

# TRIAL PROTOCOL



## OTTER

Omeprazole for Treatment of Term and preterm infants with gastro-oesophageal Reflux  
(OTTER)

Protocol Version Number: V1.0

Protocol Version Date: 05-Jun-2026

|                          |             |
|--------------------------|-------------|
| Sponsor reference number | RHM CHI1309 |
| ISRCTN number            | 31929591    |
| IRAS Project ID          | 1013233     |
| NCTU reference number    | 2372        |

## CI and Sponsor Approval Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

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

|                                     |                                                                                             |
|-------------------------------------|---------------------------------------------------------------------------------------------|
| This protocol has been approved by: |                                                                                             |
| Trial Name:                         | Omeprazole for treatment of term and preterm infants with gastro-oesophageal reflux (OTTER) |
| CI Name:                            | Professor Mark Johnson                                                                      |
| Trial Role:                         | Chief Investigator                                                                          |
| Signature:                          |                                                                                             |
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| Sponsor approval                                                                                                                                                                                                                                          |                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
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| Signature:                                                                                                                                                                                                                                                |                               |
| Date:                                                                                                                                                                                                                                                     | ___ - ___ - ___ (dd/mmm/yyyy) |
| <b>Sponsor statement:</b><br>Where University Hospital Southampton NHS Foundation Trust takes on the Sponsor role for oversight of protocol development, signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol. |                               |

| Statistical approval |                               |
|----------------------|-------------------------------|
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| Signature:           |                               |
| Date:                | ___ - ___ - ___ (dd/mmm/yyyy) |

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| Amendment number | Protocol version number | Type of amendment | Summary of amendment |
|------------------|-------------------------|-------------------|----------------------|
|                  |                         |                   |                      |

## Abbreviations

| Abbreviation | Term                                                                                                                  |
|--------------|-----------------------------------------------------------------------------------------------------------------------|
| AE           | Adverse Event                                                                                                         |
| AR           | Adverse Reaction                                                                                                      |
| CA           | Competent Authority                                                                                                   |
| CEA          | Cost Effectiveness Analysis                                                                                           |
| CUA          | Cost Utility Analysis                                                                                                 |
| CI           | Chief Investigator                                                                                                    |
| CI           | Confidence Interval                                                                                                   |
| CRF          | Case Report Form                                                                                                      |
| CTA          | Clinical Trial Authorisation                                                                                          |
| CTIMP        | Clinical Trial of Investigational Medicinal Product                                                                   |
| CUA          | Cost Utility Analysis                                                                                                 |
| DAP          | Data Analysis Plan                                                                                                    |
| DMC          | Data Monitoring Committee                                                                                             |
| DMP          | Data Monitoring Plan                                                                                                  |
| DOR          | Delegation of Responsibilities                                                                                        |
| DSUR         | Development Safety Update Report                                                                                      |
| eCRF         | Electronic Case Report Form                                                                                           |
| EOI          | Expression of Interest                                                                                                |
| EoT          | End of Trial                                                                                                          |
| EQ-5D-5L     | EuroQol 5 Dimensions, 5 Levels                                                                                        |
| GCP          | Good Clinical Practice                                                                                                |
| GOR          | Gastro-oesophageal Reflux                                                                                             |
| GORD         | Gastro-oesophageal Reflux Disease                                                                                     |
| GP           | General Practitioner                                                                                                  |
| GMP          | Good Manufacturing Practice                                                                                           |
| HCP          | Health Care Professional                                                                                              |
| HRQL         | Health-Related Quality of Life                                                                                        |
| IB           | Investigator's Brochure                                                                                               |
| ICF          | Informed Consent Form                                                                                                 |
| ICH          | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICER         | Incremental Cost Effectiveness Ratio                                                                                  |
| I-GERQ-R     | Infant Gastroesophageal Reflux Questionnaire Revised                                                                  |
| IMP          | Investigational Medicinal Product                                                                                     |
| IQI          | Infant Quality of life Instrument                                                                                     |
| ISF          | Investigator Site File                                                                                                |
| ISRCTN       | International Standard Randomised Controlled Trials Number                                                            |
| MA           | Marketing Authorisation                                                                                               |
| MHRA         | Medicines and Healthcare Products Regulatory Agency                                                                   |
| MRC          | Medical Research Council                                                                                              |
| MS           | Member State                                                                                                          |
| NCTU         | Nottingham Clinical Trials Unit                                                                                       |
| NHS          | National Health Service                                                                                               |
| NEC          | Necrotising Enterocolitis                                                                                             |
| NICE         | National Institute for Healthcare Excellence                                                                          |
| NIHR HTA     | National Institute of Health Research Health Technology Assessment                                                    |
| NNU          | Neonatal Unit                                                                                                         |

**Document Title:** Protocol  
**Trial Name:** OTTER  
**Version No:** 1.0  
**Version Date:** 05 Jun 2026

|       |                                                   |
|-------|---------------------------------------------------|
| PAU   | Paediatric Assessment Unit                        |
| PI    | Principal Investigator                            |
| PIC   | Participant Identification Centre                 |
| PICO  | Population, Intervention, Comparison, and Outcome |
| PIS   | Patient Information Sheet                         |
| PPI   | Patient and Public Involvement                    |
| PRU   | Participant Resource Use                          |
| QA    | Quality Assurance                                 |
| QALYs | Quality-Adjusted Life Years                       |
| QC    | Quality Control                                   |
| QP    | Qualified Person                                  |
| RCT   | Randomised Controlled Trial                       |
| R&D   | Research and Development                          |
| REC   | Research Ethics Committee                         |
| RSI   | Relevant Safety Information                       |
| SAE   | Serious Adverse Event                             |
| SAR   | Serious Adverse Reaction                          |
| SDV   | Source Data Verification                          |
| SDS   | Standard Deviation Score                          |
| SIV   | Site Initiation Visit                             |
| SOP   | Standard Operating Procedure                      |
| SmPC  | Summary of Products Characteristics               |
| SMS   | Short Message Service                             |
| SSI   | Site Specific Information                         |
| SWAT  | Study Within A Trial                              |
| SUSAR | Suspected Unexpected Serious Adverse Reaction     |
| TMF   | Trial Master File                                 |
| TMG   | Trial Management Group                            |
| TSC   | Trial Steering Committee                          |

