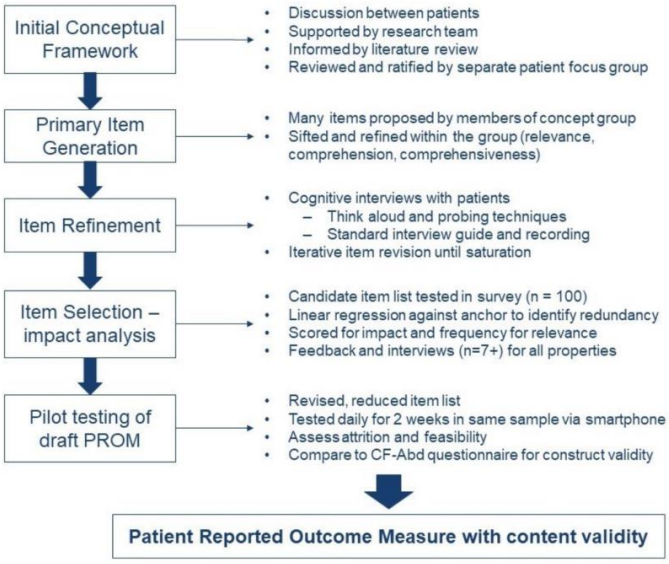

Figure 2: Flow diagram for workstream 1, patient reported outcome measure (PROM) development

STUDY PROTOCOL

A Comprehensive Approach To Relief Of Digestive Symptoms In Cystic Fibrosis: CARDS-CF

1. 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.[2] Although CF is a multi-system disorder, its impact on the respiratory tract and gastrointestinal (GI) system are of particular clinical importance.[3] In the gut, CFTR mutations result in pancreatic exocrine insufficiency in around 85% infants resulting in maldigestion and impaired nutrition,[4] with adequate nutrition in CF linked to life expectancy.[5] 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. PERT in particular contributes to this burden, with patients often having to take 25-30 capsules per day.[6] However, despite this almost all pwCF experience GI symptoms including abdominal pain, flatulence, constipation and bloating.[7] The associated burden of these GI symptoms can be disruptive to everyday life, with two thirds missing work or school because of this.[8] 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.[1]

In addition to frequent GI symptoms, other GI manifestations affecting pwCF include distal intestinal obstructive syndrome (DIOS), CF related liver disease (CFRLD) 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)[2] 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 have 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). 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.

Although our JLA PSP demonstrated that reducing GI symptoms was a research priority[8] there is currently a disconnect between this and ongoing clinical trials, with only three ongoing trials investigating GI symptoms in CF.[12] In addition, there is no agreed, validated outcome measures such as biomarkers or patient reported outcome measures in CF for measuring GI symptom burden that can be

used as a primary end point[13] for trials. The pattern of GI symptoms in CF is similar to functional GI disorders such as irritable bowel syndrome where regulatory guidance requires a daily assessment of symptoms, for efficacy assessment.[14] Therefore, the development of a specific PROM is essential and should include a daily assessment of symptoms.

2. RATIONALE

There are currently no agreed core outcome sets for trials in CF investigating the relief of GI symptoms, or no agreed, validated, patient reported outcome measures (PROM) for GI symptom burden in CF. The rationale for the proposed study is to create a framework that can be used for clinical trials investigating GI symptoms in CF. This study will comprise of PROM development (workstream 1), a registry study (workstream 2) and a systematic review (workstream 3). This protocol relates to workstream 1 only. Work will only begin once favourable ethical approval has been granted and the protocol has been uploaded onto a clinical trial database.

Workstream 2's protocol and ethics application has been developed separately and gained ethical approval by the University of Nottingham's ethics committee. Workstream 3 does not require ethical approval and a detailed protocol including search strategies will be developed separately and registered with PROSPERO database prior to commencing work on this workstream.

3. AIM: WORKSTREAM 1

3.1. Aim: To develop a patient reported outcome measure for daily measurement of gastrointestinal symptoms that can be recorded using a smartphone application (app).

3.2 Objectives

- To develop and refine a conceptual framework of the factors contributing to GI symptom burden.
- To generate a primary list of item questions, to address the conceptual framework.
- To refine the relevance, comprehensiveness, and understandability of the items in the primary list through think aloud interviews and a patient survey.
- To pilot the resulting items for the PROM over a two week period to explore the patient responses when using the PROM to assess content validity.

3.3 STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

3.4.1 STUDY DESIGN

An overview of the study design is outlined in Figure 3 below. We will follow best practice guidance from COSMIN (Consensus-based Standards for the selection of health Measurement Instruments),[15]

the US Food and Drug Administration; and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).
The study will flow from 1) an initial conceptual framework 2) primary item generation 3) item refinement 4) item selection 5) pilot testing of the PROM. Each stage informs the subsequent stage (Figure 3).

