Academic and Clinical Central Office for Research and Development

Non-CTIMP Study Protocol

Mitochondrial DAMPs as mechanistic biomarkers of mucosal inflammation in paediatric Crohn's disease and Ulcerative Colitis (Mini-MUSIC)

Mini MuSIC

Mitochondrial DAMPs as mechanistic biomarkers in paediatric Crohn's disease

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CHI	Community Health Index
CD	Crohn's Disease
CI	Chief Investigator
CRF	Case Report Form
CRP	C-reactive protein
CTIMP	Clinical Trial of an Investigational Medicinal Product
DAMPS	Damage Associated Molecular Patterns
DNA	Deoxyribonucleic Acid
ECTU	Edinburgh Clinical Trials Unit
EDTA	Ethylenediaminetetraacetic acid
eMS/MS	Endoscopic Mayo Score/Mayo Score
EEN	Exclusive enteral nutrition
FBC	Full Blood Count
FC	Faecal (stool) calprotectin
FIT	Faecal Immunohistochemistry Test
FPR	Formylated Peptide Receptor
GCP	Good Clinical Practice
IBD	Inflammatory Bowel Disease
IBD-U	IBD - Unclassified
ICH	International Conference on Harmonisation
ISF	Investigator Site File

mtDNA	Mitochondrial DNA
mtFP	Mitochondrial Formylated Peptides
PAMP	Pathogen Associated Molecular Pattern
PIBD	Paediatric Inflammatory Bowel Disease
PUCAI	Paediatric Ulcerative Colitis Activity Index
PI	Principal Investigator
PRR	Pattern Recognition Receptors
QA	Quality Assurance
RNA	Ribonucleic Acid
REC	Research Ethics Committee
SCCAI	Simple Clinical Colitis Activity Index
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOP	Standard Operating Procedure
TLR	Toll-like Receptor
TMF	Trial Master File
TNF	Tumour Necrosis Factor
U-E	Urea and Electrolytes
UC	Ulcerative Colitis
wPCDAI	Weighted Paediatric Crohn's Disease Activity Index

1. INTRODUCTION

1.1 Background

Inflammatory bowel disease (IBD) comprising of Crohn's disease (CD), Ulcerative Colitis (UC) and IBD-unclassified (IBD-U) are chronic, incurable immune-mediated conditions affecting the gastrointestinal tract. CD is the more common form of IBD in the paediatric age range (<18 years) and represents 68% of paediatric IBD (PIBD) cases.[1] CD can affect anywhere along the gastrointestinal tract, mostly commonly the last part of the small bowel (terminal ileum) and the right side of the large bowel. CD is characterized by aphthous ulcers (appearances like common mouth ulcers). UC is the second most common form of PIBD and represents 22% of total cases in Scotland[1]. In contrast to CD, it affects only the large bowel and has a diffuse, continuous inflamed appearance typified by easy bleeding from the gut lining. Patients with PIBD who do not meet the criteria of either CD or UC are described as having IBD – unclassified (IBD-U) and represent 10% of patients.[1] These three conditions are associated with debilitating symptoms and signs such as excessive tiredness, uncontrolled bowel habit, abdominal pain, growth failure and malnutrition. In severe cases, PIBD patients can develop abdominal abscesses, bowel perforation and sepsis. In children and young people this morbidity occurs at a crucial point in their life where they are developing the skills and resilience to become effective members of society. Active disease prevents optimal growth and can influence pubertal development while symptoms may prevent school attendance and limit education attainments, affecting future prospects.

The incidence and prevalence of PIBD are increasing across Europe.[2] In Scotland, the incidence is 12.0/100,000/year with the largest period prevalence recorded worldwide in 2016 at 58.9/100,000/year.[1] While PIBD patients diagnosed at less than 17 years of age account for 8.0% of all incident patients in Lothian, Scotland, those still in paediatric services (when measured in a fully inclusive all-ages population based prevalence study) represent only 1.4% of the total IBD patients locally[3]. Given that IBD is a common chronic condition with low mortality there is therefore a high population prevalence, for example 1 in 125 persons in August 2018 in Lothian, Scotland[4]. The paediatric-onset PIBD patients tend to have higher disease burden[5] and be treatment-naïve at diagnosis therefore represent an important and distinct population of patients worthy of greater study with respect to mechanistic biomarkers.

1.2 The current problem

IBD is a chronic progressive inflammatory condition. Despite recent progress in identifying factors that increase one's likelihood to (e.g. genetics), or that can trigger (e.g. drugs, stress) a flare, we do not understand why gut inflammation seen in IBD does not resolve (in comparison to other forms of gut inflammation for example, infectious gastroenteritis). Because of uncontrolled gut inflammation, IBD patients are at risk of long-term bowel wall damage and the serious complications associated with this. For example, in CD, up to 50% of patients will develop strictures (narrowing of the bowel), fistulas (abnormal connections between different parts of the bowel or to other organs) or abscesses (pockets of pus) that require surgery within 10 years of diagnosis.

Medical treatments of IBD have improved with more options available in the last 5 years. The current clinical approach follows a sequential route of conventional medical treatments with exclusive enteral nutrition (EEN; CD only), gut-specific anti-inflammatories (mesalazine; UC and IBDU only) or corticosteroids, immunomodulators, tumour necrosis factor (TNF) inhibitors and the newer biologics plus new oral small molecule drugs in that order. However, there is significant inter-individual variation in therapeutic response and our current best

standard approach involving azathioprine and TNF-inhibitors are effective in, at best, 50% of CD patients with severe CD. Loss of anti-TNF response occurs in 20-30% of CD patients within one year of treatment initiation. We lack the knowledge (or tools) underlying such molecular heterogeneity in clinical presentation and treatment response in both UC and CD.

PIBD tends to be more aggressive with patients typically presenting with more extensive areas of the bowel affected while having higher hospitalization and colectomy rates.[5] It's relapsing and remitting nature result in the accumulation of bowel damage over time with younger patients having a long disease course ahead of them. Achieving sustained remission with mucosal healing (total resolution and absence of ulceration in the gut) may reduce the frequency of complications and delay this progressive bowel damage.[6] An important tool to achieving the best outcomes is accurate disease monitoring. The current gold standard for monitoring is endoscopy* however, this carries issues of poor patient tolerance, associated complications and usage of finite NHS resources. These are compounded in paediatrics due to the need for patients to receive general anesthesia for the procedure. Established non-invasive tests are limited by reduced sensitivity and specificity. There is a need for new prognostic biomarkers that can accurately predict both the presence and severity of inflammation at diagnosis, and during a disease flare, while being able to confirm endoscopic remission; this can also be a predictive biomarker for the effectiveness of an established or novel IBD treatment.

