**GLIDE**

**GL**ycaemic **I**ndex **D**ietary **E**ducation

for glucose abnormalities in cystic fibrosis:

A feasibility study

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Glossary/Abbreviations

BRC Biomedical Research Centre

CF Cystic fibrosis

CFRD Cystic fibrosis-related diabetes

CRF Case report form

IGT Impaired glucose tolerance

OGTT Oral glucose tolerance test

PERT Pancreatic enzyme replacement therapy

PIS Participant information sheet

REC Research ethics committee

UoB University of Bristol

UHBristol University Hospitals Bristol NHS Foundation Trust

**Background and rationale**

*Cystic fibrosis*

Cystic fibrosis (CF) is a chronic, genetic disease, characterized by abnormally thick and dehydrated secretions which lead to organ obstruction, primarily affecting the lungs and digestive systems. It is the most common life-limiting, genetic disease in white populations, affecting 1 in 2500 live births worldwide [1]. Advances in medical management have led to dramatic improvements in survival such that average life expectancy is now more than 40 years of age in developed countries [2, 3].

*Management of CF*

Despite improvements in lifespan, CF continues to cause progressive digestive and respiratory dysfunction, and individuals often experience prolonged periods of ill-health before dying prematurely from lung disease. Preventative management and symptomatic treatment is instituted in early childhood and represents a significant treatment burden. Arduous and time-consuming daily treatment regimens must be adhered to, which include oral and inhaled medications, pancreatic enzyme replacement therapy (PERT), multivitamin supplements, nutritional supplements, physiotherapy and exercise. Adherence to CF therapy is variable; studies indicate a 30–70% adherence in adults [4-6], which is similar to other chronic diseases and in children overall adherence is about 50% [7]. Adherence is a complex issue [8] and the longevity and complexity of both CF and its management have been highlighted as major determinants of therapeutic adherence [9].

*Nutrition in CF*

Nutrition is a critical component of the management of CF [10] and body mass index (BMI) is an important predictor of survival [11]. The aim of dietary therapy is to optimise nutritional status. Increased energy requirements due to chronic inflammation, impaired lung function, infection and fat malabsorption mean that an energy dense diet, typically high in fat and sugar, is standard in CF management [12]. Nutritional guidelines recommend intakes of 120-150% estimated average requirements (EAR) for energy, 200% reference nutrient intake (RNI) for protein and 40% fat intake [13, 14].

*Glucose abnormalities in CF*

A spectrum of progressive glucose abnormalities is present in CF and few people with CF have normal glucose tolerance [15]. Glucose tolerance is classified as normal (CF-NGT), impaired (CF-IGT) or CF-related diabetes (CFRD) [16]. A period of progressive CF-IGT precedes diagnosis of CFRD, affecting 20% of 10-year olds and 82% of the CF population by the age of 30 years [17].

CFRD is the most common co-morbidity associated with CF [1]. It is typically diagnosed in late adolescence or early adulthood [18-20] and is associated with increasing age, affecting approximately 20% of adolescents and up to 50% of adults with CF aged over 40 years [18, 21, 22]. The combination of diabetes and CF leads to increased morbidity and a six-fold increase in mortality has been reported [23-25]. Fewer than 25% of people with CFRD survive beyond the age of 30 years, compared with 60% of CF individuals without diabetes [26]. CFRD is a distinct form of diabetes that shares features of both Type 1 and Type 2 diabetes. It occurs in association with pancreatic insufficiency and is primarily caused by pancreatic damage and the gradual loss of the insulin secreting beta cells [27]. However, glucose tolerance is also modified by factors that alter insulin resistance, such as intercurrent illness and infection [28].

CFRD is associated with decreased lung function in both the pre-diabetes and diabetes stages and there is growing evidence that early abnormalities in glucose tolerance contribute to deterioration in clinical status [29]. Cross-sectional analysis of 7,566 CF patients revealed that the rate of decline in pulmonary function is directly proportional to the degree of glucose intolerance and insulin deficiency [30]. Decline in lung function and accelerated weight loss have been shown to precede diagnosis of CFRD by up to 6 years [31, 32]. This may be because of hyperglycaemia (elevated blood glucose levels), which causes structural changes in lung tissue and predisposes to bacterial chest infections [29, 30]. An association between glycaemia and mortality has been demonstrated; hyperglycaemia has been shown to treble the risk of death in people with CFRD, providing compelling evidence to support efforts to improve glycaemic control [33].