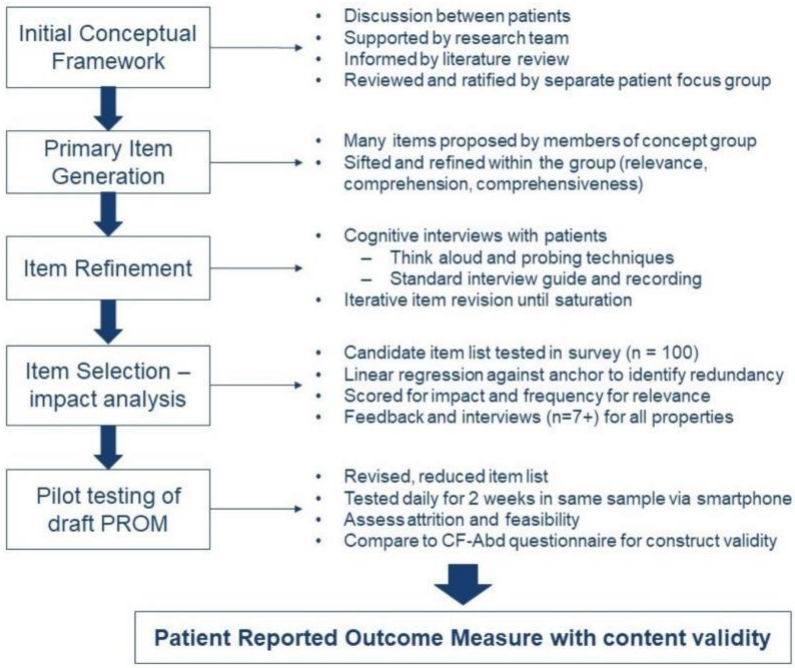

Figure 3. Flow diagram for patient reported outcome measure (PROM) development

1). Initial conceptual framework:

The first stage will be to create a conceptual framework. This will be synthesised from findings from various sources including the results of published work in the field, including an international qualitative study exploring GI symptoms and associated burden in CF.[8] This included responses from pwCF, their families and healthcare professionals. The conceptual framework will be developed by an expert panel comprising of members of the research team including health professionals caring for pwCF, those with experience in PROM development and a person with CF with experience in marketing and user experience design, in addition to an equal number of pwCF. These members of the panel are considered as co-authors involved in the design of the study, rather than participants.

The construct of interest will focus on the burden of the GI symptoms for pwCF. The intended purpose of the instrument being developed is outlined below;

Intended purpose	Description

Intended construct of interest	**A pwCF experience of their gastrointestinal (GI) symptom burden.** The severity of GI symptoms and the extent to which these GI symptoms negatively impact, disrupt or add significant burden to the life of a pwCF. This will be measured on a daily basis.
Intended target population	**PwCF aged 12 and over who are independently, or with minimal assistance, able to answer questions of the burden of their GI symptoms.** PwCF younger than 12 may require more support from a parent/ guardian in answering the questions. A parent's perception of bowel symptoms and burden may be different to that experienced by the child therefore it is not intended for use in those <12 years. It is intended for use for any sex or ethnicity.
Intended context of use	Primarily designed for use in clinical trials for pwCF to assess any type of intervention on GI symptom burden. A secondary aim is that longer term it may be appropriate for use in the clinical setting – either at home or within the healthcare setting.

We will use a formative model to capture all aspects of a patient's GI symptoms which add to their GI symptom burden. These discussions will be conducted via a variety of methods including a series of teleconferencing and videoconferencing discussions and via email until a consensus on the conceptual framework is reached. Following generation of the initial conceptual framework, a focus group will be conducted over MS Teams consisting of members of the expert panel, adults with CF and young pwCF accompanied by their parents. PwCF involved as part of the focus group will be different to those involved in the expert panel. This focus group is essential to ensure that no key concepts have been omitted from the initial framework. The meetings will be recorded using an audio digital recorder or the MS Teams function and also transcribed. Conducting the meeting in this way will allow for social distancing measures required for pwCF. Our group have experience of engaging with research participants in this way previously.[16] Recruitment of patients is detailed separately in section 4.5**.** The findings on the focus group will be discussed amongst the expert panel and any changes made to the construct finalised. This will then be used for item generation (stage 2). All transcription of audio and video recordings throughout the study will be performed by either the medical research fellow directly or by using the MS Teams transcription function and checked for accuracy by the medical research fellow.

2). Primary item generation: The expert panel involved in the development of the conceptual framework will generate a primary list of items relating to each of the concepts in the framework. Ideas for items for possible inclusion in the instrument will be submitted by members of the panel ahead of meeting and then discussed as a group. The items will be reviewed for the relevance, ease of understanding and coverage of the concepts contributing to the GI symptom burden construct. They

will be discussed and either kept for inclusion, discarded, or modified before they are used. Final decision on the items will be made by the research team, with decisions informed by pwCF and their families. Through this, a comprehensive list of key items for inclusion in the PROM will be generated. These discussions will be conducted via online methods as outlined above.