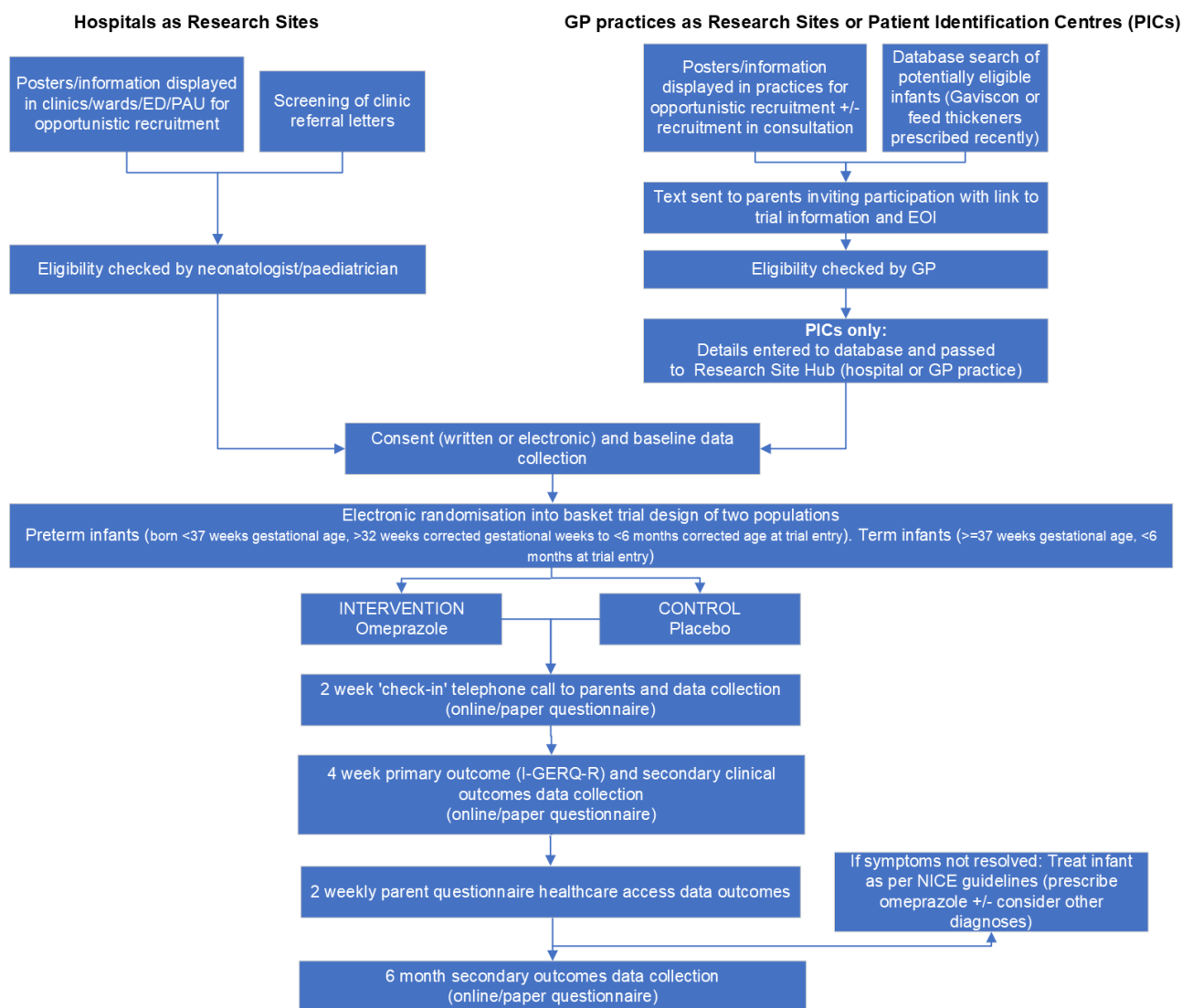
## Synopsis

|                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Trial Title                        | Omeprazole for Treatment of Term and preterm infants with gastro-oesophageal Reflux                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Internal ref. no. (or short title) | NCTU 2372 (OTTER)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Clinical Phase                     | IV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Trial Design                       | Randomised, multicentre, placebo-controlled, basket superiority trial in two patient populations with internal pilot and economic and process evaluations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Trial Participant Population       | Preterm infants (Population 1) and term-born infants (Population 2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Key Eligibility Criteria           | <p><u>Inclusion Criteria:</u></p> <p>Population 1 (Preterm infants):</p> <ul style="list-style-type: none"> <li>• Infants born &lt;37 weeks' gestation who are over 32 weeks corrected gestational age (8 weeks before their due date) and under 6 months past their due date at time of trial entry</li> <li>• Must be on full milk feeds at the time of eligibility assessment</li> <li>• Clinical diagnosis of symptomatic GOR made by a suitably qualified healthcare professional following clinical assessment</li> <li>• NICE guideline first-line interventions (including, but not limited to, feed thickeners and alginates) have either already been tried, or considered and are felt to be inappropriate by the treating clinician</li> </ul> <p>Population 2 (Term-born Infants):</p> <ul style="list-style-type: none"> <li>• Infants born ≥37 weeks' gestation and who are under 6 months of age</li> <li>• Clinical diagnosis of symptomatic GOR made by a suitably qualified healthcare professional following clinical assessment</li> <li>• NICE guideline first-line interventions (including, but not limited to, feed thickeners and alginates) have either already been tried, or considered and are felt to be inappropriate by the treating clinician</li> </ul> |
|                                    | <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> <li>• Surgical conditions affecting feeding or the gastrointestinal tract, including but not limited to repaired oesophageal or intestinal atresia, congenital diaphragmatic hernia and gastroschisis/exomphalos</li> <li>• Progressive or severe neurological conditions affecting feeding</li> <li>• Infant has received any omeprazole or other proton-pump inhibitors in the preceding 2 weeks</li> <li>• Infant has known hypersensitivity to omeprazole or any of its excipients</li> <li>• Infant with unconjugated jaundice requiring phototherapy or likely to require phototherapy during the treatment course</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                              | <ul style="list-style-type: none"> <li>• Infant has known hyperkalaemia or requiring controlled potassium intake (e.g. renal and endocrine disorders)</li> <li>• Previous participation in the OTTER trial</li> </ul>                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Investigational Medicinal Product            | Omeprazole                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Comparator                                   | Matched placebo                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Planned Sample Size                          | <p>500 infants.</p> <p>A total of 200 infants (100 per randomised group) is required to detect a 3-point difference in mean I-GERQ-R between 2 randomised groups at 4 weeks with 90% power and 5% two-sided significance level, using a standard deviation of 6.5.</p> <p>Allowing for 20% loss to follow-up in both patient populations gives a total sample size of 500 infants for the whole basket trial (250 in each population, 125 per randomised group)</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Treatment duration                           | 4 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Follow up duration                           | Infants will be followed up for 6 months post-randomisation                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Planned trial period                         | Total 41 months. 1–9 set-up, 10–27 recruitment, 18 internal pilot stop-go decision, 35 end of follow-up and data cleaning, 35–41 data analyses and reporting                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                              | <b>Objectives</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>Outcome Measures</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Primary (for full details see section 2.3)   | To conduct a basket trial in two patient populations (preterm and term-born infants) to assess the clinical effectiveness of omeprazole compared to matched placebo, for treating symptomatic gastro-oesophageal reflux in two patient populations (preterm and term-born infants)                                                                                                                                                                                  | Parent reported symptoms of GOR at 4 weeks as measured by the validated Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) score                                                                                                                                                                                                                                                                                                                                                                   |
| Secondary (for full details see section 2.4) | To assess the clinical effectiveness of omeprazole compared to matched placebo, for treating symptomatic gastro-oesophageal reflux in two patient populations (preterm and term-born infants)                                                                                                                                                                                                                                                                       | <ul style="list-style-type: none"> <li>• I-GERQ-R score at 2 weeks</li> <li>• Hospital admissions &amp; length of stay</li> <li>• Further GOR treatment</li> <li>• Growth</li> <li>• Treatment escalation (including additional investigations, referrals and treatment)</li> <li>• Evidence of oesophagitis or haematemesis</li> <li>• Length of hospital stay (where treatment started as in-patient)</li> <li>• Crying &amp; fussing, feeding difficulties and sleep quality (taken from the IQI)</li> </ul> |