*Management of glucose abnormalities in CF*

Optimising glycaemic control is known to improve clinical status, pulmonary function and reduce mortality [32]. Insulin therapy is the primary means of controlling glycaemia in CFRD but its role in CF-IGT is less clear [15]. The development of diabetes represents the onset of a second chronic disease, adding to the complexity of the daily treatment regime. Individuals are required to monitor and control their blood glucose concentrations through regular blood glucose testing and daily insulin injections. Insulin treatment for CF-IGT is controversial as it increases patient burden, but it is not yet known whether early initiation of insulin reduces morbidity and mortality in the longer term [34]. Determining the optimal therapy for pre-diabetes is regarded as an urgent priority by the CF Foundation, American Diabetes Association and Pediatric Endocrine Society [21].

*Nutritional management of glucose abnormalities in CF*

There is limited evidence to guide dietary therapy for glucose abnormalities in CF. The aim of CFRD management is to optimise nutritional status and maintain normal glycaemic control and therefore dietary therapy must incorporate the increased energy requirements of CF. Current guidelines are based on clinical consensus rather than empirical evidence [1]. There are no meta-analyses or randomised controlled trials of dietary intervention in CFRD [24]. CF nutritional recommendations are therefore applied as there is no evidence specific to the dietary management of people with CF and abnormal glucose control [15]. As in any clinical group, patients vary in their specific nutritional needs and dietary management must therefore be tailored to meet these needs. As practice varies, it is recognised that a consistency of approach and nutritional targeting is needed in this vulnerable group [35, 36].

CF clinical management emphasises the consumption of an energy dense diet, which is typically high in fat and sugar, to maintain weight. This is contrary to the low-refined carbohydrate, low-fat diet advocated for non-CF diabetes management [37]. This conflict between dietary therapy for CF and diabetes is typically resolved in favour of the traditional energy dense CF diet, but high sugar intakes result in poor glycaemic control in CF patients who have altered glucose handing.

Nutritional factors affect blood glucose levels and a possible area for dietary intervention that may offer potential benefit to individuals with CF and altered glucose handling is manipulation of the Glycaemic Index (GI) and Glycaemic Load (GL) of the diet. Different carbohydrate foods have different effects on blood glucose and can be ranked using the GIycaemic Index (GI); a numerical classification of carbohydrate-containing foods based on their postprandial effect on blood glucose levels [38]. Carbohydrates that are absorbed rapidly by the body cause higher blood glucose levels after consumption and have higher GI rankings. Examples include ‘simple’ carbohydrates such as sugar and sugar sweetened foods/drinks, white bread/rice, potatoes (baked, mashed, roasted), cornflakes etc. Carbohydrates that are slowly digested and absorbed, produce lower postprandial blood glucose excursions. These are often referred to as ‘complex carbohydrates’ and include sweet potatoes, wholegrain pasta and noodles, oats, seeded bread, basmati rice, beans, lentils, muesli [39]. By contributing a gradual supply of glucose to the bloodstream and hence stimulating lower insulin release, lower GI foods may contribute to improved glycaemic control, compared to high GI foods [38]. Low GI diets may increase insulin sensitivity by minimising fluctuations in blood glucose levels and reducing the secretion of insulin over the day [40]. The GL represents the overall glycaemic effect of the diet, taking into account the quantity of carbohydrate consumed, and is calculated by multiplying the GI by the grammes of carbohydrates [41]. The glycaemic response to a food is also affected by other factors including the method of cooking or processing, degree of ripeness, and the effect of other foods eaten at the same time. For example, combining high GI simple carbohydrates with fat and/or protein lowers their GI, as the fat/protein helps to slow the digestion and absorption of the carbohydrate [42].

It is known that low GI and GL foods consumed evenly throughout the day lead to improved glycaemic control in patients with diabetes [39]. Low GI and GL dietary intervention has demonstrated benefit in non-CF forms of diabetes, including improved insulin sensitivity, glycaemia and quality of life in both Type 1 and Type 2 diabetes and it is now recommended as part of their dietary management [43, 44]. However low GI carbohydrate foods have been associated with increased satiety and reductions in subsequent energy intake [45]. This is not consistent with the dietary aims of CF management. Dietary intervention must be able to incorporate the specific CF aim of optimising nutritional status in addition to achieving good glycaemic control. Increasing consumption of foods that combine high GI carbohydrate with fat/protein rather than encouraging consumption of low GI foods per se may be a more appropriate approach to lowering GI/GL in this patient group to ensure that the energy content of the diet is not compromised.