*Upper GI endoscopy examines the oesophagus, stomach and first and second parts of the duodenum, common sites of inflammation in paediatric CD. An ileo-colonoscopy is carried out to examine the entire large bowel (colon) and final part of the small bowel (ileum). In paediatric patients, all of the colon and approximately 10cm of the ileum (terminal ileum) respectively can be inspected by ileo-colonoscopy. This is a necessary test for patients with CD as inflammation usually affects the ileum and anywhere along the large bowel. Biopsies are taken from multiple sites during endoscopic assessment in PIBD.

1.3 What is the Mini-MUSIC study?

The Mini-MUSIC study is a multi-centre, longitudinal, translational research study set in the real world PIBD clinical setting to investigate and develop a new biomarker approach that aims to inform both patients and clinicians of the current state of the affected gut lining (how inflamed or whether the bowel wall has completely healed). It is part of the active IBD study MUSIC (Mitochondrial DAMPs as mechanistic biomarkers of mucosal inflammation in Crohn's disease) and expands on this work to therefore include all age ranges (the 'all-ages IBD' approach). Although clinical phenotype differs between PIBD and adult-onset IBD in some respects – PIBD is phenotypically most similar with elderly-onset IBD (IBD diagnosed at age 60 years or over) – there is no suggestion that the aetiopathogenic causes of IBD nor IBD treatment responses differ between PIBD and adult-onset IBD. Further, study outcomes are homogeneous between Mini-MUSIC and MUSIC where possible, so harmonising results for all-ages analyses, plus those outcomes from ileocolonoscopy which are less likely to be achieved in Mini-MUSIC (due to less sequential endoscopic assessments than in MUSIC) will be enriched within all-ages analyses.

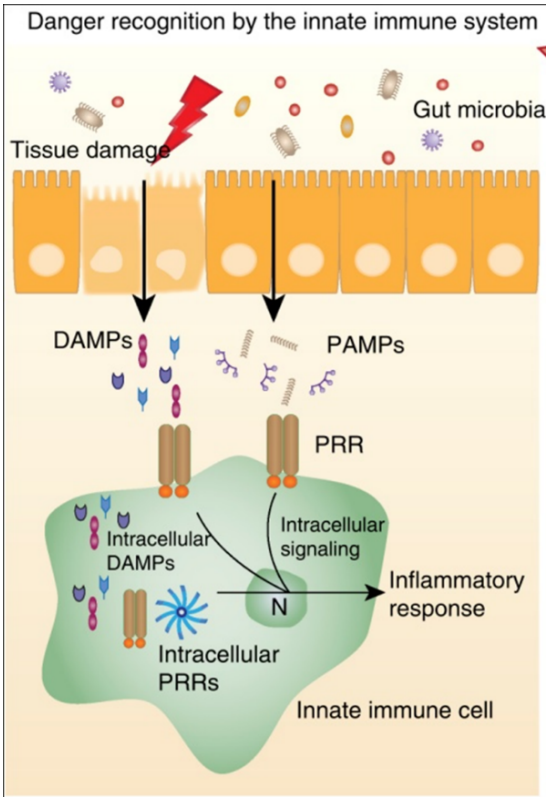
This new biomarker approach will study a panel of molecular signs in PIBD patients' blood, stools and biopsies that will be correlated to clinical status, disease activity, systemic inflammatory activity and mucosal state (by non-invasive faecal calprotectin) - and in some cases the direct appearances (via endoscopy and histopathology) of PIBD patients' gut lining will be assessed over 1 year in response to current standard nutritional and drug treatment given to them by their NHS PIBD consultant.

This approach will focus on the role of damage associated molecular patterns (DAMPs), also known as 'danger signals'. DAMPs are found in our own cells and are released during tissue stress or injury. Like the signals from bacteria, called PAMPS (pathogen associated molecular patterns, they can trigger inflammation. In the Mini-MUSIC study, we will use blood, stool, saliva and gut samples obtained from participants during active PIBD and in clinical remission in order to understand how DAMPs contribute to the development of gut inflammation.

1.4 What are mitochondrial DAMPs?

Recently, we found that DAMPs arising from the mitochondria are increased in patients with active IBD.[7] Mitochondria are the 'batteries' or 'powerstations' that reside within and provide energy for living cells. They have evolved from bacteria around 2-3 billion years ago. As such, the mitochondria have many similarities with bacteria. When our immune cells encounter mitochondria that are released, they confuse them with bacteria, become activated and trigger a prolonged inflammatory response, which is destructive to our own tissue. Of interest, we showed that these signals are mitochondrial DNA and fragments of their protein, called formylated peptides.

Mitochondrial DAMPs can also be released in severe acute tissue damage or inflammation (for example, in major trauma or sepsis respectively). Their roles as biomarkers in chronic immune-mediated conditions such as IBD have not been fully evaluated.



(a) How are DAMPs released?

Under physiological conditions, DAMPs reside intracellularly or are sequestered in the extracellular matrix and are thus hidden from recognition by innate immune cells bearing PRRs. In response to perceived danger such as tissue damage, DAMPs are liberated extracellularly, serving to signal danger to the host and promoting inflammation and repair processes. These processes are initially beneficial and protective, but in prolonged or significant DAMP release, they can be harmful.

(b) The relative importance of the specific DAMPs

DAMPs encompass a diverse range of biomolecules. Some are highly pro-inflammatory such as mitochondrial DNA (mtDNA), mitochondrial formylated peptides (mtFP) whereas others such as s100a8/9 (also called calprotectin) have less clear roles.

(c) What inflammatory pathways they activate?