|                                              |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Secondary (for full details see section 2.4) | To assess the safety of omeprazole treatment, including infections, fractures and growth, up to 6 months after trial entry                              | <ul style="list-style-type: none"> <li>• Necrotising enterocolitis (NEC)</li> <li>• Bacterial infections (prescription of antibiotics, admission for infection)</li> <li>• Suspected/confirmed bacterial respiratory infections</li> <li>• Gastrointestinal infections</li> <li>• Fractures</li> </ul> |
| Secondary (for full details see section 2.4) | To conduct a qualitative process evaluation of parental and healthcare professional experiences of the trial and treatment                              | N/A                                                                                                                                                                                                                                                                                                    |
| Secondary (for full details see section 2.4) | To assess the cost effectiveness of omeprazole use for symptomatic gastro-oesophageal reflux in two patient populations (preterm and term-born infants) | <ul style="list-style-type: none"> <li>• Healthcare use (primary care visits, secondary care visits, and medication)</li> <li>• Health-related Quality of life of infant and main parent/caregiver</li> </ul>                                                                                          |

**Flow Diagram 1: OTTER patient pathway**



## 1. Background and rationale

### 1.1. Background

Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus and is especially common in young infants because their food is liquid (milk), they spend most of their time lying flat and have underdeveloped oesophageal sphincter mechanisms. Although most GOR is asymptomatic or causes only mild problems, GOR can be more significant and cause symptoms (for example, discomfort or pain) severe enough to merit medical treatment, or complications such as oesophagitis or pulmonary aspiration, where it is termed gastro-oesophageal reflux disease (GORD). Whilst GOR improves as infants mature, some have distressing symptoms such as screaming or inconsolable crying, poor weight gain or feed refusal.

A 2019 systematic review found a mean pooled prevalence of GOR in infants <18 months' old of 26.9%, ranging from 23.1 to 40% [1]. In the UK, these data would mean that 138,000 to 240,000 infants in the UK are affected annually. One study indicated that prevalence of GOR symptoms decreased from 25.5% in the first month of life, to just 2.9% at the age of 6 months [2].

While term-born infants form the majority of infants with gastro-oesophageal reflux disease (GORD), preterm infants (<37 weeks' gestation) are at increased risk of GOR, compared to term infants, due to physiological immaturity of the lower oesophageal sphincter, impaired oesophageal peristalsis and greater gastric distension compared to term infants [3]. They also experience episodes of apnoea, acute respiratory distress or low oxygen levels as a result of GOR. Preterm infants with GORD spend around a month longer in hospital than those without GORD [3]; and US data suggests that a diagnosis of GORD in a neonatal intensive care unit (NICU) increases healthcare costs by around \$70,000 (£53,000) [4]. Estimates vary but up to 26–40% of preterm infants are diagnosed with GORD.

Our trial will focus on two patient groups (preterm and term-born infants) where GOR is most prevalent.

## 1.2. Rationale

National Institute for Health and Care Excellence (NICE) guidance for the diagnosis and management of GOR in children and young people [5] recommends using first line measures such as reducing feed volumes, adding feed thickeners or alginates, in a stepped approach for 1 to 2 weeks.

Pharmacological agents can then be considered if there is poor growth, pain or distress. The most common pharmacological agents used are proton pump inhibitor drugs like omeprazole, which act by irreversibly inhibiting the H<sup>+</sup>/K<sup>+</sup>ATPase (the acid pump) in gastric cells reducing stomach acid production. Whilst these drugs have a good evidence base in adults, evidence for effectiveness in infants is lacking, due to small underpowered trials [6].

Although acid-reducing drugs like omeprazole might reduce acid-related pain and discomfort, they may not prevent regurgitation and vomiting, which are important GOR symptoms in infants. Furthermore, there are concerns in infants that a reduction in stomach acid increases risk of infections, as stomach acid destroys ingested bacteria and viruses. Several studies in infants and children have shown an association between gastric acid reduction and an increased risk of respiratory and gastrointestinal infections [7-11]. In very preterm infants (<32 weeks' gestation), gastric acid reduction has been associated with increased risk of infection and NEC [12, 13]. Reduced gastric acid may also impair absorption of vitamins and minerals, including calcium and magnesium[7]. This can lead to impaired growth and bone development, particularly in preterm infants where growth and nutrient demands are high, and where an increased risk of fractures has been described[14, 15].

To date, there is no robust evidence that proton pump inhibitors are effective and/or safe in infant GOR management. A recent Cochrane review showed no clear benefit of omeprazole (one study of 30 infants) or esomeprazole (one study of 52 neonates) on GOR symptoms compared to placebo and recommended further studies [6]. Despite weak evidence supporting proton pump inhibitors for treating infant GOR, they are commonly prescribed. A recent study looking at trends in the prescription of proton pump inhibitors and histamine blockers in children in the UK between 1998

and 2019 shows a rising trend in the use of proton pump inhibitors, with prescription rates increasing 10% during the study period[16]. Data from NHS Business Services Authority for prescription of liquid forms of proton pump inhibitors (usually reserved for infants) shows that over 12,000 patients received them in the UK in 2019 [17]. A 2011 survey of European paediatricians found low compliance with clinical guidelines, with 82% prescribing drugs outside of guidance[18]. A 2020 survey of 156 UK neonatologists showed similar variation, with many using the response to non-pharmacological measures (38%) or anti-reflux medicines (40%) to diagnose GOR. Analysis of UK data from 2010–2017 suggests 37% of preterm infants receive anti-reflux medication, often without a diagnosis of GOR[19].

There is therefore a need to establish the evidence base for these commonly prescribed medications in infants to better inform practice.

## 2. Aims, Objectives and Outcome Measures

### 2.1. Design justification

#### 2.1.1. Justification for trial intervention

This trial will evaluate a proton pump inhibitor rather than a histamine blocker, as they are the commonest drug class used in the two chosen patient populations, based on both the literature and our recent survey of over 100 clinicians (including 56 paediatricians, 26 neonatologists and 19 general practitioners). In addition, histamine blockers are no longer easily available, especially since ranitidine (the most widely used histamine blocker) was withdrawn due to concerns about impurities. The specific proton pump inhibitor we have chosen to use is omeprazole, as it is the commonest variant in use, in the NHS, but importantly is also the only proton pump inhibitor that is available in a liquid form, allowing body weight-based dosing in infants

### 2.2. Aims

To determine the clinical effectiveness and safety of omeprazole compared to matched placebo, for treating symptomatic gastro-oesophageal reflux in preterm and term-born infants. The trial will also assess the cost-effectiveness of omeprazole when prescribed for symptomatic gastro-oesophageal reflux, and conduct a qualitative process evaluation of parental and healthcare professional experiences of the trial and of treatment.