A systematic review conducted in 2012 to assess current understanding of the effect of low GI dietary interventions in young people with CF [46] concluded that there was a dearth of evidence in this area. The authors recommended further scientific study in relation to the clinical utility of a low GI diet in CF to improve glycaemic control. A retrospective study published in 2015, evaluating the course of glucose metabolism in 12 paediatric CF patients, reported that individuals with good compliance to a low-GI diet started insulin therapy later [47]. However dietary manipulation was not the focus of this study and no details of dietary intake are provided.

Considering the current lack of evidence further research is necessary. This study is designed as an exploratory, feasibility study to investigate if appropriate GI/GL dietary education can be implemented in patients with CF and glucose abnormalities and if the study recruitment and processes are acceptable to participants and the clinical teams providing their care. The findings from this feasibility study will inform the development of a full-scale trial, as set out in the British Medical Research Council’s (MRC) framework for the development and evaluation of complex interventions [48, 49].

**Study Objectives**

*Primary Objective*

To investigate the feasibility of GI/GL dietary education (GLIDE) intervention in young people with CF and glucose abnormalities. Feasibility will be assessed through measurement of:

• Recruitment to the study

• Attendance at research visits

• Acceptability of the GLIDE dietary intervention

*Secondary Objectives*

* Measure glycaemic control before GLIDE intervention and at follow-up
* Measure energy and nutrient intake before GLIDE intervention and at follow-up

**Study Outcomes**

Primary objectives will be reported as descriptive analyses of recruitment to the study and attendance at research visits. In-depth qualitative interviews will be conducted to explore acceptability of the dietary intervention.

Outcomes for the secondary objectives, measured at baseline and at follow-up, are as follows:

• CGM results: Area under the curve (AUC) for glucose levels above the upper limit of the normal range (7.8mmol/L)

• HbA1c measurement

• Energy intake and nutrient composition (macro- and micro-nutrient) of dietary intake

• Weight, height, BMI/BMI-SDS (children & adolescents)

• Lung function: FEV1 & FVC

**Plan of Investigation**

*Study Design*

This is a mixed-methods study to evaluate the feasibility of GLIDE intervention in young people who have CF and glucose abnormalities.

*Sample*

20 young people (11-30 years) with CF and abnormal glucose control will be recruited to participate. This is an exploratory feasibility study and therefore no power calculation has been used to determine sample size; it is not designed or powered to address the effectiveness of the GLIDE intervention being evaluated [49-51]. The sample is based on the current local known populations with CF and abnormal glucose control and is considered sufficient for this evaluation of the feasibility of delivering GLIDE.

**Eligibility**

*Inclusion criteria:*

Patients aged 11-30 years, with a diagnosis of CF based on either genotype and/or phenotypic presentation, who have established CFRD or who are at risk of developing CFRD, will be invited to enter the study. All patients with a HbA1c ≥ 6.5% [21], a previously recorded abnormal oral glucose tolerance test (OGTT), defined as a 120-minute plasma venous sample ≥7.8mmol/l [52] and/or a previous abnormal continuous glucose monitoring (CGM) result, defined as CGM time above 7.8 mmol/l ≥4.5% [29] will be eligible to participate in the study.

*Exclusion criteria:*

Pregnant female patients, or those planning pregnancy, and individuals who are unable to give informed consent are not eligible for participation.

**Recruitment**

Participants will be recruited from the following sites:

***Paediatric CF services***

Bristol Royal Hospital for Children, University Hospitals Bristol NHS Foundation Trust

Royal Devon and Exeter Hospital, Royal Devon & Exeter NHS Foundation Trust

***Adult CF services***

Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust

West Midlands Adult CF Centre, University Hospitals Birmingham NHS Foundation Trust.