3). Item refinement: The items generated through this discussion will then be refined through a series of patient interviews. The interviews will be conducted by the medical research fellow with support from Professor Kim Thomas (co-investigator with experience in qualitative research). The structure of the interviews will be open-ended, semi-structured, "think aloud" interviews with probing techniques to assess the appropriateness of the items for inclusion. The aim of the interviews is to assess the items and consider their relevance, understandability and comprehensiveness to the target audience to ensure construct validity. Construct validity is the degree in which the content of the instrument being developed adequately reflects the initial construct of interest described in stage 1. The interviews will be conducted over the telephone or via phone or video call. These will be recorded either using the record function on Microsoft Teams or using a digital audio recorder, transcribed as described above, and stored securely as described in Section 6.7.

Data will be coded to identify themes within the interviews. NVivo[17] (qualitative data analysis software) may be used to help organise the data. Coding will be conducted by the research fellow with secondary coding on selected transcripts by an independent researcher within the research team. This will allow for any discrepancies in coding to be identified and discussed. We plan to conduct approximately 10 interviews; however, interviews will be continued until no further issues are identified with the items included within the PROM. Interviews will take place in "rounds" so that coding can be iterative and captures any new concepts or issues which may evolve from the data. Any instructions or items which cause confusion or are misinterpreted by pwCF during the interviews will be recorded and amended and then tested in subsequent interviews. Interviews will take place in rounds before and after survey completion (section 4, Item selection) depending on participant feedback and will continue until no new issues emerge. As the instrument is intended for use by people 12 years and over, both young people and adults with CF will be interviewed. Participants will be recruited as per section 3.6. From this, possible items for the PROM will be agreed by the expert team ready for testing within the survey (stage 4, item selection).

4. **Item selection:** The finalised extended item list of PROM questions created in step 3 will then be tested in a survey using a larger sample size (n= approximately 180). Participants will be recruited as described in section 3.6. For each item included on the list, if relevant to the question, participants will be asked;

    1) Whether they have experienced the item at any time within the last year (yes/no question) – this time frame was increased from 2 weeks to 1 year following participant interviews to allow items experienced less frequently but were felt to have an impact on the experience of GI symptoms to be captured. This time frame is also in line with previous PROM development[1].

    2) How important they think this item is when thinking about their tummy symptoms (no time frame). This will be rated using an 5 point interval scale (1 (not important at all) to 5 (very important)). This wording was amended from disruptive to importance, using methodology in other PROM development[1].

In addition, participants will also be asked the anchor question "In the last 24 hours how much have tummy symptoms bothered you?" (11 point interval scare, 0 (not at all) to 10 (severe)). This question closely relates to the conceptual model and was developed and refined through the interview stage as an overall question to assess burden.

The survey will be made available online via a web-based survey generating platform e.g. SurveyMonkey. Basic demographics of the participants such as CF centre, gender, genotype, whether they have had a transplant and medications used including creon and CFTR modulator status will also be collected. Analysis will be completed by the medical research fellow supported by the research team and team statistician using STATA (statistical data analysis software). The analysis plan was informed through previous PROM development[1].

Further Item refinement (stage 3) may be conducted if needed following the survey to address any questions which may have caused confusion (for example, if a question was commonly omitted to check for understanding). By the end of stage 4, a final item list for the PROM will be generated to be pilot tested as described in stage 5. The number of participants recruited for the survey has been increased from 100 to 180 following question generation at earlier stages with pwCF (stages 1-3) so that a sample size of at least 10 cases per predictor variable can be used.

<u>Survey analysis</u>

- The percentage of missing data for each item will be assessed. If some items appear to be particularly problematic, for example, 15% of participants don't answer this question, we will consider why this may be and if this item should still be included in any further analyses.
- The mean and distribution (SD) of the scores for each individual item will be assessed to determine if all response options are being used by the participants.
- The items will be assessed for frequency of reporting and its associated impact.

<u>Impact analysis:</u>

The aim of the impact analysis to identify those questions which are more impactful for pwCF when considering the impact of gut symptoms for pwCF and to exclude those which are less relevant (either low importance or experienced very infrequently). The impact analysis is responsible for determining the items which will be included within the PROM as this is what is perceived as most important to pwCF.

- Frequency will be calculated by the % of participants who had experienced the item in the last year (yes/no question)
- Importance of an item will be calculated by the mean score given for level of importance (1-5).
- Impact: This will be calculated by "frequency" x "importance"
- Impacted analysis will be completed for all respondents and ranked in order of impact for all participants. If there are sufficient numbers of participants not taking a modulator included, a sub-group analysis by modulator status will be performed (groups modulator, no-modulator)
- The items will be ranked in order of impact score for 1) all participants 2) sub-group analysis
    - A pre-defined impact analysis score of 2 will also be used – those items scoring <2 on impact analysis will be excluded. However, excluded items will also be open to discussion with the expert panel. Those scoring 2 or more will be considered in the regression analysis.