### 2.3. Primary objectives and Primary Outcome Measure

**Table 1: Primary Objective**

| Primary objective                                                                                                                                                                                                                                                          | Primary Outcome Measure                                                          | Time point                 | Method of collection                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------|
| To conduct a basket trial in two patient populations (preterm and term-born infants) to assess the clinical effectiveness of omeprazole compared to matched placebo, for treating symptomatic gastro-oesophageal reflux in two populations (preterm and term-born infants) | Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) score at 4 weeks | 4 weeks from randomisation | Parent or caregiver reported questionnaire completed online <sup>1</sup> |

## 2.4. Secondary objectives and outcome measures

**Table 2: Secondary objectives**

| Objective                                                                                                                                                                             | Outcome measure                                                                                                                                               | Time point                                                                                      | Method of collection                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To assess the clinical effectiveness of omeprazole compared to matched placebo, for treating symptomatic gastro-oesophageal reflux in two populations (preterm and term-born infants) | i-GERQ-R score at 2 weeks                                                                                                                                     | 2 weeks from randomisation                                                                      | Parent or caregiver reported questionnaire completed online <sup>1</sup>                                                                                    |
|                                                                                                                                                                                       | Need for treatment escalation (including additional investigations, referral and treatment)                                                                   | 4 weeks and 6 months from randomisation                                                         | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup> |
|                                                                                                                                                                                       | Evidence of Oesophagitis or haematemesis (blood in the baby's vomit or if inflammation of the food pipe was found through endoscope imaging during treatment) | 4 weeks and 6 months from randomisation                                                         | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup> |
|                                                                                                                                                                                       | Length of hospital stay                                                                                                                                       | At hospital discharge (only preterm and term-born infants where treatment started as inpatient) | Case Report Form completed by research nurses/PI from clinical records                                                                                      |
|                                                                                                                                                                                       | Hospital admissions and length of stay                                                                                                                        | 6 months from randomisation                                                                     | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup> |
|                                                                                                                                                                                       | Any further treatment with medication for GOR                                                                                                                 | 4 weeks to 6 months from randomisation                                                          | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup> |

| Objective                                                                                                               | Outcome measure                                                                      | Time point                                                                                                                                                                                          | Method of collection                                                                                                                                                                                                            |
|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                         |                                                                                      |                                                                                                                                                                                                     |                                                                                                                                                                                                                                 |
|                                                                                                                         | Crying and fussing (part of Infant Health-related Quality of Life Instrument, IQI)   | 4 weeks and 6 months from randomisation                                                                                                                                                             | Parent or caregiver reported questionnaire completed online <sup>1</sup>                                                                                                                                                        |
|                                                                                                                         | Feeding difficulties (part of Infant Health-related Quality of Life Instrument, IQI) | 4 weeks and 6 months from randomisation                                                                                                                                                             | Parent or caregiver reported questionnaire completed online <sup>1</sup>                                                                                                                                                        |
|                                                                                                                         | Sleep quality (part of Infant Health-related Quality of Life Instrument, IQI)        | 4 weeks and 6 months from randomisation                                                                                                                                                             | Parent or caregiver reported questionnaire completed online <sup>1</sup>                                                                                                                                                        |
|                                                                                                                         | Growth (change in weight standard deviation score (SDS) from trial entry)            | 4 weeks and 6 months from randomisation                                                                                                                                                             | Clinical measurements taken as part of routine care (date/result of most recent measure reported by parents from child health record) within a 1 week window, or parent measurement where clinical measurement is not available |
| To monitor safety of omeprazole treatment, including infections, fractures and growth, up to 6 months after trial entry | Necrotising enterocolitis (Modified Bell Stage 2 or 3)[20, 21]                       | At hospital discharge (for infants' diagnoses where treatment started as an inpatient) or at 6 weeks post randomisation (for infants' diagnoses where treatment was outpatient reported as an SAE.) | Case Report Form                                                                                                                                                                                                                |
|                                                                                                                         | Any bacterial Infections (prescription of antibiotics,                               | 6 months from randomisation                                                                                                                                                                         | Parent or caregiver reported questionnaire completed online <sup>1</sup>                                                                                                                                                        |

| Objective                                                                                                                                               | Outcome measure                                                                                                         | Time point                                                                                                        | Method of collection                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                         | admission where infection was admission or discharge diagnosis)                                                         |                                                                                                                   | Case note review and Case Report Form completion where appropriate <sup>2</sup>                                                                                         |
|                                                                                                                                                         | Any gastrointestinal infections (vomiting or diarrhoea which required medical attention)                                | 6 months from randomisation                                                                                       | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup>             |
|                                                                                                                                                         | Suspected/confirmed bacterial respiratory infections (defined by prescription of antibiotics for a respiratory illness) | 6 months from randomisation                                                                                       | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup>             |
|                                                                                                                                                         | Fractures (defined as a fracture diagnosed on x-ray following a consultation with a medical professional)               | 6 months from randomisation                                                                                       | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup>             |
| To conduct a qualitative process evaluation of parental and healthcare professionals' experiences of the trial and of treatment                         | Parent and professional experiences of trial, by interview                                                              | Throughout recruitment and follow-up (until 30 parents and 25-30 healthcare professionals have been interviewed). | Semi-structured interviews                                                                                                                                              |
| To assess the cost-effectiveness of omeprazole use for symptomatic gastro-oesophageal reflux in two patient populations (preterm and term-born infants) | Healthcare use (primary care visits, secondary care visits, and medication)                                             | 4 weeks and 6 months from randomisation                                                                           | Parent or caregiver reported questionnaire completed online <sup>1</sup> and Case Report Form completion.<br>Case note review completion where appropriate <sup>2</sup> |

| Objective | Outcome measure                                                                                                     | Time point                              | Method of collection                                                     |
|-----------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------------------------|
|           | Infant Health-related Quality of Life Instrument (IQI)                                                              | 4 weeks and 6 months from randomisation | Parent or caregiver reported questionnaire completed online <sup>1</sup> |
|           | EQ-5D-5L (European Quality of life 5 Dimensional 5 level) Questionnaire for parental health related quality of life | 4 weeks and 6 months from randomisation | Parent or caregiver reported questionnaire completed online <sup>1</sup> |

1 – a paper version will be provided if needed

2 – where there is partial or complete missing data from the parent or caregiver reported questionnaire

### 3. Trial Design and Setting

#### 3.1. Design

A Phase IV, two-arm parallel group, multicentre, randomised (allocation ratio 1:1), placebo-controlled, basket superiority trial in two patient populations: preterm infants (Population 1) and term-born infants (Population 2) with an internal pilot phase and concurrent economic and process evaluations. Parents and healthcare professionals will be blinded to randomised treatment allocation.