Specific DAMPs have distinct roles on established inflammatory pathways. Our recent work has focused on mitochondrial DAMPs on toll-like receptor (TLR)-9 and Formylated Peptide Receptor (FPR)-1 signaling

1.4.1 Mitochondrial DAMPs in IBD

We recently found two classes of mitochondrial DAMPs: DNA and formylated peptides that were significantly higher in IBD (prospective cohort of 67 UC and 30 CD patients).[7] In CD, Plasma mtDNA levels were significantly higher (136.7 copies/µl [IQR 88.0-370.9]) compared to non-IBD controls (61.5 copies/µl [IQR 32.8-104]) ($p<0.0001$).[7] Higher mtDNA levels were observed in those with severely active CD (159.1 copies/µl [IQR 90.17-421]) compared to

those in clinical remission (79.92 copies/µl [IQR 30.94 – 145.9] (p=0.04).[7] In our overall IBD cohort, we found that mtDNA levels were significantly correlated with severe disease markers C-reactive protein (r=0.33, p<0.0001), albumin (r=-0.32, p<0.0001), and white cell count (*r*=0.37, p<0.0001).[7] We also detected significantly higher levels of stool mtDNA and mitochondrial formylated peptides (that activates the pro-inflammatory formylated peptide receptor-1, [FPR1]) during active disease (vs. remission).[7]

There are now more than 270 genes that are associated with increased susceptibility to IBD in humans. Many of these IBD genes have direct roles in regulating mitochondrial function. One of the strongest genetic signals from GWA-studies arises from genes regulating autophagy (*Atg16l1, Irgm, Atg5, Lrrk2, Park7*).[8,9] Autophagy is the major biological process to remove damaged mitochondria. We (and others) have shown that mice models with autophagy defects (*Irgm*$^{-/-}$, *Atg16l1*$^{-/-}$, *Xbp1*$^{-/-}$, *NLRP6*$^{-/-}$ *and mdr1a*$^{-/-}$)[10] accumulate damaged mitochondria in the gut. Failure to clear increases the burden and inflammatory potential of these damaged mitochondria. Related studies show that this results in higher pro-inflammatory mtDAMP release.[11] This pathologic process is amplified in defective autophagy. Hence, genetic susceptibility may influence the level of mitochondrial DAMPs release, which in turn, play a role in determining the severity of gut inflammation. Mitochondrial DAMPs therefore, also identifies the pathologic process IBD.

1.5 Oral and intestinal microbiome

The innate immune system has evolved to protect epithelial surfaces from microbial pathogens, with the ability to recognise PAMPs (pathogen associated molecular patterns). As noted earlier, mitochondria are derived from bacteria so bacterial infection through PAMPs and damaged tissue mitochondria through DAMPs will both promote inflammation and repair.

The key role of the gut microbiota in the establishment and maintenance of health, as well as in the pathogenesis of disease, has been identified over the past two decades. Shifts in the microbiome have been linked to the rise of incidence of IBD in countries undergoing industrialisation and Westernisation; the microbiome has a central role in current proposed models of IBD pathogenesis.

Oral bacteria have been shown to be enriched in the intestine in IBD.[12] Current hypotheses suggest that once established, IBD can be driven by microbiomial and inflammatory changes originating specifically from the gingival niche in the oral cavity through saliva, worsening IBD outcomes; this concept has been termed the “gum–gut axis”.[13] In preliminary studies, the oral microbiome in treatment-naïve PIBD patients has been shown to exhibit dysbiosis which is related to disease severity and which resolves following therapy.[14] Tongue swabs were used in this study; Somineni at al. have indicated that saliva may be more effective than mucosal surfaces for measuring oral dysbiosis.[15]

2 WHY IS THE Mini-MUSIC STUDY NEEDED?

We hypothesise that mitochondrial DAMPs are good mechanistic biomarkers for mucosal inflammation and healing in IBD at all ages, paediatric and adult patients alike.

Complete mucosal healing is the most sought-after treatment target with the best long-term implication in prognosis.

Up to now IBD clinicians rely on (1) clinical symptoms (how they feel, their bowel habit, presence of blood in stools), (2) clinical tests such as stool calprotectin (FC) and blood C-reactive protein (CRP) to inform both themselves and the patients, how well the drug treatment is working and importantly, whether the ulcers and inflammation seen in the gut lining have healed or not.

Current evidence shows that these approaches are not fully informative. For example, 30% of patients with significant subjective improvement in their symptoms following treatment of active CD have evidence of active inflammation in their gut lining when further assessed with an ileo-colonoscopy. Blood and stool tests to predict mucosal healing are only useful in around 60-70% therefore limited in their use in guiding doctors to how severely inflamed the bowel wall is during active IBD.

Direct visualisation using ileo-colonoscopy is the most accurate approach to assess disease activity and mucosal healing in response to medical treatment. By knowing precisely, how the gut wall inflammation is responding to treatment, the clinician can accurately manage the IBD patient (by either changing the dose and type of treatment, and whether to carry on with expensive, strong medications with potentially serious side effects). However, in the real world, follow-up endoscopic tests are difficult to carry out as they are expensive and we lack the capacity to undertake these examinations within NHS. This difficulty is further compounded in children due to poor acceptability and the additional risks and costs of general anaesthesia.

The MUSIC trial aims to recruit 250 adult IBD patients from three centres in Scotland. The Mini-MUSIC trial will add to this prospective cohort and include patients aged between 6 - 17 years from within paediatric IBD services. Expanding the trial to include all ages will provide additional data on this important group of PIBD patients who often have more severe disease at presentation. Given that the population of children and young people with IBD is significantly smaller than in adult practice, we will mitigate this by expanding Mini-MUSIC to include all PIBD centres in Scotland. In a later stage, we also aim to utilise a biobank (the UK PIBD bioresource) to expand our access to PIBD samples (blood, urine, stool, saliva, and biopsy) when using the same inclusion criteria (given below).

3 PROJECT GOALS

The main goal for the Mini-MUSIC study is to investigate the role of mitochondrial DAMPs in the clinic as an indicator of gut inflammation and subsequent mucosal healing in response to medical (nutritional and drug) treatment in PIBD.

Secondly, we will carry out further scientific studies using blood, stool, saliva and gut biopsy samples to investigate how mitochondrial DAMPs (and all known biomarkers and biological data such as genetics) contribute to the abnormal development of gut inflammation in PIBD.

Thirdly, we will investigate the role of the oral microbiome and the duodenal microbiome as prognostic biomarkers in PIBD, the relationship of the oral and the duodenal microbiomes with the ileal and rectal microbiomes, and any resolution of oral and duodenal dysbiosis with medical (nutritional and drug) treatment of PIBD over time.

3.1 Primary research questions:

- Do mitochondrial DAMPs predict the activity and severity of PIBD-inflammation?
- Does normalisation of mitochondrial DAMPs reflect complete endoscopic mucosal healing in PIBD?