This is an initial study to evaluate the feasibility and acceptability of GLIDE intervention and therefore for pragmatic reasons we will aim to recruit patients with a confirmed CFRD diagnosis who are established on insulin therapy and who are therefore known to the clinical CF teams. However, if sufficient numbers of patients with established CFRD cannot be recruited, individuals who are at risk of developing CFRD will be invited to participate in this feasibility study. These individuals will be identified by the clinical CF teams through review of clinic lists using the following screening criteria:

• HbA1c ≥ 6.5% [21]

OR

• OGTT: 120 min venous blood sample ≥ 7.8mmol/l [52]

OR

• CGM time above 7.8 mmol/l ≥4.5% [29]

Purposive sampling will be employed to ensure maximum variation of genders and ages. A study invitation letter and participant information sheet will be distributed by members of the CF clinical teams to individuals who fulfil the inclusion criteria during routine clinic appointments. Individuals willing to consider participation will be able to contact the research dietitian using the details on the study paperwork or, with consent, the research dietitian will contact these individuals via telephone or email at their preference, one week later to confirm study participation.

**Informed Consent**

All participants are required to give written informed consent to participate in this study. When obtaining consent to take part in the main study, participants will also be asked to consent to being interviewed. Informed consent will be sought at the first research visit, prior to commencing any data collection. A member of the research team will be responsible for the consent process. At the point that consent is obtained, the participant will have had the relevant information and time to discuss the information with family, friends and their CF clinical care team for a minimum of one week. There will be an opportunity to discuss any remaining questions the participant may have with a member of the research team prior to signing the consent form. For individuals under 16 years of age, their parent/carer will be the main point of contact and will be required to give informed consent. However, participant assent will also be obtained from young people under the age of 16 where appropriate. A copy of the signed consent form will be filed in the participants’ medical records to ensure that the clinical care teams are aware of their involvement in the study. Participants will also be provided with a copy of the signed consent form.

**Data collection**

The study comprises four participant research contact sessions. Data will be collected on a purpose-designed case record form (CRF). All participants will be allocated and identified by a unique study number.

**Research Contact 1 - Baseline measurements**

Research Contact 1 will take approximately 1-1.5 hours and will be conducted at the participants usual CF care centre.

*Glycaemic control:*

Glycaemia will be measured for 5-days (including a weekend) using a continuous glucose monitoring (CGM) system (Appendix 1: Ipro2®, Medtronic). CGM monitoring will be conducted when participants are clinically stable; clinical status will be assessed via telephone using the modified criteria of Fuchs et al [56] prior to Research Contact 1 to identify any exacerbations/steroid use. If any change in usual clinical status has occurred, the time to Research Contact 1 will be extended to allow recovery of the participant’s usual clinical status.

CGM measures and records interstitial glucose levels every 5 minutes whilst in situ. It has been validated in CF [53] and is increasingly being used to monitor glycaemia in clinical practice, identifying growing numbers of CF patients with altered glucose handling. The CGM sensor will be inserted by the CF clinical nurse specialist/research dietitian at Research Contact 1. Three calibration finger prick blood tests are required each day the CGM sensor is in situ. Participants will receive training and a glucose monitor to facilitate this.

*Dietary intake:*

Dietary intake will be recorded over the same 5-day period using an on-line, 24-hour dietary recall tool (Appendix 2: INTAKE24). INTAKE24 is a validated, self-completed computerised dietary recall system based on multiple-pass 24-hour recall. Data collection has been demonstrated to be of similar quality to interviewer-led recalls at a significantly lower cost [54]. Unlike the traditional paper-based methods of dietary assessment, this technology-based method has benefits such as pre-programmed completeness checks and food photographs to enhance food recognition and portion size estimation. Evidence has demonstrated newer methods of dietary assessment to be preferred over traditional methods by an array of population groups, including adolescents and adults [55, 56]. An interactive tutorial on how to use the tool will be provided by the research dietitian at Research Contact 1. Each participant will be issued with an individualised log-in code and will be asked to access the tool once a day for the duration of the measurement period, commencing on the day of Research Contact 1. It takes approximately 20 minutes to record one day’s dietary intake.

If participants are unable to access the internet to use INTAKE24, a paper food diary will be provided, and the research dietitian will provide training on how to complete this. The participant’s paper food diary will then be inputted into INTAKE24 by the research dietitian at the end of the data collection period. This may involve a telephone call to the participant to clarify/obtain any missing data.

