Study Protocol

A mixed methods feasibility study into the use of physiological assessment in eosinophilic oesophagitis (EoE)

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1. INTRODUCTION

1.1. Background and Rationale

Eosinophilic oesophagitis (EoE) is an antigen-mediated, inflammatory condition with a prevalence of 10-40/100,000 people in Europe[1]. Though rare, incidence is increasing, in keeping with trends seen in other allergic conditions such as asthma[2]. Whilst increased awareness results in better recognition, the increasing prevalence of EoE exceeds this explanation[1,3]. EoE frequently presents as dysphagia, often with food bolus obstruction, which can lead to emergency hospital admissions. Others present with treatment-resistant chest-pain and heartburn. The cause of varied symptoms in EoE is a hot topic of debate. Diagnosis is based on histological assessment of eosinophil infiltration of the oesophageal mucosa and index oesophageal symptoms. Despite histological remission in 90% of cases after treatment, at least 30% of patients remain symptomatic[4,5]; however, currently there are no methods of investigating these symptoms further within routine care pathways. EoE is a chronic condition, managed primarily with medical treatment, i.e. topical steroids or proton pump inhibitors, or food elimination diets. In non-responsive cases, oesophageal dilation is required[2]. This latter approach carries a non-trivial risk of side effects including bleeding and oesophageal perforation. Additionally, EoE is associated with increased demand on endoscopy units, with 25% of individuals undergoing endoscopy for food bolus obstruction, presenting with EoE[2].

These observations highlight limitations of current assessment and management of EoE, a condition that carries significant quality of life (QOL) burden for affected individuals, including difficulties coping with symptoms of unknown cause, challenges with eating and subsequent impact on social interactions[6]. Individuals with EoE responding to a survey I conducted voiced that they felt the condition is poorly understood, live with "fear of making mistakes" and feel frustrated due to a "lack of information". Although it is known that symptoms in EoE occur for various reasons, the causes of symptoms are often not assessed, with emphasis on histology and endoscopic appearance. With global movement towards precision medicine and patient-directed therapy, this work will explore how assessments of oesophageal motility and function may be used to define pathophysiological processes that cause patient symptoms in EoE. Oesophageal physiology investigations are used routinely to diagnose primary motility disorders and gastro-oesophageal reflux disease (GORD); however, their role in EoE is undefined. If these tools were deemed informative for EoE, they could enable future treatment to be targeted at specific disease manifestations.

This feasibility research will focus on four problems not addressed by current EoE management:

1. Oesophageal motility has not been formally studied when individuals with EoE swallow food. This may provide much-needed explanation for symptoms that persist despite histological remission.
2. Monitoring of treatment response requires invasive, expensive interventions using endoscopy. Alternative approaches to monitor EoE may reduce patient burden and strain on endoscopy units.

3. Patient acceptability of interventions used to monitor EoE is unknown.
4. The relationship between objective investigation results, reported symptoms and changes in response to treatment are poorly understood.

2. STUDY OBJECTIVES

2.1.Research Aim

To assess the use and acceptability of physiological investigations of oesophageal function in understanding symptoms in EoE and to assess the relationship between physiological parameters, symptom profiles and response to treatment.

2.2.Objectives

The feasibility of a more comprehensive approach for the assessment of EoE using physiological investigations of oesophageal function will be assessed with the following objectives:

1. Describe oesophageal motility in EoE when solid food is swallowed and assess motility during symptomatic episodes that occur contemporaneously during eating.
2. Evaluate an alternative method of measuring response to treatment in EoE using the parameter mean nocturnal baseline impedance (MNBI), obtained during 24 hour ambulatory pH/impedance monitoring.
3. Determine the feasibility of performing oesophageal physiology investigations within the patient pathway and understand challenges associated with acceptability using qualitative interviews.
4. Describe the relationship between physiological assessments, symptom profiles, parameters from routine clinical care and changes following a treatment period.