- How do mitochondrial DAMPs compare to current biomarkers (FC, CRP) and clinical symptoms (paediatric ulcerative colitis activity index (PUCAI)/Weighted paediatric Crohn's disease activity index (wPCDAI)) in assessing PIBD inflammation and mucosal healing?

- Can we develop a simple PIBD decision-making model to predict mucosal healing based on mitochondrial DAMPs, together with relevant biological data such as genetics, blood transcriptomics, microbiome; and current clinical biomarkers such as calprotectin, faecal haemoglobin and blood CRP?

- Are oral and duodenal microbiomes prognostic biomarkers of failure to achieve mucosal healing?

- Does resolution of oral and duodenal dysbiosis (upper GI microbiome) with medical (nutritional and drug) treatment of PIBD over time occur?

3.2 Secondary research questions:

- How are mitochondrial DAMPs released from cells in the IBD gut?

- What types of cells are important in mitochondrial DAMP release? They are many forms of inflammatory cells in affected IBD gut (e.g. macrophage, epithelial, neutrophils). We think different cell types may contain more inflammatory DAMPs.

- Which type of mitochondrial DAMPs are important in causing inflammation? Can mitochondrial DAMPs pinpoint a specific underlying genetic susceptibility (e.g. autophagy) or inflammatory mechanism in IBD?

- What are the relationships of the oral and the duodenal microbiomes with the ileal and rectal microbiomes?

3.3 Rationale

Our focus is to investigate mitochondrial DAMPs' utility in two clinically relevant PIBD scenarios: (a) How severe or active is the disease? (b) How well are we treating IBD? At the initial diagnosis this will follow current standards of care as outlined in the ECCO-ESPGHAN guidelines for treatment of paediatric CD[16] and paediatric UC[17]. PIBD clinical status in terms of disease severity, response to treatment and attainment of remission will be via clinical measures (PGA – physician global assessment), disease activity scores ((PUCAI and wPCDAI for UC and CD respectively)[17,18], laboratory blood tests (e.g. CRP) and stool tests (faecal calprotectin). If endoscopy is performed, endoscopic endpoints of mucosal inflammation and healing can therefore be used - the Simple Endoscopic Score for Crohn's Disease (SES-CD) and Endoscopic Mayo Score (eMS) for CD and UC respectively. Both have been validated and used widely in research and in clinical trials. By using these objective endoscopic endpoints, we can test mtDAMPs (and in combination with current biomarkers FC and CRP) across a range of mucosal inflammation (full healing to severe). Due to the reduced acceptability of frequent repeat endoscopy in paediatric practice the additional endoscopies at both 3 and 12 months in the MUSIC trial will be replaced with documentation of disease severity scores (PUACI and wPCDAI for UC and CD respectively) in all cases, with SES-CD and eMS only documented if paediatric endoscopy is performed at these time points.

In addition to this, we will investigate if mitochondrial DAMPs can identify a subclinical pathogenic mechanism (e.g. [a] defective autophagy to clear damaged mitochondria; [b] de-regulated innate immune response to mitochondrial DAMPs.) These data will pave the way for future use of mitochondrial DAMP biomarkers as part of a stratified approach for new treatments targeted at mitochondrial DAMPs and their downstream inflammatory mechanisms in IBD.

4 STUDY POPULATION

Presently within usual UK NHS paediatric IBD care, all children and young people 17 years of age and younger with active IBD are followed up in PIBD centres or in district general hospitals (DGHs) working in shared care with the PIBD centres. Within Scotland, all PIBD patients are investigated and managed via the 3 regional centres (Edinburgh, Glasgow and Aberdeen/Dundee) providing a virtual national PIBD network. In 2022, the prevalent number of patients in PIBD centres in Scotland was 800, with 175 incident PIBD patients in the 2022 calendar year (unpublished data). Scotland has seen an inexorable rise in biologic prescribing in the last decade[19], and currently more than 50% of prevalent PIBD patients are currently or have been exposed to 1 or more biologic or new small molecule drug (unpublished data). PIBD patients will have documentation of disease activity (PUCAI, wPCDAI), plus simple laboratory tests (stool calprotectin, C-reactive protein, albumin and blood count) to assess their well-being and response to medical treatment.

Within Mini-MUSIC, our patients will be followed up prospectively (aligning the usual NHS clinical care above) and will receive additional clinic follow-up to assess mucosal healing in response to medical treatment.

All participants will have active IBD at the time of recruitment.

There will be 3 main groups:

1. The incident cohort - newly diagnosed PIBD patients with active disease prior to initiating medical therapy

2. The relapse cohort - PIBD patients with acute flare requiring medical treatment (exclusive enteral nutrition, corticosteroids, immunomodulator or biologics)

3. The biologic cohort - PIBD patients on established medical treatments (biologics or immunomodulators) that require either escalation to 1st biologic or change of biologic to another biologic or a new oral small molecule drug due to poor control of disease activity

We aim to capture a wide spectrum of IBD patients with active disease, hence strict criteria for IBD disease severity/extent/activity ***is not applied***.

Suitable potential participants must have active IBD based on clinical evaluation of referring clinician and any one of the below from investigations which have been carried out within 6 weeks of screening (see inclusion criteria below).

5. PATIENT SELECTION AND ENROLMENT

5.1 Number of participants

We aim to recruit 60 PIBD patients in total (15 incident cohort, 30 relapse cohort and 15 biologic cohort patients) from the participating gastroenterology units in Scotland. The proposed patient recruitment period will be from 01/04/2023 – 30/06/2024, with follow up to 30.06.25.

5.2 Inclusion Criteria:

1. All patients must be aged 6-17 years and be able to either give consent or have a parent/guardian with parental rights that is able to give consent on their behalf.

2. All patients must have a diagnosis of IBD (CD, UC or IBD-U as determined by the ESPGHAN Porto criteria[20])

3. All patients must have active IBD at the time of screening:
    - Active IBD symptoms by referring clinician's judgement in addition to one of the below criteria (within 6 weeks of screening):
        - FC level of >100ug/g
        - Blood CRP >5mg/l
        - Endoscopic, radiological or histological evidence of active IBD

4. All new diagnosis PIBD patients will require a recent ileo-colonoscopy within 6 weeks of recruitment that has:
    - Clear documentation of endoscopic disease activity and extent (SES-CD for CD; Mayo Score for UC)
    - Photographs of endoscopic mucosal IBD disease activity

5. If patients have undergone an ileo-colonoscopy within 6 weeks but with an endoscopic report that is insufficient in endoscopic disease activity data as per (4), potential participant can still be considered providing there is:
    - Supporting objective evidence of IBD disease activity (FC, CRP) **within 2 weeks** of index endoscopic assessment

6. Patients who have evidence of an active IBD flare (as per 3) or are changing IBD therapies due to treatment failure can be included in the study without a recent ileo-colonoscopy if the referring clinician considers omitting it as their local standard of care.