*Clinical measurements:*

The following clinical measures will also be performed:

• Blood sample for baseline Glycated Haemoglobin (standard measure of glycaemia in previous three months) - details provided below

• Weight

• Height

• Lung function (FEV1, FVC)

* CF-Quality of Life Questionnaire [57]

*Blood sample:*

Blood will be sampled by a trained Doctor/Phlebotomist/Clinical Nurse Specialist in the participants CF centre. Blood samples will be stored locally in hospital freezers designated for storage of samples or similarly secure storage arrangement at -80°c until collected for analysis. Local storage is temporary, and samples will be regularly transferred to central storage at the co-ordinating centre (UHBristol) in accordance with appropriate health and safety guidance and study procedures. At the co-ordinating centre, samples will be placed in designated freezers located at the Bristol Royal Infirmary. These freezers will remain locked when not in use to ensure no other parties can gain unauthorised access. Access to the building is strictly controlled by use of an ID card and PIN number.

Aliquots of the samples will be sent in batches from the co-ordinating centre to the analytical and collaborating laboratories. Once the samples have been tested, the remainder of the aliquot will be destroyed by the commercial testing laboratory. Once the study is complete, any remaining samples at the co-ordinating centre will be disposed of in accordance with the Human Tissue Authority’s Code of Practice.

*CGM sensor removal:*

After the 5-day measurement period the CGM sensor will be removed. CGM sensor removal is quick, easy and painless; the research dietitian/member of the clinical CF team can do this, or the participant can remove the sensor at their preference. If removing the sensor themselves, participants will be provided with pre-paid postage to return the sensor to the chief investigator. If the participant prefers a member of the research team to remove the sensor, a home visit can be arranged to facilitate this. Following sensor removal, the data generated will be downloaded by the chief investigator for analysis. Dietary intake and glycaemia data will be reviewed concurrently to examine the effects of usual diet on glycaemic control.

**Research Contact 2 - GLIDE intervention**

Research Contact 2 will be conducted approximately 2 weeks after Research Contact 1. Clinical status will be re-assessed via telephone using the modified criteria of Fuchs et al [58] prior to Research Contact 2 to identify any exacerbations that may have occurred. If any change in clinical status has occurred, the time to Research Contact 2 will be extended to allow recovery of usual clinical status.

It is anticipated that Research Contact 2 will take around 1 hour. Research Contact 2 can be conducted either as a home visit or at the participants CF centre at their preference.

Tailored GLIDE intervention will be delivered using the participants baseline diet and glycaemia data. GLIDE intervention will focus on manipulation of the GI/GL of dietary intake. This will be designed to lower the GI/GL of the participants diet whilst maintaining energy intake through increasing consumption of foods and drinks that combine 'simple' high GI carbohydrate with fat and/or protein and use of alternative foodstuffs that the individual finds acceptable. For example, where high GI carbohydrates such as sugar-sweetened beverages are regularly consumed, substitution with a milkshake will combine both fat and protein with the refined carbohydrate and will lower the GI, slowing glucose absorption, whilst still providing the necessary energy contribution required for CF management.

In-depth dietary planning will be conducted, in addition to the provision of behaviour change advice and practical advice to address any challenges that implementing dietary change may provoke. Implementing dietary changes may impact participants PERT regimes and this will be evaluated. Education and advice in relation to any necessary changes to pancreatic enzyme doses will be provided.

Following Research Contact 2, agreed GLIDE dietary changes will be implemented for 12 weeks. Participants will be provided with written advice to guide their dietary modification and they will be contacted by the research dietitian after week 1 of the implementation period via phone/email at their preference.

**Research Contact 3 - Follow-up**

Research Contact 3 will take place at the participants CF centre and is anticipated to take approximately 45 minutes.

All measurements conducted in Research Contact 1 will be repeated during the final week of the 12-week GLIDE implementation period, or as close to this time as possible. Dietary intake and glycaemia will be re-measured for a consecutive 5-day period. A blood sample for glycated haemoglobin will be taken as previously described. Weight, height (participants aged 11-18 yrs) and FEV1/ FVC will be recorded. The same methods as described in Research Contact 1 will be used for all procedures.

**Research Contact 4 - Feasibility assessment of GLIDE intervention: Qualitative interview**

Research Contact 4 can be conducted at the participants CF centre, as a home visit or via internet video calling tool (Skype/Facetime). It is anticipated to last up to 1 hour.