3. STUDY DESIGN

3.1.Overview

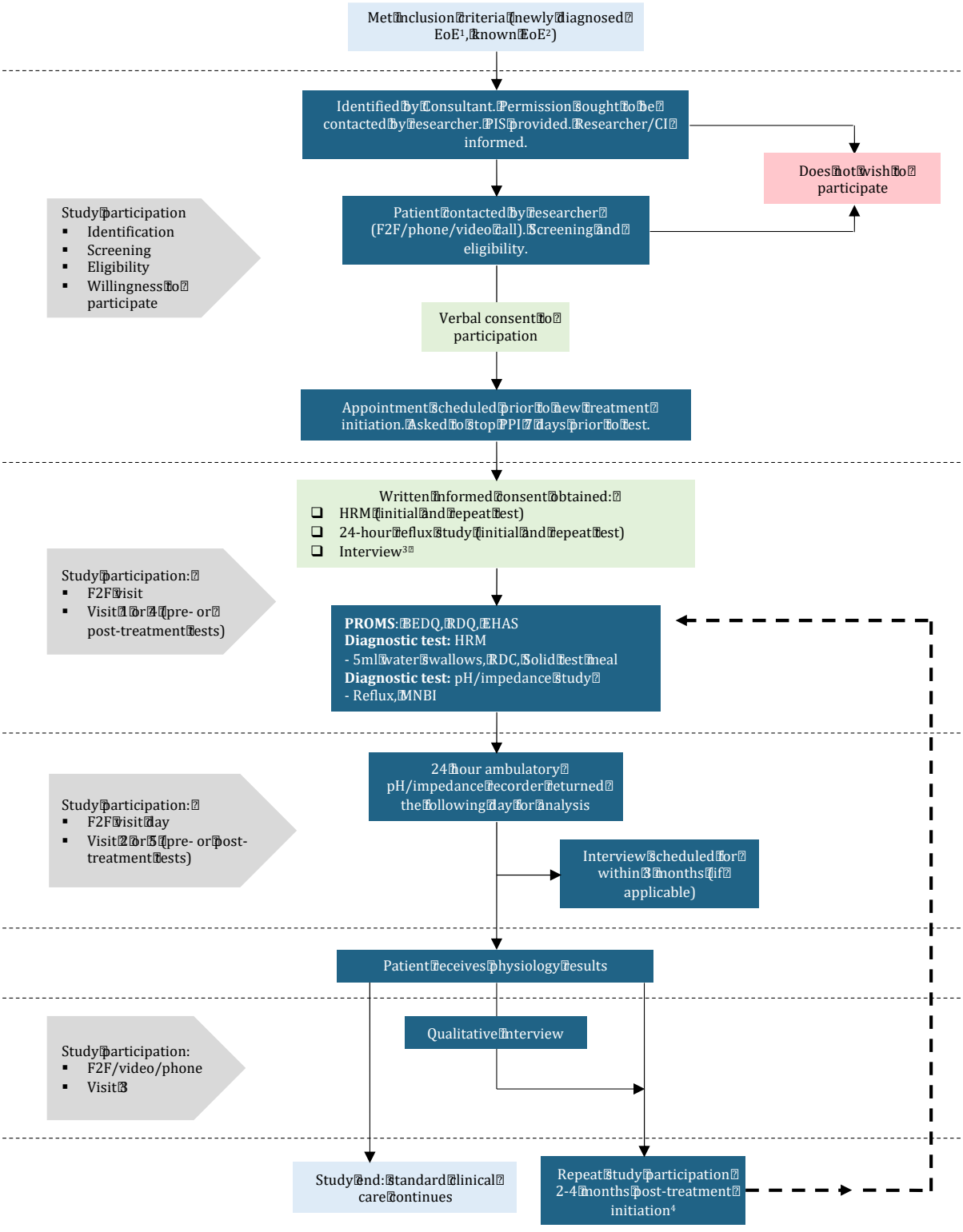
A dual-site exploratory, mixed-method feasibility study comprising a serial diagnostic observational study with embedded qualitative design[7].

The sites are:

- County Durham and Darlington NHS Foundation Trust (CDDFT)
- University College London Hospital NHS Foundation Trust (UCLH)

Three elements (high-resolution manometry (HRM), pH/impedance monitoring and qualitative interviews) will be completed in a longitudinal format with 3 overlapping phases, with a recruitment and data collection period of 21 months. Eligible patients will be identified by lead Consultants at CDDFT or UCLH, with initial study participation for those with a new diagnosis within a 3-week period, prior to standard care treatment initiation.

3.2.Study Flow Chart



Legend

1. Eosinophilia ≥15/high powered field or 0.3mm². Not specifically treated with locally acting steroids. May have had proton pump inhibitor.
2. Previous diagnosis of EoE.
3. Must have at least one physiology test to consent to interview.
4. Individuals with EoE in remission will provide control data and will not undergo repeat physiology testing.

Acronyms

EoE: Eosinophilic esophagitis
PIS: Participant Information Sheet
CI: Chief Investigator
F2F: Face to Face
PPI: Proton Pump Inhibitor
HRM: High resolution manometry
PROMS: patient reported outcome measures
BEDQ: Brief Esophageal Dysphagia Questionnaire
RDQ: Reflux Disease Questionnaire
EHAS: Esophageal Hypervigilance and Anxiety Scale
RDC: Rapid drink challenge
MNBI: Mean Nocturnal Baseline Impedance