5.3 Exclusion Criteria:

1. IBD patients with severe/fulminant disease at screening:

    - Subjects displaying evidence of toxic megacolon (transverse colon diameter >5.5cm in those >10 years or >4cm in those <10years on plain abdominal X-ray in the presence of acute severe colitis and systemic upset). An accompanying full radiological report must be attached. Note – abdominal X-ray will be carried out if clinically indicated by referring clinician

2. Referring clinician's judgement where surgical intervention (colectomy or resection) is deemed likely within 1 month of screening

3. Evidence of intestinal dysplasia or malignancy (histologic, endoscopic or radiologic)

4. UC patients who have had a colectomy (total and subtotal)

5. UC patients with an ileo-anal pouch

6. Participants, where there are limitations to language communication for the patient or parent/guardian so the information sheet cannot be reliably understood and/or the patient/carer, cannot provide full informed consent.

5.4 Identifying Participants

Potential participants will be identified by responsible NHS IBD clinicians and then be referred to the Mini-MUSIC research team or local Principal Investigator in typical scenarios below:

1. IBD patients referred due to active disease for the initiation of, or switch, in biologic or new oral small molecule drug treatment
2. IBD patients who are newly diagnosed (following full diagnostic assessment) requiring exclusive enteral nutrition, corticosteroids (oral or intravenous), biologic treatment or immunomodulator treatment
3. IBD patients who are on medical follow-up, requiring endoscopic re-assessment of IBD activity due to worsening of their IBD symptoms
4. IBD patients who have contacted IBD service or seen in clinic/emergency department/attendance on day case ward (for infusion or injection or unscheduled review) or admitted to hospital with symptoms suggestive of an IBD flare.

The clinical team will inform the research team of any potentially suitable patients who have expressed interest in taking part in the study, and have given permission to be approached by telephone or in person. The first approach to the participant will be performed by the Mini-MUSIC research team (gastroenterologist, clinical research fellow, research assistant or nurse) following:

1. IBD clinical review (in physical or virtual clinics; or IBD Helpline contact by patients) or during in-patient stay for management of active IBD
2. IBD patients' hospital appointments for counselling for biologic therapy

Age specific participant information sheets (PIS - see appendix 2) will explain the aims and the potential risks/benefits of the study, are provided to all patients and parents/guardians. Potential participants and their parents/guardians will be given at least 24 hours to consider participating in the study.

A study specific website will be created to keep participants informed of study news. Social media may also be used to communicate study information online.

5.5 Consent and enrolment

Following initial screening and PIS allocation, the Mini-MUSIC research team will invite interested potential participants to attend a research appointment where eligibility will be confirmed and consent received. See appendices 3 and 4 for consent and assent documents**.** The ethical issues surrounding the recruitment of children will be addressed by means of consent and assent with the use of age-appropriate PIS forms Consent will be obtained by a child / young person if they are deemed, by a medical practitioner using informed judgment, to have the capacity to understand the specific details and risks of the study. As a guide, young people that are competent and aged 16 and over are usually deemed to be competent to give consent; although this age is a guide. Even if a child or young person is competent, it is still normally good practice to involve the family in the decision-making process: however, if the child / young person objects, their view will be respected. Parent/guardian consent will be given for children and young people younger than 16 years who are determined not to have the capacity to understand the study and risks fully. If a child or young person is not deemed to be sufficiently competent to give consent themselves; they will be informed to the fullest of their understanding to enable them to participate in an assent process whenever this is appropriate. Whenever practical and appropriate, a child / young person's assent will be sought before including them in the study. The medical practitioner using informed judgment will determine when seeking assent is appropriate; the age of a child can only be taken as a guide. As a guide, children over the age of 12 are usually considered to be sufficiently mature to form a view, even if they are not considered fully competent to give consent. A delegation log will be set up for local PIs and other relevant clinical research team members to take consent from potential participants. Only trained and delegated members of the trial team will take consent. All PIS and consent documents will also be available on the study website which can be accessed at any time before meeting the research team. A specific age appropriate PIS will be given to the following groups of people - parents/guardians, young people aged 16-17 years, children aged 12-15 years of age, children aged 9-11 years of age and children aged 6-8 years attending the appointment who are capable of understanding it. Either the parents/guardians or competent young person will be asked to sign the informed consent form (ICF). All Children and young people not appropriate to give consent and are determined to be capable of giving assent will be asked to sign the assent form. Parents/guardians will give consent for all children and young people who have provided assent. All consent documents will be signed and dated by all, including the person delegated to take consent. The original signed CF must be kept by the Researcher in the Research Study File, 1 copy is provided to the parent/guardian, and 1 copy is placed in the electronic health record. The same will apply when assent is given. Following this, the Mini-MUSIC research team will plan subsequent steps for the Mini-MUSIC study entailed below (Figure 1).

5.6 Co-enrolment

Co-enrolment to other research studies, including drug, interventional and long-term follow-up studies will be permitted if this has been agreed and documented by the Chief Investigators of co-enrolling studies.

Any co-enrolment will follow the Sponsor Guidelines GL001.

6. STUDY VISITS, ASSESSMENTS AND FOLLOW-UP

6.1 Study visits

Clinical data and sample collection will take place at baseline week 0, 3 months and 12 months for all 3 cohorts. At each visit the participants will provide clinical activity scores, blood samples, optional saliva samples and optional stool samples. Participants may be contacted by the Mini-MUSIC research team by phone or text to remind them of appointments or sample collection.

The visit schedule and patient requirements are outlined in figure 1, table 1 and table 2.

Baseline Week 0 - The research team will complete the baseline Week 0 case report form (CRF – appendix 5). Participants have their index blood and optional saliva/stool tests taken. Participants may have had a recent index ileo-colonoscopy as part of their routine clinical care prior to recruitment (<6 weeks before recruitment).