Research Contact 4 will involve removal of the CGM sensor, completion of the CF-Quality of Life Questionnaire and an in-depth qualitative interview to explore a) acceptability of the dietary intervention (GLIDE) and the study processes and b) experiences of managing diet for CF and glucose abnormalities.

*Qualitative interviews*

Semi-structured interviews will be held with all participants in order to explore a) acceptability of GLIDE intervention and the study processes and b) experiences of managing diet for CF and glucose abnormalities. Semi-structured interviews allow in-depth reporting of views and experiences according to an individual’s priorities, understanding and interpretations. They ensure key areas are covered whilst allowing the participant to raise issues that are salient to them but not predicted by the researchers.

A topic guide will be used to ensure consistency across the interviews. The topic guide has been developed using previous literature and qualitative expertise within the research team and will cover areas including any previous dietary management, experience of the study dietary intervention and the study processes. It will be used in an open and flexible manner to allow participants to raise issues that are salient to them. It is anticipated that interviews will last approximately 30-45 minutes. All participants will have given consent to be interviewed when consenting to take part in the study.

A sample (n≈8) of participants’ carers (parents/guardians and/or partners) will also be interviewed to capture their perspectives on managing diet for glucose abnormalities on CF, as differing priorities of diet between young people with CF and their parents/carers have been identified [59]. The final number of interviews will depend on when data saturation is researched.

Interviews will be conducted in private, either face-to-face or via Internet video calling tools (e.g. Skype/Facetime), according to the participants preference, and will be audio-recorded. Young people will be interviewed independently to facilitate open and honest discussion. However, if younger participants (<16 years) want to be interviewed with a parent/carer present this preference will be respected. Interviews with carers will take place immediately after interviews with participants.

*Focus groups – CF clinical teams*

Focus groups will be conducted with healthcare professionals from the CF clinical teams participating in this study at the end of the participant recruitment period. These focus groups will be used to explore their views and experiences of the dietary intervention and the study processes. The clinical teams have advised that scheduling these focus groups during protected time for clinical/research updates in team meetings would be appropriate and will provide opportunity for group discussion. A topic guide for these focus groups will be developed, informed by the findings from the qualitative interviews with participants.

**Discontinuation/withdrawal of participants**

Each participant will have the right to withdraw from the study at any time. The study design aims to minimise attrition by not overburdening participants but if there is significant attrition (loss of more than five individuals) over the study period then additional individuals with similar characteristics to those lost will be recruited.

If a participant wishes to withdraw, data collected up until this point will be included in the analyses, unless the participant expresses a wish for their data to be destroyed. If a reason for withdrawal is given this will be documented in the participants CRF.

Participants will be withdrawn from the study if their CF clinical team feel that their participation is in any way negatively affecting their clinical status.

**Expenses**

Participants will be reimbursed for any travel expenses/parking costs they incur as a result of participating in the study.

**Data Analyses**

*Qualitative data*

Interviews will be audio recorded and fully transcribed. NVivo data management software will be used to facilitate electronic coding and retrieval of data. Data will be analysed thematically using an approach based on Framework [60]. Using this method, data pertaining to each code will be summarised in tables, allowing comparisons to be made within and across interviews to identify thematic patterns and deviant cases and to highlight participants’ views of specific issues. The CI will receive full qualitative support throughout data collection and analysis by her supervisor, Dr Katrina Turner, a senior qualitative methodologist and joint head of the Centre of Academic Primary Health Care, University of Bristol.

*Quantitative data*

Descriptive analyses of recruitment to the study and attendance at Research Contact sessions will be presented. Participants’ baseline characteristics and CGM and dietary data recorded at baseline and at 12-week follow-up will be tabulated using means and standard deviations for normally distributed data, medians and interquartile ranges for non-normally distributed data, and percentages and counts for categorical data. Area under the curve (AUC) for glucose levels above the upper limit of the normal range (7.8mmol/l) and energy content and nutrient composition of dietary intake pre-GLIDE intervention (baseline) and at 12-week follow-up will be calculated. Paired tests will be used to assess whether there has been any change in glycaemic control and energy and nutrient intake between baseline and the 12-week follow-up time point. Changes in glycaemia will also be examined in relation to changes from baseline of glycated haemoglobin (HbA1c). Statistical advice and input will be provided by the NIHR Bristol Biomedical Research Centre’s statistician.