3.3.Schedule of events

	1) Outpatient appointment	**2) Checking eligibility**	**3) Discussion with potential participant**	**4) Appointment scheduled at local site**	**5) Visit 1**
What will happen?	☐ Patient identified as potentially eligible ☐ Patient accepts patient information sheet (PIS) and is willing to be contacted by telephone to discuss the project ☐ Patient does not accept PIS. Asked if willing to answer question on reason for not wishing to participate. ☐ If yes, written response obtained	☐ Pre-screen confirmation of eligibility using medical records	☐ Patient contacted a minimum of 48 hours after being given PIS ☐ Project discussed ☐ Eligibility discussed ☐ Patient accepts or declines participation **Declines**: ☐ Willing to answer question on reason for not wishing to participate? ☐ If yes, transcribe this **Accepts**: ☐ Appointment date to be scheduled for visit 1	☐ Date established with return visit next day ☐ Pre-test preparation explained: ○ PPI – stop 1 week before ○ Anti-histamine – stop 3 days before ○ Other antacids – stop 24-hours before ○ Fast for 4 hours before tests	☐ Written informed consent ○ Physiology ○ Qualitative ☐ Participant completes 3 questionnaires ☐ HRM Study as per local SOP ☐ Start of 24-hour pH/impedance study as per local SOP Clinical information relevant to study documented (including endoscopy & biopsy results)
Who?	PI (Consultant Gastroenterologist)	Researcher (CI)	Researcher (CI)	CDDFT: Researcher (CI) UCLH: Administrative Staff or local Clinical Scientist/GI Physiologist	CDDFT: Researcher (CI) UCLH: Clinical Scientist/GI Physiologist
Where?	Outpatient Gastroenterology appointment at CDDFT or UCLH	Computer based admin task. Documented in pre-screen log	Telephone conversation	Telephone conversation	CDDFT: Medical Physics department, UHND UCLH: GI Physiology Unit, UCLH

	6) Visit 2 (day after visit 1)	7) Results discussion	8) Qualitative interview arranged	9) Visit 3	10) Repeat physiology appointment scheduled at local site	11) Visit 4 (2-4 months post-treatment)	12) Visit 5 (day after visit 4)
What will happen?	☐ pH/ impedance monitor and diary sheet returned	Major results contextualised with patient	☐ Qualitative interview scheduled in participants' preferred medium (telephone, video call, face to face)	Qualitative interview	☐ Date established with return visit next day ☐ Pre-test preparation explained: ○ PPI – stop 1 week before ○ Anti-histamine – stop 3 days before ○ Other antacids – stop 24-hours before Fast for 4 hours before tests	☐ Participant completes 3 questionnaires ☐ HRM Study as per local SOP ☐ Start of 24-hour pH/ impedance study as per local SOP	☐ pH/impedance monitor and diary sheet returned
Who?	CDDFT: Researcher (CI) UCLH: Clinical Scientist/GI Physiologist	Consultant Gastro-enterologist at local site	Researcher (CI)	Researcher (CI)	CDDFT: Researcher (CI) UCLH: Administrative Staff or local Clinical Scientist/GI Physiologist	Researcher (CI)	Researcher (CI)
Where?	CDDFT: Medical Physics department, UHND UCLH: GI Physiology Unit, UCLH	Outpatient appointment /Telephone	Telephone	☐ Telephone ☐ Video call ☐ Face to face	Telephone conversation	CDDFT: Medical Physics department, UHND UCLH: GI Physiology Unit, UCLH	CDDFT: Medical Physics department, UHND UCLH: GI Physiology Unit, UCLH

3.4.Practicalities

3.4.1. Setting up sites

Feasibility reviews will be conducted at CDDFT and UCLH to ensure confirmation of capacity and capability, once national regulatory approvals are received. Each site (CDDFT and UCLH) will have a site visit prior to study commencement with PI (lead Consultant) present. The suitability of the two sites and formal decision for inclusion in the study will be documented in the trial master file. The CI and research fellow (Catherine Sykes) will liaise with the two sites on a regular basis. The trial master file and individual site files will be created.

3.4.2. Participation

Participants will be asked to give consent to participate in Oesophageal Physiology investigations (HRM & pH/impedance monitoring) and to be interviewed separately. However, certain study elements are pre-requisites to others (see section 3.5).

Recruited patients will be reimbursed for travel to and from sites for study involvement.

3.5.Investigations

The acceptability and practicability of carrying out physiological assessments in EoE will be evaluated across the study. Limited efficacy testing will also be used to gain insight into the potential value of physiological tests (HRM and pH/impedance monitoring). A qualitative approach will explore the broader picture of the role of diagnostic assessments in EoE and also patient experiences of living with this chronic condition.

3.5.1. High-resolution manometry (HRM)

The use of advanced tests of oesophageal function in EoE will be assessed. High-Resolution Manometry (HRM) with a solid test meal will be compared with standard testing with water swallows[8]. Assessment will be made before and after therapy. Patient Reported Outcome Measures (PROMs), using validated questionnaires for benign oesophageal motility disorders will be used to assess overall symptoms[9–11], in addition to assessment of contemporaneously occurring symptoms during HRM testing.

3.5.2. pH/impedance monitoring

The use mucosal impedance measurements in monitoring EoE status will be evaluated, before and after standard therapy, with patients undergoing tests directly following HRM. Mucosal impedance will be measured to assess its practicability as a marker of mucosal integrity during quiescent nocturnal periods. Evaluation of gastro-oesophageal reflux burden will also be assessed[12].

Participation in HRM is a pre-requisite of pH/impedance monitoring.

3.5.3. Qualitative interviews

The acceptability of tests used in EoE and also the wider context of living with EoE will be explored using qualitative interviews.