Regression analysis

Aim: Regression analysis will be used to understand the relationship between the items with each and also their contribution to the model.

The questions identified in the impact analysis as scoring 2 or greater will be included in the regression analysis. These will be the independent variables and "in the last 24 hours how much have tummy symptoms bothered you?" the dependent variable. We will use multivariable linear regressions for each item and regression analysis may further refine the PROM if there is evidence of significant collinearity between certain items within the PROM.

- Missing data will be handled by using complete case (listwise) analysis. A sensitivity analysis including those with missing data (pairwise) will also be completed.

- Test assumptions of multivariable regression analysis: linearity, multicollinearity, independence of residuals, homoscedasticity, normality and outliers.

- A backwards elimination technique will be used. A stopping criterion of 0.157 will be used, which is recommended for use in STATA as a proxy for Akaike's information criteria (AIC) and as the appropriate criterion for our sample size.[2, 3]

5). Pilot testing of the PROM: Following final item selection for the PROM, these will be piloted over a 2-week period using a smartphone app. The items will be hosted on an app provided by uMotif® - a medium sized UK company specialising in data recording for clinical trials. The platform is compliant with Good Clinical Practice and Title 21 Code of Federal Regulation part 11. This will ensure that we capture adequate data for later registration of any PROM with the US Food and Drug administration and similar regulators.

We aim to have approximately 100 participants have good completion (at least 11 out of 14 days) of the app. In view that not all people who sign up will likely complete the full 14 days we will over recruit participants to minimise the risk of missing data within the study. We plan to recruit up to 150 people, in order to achieve 100 participants with satisfactory completion of the app over the two weeks. These will be recruited through a variety of means including those who took part in the initial focus groups, interviews and survey, through participating CF clinics, social media and via the study website. Recruitment is described in section 3.6. Participants will be asked to complete the app daily and record data over a 2-week period which can be viewed by researchers through a research portal presented through the uMotif app. We will collect feedback on the PROM such as engagement and participant attrition rate through this research portal feedback facility. This information may also be used during the study period to contact the participants if engagement drops to encourage engagement and to give the opportunity for participants to raise any issues they may be having with the app. Participants will also be asked to give feedback on their experiences of using the PROM on days 7 and 14 to ascertain its usability. This will help evaluate the participant experience and feasibility of completing the PROM daily using this platform.

The scores from the PROM will be provided by the company uMotif at the end of a participant's involvement in the study. Descriptive analysis and non-parametric tests will be used to assess the PROM scores. Each question will be scored from 1 – 5 (worst – best). The hypothesis is that higher scores would indicate reduced gut symptom burden for a participant.

For each item, the mean and distribution of the individual item scores chosen as part of the PROM will be assessed and we will consider if floor or ceiling effects have occurred (defined as >15% of participants achieving the highest or lowest possible score). This will be calculated for each item per day, as well as a mean over the 14-day study period (denominator = number of completed days). The overall mean and distribution of scores for the PROM each day, and over the study period will also be calculated.
To begin to assess construct validity participants will also complete the CFAbd-score at the beginning and end of the two weeks which will be made available electronically on the app. This is a validated 28-point questionnaire which captures CF GI symptoms over the preceding fortnight, as opposed to the daily burden caused by the GI symptoms proposed for this PROM development. We will use descriptive analysis and non-parametric tests to compare the results with the CFAbd-score. This will also give an indication of the construct validity of our prototype PROM and may also allow us to assess whether any correlation between the CFAbd-score and our PROM is seen. We hypothesis that a reduction in the

CFAbd-score, indicating better/ improved GI symptoms, will correspond with an increase in scores for our PROM.
Participants will also be asked the anchor question on day 1, 7 and day 14 (developed as part of this PROM development and originally used in the online questionnaire) to further assess construct validity. The anchor question that will be used is "In the last 24 hours, how much have tummy symptoms bothered you?" answered on an 11 point Likert scale (0 Not bothered you at all to 10 very severely bothered you). In order to test test-retest reliability on day 7 in addition to the motif, participants will also be asked the question "How much have your tummy symptoms bothered you today compared to yesterday?" On a 5 point Likert scale.

A person will be considered as having completed the motif for a day if they have completed at least 9 out of the 10 questions on the motif. A person will be considered as having adequate completion of the study if they have completed at least 10 out of the 14 days. As a feature within the app allows for a participant to complete multiple motifs per day, where a participant has completed more than 1 motif, we will use the most completed motif for that day in the analysis. If multiple motifs have the same number of completed questions in a day (i.e. 9 out of 10 sections completed), we will then use whichever of these scores were completed first that day. If a question if commonly omitted for participants, we will consider why this may be and whether any further development of this question is required. As a formative model was used in the PROM development, internal consistency, structural validity and measurement invariance will not be assessed. Further validation of the PROM will be performed in subsequent studies in an independent population.