**Dissemination of findings**

Summaries of preliminary findings will be produced for study participants, the NIHR and the clinical CF services participating in this study. Manuscripts reporting the findings will be produced for publication in high impact factor, relevant, peer-reviewed journals (e.g. paediatric, respiratory and diabetes journals). Preliminary work will be disseminated locally through the NIHR Bristol Biomedical Research Centre’s ‘Present and Discuss’ programme and seminar series and will be submitted for presentation at the UK CF Trust Conference, the European CF Society Conference and the North American CF Conference.

**Regulatory Issues**

*NHS Ethical Review*

Ethical review of the study protocol and all other study related essential documents (e.g. Patient Information Leaflet, consent/assent forms) will be carried out by a UK NHS NRES REC. All members of the research team are trained in and will adhere to Good Clinical Practice.

*Site−specific information (NHS sites)*

This study will involve four NHS sites (Bristol Royal Children’s Hospital, Royal Devon and Exeter Hospital, Bristol Royal Infirmary, Birmingham Heartlands Hospital). All site-specific information will be reviewed and approved by NHS HRA and contracts confirmed prior to the study commencing.

*Informing study participants of possible benefits and known risks*

The information from this feasibility study will inform future studies to establish if Gl/GL dietary intervention can improve glycaemic control in people with CF and glucose abnormalities without negatively affecting energy intake.

All potential participants will be provided with age-appropriate written participant information. This will provide information on why the research is being conducted, what it will involve, the possible benefits and any known risks of taking part in the study. The opportunity to discuss the study before deciding on participation will be afforded to all either through direct contact or telephone contact with the research dietitian as the participant/family wish. The research dietitian or CF clinical care teams will inform participants if any new information comes to light that may affect their willingness to take part in the study.

*Adverse events/safety reporting*

Details of any adverse events which arise whilst the participant is taking part in the study will be recorded and reported as per the definitions and reporting guidance outlined below:

Definitions

An adverse event is any unexpected effect of an untoward clinical event affecting the participant. This is classified according to severity:

a) Non-serious adverse event (AE) – includes discomfort or slight worsening of symptoms

b) Serious adverse event (SAE) – may be particularly harmful, dangerous or require hospitalisation

An SAE is defined as one of the following:

1) results in death

2) is life-threatening

3) requires hospitalisation, or prolongation of existing hospitalisation

4) results in persistent or significant disability or incapacity

5) consists of a congenital anomaly/birth defect

6) is otherwise considered medically significant by the investigator

*Reporting*

Adverse Events (AE)

All AEs will be reported by the chief investigator from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure. Those occurrences meeting the definition of SAEs will be reported using the Serious Adverse Event Form (available from UHBristol), including SAEs spontaneously reported to the Investigator within 30 days after the participant has completed the study (including post study follow-up). UHBristol, on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by the chief investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to the study, will be recorded in the source document and the CRF, together with any measures taken. The chief investigator will record in the CRF their opinion concerning the relationship of the adverse event to study therapy. UHBristol, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities.

Serious Adverse Events (SAEs)

All SAEs will be reported to the UHBristol contact (research@uhbristol.nhs.uk or fax 0117 3420239) by investigational staff within 24 hours of their knowledge of the event.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant’s participation in the study, will be followed until any of the following occurs:

• the event resolves

• the event stabilizes

• the event returns to baseline, if a baseline value is available

• the event can be attributed to factors unrelated to study conduct

• when it becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The death of a participant is considered an SAE, as is any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant’s participation. Exceptions to this are hospitalizations for:

• social reasons in absence of an adverse event

• the in-clinic protocol procedures

• surgery or procedure planned before entry into the study (must be documented in the CRF)

**Research Governance**

*Study Sponsorship and Indemnity*

The University of Bristol will act as sponsor for the study. The University of Bristol will be responsible for and administer the financial aspects of the grant. The University of Bristol has arranged public liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University. The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University. The University of Bristol’s Public Liability insurance policy provides an indemnity to our employees for their potential liability for harm to participants during the conduct of the research.

The study will be conducted in accordance with:

• International Conference for Harmonisation of Good Clinical Practice (ICH GCP)

• Research Governance Framework for Health and Social Care

*Sponsor/NHS approval*

All trial documents and any amendments to these will be approved by the Sponsor (University of Bristol) prior to submission to the NHS REC or HRA.