Purposive sampling will be used to recruit participants, reflecting a diverse cohort of individuals accounting for different demographics, genders, age and ethnicity. This will enable exploration of cultural differences regarding the impact of living with this rare, chronic disease and the value placed on investigations for monitoring EoE. Sampling will also acknowledge diagnosis history, reflecting those with a new diagnosis and those with treatment refractory disease (defined in section 4.2) to ensure that interviewees represent individuals at different points within the patient journey.

Interviews will commence between initial and repeat physiology tests (during treatment period). This will capture people when they have first-hand experience of the tests and the available treatment options, thus providing an opportunity to explore people's views on their short-term management. Participation in at least one physiological assessment (HRM) is therefore required for participation in a qualitative interview. Participants will have received the results from their initial HRM and pH/impedance investigations prior to interview.

3.6.Planned recruitment

60 patients (30/site) will be recruited. Initial investigations at UCLH will be conducted by a local Clinical Scientist, ensuring a timely approach. The study research fellow will perform post-treatment investigations at UCLH during planned visits, enabling multiple patients to be seen on a single day. Major results/findings from HRM and pH/impedance studies will be discussed and contextualised with patients once formally reported.

Qualitative interviews will be conducted with a subset of 20 recruited patients following initial HRM and 24-hour ambulatory pH/impedance investigations. Individuals declining participation will be asked if they would be willing to answer an open-ended question on reasons for not wishing to participate, with consent sought to use responses anonymously to further understand acceptability.

3.7.Patient Public Involvement

A PPI advisory group comprising 5 adults, 3 with experience of EoE, one without lived experience of the condition and the founder of the national UK EoE charity (EOS Network) has been convened. The direct experience of EoE for the majority of the group will be used to optimise the project. One challenge of this project may be recruitment, due to requirements to attend additional hospital appointments to undergo invasive tests. The advisory group's own experiences of diagnostics surrounding EoE will be drawn upon to address this.

Meetings will be quarterly and predominantly carried out via video conference, with one annual face-to-face meeting per year. Individuals will be reimbursed for involvement as per NIHR guidance. Individuals can choose their preferred form, ensuring no-one is

excluded from participation due to issues surrounding payment. The role of the advisory group will evolve during the course of the project; however, anticipated roles are:

- Advising on development of patient information leaflets
- Discussing recruitment barriers and ways to approach this
- Contribution to writing/design of the interview guide
- Study management
- Identification of important areas for analysis
- Raising awareness of the study and dissemination
- Contributing to study outputs e.g. conference presentations and talks for members of the EoE community, ensuring outcomes are presented effectively.

An initial meeting with the PPI advisory group will provide training and support for involvement.

4. STUDY POPULATION

4.1.Number of participants

Recruitment aim of 60 patients (30/site). 20 of these participants will be recruited to semi-structured, qualitative interviews.

4.2.Inclusion criteria

Patients from CDDFT or UCLH with:

- New diagnosis of EoE (>15/high-powered field (hpf) or 0.3mm^2 on oesophageal biopsy and index oesophageal symptoms).
- Known diagnosis of EoE (current histological and symptom status documented but does not impact inclusion).

4.3.Exclusion criteria

- <18 years old
- Current involvement in a Clinical Trial of an Investigational Medicinal Product (CTIMP) for EoE.
- Eosinophilia as a result of other known cause (local or systemic)
- Oesophageal stricture on oesophago-gastric duodenoscopy
- Previous upper GI surgery
- Active comorbidity including: Barrett's oesophagus, oesophageal varices, coagulation disorders
- Significant nasopharyngeal pathology, preventing nasogastric intubation
- Opiate use
- Unable to provide informed consent
- Limited verbal communication
- Non-English language speaker

5. PARTICPANT SELECTION AND INFORMED CONSENT

5.1.Identifying Participants

Eligible patients will be identified by lead Consultants/PI at CDDFT or UCLH who will discuss research participation with the patient initially and provide the Patient Information Sheet (PIS) and a copy of the consent form if the patient is willing to consider participation. The PI will inform the research fellow of patients interested in being contacted about the study.

Prior to contacting the patient, the research fellow will use the patient's medical records to ensure study eligibility is met from a medical perspective. The research fellow will then contact the patient after a minimum of 48 hours, to ensure the participant has had time to read the PIS and discuss with others if desired. If the individual chooses to participate, an appointment will be scheduled with the participant. For those with a new diagnosis of EoE, initial study participation would occur within a 3-week period to prevent significant delay to standard care treatment initiation which would be paused until after initial tests. Those with a known EoE diagnosis would be scheduled for physiology testing after a minimum of 2 months following initiation of EoE specific treatment. Patients will be asked to stop proton pump inhibitors (if taking) for 1 week prior to physiological tests; however, stopping for 3 days will be accepted.

Individuals declining participation will be asked if they would be willing to answer an open-ended question on reasons for not wishing to participate, with consent sought to use responses anonymously to further understand acceptability.