3.4.2 ENDPOINTS

PRIMARY ENDPOINTS

- Development of a conceptual framework for GI symptom burden in CF
- Use this conceptual framework to develop a patient reported outcome measure in CF for GI symptom burden

SECONDARY END POINTS

- Feasibility of daily data capture of the PROM through a smartphone app
- Usability of the PROM on the smartphone app
- Participant attrition rate

3.4.3 STUDY SETTING

Research activities will primarily take place either online or over the telephone as described in detail in section 3.4.1 above. Focus groups will be completed online via MS Teams, and interviews will be conducted via MS Teams, with the option for a telephone call also given to participants. This is important for pwCF who are advised to never meet face to face due to the risk of cross infection of particular bacteria resulting in potentially serious respiratory infections. It also will help to mitigate

against any risks posed from social distancing guidance or restrictions in relation to Covid-19. Our group has experience of conducting research in this way.[16] Researchers involved in the focus groups and interviews will conduct these within their home in a private setting, or within the School of Medicine at the University of Nottingham depending on Covid-19 working from home guidance. If MS Teams is unable to be used for any reason, Cisco WebEx will be used, a secure platform for video conferencing supported by the sponsor, Nottingham University Hospitals NHS Trust.

Study recruitment will take place at Nottingham University Hospitals NHS Trust which has two main campuses. These are Queen's Medical Centre (QMC) and City Hospital, Nottingham (CHN) which have paediatric and adult CF centres. This recruitment will be supported by 4 Participant Identification Centres at Leeds Teaching Hospital NHS Trust (Leeds Adult CF Centre), Manchester University NHS Foundation trust (Manchester Adult CF Centre), the Royal Brompton and Harefield NHS Foundation Trust (Royal Brompton Paediatric CF Centre) and Kings College Hospital NHS Foundation Trust (Adult CF Centre). Each site will be able to identify participants based on the inclusion criteria. Patients will also be recruited via social media.

3.5 SAMPLE AND RECRUITMENT

ELIGIBILITY CRITERIA

3.5.1. Inclusion criteria

- Age 12 years or older
- Confirmed diagnosis of CF based on genotype or sweat chloride testing
- Capacity to consent, or to understand the requirements of the study where parental consent is required

3.5.1 Exclusion criteria

- < 12 years age
- Unable to give informed consent

3.6SAMPLING AND RECRUITMENT

Stage 1+2: We will recruit a representative sample of participants for the focus group and interviews through one of the six tertiary CF clinics involved in this study. The six tertiary care cystic fibrosis centres included are listed in section 3.4.3. Potential participants will be identified by their usual care team who will discuss the focus groups and interviews with the patients and provide a Patient Information Sheet (PIS) containing the study teams contact details. Potential participants can either opt in by directly contacting the study team themselves after taking time to consider the information on the PIS, or they can give their consent for the clinical team to pass their contact details to the study team via a secure email for the study team to contact the potential participant. A member of the research team will contact the potential participant, discuss the study, and seek to gain consent as described in section 3.6.2. We plan for 1 focus group, and approximately 10 interviews, although this will continue until no new issues are identified.

Stage 4: Participants will be identified by their usual CF care team whilst in clinic as described above, as well as via social media. The study will also be advertised via posters displayed in clinics. They will be given a QR code taking them to the PIS and survey. Consent is detailed in section 3.6.2 below. As part of the participant information and consent, participants will be made aware they will be given the option to leave their contact details if they would like to hear more about future research and to advertise recruitment for Stage 5. We aim to recruit approximately 180 participants to complete the survey. Participants may also be recruited through a study website. The aim of the website is to provide information about the study, a location for the PIS to be accessed online, as a means to be able to contact the study team directly for any further information (a generic study email address and researcher's email addresses will be made available) and to provide links for participants who wish to access the survey or download the app (stage 5). The website will be called CFTummyTracker or similar after work and was developed through the expert panel (including pwCF) through the PROM development process.

Stage 5: Participants will be identified by their usual CF care team whilst in clinic as described above, as well as via social media/clinic posters and via the study website as described in stage 4 above. QR codes will be made available to the app for potential participants taking them to the app store to download the uMotif app, available for iphone or android. Participants will be provided with an invite code and asked to sign up using an email address and setting a password. The app will contain a page displaying an overview of the PIS, a link to a detailed PIS and electronic consent. Patients will be asked to read the PIS and give econsent before giving basic demographics about themselves.

We aim to recruit approximately 100 participants with adequate data completion for the pilot testing phase of the PROM on the app. Those completing the app may, but do not have to have taken part in previous stages of PROM development. We will undertake purposive recruitment to aim that we have;

- Approximately 20% of the sample aged 20 years or younger
- Some participants who have had a transplant
- Approximately 10% of participants are not taking CFTR modulators (which may include, but is not restricted to transplanted patients).