Follow-up visits at 3 and 12 months - Participants will complete a follow-up CRF (appendix 6) with the researcher, have bloods samples and optional saliva/stool samples taken as outlined in table 1. These appointments can be conducted either in a routine, dedicated research, telephone or virtual clinics. If not seen in person at a hospital, appointments for further blood, saliva and stool tests will be arranged for participants at dedicated clinic appointments at a convenient time for the participant.

If a study participant is admitted to hospital for further in-patient management during the study period, our Mini-MUSIC research team will record the clinical and laboratory investigations pertaining to the hospital admission event. Further optional research stool, saliva and blood tests will also be carried out during the hospital admission with patient/parent/guardian agreement.

Participants are free to withdraw from the study at any point or the Investigator can withdraw a participant. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible.

Samples will be linked to the established MUSIC system by use of patient-specific barcodes or QR codes generated by the study team. Some study assessment results may be obtained from participants' medical records.

Figure 1: Patient identification, study visits and follow up

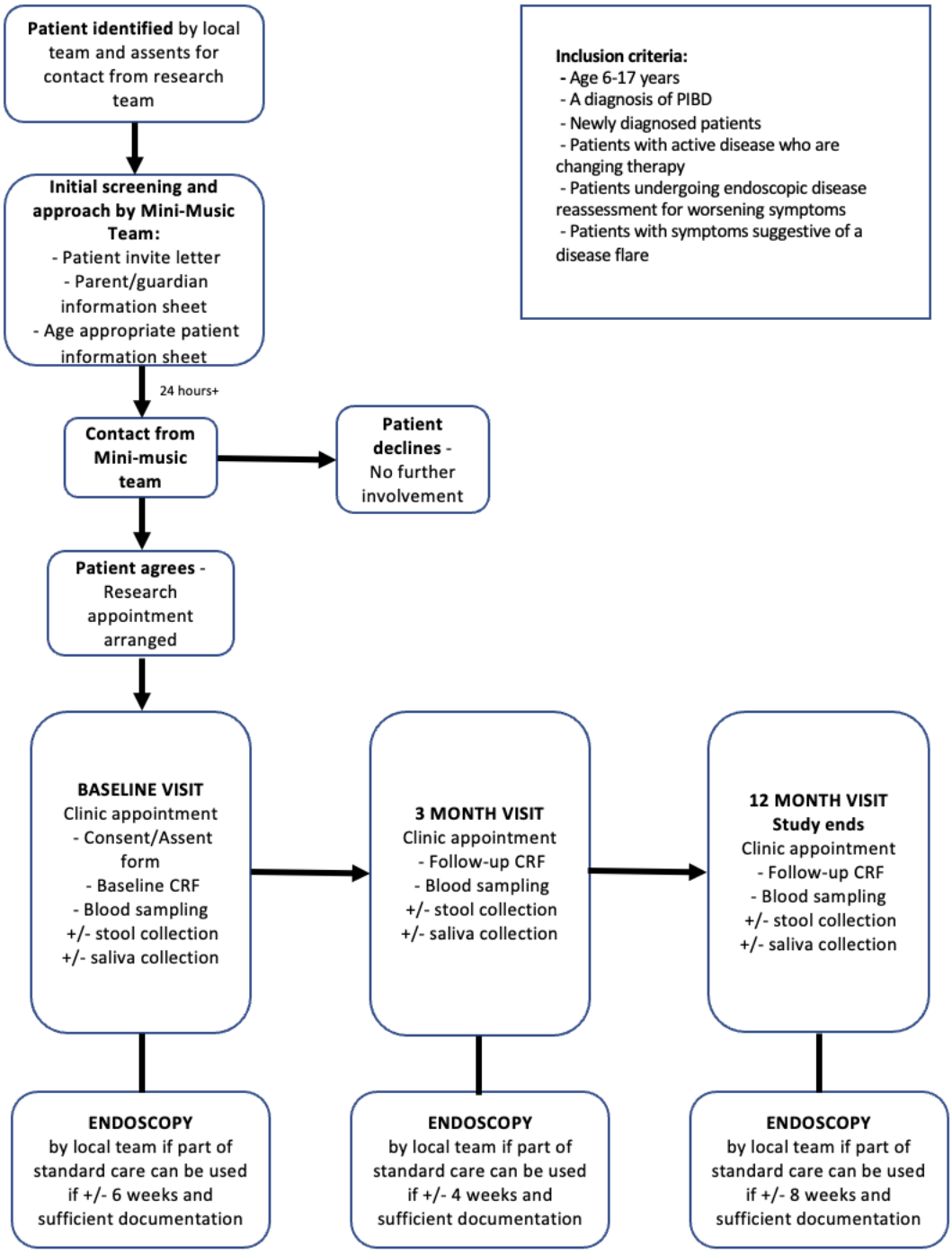


Table 1: Summary of visits and sample requirements

	Baseline visit	3 Months ^	12 Months^
Consent/Assent Baseline assessment form (Baseline CRF) [1]	√		
Follow-up assessment form (Follow-up CRF)		√	√
Symptom assessment and record of disease activity [2]	√	√	√
Ileo-colonoscopy +/- upper GI endoscopy[3] [4] [5] [6]	Optional (+/- 6 weeks) [6]	Optional (+/- 6 weeks)	Optional (+/- 8 weeks)
Blood samples [7] [8]	√	√	√
Saliva sample [8] [9]	√	√	√
Stool samples [8] [9]	√	√	√

^ Visits can occur ± 4 weeks of time point

[1] Includes relevant medical history

[2] The symptom assessment can be performed via telemedicine or phone call if necessary.

[3] Including optional video of the endoscopic procedure

[4] Additional research biopsy samples as consented by participant

[5] Ileo-colonoscopy +/- upper GI endoscopy visits can occur within 6 (3 months) and 8 (12 months) weeks of time point

[6] Data will be collected if endoscopic assessment has occurred within 6 weeks of recruitment. Please see inclusion/exclusion criteria.