All study participants will be recruited from NHS sites and therefore confirmation of capacity and capability from the local NHS Trusts (University Hospitals Bristol NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust and Royal Devon & Exeter NHS Foundation Trust) is required prior to study commencement. Any amendments to the trial documents approved by the REC or HRA will be submitted to NHS trusts involved in the study for information or confirmation of continued capacity and capability as directed by HRA categorisation.

*Monitoring*

University of Bristol, as Sponsor of this study, has a Service Level Agreement in place with University Hospitals Bristol NHS Foundation Trust. As part of this agreement, University Hospitals Bristol NHS Foundation Trust will undertake monitoring of research projects where University of Bristol is fulfilling the responsibilities of Research Sponsor. A minimum of 10% of projects will be monitored.

*Patient and Public Involvement*

Three young individuals with CF and glucose abnormalities under the care of the Bristol CF services have participated in the development work underpinning this research. These individuals have advised that they will continue to support this research in an advisory capacity and will form the research steering group. The group are unable to meet in person due to CF cross-infection restrictions, but all have advised that they are willing to receive email and phone communication and to comment on study documents etc via email. The Bristol Young Persons Advisory Group (YPAG) has been consulted and has provided useful advice and input into the development of the study documents and the study processes.

*Confidentiality*

All data collected in this study will be stored and maintained in strict accordance with the UK Data Protection Act 1998. All participant identifiable information (i.e. names, addresses, dates of birth etc.) will be stored in a separate database from those that hold the study data collected and participants will be identified by a unique study number.

Data will be stored in the NIHR Bristol BRC on level 3 of University Hospitals Bristol (UHBristol) NHS Foundation Trust Education and Research Centre, Bristol. This is a secure site within the UHBristol NHS Trust. Anonymised data will be kept on a database within the BRC on a password protected University of Bristol computer and the University network is itself firewalled, IP and password authenticated. All paper records will be stored in secure storage facilities in the BRC. Personal identifiable paper records will be stored separately from anonymised paper records. No personal data will leave University Hospitals Bristol NHS Foundation Trust/University of Bristol property.

**Study Management**

*Finance*

This study is funded by an NIHR Clinical Doctoral Research Fellowship (C-DRF) award and supported by a CF Trust Venture and Innovation Award (VIA).

*Day-to-day Management*

Day-to-day management of the study will be the responsibility of the chief investigator, Laura Birch, under the supervision of the Co-Investigator, Professor Julian Hamilton-Shield. Study progress will be discussed at the chief investigators monthly C-DRF supervision meetings within the NIHR BRC.

*Protocol Amendments*

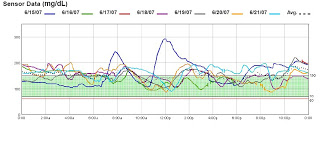
Any amendments to the protocol will be submitted to the REC or HRA as advised by the Sponsor (University of Bristol). Protocol amendments may be substantial (requiring full review and favourable ethical opinion from the REC) or Non-substantial (requiring review by HRA). Only once the amendment has been approved by the REC and/or HRA and confirmation of continued capacity and capability provided by trusts involved will the amended protocol be implemented.

*End of the Study*

For the purpose of REC approval, the study end date is deemed to be the date of last data collection. The study will be reported to the REC within 90 days of completion, or 15 days if it is stopped early for any reason.

**Appendix 1: Continuous Glucose Monitoring (CGM)**

CGM works via insertion of a small subcutaneous sensor on the abdomen, which measures glucose levels in the interstitial fluid every five minutes, 24-hours per day, providing a more complete picture of glycaemia compared to the standard oral glucose tolerance test (OGTT) or using daily fingerstick blood testing. CGM sensors require daily calibration using fingerstick blood samples (x3/day). Glucose measurements are sent from the sensor via a wireless transmitter to a small monitor that can be worn in a pocket or on a belt. The data is then downloaded from the monitor and is presented quantitatively and graphically as plotted daily glucose curves.



**Appendix 2: INTAKE24**

INTAKE24 is an on-line, dietary recording tool, developed by Newcastle University, designed specifically for young people. This is a secure tool, accessed by individually issued log-on details. No personal data is collected; participants are identified through their unique user number. Completion of one day’s dietary intake record takes approximately 15 minutes. The tool provides prompts and visual aids to assist the user and to improve data capture.

<https://intake24.co.uk/>



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