To achieve this, participants will be asked to enter baseline characteristics the first time they use the app, such as age, gender, ethnicity, genotype, country, CF centre, transplant status and history of gut surgery and other GI related co-morbidities, CFTR modulator status and the use of pancreatic enzymes. Finally, participants will be asked if they had been involved in any of the earlier development stages. The Chief Investigator or a nominee, i.e. the medical research fellow is responsible for ensuring recruitment fulfils these criteria through regular reviews of the enrolment of participants and liaising across the CF centres. Recruitment will be primarily based with the UK, but we will not exclude international participants providing they are able to read the PIS, consent process and PROM questions which will be written in English.

Separate participant information sheets (PIS) have been generated for stage 1 (focus group), stage 2 (interviews), stage 4 (survey) and stage 5 (app use). For the focus group and interviews PIS, 3 types have been generated; a 12-15 years, 16 years+ and a parent/carer PIS. The PIS will inform the potential

participant or their representative (such as a parent in the case of children with CF) of all aspects relating to participating in that aspect of the study. It will be explained that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. For piloting testing the PROM on the app, this PIS this will also be displayed electronically. As it will not be possible to determine whether a young person or adult has downloaded the app, this information sheet will be written to be accessible to a reading age of 12 years therefore should be appropriate for all participants. Stage 4 PIS is described in section 3.6.2. Although it is also possible that recruitment via social media may allow the potential for people outside our targeted population (i.e. people who do not have CF or less than 12 years) to fill in the survey or use the app, by asking for basic demographic information such as their age, CF centre, and CFTR modulator status, we feel that this is unlikely.

Participants will be made aware that in the event of their withdrawal from the study their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate. Only English-speaking participants will be enrolled into the study due to the lack of availability of funding to conduct the interviews via interpreters and that also the pilot app will be developed in English. Further work to develop translations into other languages and cross-cultural validation studies will be required at a later stage once an English version of the PROM has been developed. We will aim to include people within our expert panel that speak common languages to help highlight any words which may not be easily translated.

Participants involved in the focus group and interviews will be compensated for their time with a £30 shopping voucher made available in the appropriate format for the patient as a mark of thanks. The first 100 people to complete the pilot testing of the PROM in the app will receive a £10 electronic shopping voucher in the appropriate format to their registered email address. Participants will be made aware as part of the sign up and consent process their email address will be used for this purpose. No reimbursements will be given for participants involved in completion of the survey as participants can complete it at a time and place suitable for them and will likely have minimal impact on the individual's time.

3.6.2 CONSENT

<u>Stage 1+2</u>

All participants involved in the focus groups and interviews will be identified by their clinical care team who will provide information to the potential participants and the PIS with the study team's contact details on. Participants can either take the information away to read at a time convenient to them before contacting the study team themselves therefore having time to consider whether to participate or not. They can also give consent for the clinical team to pass on their information to the study team who will make contact, check eligibility criteria, gain electronic consent for the study and arrange a date for the focus group or interview. Participants will be made aware as part of the consent that these will be recorded. Consent will be completed electronically following HRA/MHRA guidance on seeking consent by electronic methods.[18] Informed consent will be taken prior to conducting the interview. In the case of a young person with CF, an e-consent from a person with parental responsibility is required,

but the child may also provide assent (optional, depending on the young person's ability to do so). A parent/ guardian will be responsible for their child's safety to monitor their child to ensure they are safe when online. The medial research fellow anticipated to conduct these interviews has an up to date DBS check.

Stage 4

We will recruit adults and young people 12 years and over with CF. Participants who are interested in completing the survey will use a QR code to the survey where they will first be provided with more information for the study. They will be asked to read the information, which will include eligibility criteria, research aims, voluntary nature of taking part, what will happen to the data they provide and withdrawal procedures. There will be an option to select to confirm that they have read the information and are happy to proceed. It will be made clear to them that by ticking the box or completing any part of the survey that they are providing their consent to take part in the survey. For young people under the age of 16 they will be asked to confirm they have discussed the information with their parent/ guardian and they have given their permission to take part in the survey. Although it is possible a child will participate without the informed consent of a parent/ guardian monitoring this will be beyond the control of the researchers.

Stage 5

The participant information sheet as described in section 3.6.1 will be displayed on the app front page detailing the study aim, eligibility criteria, aims, what participants are required to do as part of piloting testing the PROM on the app, and how their data will be used. There will also be a link available to a full PIS. The research study team's contact details will be made available if participants require any further information and will also be able to request a call back from the study team. Participants will be asked to read a series of statements to show that that have read and understood the information and complete a simple electronic consent prior to using the app. If a young person takes part in the use of the app, they will require a parent/ guardian to provide consent for them. It is the parents' responsibility to monitor their child to ensure their child is safe online.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation, continuing consent will be obtained using an amended consent form which will be signed by the participant.