A basket trial design has been selected to efficiently compare the same intervention and comparator in two distinct populations of infants, evaluating the same outcomes, therefore avoiding the need for two separate trials. Details on the internal pilot phase and pre-specified progression criteria are provided in section 3.4.

**Table 3: Population, Intervention, Comparator and Outcome (PICO)**

|                        |                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population</b>      | <b>Population 1:</b> Preterm infants born <37 weeks' gestation who are over 32 weeks corrected gestational age (8 weeks before their due date) and under 6 months past their due date at time of trial entry. Preterm infants must also be on full milk feeds before entering the trial.<br><b>Population 2:</b> Term-born infants ≥37 weeks' gestation and who are <6 months of age |
| <b>Intervention</b>    | Omeprazole 1mg/kg once daily for 4 weeks given as an oral suspension                                                                                                                                                                                                                                                                                                                 |
| <b>Comparator</b>      | Matched placebo                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Primary Outcome</b> | Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) score at 4 weeks. The I-GERQ-R is a 12-item, caregiver completed questionnaire that provides a measure of severity of symptoms of GOR, validated for use in infants.                                                                                                                                                 |

### 3.2. Setting

Primary care (10 General Practice (GP) research sites) and secondary care (35 hospital sites with in- and outpatient settings, including neonatal units). Recruitment will also be facilitated by additional GP practices acting as Participant Identification Centres (PICs).

### 3.3. Type of trial by risk category

CTIMP: type A – the risk is no higher than the risk of standard medical care

### 3.4. Internal pilot phase

The funder feasibility assessment will take place 9 months after recruitment of the first infant. Progression criteria are given in Table 4.

**Table 4: Internal pilot phase metrics to assess feasibility**

| % Threshold                                                                                                                                                                                                                                                                                                                                                                                                           |                                              | Red                                                                                                                    | Amber                                                                                                                                               | Green                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Number of sites opened                                                                                                                                                                                                                                                                                                                                                                                                |                                              | 14<br>( $< 60\%$ )                                                                                                     | 15–23<br>(60%–99%)                                                                                                                                  | 24 (100%)                                 |
| Preterm population                                                                                                                                                                                                                                                                                                                                                                                                    | Total participants randomised                | 34<br>( $< 60\%$ )                                                                                                     | 35–55<br>(60%–99%)                                                                                                                                  | 56 (100%)                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                       | % of expected primary outcome data collected | $< 80\%$                                                                                                               | 80%–99%                                                                                                                                             | 100%                                      |
| Term-born population                                                                                                                                                                                                                                                                                                                                                                                                  | Total participants randomised                | 43<br>( $< 60\%$ )                                                                                                     | 44–70<br>(60%–99%)                                                                                                                                  | 71 (100%)                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                       | % of expected primary outcome data collected | $< 80\%$                                                                                                               | 80%–99%                                                                                                                                             | 100%                                      |
| Action required                                                                                                                                                                                                                                                                                                                                                                                                       |                                              | rescue strategy or closure plan will be implemented following consultation with trial oversight committees and Funder* | strategy for improvement will be implemented with the support of the trial oversight committees (TMG, DMC and TSC) and consultation with the funder | trial will continue without modifications |
| <p>*If trial progression criteria relating to total infants randomised is red for both populations, even if the other categories are amber or green the trial should be categorised as red and associated strategies implemented.</p> <p>The progress of the trial will be continually monitored by the trial team and funder. Recruitment and trial procedures will continue during the decision-making process.</p> |                                              |                                                                                                                        |                                                                                                                                                     |                                           |

## 4. Eligibility criteria

### 4.1. Inclusion criteria

#### 4.1.1. Preterm infants

- Preterm infants born <37 weeks' gestation who are over 32 weeks corrected gestational age (8 weeks before their due date) and under 6 months past their due date at time of trial entry
  - Must be on full milk feeds\* at the time of eligibility assessment
  - Clinical diagnosis of symptomatic GOR made by a suitably qualified healthcare professional following clinical assessment
  - NICE guideline first-line interventions (including, but not limited to, feed thickeners and alginates) have either already been tried, or considered and are felt to be inappropriate by the treating clinician
- \* hospitalised infants must be receiving full milk feeds defined as at least 140 mL/kg/day of milk, with final eligibility determined based on clinical assessment.

#### 4.1.2. Term-born infants

- Infants born ≥37 weeks' gestation and who are under 6 months of age
- Clinical diagnosis of symptomatic GOR made by a suitably qualified healthcare professional following clinical assessment
- NICE guideline first-line interventions (including, but not limited to, feed thickeners and alginates) have either already been tried, or considered and are felt to be inappropriate by the treating clinician

#### 4.1.3. Parent or Caregiver

- Aged 16 years or over
- Able to provide informed consent for participation

### 4.2. Exclusion criteria (infant)

- Surgical conditions affecting feeding or the gastrointestinal tract, including but not limited to repaired oesophageal or intestinal atresia, congenital diaphragmatic hernia, gastroschisis/exomphalos
- Progressive or severe neurological conditions affecting feeding
- Infant has received any omeprazole or other proton-pump inhibitors in the preceding 2 weeks
- Infant has known hypersensitivity to omeprazole or any of its excipients
- Infant with unconjugated jaundice requiring phototherapy or likely to require phototherapy during the treatment course
- Infant has known hyperkalaemia or requiring controlled potassium intake (e.g. renal and endocrine disorders)
- Previous participation in the OTTER trial

## 5. Identification, consent and recruitment

Infants can be identified and recruited into the trial via four different pathways. The process for identifying eligible infants in each pathway is outlined below:

1. Secondary care inpatient Section 5.1
2. Secondary care outpatient Section 5.2
3. Primary care recruitment centres Section 5.3
4. Primary care identification centre Section 5.4
5. Publicity materials 5.5

### 5.1. Secondary care inpatient recruitment

#### 5.1.1. Identification and screening

Potentially eligible infants will be identified within Neonatal Units (NNU) and paediatric units (emergency departments, assessment units and inpatient wards) by screening admissions, and by electronic health record searches in secondary care. Screening will be completed by trained delegated site research staff. In addition, publicity materials raising awareness of the trial may be displayed and there will be the opportunity to recruit parents/caregivers during discussions with clinicians. For families who are interested in participating, eligibility will be assessed and trial information provided. For preterm infants yet to reach 32 weeks corrected gestational age, trial information can be given, but the infant would not be eligible to enter the trial until 32 week corrected gestational age.

Trial eligibility must be confirmed by a medically qualified doctor, and informed consent must be provided and signed by both a parent/caregiver of the potential participant and the investigator or delegate (please go to Section 5.6 onwards for information on participant information, consent and randomisation).