[7] See core sample set in Table 2 below

[8] If participant is admitted to hospital for in-patient management of active IBD, additional research blood and stool samples can be taken during hospital admission with the patients assent

[9] Optional additional samples for biomarker studies

6.2 Sample Requirements

Table 2: Sample requirements

CORE SAMPLE SET	Processing/ storage	Purpose
Blood in lithium heparin tube(1)	Local NHS laboratory	Routine sampling as part of normal IBD care
Blood in clotted tube(1)	Local NHS laboratory	Routine sampling as part of normal IBD care
Blood in EDTA tube(1)	Local NHS laboratory	Routine sampling as part of normal IBD care
Blood in EDTA tube	Processed as per site specific Blood Sampling SOP	DNA extraction for Whole Genome Sequencing
Blood in EDTA tube	Plasma Processed as per site specific Blood Sampling SOP	Mediators, biomarkers, metabolites and LC-MS
Blood in blood RNA tube (PAXgene®)	Processed as per site specific Blood Sampling SOP	RNA sequencing of host transcriptome
Blood in blood ccfDNA tube (PAXgene®)	Plasma Processed as per site specific Blood Sampling SOP	Quantification of mitochondrial genes and sequencing of blood DNA
Stool in OMNI gut	Processed as per Non-Blood Sampling SOP	Microbiome Next Generation Sequencing/Stool biomarkers
Stool faecal calprotectin	Local NHS Laboratory	Routine sampling as part of normal IBD care
Saliva sample	OMNIgene ORAL 505 tube	Microbiome Next Generation Sequencing
Upper GI tract biopsies Formalin and OMNIgut	Pathology for paraffin-block embedding Formalin	Immunohistochemistry; microbiome Formalin; RNA Later
Upper GI tract biopsies RNA later Medium	Processed as per Non-Blood Sampling SOP	Gene expression studies
Ileo-colonic biopsies Formalin and OMNIgut	Pathology for paraffin-block embedding Formalin	Immunohistochemistry; microbiome Formalin; RNA Later
Ileo-colonic biopsies RNA later Medium	Processed as per Non-Blood Sampling SOP	Gene expression studies

(1) The research team will endeavour to take routine NHS sample at the same time as research samples.

BLOOD SAMPLES:

At each time point above, 25 - 30mls of blood for both NHS care and research bloods (approximately 3-4 additional standard blood tubes for research) will be taken either at usual IBD, research or phlebotomy clinic during the hospital visit or within the community.

SALIVA SAMPLES:

During study period, participant will be asked to provide 1 saliva sample, which will be collected for DNA sampling and an optional saliva sample at each visit for microbiome next generation sequencing.

STOOL SAMPLES:

At each time point above, an optional stool sample will be requested for faecal biomarkers and microbiome next generation sequencing.

ILEO-COLONOSCOPY:

If a participant requires an ileo-colonoscopy +/- upper GI endoscopy at baseline, the local team will carry out this procedure as part of our research study.

If a participant has had an ileo-colonoscopy +/- upper GI endoscopy as part of routine clinical care within 6 weeks of study approach, he/she can still be recruited into the study, providing that the ileo-colonoscopy has adequate record of endoscopic activity of mucosal inflammation (SES-CD/Mayo Score) with supporting image data. We will use this ileo-colonoscopy as baseline (0 month).

In certain clinical situations, if NHS clinical team require a further ileo-colonoscopy +/- upper GI endoscopy to assess IBD activity, this will be performed by the local team.

ILEO-COLONOSCOPY SAMPLES:

A standard ileo-colonoscopy requires 14 biopsies to be taken: 2 from each of the terminal ileum, caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum. For research, up to 9 additional pinch biopsies will be collected. This involves 3 biopsies (2 for formalin fixation and 1 for RNA-later) from the ileum (the small bowel), the right side colon and rectum respectively.

As there are extra research biopsies taken, there is a slightly higher risk of excessive bleeding (<1%). Most bleeding will settle spontaneously and if there is more bleeding than expected, this can usually be treated by cauterisation or clipping during the same procedure by the Endoscopist.

UPPER GASTROINTESTINAL ENDOSCOPY:

If a participant has had an upper GI endoscopy as part of routine clinical care within 6 weeks of study approach, he/she can still be recruited into the study, providing that there is adequate record of endoscopic activity of mucosal inflammation with supporting image data. We will use this upper GI endoscopy as baseline (0 month).

UPPER GI ENDOSCOPY SAMPLES:

A standard upper GI endoscopy requires 8 biopsies to be taken: 2 from each of the oesophagus, gastric body, gastric antrum, 2nd part of the duodenum. For research, up to 6 additional pinch biopsies will be collected. This involves 3 biopsies (2 for formalin fixation and 1 for RNA-later) from the oesophagus and the 2nd part of the duodenum.

ENDOSCOPIC IMAGES:

Photographic and video images of the inflamed and uninflamed bowels can be taken as an option during ileo-colonoscopy and upper GI endoscopy for further analysis to provide an objective score for disease activity and severity. Photographic images are usually taken during standard endoscopy.

SURGICAL SAMPLES:

If during duration of Mini-MUSIC study follow-up, surgery to remove affected part of IBD bowel is necessary, surplus tissue may be obtained from specimens of the large bowel (colon) and lower small bowel (ileum) that have been surgically removed either at the time of operation or during histopathological evaluation.

6.3 Storage and analysis of samples

All research samples will be anonymised and given a study code. Samples will be transferred between participating sites to allow for storage or analysis by members of the research team.

SALIVA SAMPLES will be hand delivered or posted directly to the Gut Research Unit, University of Edinburgh for processing and storage.

STOOL SAMPLES will be hand delivered or posted directly to the Gut Research Unit, University of Edinburgh (OmniGUT) for dedicated analysis in special envelopes.

BLOOD SAMPLES will be processed and stored initially at the participating centres using an agreed Standard Operating Procedure (SOP) before being transported to the Gut Research Unit, University of Edinburgh.

ENDOSCOPIC BIOPSIES in RNAlater are processed and stored in appropriate temperature controlled storage at the Gut Research Unit, University of Edinburgh using an agreed Standard Operating Procedure (SOP). Endoscopic biopsies are also stored in formalin and sent to the local Pathology Department to be processed initially. The coded pathology blocks will then be sent to and stored at the Gut Research Unit, Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh

At 3-4 monthly intervals, depending on progress of recruitment, these samples will then be processed as a batch to process supernatants (**STOOL**), plasma and serum (**BLOOD**) and RNA/protein extraction (**ENDOSCOPIC BIOPSIES**) for planned experiments.

7 DATA COLLECTION AND MANAGEMENT

Research data will be collected using the MUSIC application system designed and developed in the REDCap platform, which is maintained by the University of Edinburgh IT department based at the Institute of Genetics and Molecular Medicine (IGMM) at Western General Hospital campus in Edinburgh.

In the Mini-MUSIC system, we will use the REDCap secure web application for managing non patient identifiable information and CRFs. It is encrypted using AES-256 in counter mode and authenticating it using Poly1305-AES. Day to day management of this database is maintained by a dedicated Data Scientist in the Mini-MUSIC team and can only be accessed by members of the research team.