3.6.3 WITHDRAWAL

Participants may be withdrawn from any aspect of the study at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

ETHICAL AND REGULATORY CONSIDERATIONS

4.1 ASSESSMENT AND MANAGEMENT OF RISK

There is a low level of risk or burden for participants in the study. No investigational medicinal product will be used, and participants will not be asked to alter or abstain from any of their medications related to their CF or GI symptoms. App completion over a 2-week period is not anticipated to add significantly to treatment burden.

A possible risk identified is the identification of patients through the focus group, interview, survey or app suggestive of needing medical attention, for example exacerbation of symptoms or symptoms indicating potential DIOS. It will be made clear to participants at study entry that data collected via the survey and app will not be reviewed regularly by clinicians and their results are for research purposes only. They will be advised on study entry that any worsening symptoms should prompt them to seek advice from their usual healthcare professional. A reminder of this will also appear within the app. For the patient interviews where participants will have direct contact with the research team, no advice on symptom management will be given. However, if through discussion worsening clinical symptoms are noted they will be advised to speak to the relevant healthcare professional from their usual CF team. These participants will also be discussed with the Chief Investigator who will pass information if appropriate to their usual CF centre with the patient's consent. Similarly, if during participation of the interviews or app it raises any feelings of distress to participants, they will be directed to their CF Team and relevant support services which will be provided by the research team at the end of the focus groups, interviews, or within the app.

5.1 RESEARCH ETHICS COMMITTEE (REC) REVIEW AND REPORTS

This study will not start before ethical approval has been gained from the National Research Ethics Service, through the Health Research Authority. The review by National Research Ethics Service will include a review by a Research Ethics Committee (REC). The REC will include review of the protocol, participant information sheets and consent form.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

6.1 PEER REVIEW

The study design has been formulated through collaboration of co-applicants at the six involved CF centres as well as with co-applicants within the US and Germany who are experts within the field of Cystic Fibrosis. Independent internal peer review was completed through the School of Medicine as part of the funding application and submission process for external grant applications. NIHR peer review was also undertaken prior to awarding funding as part of the programme development grant.

6.2 PATIENT AND PUBLIC INVOLVEMENT

This study is in response to a James Lind Alliance Priority Setting Partnership for CF.[1] "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 this study is a person with CF. She will have continued involvement and will sit on the management group for workstreams 1 and 2. She will advise on PROM development, recruitment, and retention of participants. Along with members of a Young Person's Advisory Group, she has contributed to the content of the PIS and consent. The development of the PROM through focus group, interviews, surveys and trialling its use within the app is only possible through engagement with pwCF and their families. Our initial priority setting partnership work developed social media tags that can be used to disseminate the results through patient networks.

6.3 REGULATORY COMPLIANCE

Before any site can inform patients about the study, the Chief Investigator/Principal Investigator or designee will apply for Health Research Authority (HRA) approval for the study and will contact all potential site R&D department and, if applicable, the local Clinical Research Network. Prior to commencing recruitment, sites must confirm their capacity and capability to conduct the study, as per the HRA approval letter.

Any amendment to the protocol should be considered that it may potentially affect a site's capacity to continue in the study, the Chief Investigator or designee will inform the Sponsor of the proposed amendment. The amendment will be submitted as per Section 6.7.

6.4 PROTOCOL COMPLIANCE

Accidental protocol deviations can happen at any time. If this occurs, they must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

6.5 AMENDMENTS

Proposed amendments will be presented to the Sponsor prior to their enactment. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. Site R&D departments will also need to be provided with the information on the amendment in order to assess their continued capacity and capability.
Non-substantial amendments also need to be notified to the REC as well as the relevant R&D departments of participating sites to assess whether the amendment affects the continued capacity for that site.
The amendment history will be numerically tracked to identify the most recent protocol version.

6.6 ADVERSE EVENTS

Reporting Procedures: Proportionate to the type of study and participant involvement**,** all adverse events will be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.

Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Non serious AEs: All such events, whether expected or not, should be recorded.

Serious AEs: An SAE form should be completed and sent to the Chief Investigator within 24 hours. However, relapse and death due to Cystic Fibrosis and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported by the Chief Investigator directly to REC where in the opinion of the Chief Investigator, the event was:

'related', ie resulted from the administration of any of the research procedures; and

'unexpected', ie an event that is not listed in the protocol as an expected occurrence

In this instance, RDSAE@nuh.nhs.uk should be copied into all correspondence with the REC. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the TAFR01910 SAE form for non-IMP studies. Local investigators should report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Sponsor Contact Details for SAEs:

I. Email (RDSAE@nuh.nhs.uk)

II. Hand delivered not mailed (R&I, NHSP, C Floor, South Block, QMC)

Any queries please contact a member of staff in the Research & Innovations department:

Email: researchsponsor@nuh.nhs.uk

6.7 DATA PROTECTION AND PATIENT CONFIDENTIALITY

GENERAL PRINCIPLES

All investigators and study site staff will comply with the requirements of the General Data Protection Regulation 2018 and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's/Act's core principles. Nottingham University Hospitals NHS Trust will act as Data Controller for the study.