### 5.2. Secondary care outpatient recruitment

#### 5.2.1. Identification and screening

Potentially eligible infants will be identified by screening paediatric out-patient referrals and weekly clinic lists to check eligibility in addition to opportunistic recruitment arising from emergency department and assessment units and during discussions with clinicians or from trial information (e.g., posters, flyers, information cards etc). Screening will be completed by trained delegated site research staff. Short summary information leaflets will be provided to these families where possible, by their usual care team, so they are aware of the trial before coming into clinic. At the visit more information will be given to families and eligibility fully assessed.

### 5.3. Primary Care recruitment sites

#### 5.3.1. Identification and screening

In GP research sites, potentially eligible infants may be identified through searches of electronic health records to identify infants prescribed alginates or feed thickener in the previous two weeks but haven't improved or with a diagnostic coding of GOR. Screening will be completed by trained delegated site research staff, including local RRDN staff. The initial search should identify infants who meet these criteria in the previous one month, with weekly searches for the previous 7 days

once the site is open to recruitment. Where weekly searches cannot be conducted, the minimum requirement for the trial is one search per month covering the previous month. A text message, phone call, email or letter will go out to parents/caregivers. Interested parents/caregivers will need to complete an expression of interest (EOI) form where they'll consent to the NCTU and GPs and to hold their contact details. Publicity materials raising awareness of the trial may be displayed and parents/caregivers may also be introduced to the trial during a routine GP appointment. GPs will check eligibility of those who have expressed interest and invite them for an appointment where eligible. Where an infant is not eligible GPs will contact the parent/caregiver to explain that the eligibility criteria has not been met and thank them for their time.

## 5.4. Primary Care Participant Identification Centres

### 5.4.1. Identification and screening

In GP participant identification centres (PICs), potentially eligible infants may be identified through searches of electronic health records to identify infants prescribed alginates or feed thickener in the previous two weeks but haven't improved, or with a diagnostic coding of GOR. Searches will be completed by healthcare or research staff at the PIC, or local RRDN staff. The initial search should identify infants who meet these criteria in the previous one month, with weekly searches for the previous 7 days once the site is open as a PIC. Where weekly searches cannot be conducted, the minimum requirement for the trial is one search per month covering the previous month. A text message, phone call, email or letter will go out to parents/caregivers of identified patients. Publicity materials raising awareness of the trial to potential parents/caregivers may be displayed in PICs and there may also be opportunistic identification during appointments. Interested parents/caregivers will need to complete an expression of interest (EOI) form where they'll give their consent to the NCTU to store their contact details and recruiting sites to access the details on the trial database in order to contact them about participation. Recruiting site research staff will have a conversation with the parent/caregiver by email or phone call, to discuss the trial and check the infant's eligibility. If the infant meets the eligibility criteria they will be invited to attend a baseline appointment. If the infant is not eligible GPs will contact the parent/caregiver to explain that the eligibility criteria has not been met and thank them for their time.

## 5.5. Publicity materials

Publicity materials will be used to raise awareness of the trial to potential participants. The trial will have a public facing website, social media pages (e.g., Instagram/Facebook, X,) and posters will be used to share information regarding the trial and the active recruiting sites. Posters will include QR codes linking to the trial website, which will include both trial information as well as general GOR information. Information on the website will be produced using a variety of media (e.g., written, animated) to encourage increased understanding of both the trial and GOR in parents of potentially eligible infants. Online publicity may include information on individual site activity such as date of opening and recruitment data. These publicity materials will help to inform potential participants and update existing participants whose identification and recruitment has taken place in GP recruiting sites, PICs, and secondary care recruiting sites. Direct recruitment of parents and infants from social media platforms or websites will not take place on this trial.

Members of the trial team and other health professionals may also share details of the trial at relevant events and conferences.

OTTER will apply for inclusion to the NIHR Be Part of Research service to raise further awareness of the trial to its members across the UK.

## 5.6. Screening logs

Brief data of all parents/caregivers and their infants who are approached about the trial will be recorded by sites on the Participant Screening Log, for example, date approached, initials, date of birth, whether their parent/caregiver gave their consent, reason if they did not consent (where given), whether the infant was randomised and reason if they were not randomised (where given). Summary information (no identifiers) will be transferred to REDCap by site staff. When infants are ineligible, this will be explained to the parent/caregiver, including that non-participation will not impact on their clinical care, which will continue as per usual care.

## 5.7. Participant information

A Participant Information Sheet (PIS) will be provided to the parents/caregivers of all eligible infants who have expressed an interest in their infant participating in the trial. PIs or delegate(s) will ensure that they adequately explain the aim, treatment, anticipated benefits, and potential hazards of taking part in the trial to the parents/caregivers. They will also stress that participation is voluntary and so the parents/caregivers are free to decline participation and may withdraw their infant from the trial at any time. The OTTER trial PIS will be available in English and translated into the five most widely spoken languages across the country.

In line with routine clinical care, eligible infants can be enrolled at the single face to face visit and randomised at this time if all eligibility criteria can be ascertained. Parents/caregivers of potentially eligible infants may choose to take away trial information to discuss the infant's participation with others (i.e., other parent or caregiver, family members, GP or other healthcare professionals outside of the site research team, if they wish), and enrol at a later time/day. A letter with a EOI link will be given with the PIS.

## 5.8. Consent/e-consent

If the parent/caregiver expresses an interest in their infant participating in the trial, they will be asked to sign and date the latest version of the written Informed Consent Form (ICF) or e-consent form in the trial database. E-consent may be used at the recruiting sites convenience, but consent will always still be given in the presence of the Investigator or delegate(s). All parent/caregivers must provide consent prior to their infant participating in the trial. The parent/caregiver must give explicit consent for the regulatory authorities, members of the trial team and representatives of the Sponsor to be given direct access to their infant's medical records.

The Investigator "or delegate(s)" will then sign and date the form. Informed Consent Form copies will be retained by the Parent/caregiver (personal copy), the Site (infant medical notes), and the NCTU (to be uploaded to the trial database). Where e-consent is used, a copy of the e-consent form will be emailed to the participant.

Where a paper Informed Consent Form is signed, once the infant is entered into the trial, their unique trial identification number will be entered onto the paper Informed Consent Form maintained in the ISF. In addition, if the parent/caregiver has given consent, a copy of the signed Informed Consent Form will be uploaded to the trial database for review.

Details of the informed consent discussions and trial procedures will be recorded in the infant's medical notes. This will include a copy of the signed and dated ICF detailing the version number of the PIS that parents/caregivers provided their consent to.

Throughout the trial the parent/caregiver will have the opportunity to ask questions about the trial. Any new information that may be relevant to the infant's continued participation will be provided. Where new information becomes available which may affect the parent/caregiver's decision to continue, they will be given time to consider and if happy to continue will be re-consented if appropriate. Re-consent will be documented in the medical notes. The parent/caregiver's right to withdraw their infant from the trial will remain.

Electronic copies of the PIS and ICF will be available from the NCTU and will be localised to include the relevant logos for the local institution on both printed and electronic documentation.