Hard copies of consent forms (with linked patient name and unique numbered code) and CRFs (with allocated specific study ID) will be filed separately in locked filing cabinets in secure locations at each research site.

Routine clinical data on IBD activity during the follow-up period will be updated in the Mini-MUSIC database.

All biological samples collected will be kept within the Gut Research Unit, Centre for Inflammation Research, Queens Medical Research Institute, University of Edinburgh and the Clinical Research Facility at the Royal Hospital for Children and Young People, Edinburgh under the oversight of the Lothian Gastroenterology Bioresource, University of Edinburgh and be processed every 2-3 months; or for certain experimental work, be used immediately in the Gut Research Laboratories, Centre for Inflammation Research, University of Edinburgh. Here, we will carry out new biomarker analysis from blood, stools and biopsies working together and in combination with our studies in Edinburgh. Samples and related clinical data may be shared with other researchers for use in other related projects on agreement with the Chief Investigator. At the end of the study, anonymised samples that are not directly used by our research will be transferred to South East Scotland SAHSC BioResource under the guardianship of NHS Lothian or disposed in accordance to the Human Tissue Authority Code of Practice.

All ileo-colonoscopic and upper GI endoscopy images images/videos will be anonymised and coded according to allocated specific Study ID. All images/videos will be stored in a secure database in the University of Edinburgh server.

7.1 Personal Data

The following personal data will be collected as part of the research:

Community Health Index (CHI) number, date of birth, initials, gender, age and family history of relevant medical conditions will be collected as part of the research. Patient addresses and phone numbers may also be collected if they wish to be reminded of samples or appointments by mail or text message. The CHI number is a unique identifying number assigned to each patient within NHS Scotland. The results of investigations performed routinely during the standard care of NHS patients (full blood count, CRP, electrolytes, faecal calprotectin) will be stored in the patients NHS electronic medical record, or patient notes. Use of the CHI number allows the research team to identify participants for clinical note review and inclusion of these essential investigation results in the research database. Specific consent is taken for both the use of the CHI number by the research team and for storage on University of Edinburgh servers.

All data is stored on an established encrypted database held as above. The electronic database has the recommended encryption (AES256) and can only be accessed by members of the research team. The key or code that links study ID no to CHI or identifiable personal data will be stored in a separate encrypted database also held on a University of Edinburgh server. Only the Chief Investigator (Dr Gwo-tzer Ho), Paediatric Investigator (Prof. David Wilson) and named PIs will have the code for this database.

Hard copies of consent and assent forms and case report forms (with allocated specific study ID) will be filed separately and securely in locked filing cabinets at each study site.

7.2 Transfer of Data

Data from this project may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS

organisations or companies involved in health and care research in this country or abroad. Information will only be used by organisations and researchers to conduct research in accordance with the HRA UK policy framework for health and social care research; https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/. This data could be used for research in any aspect of health or care, and could be combined with information from other sources held by researchers, the NHS or government.

7.3 Data Custodian

Gwo-Tzer Ho, as Chief Investigator, will act as data custodian for this study based in Scotland. We will use information from participants and/or their medical records in order to undertake this study and the co-sponsors will act as the data controller for this study. This means that the Chief Investigator is responsible for looking after information and using it properly. The co-sponsors will keep identifiable information about participants for 5 years.

The data custodian is the person who will be responsible for the use, security and management of all data generated by the study.

7.4 Data Controller

The data controller is University of Edinburgh

7.5 Data Breaches

The online database is hosted on a secure University of Edinburgh server. Any data breaches will be reported to the University of Edinburgh who will onward report to the relevant authority.

7.6 Identifiable Data for future research

University of Edinburgh and NHS Lothian are the co-sponsors for this study based in Scotland. The co-sponsors are responsible for any identifiable information about participants for 5 years and are strictly governed by UK Policy Framework for Health and Social Care Research.

8 OVERSIGHT ARRANGEMENTS

8.1 Inspection of records

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

8.2 Study monitoring and audit

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

9 GOOD CLINICAL PRACTICE

9.1 Ethical conduct

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

9.2 Investigator responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

9.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participant/Parent/Guardian must receive adequate oral and written information – appropriate Participant Information and Informed Consent and Assent Forms will be provided as documented earlier.

The oral explanation to the participant/parent/guardian will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent and Assent Form.

The participant/Parent/Guardian must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant/parent/guardian must be given sufficient time to consider the information provided. It should be emphasised that the participant/parent/guardian may withdraw consent at any time without loss of benefits to which they or their child otherwise would be entitled.

The participant/parent/guardian will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant/parent/guardian will sign and date the Informed Consent and Assent Form(s) to confirm that consent and assent has been obtained. The participant/parent/guardian will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

As highlighted in the earlier patient recruitment section, the process of consenting will be carried out by individuals within the Delegation Log for consent. This will include the Principal Investigator, named Investigators, Mini-MUSIC research doctors, nurses and/or research associates.

In most circumstances, consenting process will be carried out within dedicated Mini-MUSIC outpatient clinic appointments that have been agreed and arranged (following referral). Otherwise, less commonly they will take place during dedicated clinic time following clinic appointments with routine consultant review or as an in-patient during concomitant hospital admission. Every effort will be made to minimise inconvenience for the participant.

9.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

9.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

9.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

9.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

9.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords. Patients' or research participants' personal data should not be stored on a home or other personal computer.

Published results will not contain any personal data that could allow identification of individual participants.

All University of Edinburgh employed researchers and study staff will undergo mandatory data protection training through the University of Edinburgh. This includes the online Data Protection package and the Information Security Essentials through Learn as well as a minimum reading list outlined by the University.

10 STUDY CONDUCT RESPONSIBILITIES

10.1 Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

10.2 Management of protocol non-compliance

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

10.3 Serious breach requirements

A serious breach is a breach, which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

10.4 Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor. The sponsor SOP for study archiving will be followed.

10.5 End of study

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

10.6 Insurance and indemnity

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

11 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

11.1 Authorship policy

Ownership of the data arising from this study resides with the study team.

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14 APPENDICES

Appendix 1 – Patient invite letter

Appendix 2 – Patient information sheets

Appendix 3 – Consent form

Appendix 4 – Assent form

Appendix 5 – Baseline clinical research form

Appendix 6 – Follow-up clinical research form