5.2.Screening Logs

5.2.1. Pre-Screen Log

Participants identified by PI in outpatient clinic who accept a PIS will be included on the pre-screening log. This log will provide the following information:

- Patient initials
- Sequential screening number
- Date of appointment with Gastroenterologist when potential study eligibility determined
- Site (CDDFT or UCLH)
- Eligibility based on clinical history (yes/no)
- Initial screening outcome: recruited, declined, with reason if given
- Telephone discussion with researcher outcome: recruited, declined, with reason if given

5.2.2. Participant Identification Log

Participants recruited to the study will be documented within the participation identification log which will include the following information:

- Participant name
- Participant initials
- Sequential screening number
- Participant number

- NHS number
- Confirmation of eligibility
- Date of consent
- Personal details (address, phone number, email address)
- Withdrawal (yes/no) if yes, when and why

The researcher will use a checklist to determine clinical eligibility. If recruited, patients will then be assigned a Case Report Form (CRF).

5.3.Consenting Participants

5.3.1. Informed consent

Eligible participants willing to consider participation will be provided with the study Participant Information Sheet (PIS) by their local PI. If a patient is about to try a new treatment, the PI will explain to the patient that this would commence after the first study visit, to provide baseline measurements. Patients will have a minimum of 48 hours to consider the information before being contacted by the research fellow to discuss the information. This time is kept to a minimum to prevent significant delays to participation and thus treatment initiation. Those wishing to participate will then be provided with an initial appointment date/time. Written informed consent will be obtained at visit 1 by the research fellow or delegated clinical scientist at UCLH, prior to involvement in any part of the study protocol.

A copy of the consent form will be given to the participant, another copy will be stored in the patient's medical records and the original copy will be stored in the site file. The patient's GP will be contacted by letter following the first study visit to inform them that the patient is participating in this research study.

5.3.2. Withdrawal of study participants

Participants may withdraw from the study at any point. If this occurs, the primary reason for withdrawal will be documented in the patient's CRF if the participant is willing to provide this information. The individual will be asked whether they wish to:

i. Withdraw from some aspects of the study but continue in other elements
ii. Withdraw from all aspects of the study

6. STUDY PROCEDURES

6.1.Covid-19 (Sars-CoV-2)

Local regulations (CDDFT and UCLH) will be adhered to regarding the Covid-19 pandemic.

6.2.Pre-treatment tests

6.2.1. Visit 1

PROMs will be collected using three validated questionnaires completed by the patient. These will assess dysphagia, reflux burden and oesophageal hypervigilance and anxiety using the Brief Esophageal Dysphagia Questionnaire/BEDQ[10], Reflux Disease Questionnaire/RDQ[11] and Esophageal Hypervigilance and Anxiety Scale/EHAS[9] respectively.

HRM: HRM involves placement of a nasogastric catheter. Testing will follow standard procedures with additional provocation tests:

- Assessment of 5 mL water swallows
- Rapid drink challenge - 200 mL water drunk continuously through a straw. This is used to further assess lower oesophageal sphincter relaxation and oesophageal body pressurisation
- Solid test meal - 200g rice eaten to assess oesophageal function using a physiologically relevant test meal

Symptomatic episodes during swallowing will be recorded to determine if reported symptoms correspond with abnormal HRM events, thus assessing the clinical relevance of motility findings. Findings will be classified using the Chicago Classification (CCv4.0)[8].

pH/impedance monitoring: Following PROMs and HRM, 24-hour ambulatory pH/impedance monitoring using a nasogastric catheter will commence. This involves placement of a second naso-gastric pH/impedance catheter. Testing will follow standard procedures. Patients will be provided with a paper diary to complete and an explanation will be given as to how to use the ambulatory recorder.

6.2.2. Visit 2

Participants will return the ambulatory recorder the following day (24 hours after initiation of ambulatory pH/impedance test).

Individuals will begin treatment course after physiology tests have been performed. Treatment will be standard care (usually locally acting steroids and/or proton pump inhibitors), decided upon by patient and clinician (study does not influence treatment choice). Those patients with an established diagnosis of EoE who are in symptom remission may not begin new treatment course and in this case would only participate in initial tests.

6.3.Qualitative interviews

6.3.1. Visit 3

Qualitative interviews: Semi-structured interviews will be conducted in a sub-set of patients in their preferred medium (telephone/video-conference call/face to face (Sars-CoV-2 permitting)) with support provided. Audio recordings will be made with consent

and transcribed verbatim, forming the basis for analysis. Interviews will commence between pre- and post-treatment HRM and pH/impedance tests.

An iterative approach will be taken during the interview process, with data collection and preliminary coding of themes and subthemes to enable the integration and refinement of occurring themes into subsequent interviews.

6.4.Post-treatment tests

6.4.1. Visit 4

HRM: PROMs and HRM will be repeated as described in pre-treatment tests (6.2), two-four months following a course of treatment, to assess physiological changes. Around a similar time, participants will also receive repeat endoscopies with biopsies and clinical assessment as part of standard care.

pH/impedance monitoring: 24-hour ambulatory pH/impedance measurements will be repeated as described in pre-treatment tests (6.2), two-four months following a course of treatment, to assess physiological changes. Again, this will be performed after repeat HRM study. However, should a patient withdraw consent to repeat HRM but wish to repeat the 24-hour ambulatory pH/impedance study, this is acceptable.