Where infants are recruited in secondary care, their General Practitioner (GP) will also be informed that they are taking part in the trial.

Consideration will be given to whether participants are able to take part in other studies.

## 6. Randomisation

### 6.1. Randomisation and allocation concealment

Randomisation will be provided by REDCap, a secure online randomisation system at the Nottingham Clinical Trials Unit (NCTU). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising infants into the trial as detailed on the OTTER Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. Full details of the randomisation specification will be filed within the Trial Master File (TMF).

After infant eligibility has been confirmed and parent/caregiver informed consent has been received, the infant can be randomised into the trial. If data items are missing, randomisation will be suspended but can be resumed once the information is available.

Following randomisation, an email will be sent to the randomising site researcher, local Principal Investigator, and the central/site pharmacy confirming the blinded randomisation of the infant and IMP pack number (where relevant). A blinded randomisation notification will be sent to the Chief Investigator (CI) and NCTU.

Infants will be randomised in a 1:1 allocation ratio to either omeprazole or placebo separately for the two populations. A probabilistic minimisation algorithm will be used to ensure balanced allocation over the following factors:

- Prescribing site
- Setting (inpatient / outpatient)
- Infant sex
- Milk feeding mode at randomisation

- breast
- bottle
- nasogastric tube
- combination nasogastric tube + bottle
- combination breast + bottle
- combination nasogastric tube + breast
- Age at randomisation (term-born population only) and gestational age at birth (preterm population only)

**NOTE:**

- 1) Infants from a multiple pregnancy will be randomised separately, with the infant as the unit of randomisation.
- 2) Prescribing site is included for logistical reasons to aid stock management within sites. Inclusion of recruiting site as a minimisation factor was deemed impractical given the large number of recruiting sites with expected low recruitment numbers.

**6.2. Blinding**

Table 5 provides an overview of the blinding status of all individuals involved in the management and delivery of the trial.

**Table 5: The blinding status of individuals involved in the trial**

| Role                                         | Status  | Comments                                                                                                                                                                                                                                                 |
|----------------------------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Parent/caregiver(s) of participating infants | Blinded | Parents/caregivers will not be told whether their baby has been randomised to the IMP or matched placebo.<br>Parent/caregivers may be unblinded to the treatment allocation at the end of the trial if they have given consent to have this information. |
| Chief Investigators                          | Blinded | The CI will remain blinded to treatment allocation overall, except in their role as medical monitor, should there be a SUSAR                                                                                                                             |
| Trial Management staff                       | Blinded | Trial management staff within the NCTU will remain blinded to treatment allocation, except Senior Trial Manager in the instance they are required to submit a SUSAR                                                                                      |
| Statistician(s)                              | Blinded | The trial and senior trial statisticians will not have access to treatment allocations or data which have the potential to unblind them until after the database lock for the analysis                                                                   |

|                                             |           |                                                                                                                                                                                                                                                      |
|---------------------------------------------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Trial Pharmacist                            | Blinded   | The Trial Pharmacist will remain blinded to treatment allocation overall                                                                                                                                                                             |
| Principal Investigator and other site staff | Blinded   | Blinded to treatment allocation to minimise the chance of unconscious treatment bias                                                                                                                                                                 |
| Database Systems Developer(s)               | Unblinded | The database programmer will be responsible for the management of the randomisation system and Investigational Medicinal Product (IMP) pack system and will have access to unblinded datasets within the trial database                              |
| Data Management staff                       | Unblinded | Data management staff will have access to the unblinded datasets within the trial database to ensure data quality and undertake central monitoring activities                                                                                        |
| Health economist(s)                         | Blinded   | The health economists will be blinded until they undertake the incremental analysis                                                                                                                                                                  |
| Process evaluation research fellow          | Blinded   | The process evaluation researcher will have access to a blinded dataset to purposively select parents/caregivers from each intervention arm to interview about their experience of the trial and their trial medicine.                               |
| Independent statistician                    | Unblinded | A statistician, independent of the trial team, will be responsible for the generation of confidential reports for the Data Monitoring Committee (DMC) and other potentially unblinding data, and will therefore be unblinded to treatment allocation |

### 6.3. Unblinding procedure

Unblinding is the process that relates to revealing the intervention that was allocated to an infant during their randomisation onto the trial. For the OTTER trial, unblinding each infant's treatment allocation will occur routinely at the end of the trial (after database lock), or unblinding prior to the end of the trial may occur if the infant experiences a Suspected Unexpected Serious Adverse Event (SUSARs). Unblinding will occur on an individual basis. Unblinded data management staff will be able to provide the allocation by email when requested during the working hours of 9am-5pm

Monday to Friday in line with the reporting timeline for SUSARs. Parents/caregivers who have given their consent to reveal the treatment their infant was allocated to at the end of the trial, will receive this information when the results have been shared with participants unless there is a reason to inform them due to a SUSAR. If a participant develops a condition other than GORD, where there is a need for omeprazole treatment, and the trial results have not yet been shared, there will be an option to request unblinding. This would only be considered where the IMP had been stopped due to clinical concerns of adverse reaction. Unblinding in this situation should be requested through the trial management team, assessed by the CI, and if necessary for the participants clinical care, treatment allocation will be provided to the participants clinician by unblinded data management staff.

#### 6.4. Emergency unblinding

Emergency unblinding is not required in the OTTER trial. Omeprazole is a licensed medicine for children from 1 month of age for the treatment of reflux oesophagitis. Although its use in neonates, including preterm neonates, is off-label, it is well established in clinical practice. Omeprazole has a well-characterised safety profile, and serious acute adverse reactions for which management depends on confirmed exposure are rare.

In the event of a serious adverse event, emergency unblinding is not anticipated to be necessary, as knowledge of treatment allocation would not alter the participant's immediate clinical management. There is no specific antidote or treatment strategy that depends on confirmation that the participant received omeprazole. Management would be guided by the participant's clinical presentation and would include discontinuation of the IMP where clinically indicated and standard supportive care, irrespective of treatment allocation.

Although omeprazole has recognised interactions with some medicines that may be used in an emergency in this population, such as diazepam and phenytoin, these interactions would not be expected to affect the selection, initial dosing or immediate administration of emergency treatment. There is no specific intervention that would immediately reverse CYP2C19 inhibition by omeprazole. Once the IMP is discontinued, the potential for interaction would progressively diminish as omeprazole and its metabolites are eliminated and CYP2C19 activity recovers. During this period, clinical management would comprise appropriate monitoring and adjustment of the concomitant medication as required and would not be dependent on knowledge of treatment allocation.

#### 6.5. Unblinding for SUSAR

Where unblinding is required in the event of a potential SUSAR being reported, the trial management team will request that unblinded data management staff provide the allocation by email for the Medical Monitor to view. To ensure medical oversight the CI and/or Deputy Medical Expert will be unblinded as necessary, as per section 9.3.