Commercial software packages will be used throughout the project. For all software used, the appropriate usage licences will be held through the University of Nottingham. Statistical analysis will be performed using NVIVO, Stata or PRISM software. Microsoft Teams will be used for the video and audio recording and transcription of the focus group and interviews. Microsoft Teams is an ISO 27001, information-security-management compliant service that allows secure and controlled sharing of data, including video and audio recordings. Microsoft Teams encrypts data both in transit and at rest and is approved against the University's Handling Restricted Data Policy. The service provides continual failover support. Microsoft Teams also allows for data segregation via private channels, meaning that sub-project folders can have strict access controls. In addition, the University of Nottingham provides access to central performance storage; approved for storage of very large data or those which require

on-premise storage. It is approved against the University's Secure Data Handling Standards. Any off site working with the data will be backed up and stored on the University central storage as soon as possible. If MS Teams is unable to be used for any reason, Cisco WebEx will be used, a secure platform for video conferencing supported by the sponsor, Nottingham University Hospitals NHS Trust.

Data will be stored in the overall umbrella folder "CARDS-CF" in which a README folder will be created with a file describing the project aim, objectives, statistical analysis plan along with a detailed protocol. A descriptive metadata will also be included within this folder. The metadata will be sufficient to allow others to understand what research data exists and how to access them. Version control will be accounted for by labelling the file as "FILE NAME_DATE_"

For all aspects of the study, to maintain anonymity participants will be pseudonymised and assigned a study ID number (random 3 digit number). This will be used to allow the separation of personal data from the participant responses to maintain confidentiality. Video and audio recordings for the interviews will be labelled with the study ID number only with the files only accessible to researchers at the University of Nottingham. A data file matching the study ID number to the participant's identifiable information will be held in a separate, secure, password-protected University of Nottingham file in the University central storage. For the focus group, as there will be a number of people participating, participants will still be assigned a study ID number with their details stored in a separate data file as outlined above. The recording will also be labelled with a generic 3 digit code and this code stored in the data file. Participants will be made aware through the participant information sheet and during the focus groups to maintain confidentiality of other members of the focus group and not share their information or the content of the focus group outside the session.

The Chief Investigator will decide on the appropriateness of sharing data related to this study following a formal request for data or collaboration. Microsoft OneDrive and SharePoint allows for secure and controlled sharing of data if a request for data sharing is approved. Following study competition, the Investigator Site File, Sponsor Trial Master File and study documents shall be finally archived by the sponsor at secure archive facilities according to Sponsor SOP's.

STAGE SPECIFIC DATA MANAGEMENT

Stages 1 and 2

All data generated as part of focus groups or interviews will be transcribed verbatim. The audio recording and electronic copies of the data will be stored on the University central storage. These will be stored separately in password protected files.

Stage 4

Data will be generated using a secure web-based survey generating platform. Data will be downloaded and stored securely on the University central storage. For participants who gave their contact details to be contacted about further work relating to the study, these will be separated from the results and stored as a separate password protected file prior to analysis of the results. This will preserve confidentiality of the participant responses and provide anonymity of the participants.

Stage 5

The sponsor will remain the data controller and uMotif is the Processor. Data processing and the management of the data provided by uMotif via use of the app is outlined in detail as a separate Data Processing document. Only basic participant demographic information will be collected, and any personal identifiable information provided by the participant such as contact details will be separated from the to the participant's responses to maintain confidentiality. A sub-contract is in place between the University of Nottingham and uMotif in which the University of Nottingham is the data controller and owns the Intellectual Property in order for the University of Nottingham to give this in turn to Nottingham University Hospitals NHS Trust who are leading the study.

6.8 INDEMNITY

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

6.9 ACCESS TO THE FINAL STUDY DATASET

All investigators at the University of Nottingham will have access to the full dataset. Decision to grant access to study investigators at other sites to the full dataset will be at the discretion of the Chief Investigator.

7 DISSEMINATION POLICY

Access to the data generated will be granted to all named co-investigators at the University of Nottingham. Anonymised data from the study will be made available subject to reasonable request to the Chief Investigator. On completion of the study, the data will be analysed and a Final Study Report prepared and sent to NIHR. Funders will be acknowledged within the publications but do not have any rights for review or approval of data for publication. Participating investigators can only publish any of the study data following approval from the chief investigator. At the end of the study we will also hold an online

dissemination event for pwCF in addition to preparing a lay summary of the findings and also disseminating the results via social media accounts.

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7.1 Appendix 1- Required documentation

- Participant Information Sheets (paper copy and electronic) – Focus Group (12-15 years, parents/carer, 16years+)
- Participant Information Sheets (paper copy and electronic) – Interview (12-15 years, parents/carer, 16years+)
- Participant Information Sheets (electronic) – Survey
- Participant Information Sheets (paper copy and electronic) – App use
- Consent forms – Focus group (parents/carer, 16years+)
- Consent forms – Interview (parents/carer, 16years+)

7.2 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made