6.4.2. Visit 5

Patients will again be required to return the ambulatory recorder 24 hours after the initiation of the pH/impedance test.

7. DATA COLLECTION

7.1.Source Data Documentation

Source data associated with the study is anticipated to include (non-exhaustive list) documents relating to consent, demographics, medical data, adverse events and communications. This will only be accessed by the direct healthcare team. Source data relating to medical information will be recorded within the participant's CRF.

A source data log will be included in the site file to enable easy identification of source data associated with the study. This will include the origin and destination of data, date of data transfer, parties with access to the source data and the type of document. Management of source data will be in line with Good Clinical Practice (GCP) guidance and accordingly, source data will remain accessible to investigators, monitors, auditors and inspectors.

7.2.Case Report Forms

Each participant will have a CRF which will be kept in the site file. This will contain summarised source data relating to an individual's involvement in the study.

8. DATA ANALYSIS

8.1.Sample Size

A dual-site recruitment approach will ensure valuable data on recruitment, retention and acceptability are explored, with appreciation of potential differences between secondary care (UHND) and large tertiary referral centres (UCLH). A total of 60 participants will be recruited (30 per site), in keeping with recommendations for feasibility studies[13]. Total eligible EoE cases across sites are approximately 55/year. We envisage at least 60% of patients will consent based on previous experience and PPI input from individuals with EoE, indicating that intended recruitment will be possible over the 21 months. This approach will enable Objectives 1,2 and 3 to be met and ensure a range of symptom profiles are represented (Objective 4), whilst accounting for drop-out (Objectives defined in section 2.2).

A sample size of 20 participants will be recruited to the qualitative interviews. Due to small sample size, information power may not be reached; however, there is evidence to suggest a 20 person cohort would be sufficient to capture the range of perspectives surrounding the acceptability of tests to monitor EoE, with a shared experience of this rare condition forming the focus of the study[14].

8.2.Outcomes and Analysis

8.2.1. HRM

The following outcomes will be assessed:

- Study recruitment, including practicalities and acceptability of conducting tests prior to treatment initiation (time to test) and site differences. Partial information will be reported, increasing understanding of acceptability.
- Successful completion of test meal during HRM.
- Successful completion of questionnaires for PROMs data.
- Drop-out between initial and post-treatment tests, using information from qualitative interviews to understand barriers.
- Description of changes to diagnostic yield (categorical data) as a result of solid swallows compared to water swallows during HRM, classified in line with routine clinical practice using CCv4.0[8,15].
    - This will be described both pre- and post-treatment, providing insight into possible effect size of change in motility classification in EoE (currently unknown) for future study.
    - Differences will be described in relation to previous treatment exposure and overall symptom status from PROMs.
    - Changes will be described in those recruited with a new diagnosis of EoE versus those recruited as treatment refractory.
- Temporal relationships between patient-reported symptoms and abnormalities identified on HRM will be defined using the oesophageal dysfunction symptom index (D-SI), whereby number of symptoms associated with oesophageal dysfunction is divided by total number of symptoms[16] and numbers in whom typical symptoms are reproduced will be reported.

8.2.2. pH/impedance monitoring

The following outcomes will be assessed:

- Recruitment, including practicalities of conducting tests prior to treatment initiation (time to test) and site differences.
- Drop-out between initial and post-treatment tests, using information from qualitative interviews to understand barriers.
- Tolerance of a 24-hour test by patients with EoE.
- Description of mucosal impedance/MNBI as a marker of ongoing inflammation in relation to eosinophilia pre- and post-treatment, with quantitative outcomes described by confidence intervals and treated as preliminary findings.
    - Differences will be described in relation to previous treatment exposure and overall symptom status from PROMs.
- Presence of reflux disease, described using the Lyon Criteria[12].
- Descriptive comparison of histological findings (EoE histologic scoring system/HSS[17]) to mucosal impedance results.

8.2.3. Qualitative interviews

An inductive approach to analysis will be used to identify themes from the data corpus, drawing on the six phases of thematic analysis outlined by Braun and Clark[18]. Broadly, the following pre-defined topics will be explored: impact of living with EoE, acceptability of routine follow-up investigations once a diagnosis of EoE has been made (endoscopy, biopsies, imaging) and the additional testing performed as part of this study (HRM and pH/impedance monitoring). Further exploration of influences on acceptability will be explored, including whether participants felt that tests provided realistic insight into their problems, cultural factors surrounding the test meal and socio-economic factors on how people manage on a daily basis with a condition that affects eating. Data collected will also be used to understand the recruitment patterns of the study.

NVivo software will be used to organise and analyse pseudonymised interview transcripts. Codes used to organise the data will be refined iteratively and degree of saturation will be assessed in order to report on the extent to which interviews captured participant views. Prior to processing, themes will be discussed with colleagues to ensure validity and reduce the impact of interpretation bias.

8.2.4. Cross-study analysis

Information on symptoms, oesophageal muscle function and inflammation identified within the study will be collated to provide preliminary insight into potential relationships. This includes reported symptom types and severity (PROMs data[9–11]), motility findings (HRM), mucosal impedance, results from standard care (endoscopy, histology) and disease duration, in relation to treatment. This will inform on the practicalities of collecting meaningful multi-factorial data, with a view to future work defining factors relating to EoE disease profiles. Patient numbers in whom objective physiology and subjective symptoms relate will provide preliminary insight into proportions of individuals who could, in the future, respond to treatment targeted at the specific pathophysiology.

9. DATA MANAGEMENT AND CONFIDENTIALITY

9.1.Data Management

Clinical data pertaining to an individual participant will be stored within their CRF. Members of the study team involved in data entry into the CRF will receive appropriate training. A copy of each CRF will remain at the study site (CDDFT or UCLH) and a copy scanned, emailed from nhs.net to nhs.net account and stored in the Trial Master File.

Patient data will remain on NHS computers and a Microsoft Excel spreadsheet will be used to collate information from the CRF. Any electronic transfer of data will be via encrypted email accounts (nhs.net to nhs.net).

An external body (UK Transcription Ltd) will be used for transcription of data collected from participant interviews. Audio files will be anonymised prior to being transferred to UK Transcription Ltd. A non-disclosure agreement is in place, including the relevant data protection safeguards in line with GDPR. Once transcribed, audio data from recorded interviews will be deleted.

9.2.Confidentiality

The Newcastle upon Tyne Hospitals NHS Foundation Trust is the sponsor for the study and will act as the data controller. Research will be conducted in line with Caldicott Principles, General Data Protection Regulation (2018) and GCP. Encrypted, password-protected NHS IT devices will be used within local sites. Physical records other than those forming the site files will be scanned, saved and destroyed. Unique, anonymised identification codes will be used for study information leaving an NHS device (i.e. interview transcripts).

9.3.Missing Data and Data Queries

Any self-evident corrections made will be documented in the Trial Master File and will be approved by the CI. Data queries and subsequent changes made will be documented in an audit trail. Any changes will be initialled, dated and explained where necessary.

10. SAFETY REPORTING

10.1. Reporting Adverse Events

HRM and 24-hour pH/impedance investigations are low risk investigations conducted in routine practice for indications other than EoE. Procedure risks will be discussed in line with routine practice. The sponsor would be notified of any adverse events occurring during the study period including the patient ID, event, review of causality, whether it is resolved/ongoing. If deemed to have occurred as a result of the study, the adverse event will be reported on local incident reporting systems.

Any adverse events occurring will be recorded in the adverse events log and the participant's CRF and will also be documented within the Trial Master File. Details kept

will include the event, date and time, timeframe in which the event occurred, severity, actions taken, relationship of the event to the study and those involved in the event.

Any Serious Adverse Event (SAE) occurring as a result of the study will be reported by the CI to the Research Ethics Committee (REC) within 15 days of becoming aware of the event. The National Health Service Health Research Authority Non-CTIMP Safety Report to REC form should be used to do this. Any SAE will also be included in the Annual Progress Report to the REC.

11. STUDY MANAGEMENT & SPONSOR OVERSIGHT

11.1. Sponsorship, Monitoring and Auditing Arrangements

The CI or research fellow will monitor the informed consent process to ensure that consent forms are appropriately counter signed at both sites. The study team will also conduct internal monitoring to ensure the study is run in line with GCP. The study may fall under the sponsor's QA audit programme as per NJRO-QA-SOP-001 and data will be made available if requested.

12. STUDY CONDUCT RESPONSIBILITIES

12.1. Protocol Amendments

Protocol amendments must be reviewed and approved by the CI, PIs and the study team.

12.2. Management of Protocol Non Compliance

Non-compliances identified will be reported to the Sponsor (Newcastle upon Tyne Hospital NHS Foundation Trust) in a timely manner.

12.3. Serious Breach Requirements

A serious breach is defined as something that is likely to significantly effect:

- The physical or mental safety of participants; or
- The scientific value of the study

12.4. Study Retention Record

All documents will be kept for a minimum of 5 years from the study end point. Permission from the sponsor will be sought before any information is destroyed.

12.5. End of Study

End of study is defined as the final visit of the last participant. The study can be terminated by the investigators or sponsor at any time for clinical or administrative reasons.

12.6. Continuation of Treatment Following End of Study

Not applicable.

12.7. Insurance and Indemnity

Newcastle University will cover the indemnity for the design of the research. Management and conduct of the study will be covered by the NHS.

13. TRIAL FUNDING

Funding for this study has been obtained from the National Institute for Health Research's (NIHR) Integrated Clinical Academic (ICA), Clinical Doctoral Research Fellowship (CDRF) scheme (NIHR302158).

14. PUBLICATION AND DISSEMINATION PLANS

Quarterly meetings with the study advisory group will ensure regular updates on study output. Study findings will be disseminated as follows:

- Events: Two dissemination events (North East, London) for participants and members of the advisory group. As a rare condition, many have never met someone else with EoE. This will therefore provide an opportunity for people to connect and support groups to be established.
- Presentation: At events specifically for people affected by EoE (i.e. EOS Network) and within the GI Physiology community via the Association of Gastrointestinal Physiologists (AGIP).
- Conference presentations: One major gastroenterology conference in years two and three, including the British Society of Gastroenterology's annual conference, enabling dissemination to NHS professionals.
- Publications: Open-access, peer-reviewed publications to contribute to scientific and clinical communities with contingent titles of: Feasibility of enhanced motility assessment in EoE using HRM with solid test meal, Integration of mucosal impedance in the EoE assessment pathway, Qualitative findings in EoE from existing standard of care with augmented physiological assessments.

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16. APPENDIX

16.1. Brief Esophageal Dysphagia Questionnaire

Brief Esophageal (oesophageal) Dysphagia Questionnaire

We would like to ask about your dysphagia (difficulty swallowing) symptoms over the past 2 weeks (14 days) and two experiences over the last 12 months. Please think about your symptom experiences and choose the best answer.

Over the **past 14 days**, on average, how often have you had the following? If your response falls between two categories, please make your best guess. If you are unable to eat the type of food in the question, please choose "Cannot eat this". Please place a tick in the relevant box.

	Cannot Eat This	*0 Rarely/ Never*	*1 Once or twice a month*	*2 1-2 times per week*	*3 3-5 times per week*	*4 Daily or almost daily*	*5 Several times per day*
Trouble eating solid food (meat, bread, vegetables)							
Trouble eating soft foods (yogurt, jelly, pudding*)							
Trouble swallowing liquids							
Pain while swallowing	--						
Coughing or choking while swallowing foods or liquids	--						

Over the **past 14 days**, on average, how would you rate your discomfort or pain during swallowing? If you are unable to eat the type of food, please choose "Cannot eat this".

	Cannot Eat This	*0 None*	*1 Very Mild*	*2 Mild*	*3 Moderate*	*4 Moderately Severe*	*5 Severe*
Eating solid food (meat, bread, vegetables)							
Eating soft foods (yogurt, jelly, pudding*)							
Drinking liquids							

**Pudding refers to a soft dessert such as mousse*

Approximately how many times in the **past 12 months** have you -

Had food stuck in your throat or oesophagus for a period lasting longer than 30 minutes? ____
Had to visit the emergency room* because of food stuck in your throat or oesophagus? ____
**Accident and Emergency Department/A&E*

Participant Initials ☐☐☐ Screening Number ☐☐☐ Participant Number ☐☐☐

16.2. Reflux Disease Questionnaire

Reflux Disease Questionnaire (RDQ)

Please answer each question by ticking **one** box per row

1. Thinking about your symptoms over the past week, how often did you have the following?

		Did not have	Less than one day a week	One day a week	2-3 days a week	4-6 days a week	Daily
a.	A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b.	Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c.	A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d.	A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e.	An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f.	Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

2. Thinking about symptoms over the past week, how would you rate the following?

		Did not have	Very mild	Mild	Moderate	Moderately severe	Severe
a.	A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b.	Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c.	A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d.	A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e.	An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f.	Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

TOTAL Score:
Subgroups Scores: ***Heartburn:*** ***Regurgitation:*** ***GERD:*** ***Dyspepsia stomach:***

16.3. Esophageal Hypervigilance and Anxiety Scale

Esophageal (oesophageal) Hypervigilance and Anxiety Scale

We are interested in the way people think when they are experiencing unpleasant or painful oesophageal symptoms. The word oesophagus refers to the food pipe. Below is a list of common thoughts, beliefs and attitudes associated with having symptoms such as heartburn, chest pain, regurgitation, difficulty swallowing or throat burning, among others.

Please rate, using the following scale, the degree to which you agree with each of the following statements, based on your experiences with oesophageal symptoms **over the past month**.

Date completed: _____	0 Strongly Disagree	1 Somewhat Disagree	2 Neither Agree nor Disagree	3 Somewhat Agree	4 Strongly Agree
1. I can't seem to keep my symptoms out of my mind.					
2. I have a difficult time enjoying myself because I cannot get my mind off the discomfort in my throat/chest/oesophagus.					
3. These symptoms are awful and they overwhelm me.					
4. As soon as I awake, I worry that I will have discomfort in my throat/chest/oesophagus during the day.					
5. I often worry about problems in my throat/chest/oesophagus.					
6. These symptoms are terrible and I think things are never going to get any better.					
7. There is nothing I can do to reduce the intensity of my symptoms.					
8. When I feel discomfort in my throat/chest/oesophagus, it frightens me.					
9. I anxiously want the symptoms to go away.					
10. I am quick to notice changes in the location or extent of my oesophageal symptoms.					
11. I am aware of sudden or temporary changes in my oesophagus.					
12. I notice my symptoms even if I am busy with another activity.					
13. I focus on oesophageal sensations.					
14. I am very sensitive to oesophageal sensations such as heartburn or chest pain.					
15. I keep track of my symptom levels.					

Participant Initials ☐☐☐ Screening Number ☐☐☐ Participant Number ☐☐☐