## 7. Trial interventions

### 7.1. Name and description of Investigational Medicinal Product IMP

**Table 6. Description of the Investigational Medicinal Product**

| Treatment group | Omeprazole | Placebo |
|-----------------|------------|---------|
| IMP or NIMP     | IMP        | IMP     |

|                                                                                   |                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Description of active substance</b>                                            | Chemical origin                                                                                                                                                                                                                                                                                                                                                         | Chemical origin                                                                                                                                                                                                                                                                                                                                                         |
| <b>Pharmaceutical form</b>                                                        | Powder for Oral Suspension                                                                                                                                                                                                                                                                                                                                              | Powder for Oral Suspension                                                                                                                                                                                                                                                                                                                                              |
| <b>Omeprazole Concentration</b>                                                   | 2 mg/mL                                                                                                                                                                                                                                                                                                                                                                 | 0 mg/mL                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Unit size</b>                                                                  | Once reconstituted the bottle contains 90 mL of oral suspension, of which 75 mL is intended for dosing and administration                                                                                                                                                                                                                                               | Once reconstituted the bottle contains 90 mL of oral suspension, of which 75 mL is intended for dosing and administration                                                                                                                                                                                                                                               |
| <b>Excipients</b>                                                                 | Sodium hydrogen carbonate, Potassium hydrogen carbonate, Sodium alginate, Maltitol, Mannitol, Sucralose, Xanthan gum, Natural Vanilla Flavouring containing Maltodextrin (Maize), silicon dioxide and vegetable oil fats, Natural Mint Flavouring containing Gum Arabic / Acacia Gum, and pulegone Titanium dioxide, Sodium benzoate, Sodium methyl parahydroxybenzoate | Sodium hydrogen carbonate, Potassium hydrogen carbonate, Sodium alginate, Maltitol, Mannitol, Sucralose, Xanthan gum, Natural Vanilla Flavouring containing Maltodextrin (Maize), silicon dioxide and vegetable oil fats, Natural Mint Flavouring containing Gum Arabic / Acacia Gum, and pulegone Titanium dioxide, Sodium benzoate, Sodium methyl parahydroxybenzoate |
| <b>Appearance</b>                                                                 | White / off-white / slightly yellow powder                                                                                                                                                                                                                                                                                                                              | White / off-white / slightly yellow powder                                                                                                                                                                                                                                                                                                                              |
| <b>Manufacturer</b>                                                               | Xeolas Pharmaceuticals                                                                                                                                                                                                                                                                                                                                                  | Xeolas Pharmaceuticals                                                                                                                                                                                                                                                                                                                                                  |
| <b>Regulatory status</b>                                                          | Licensed                                                                                                                                                                                                                                                                                                                                                                | Not licensed                                                                                                                                                                                                                                                                                                                                                            |
| <b>Labelling</b>                                                                  | In compliance with Medicines for Human Use (Clinical Trials) Regulations (Amended) 2025                                                                                                                                                                                                                                                                                 | In compliance with Medicines for Human Use (Clinical Trials) Regulations (Amended) 2025                                                                                                                                                                                                                                                                                 |
| <b>Sourcing</b>                                                                   | Provided centrally from the sponsor via Sharp Clinical Service (UK) Limited                                                                                                                                                                                                                                                                                             | Provided centrally from the sponsor via Sharp Clinical Service (UK) Limited                                                                                                                                                                                                                                                                                             |
| IMP=investigational medicinal product; NIMP=non-investigational medicinal product |                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                         |

Each treatment kit will contain two bottles of Omeprazole or Placebo (each bottle is enclosed in an aluminium foil pouch), two oral dosing syringes, two bottle adaptors, and two replacement caps. Each treatment kit will be labelled with a unique kit number. This unique kit number will be assigned to an infant and encodes the appropriate IMP to be dispensed in accordance with the treatment assignment for the infant.

#### 7.1.1. Regulatory status of drug

The regulatory status of each IMP is detailed in Table 6.

#### 7.1.2. Product characteristics

The product characteristics of each IMP are detailed in Table 6.

#### 7.1.3. Drug storage and supply

The investigator, or an authorised designee (e.g., pharmacist) will ensure that all IMPs are stored in a secured area under recommended storage conditions, with access limited to the investigator and authorised personnel. The IMPs are for clinical trial use only and are to be used only within the context of this protocol.

The IMPs should be stored below 25°C, prior to reconstitution, in its secondary packaging to protect from light and moisture.

The site pharmacy team (or central pharmacy services provided by IPS Pharma for primary care sites) will reconstitute the IMP at the point of dispensing, providing infants and parents/caregivers with a ready-to-use product. The reconstituted suspension may be stored for up to 2 days, below 25°C whilst pick up or delivery takes place. Parents/caregivers should store the reconstituted suspension in a refrigerator (2°C - 8°C), in the original container to protect from light. The bottle should be tightly closed. Temperature monitoring is not necessary.

#### 7.1.4. Preparation and labelling of IMP

IMP will be packaged and labelled according to Good Manufacturing Practice (GMP) guidelines and the Medicines for Human Use (Clinical Trials) Regulations (Amended) 2025, in secondary containers as individual treatment kits as described in section 7.1.

The preparation and administration of IMP is summarised in Table 7. Further information is detailed in the IMP manual.

**Table 7. Preparation and administration of Investigational Medicinal Product**

| Treatment group         | Omeprazole                                                                                                                                                                                                                                     | Placebo |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Route of administration | Oral                                                                                                                                                                                                                                           | Oral    |
| Dose preparation        | The site pharmacy team (or central pharmacy for primary care sites) will reconstitute the IMP at the point of dispensing, providing infants and parents with a ready-to-use product.<br><br>Further information is detailed in the IMP manual. |         |
| Duration of treatment   | 28 days                                                                                                                                                                                                                                        |         |

#### 7.1.5. Dosing schedules

The dose administered will be based on body weight recorded at the baseline appointment, or up to one week prior to the baseline if recorded by a healthcare professional. The dose will be 0.5 mL/kg once a day for 28 days. For infants randomised to the omeprazole group, this translates to a dose of 1mg/kg.

#### 7.1.6. Dose modifications

Dose modification will not be used in this trial.

#### 7.1.7. Known drug interactions and other therapies

Nelfinavir is listed as a contraindication in section 4.5 of the SmPC however this should not be used in the treatment of infants, and has been unavailable in the UK since 2013.

#### 7.1.8. Concomitant medications

Omeprazole is metabolised by CYP2C19 and CYP3A4 enzyme, but it also functions as a moderate inhibitor of CYP2C19. Thus:

- Medications known to inhibit CYP2C19 or CYP3A4 (e.g., clarithromycin and voriconazole) may lead to increased omeprazole serum levels.
- Medications known to induce CYP2C19 or CYP3A4 (e.g., rifampicin) may lead to decreased omeprazole serum levels.
- The systemic exposure of concomitant medications metabolised by CYP2C19 (e.g., vitamin K antagonists, cilostazol, diazepam and phenytoin) may increase.

Caution should be exercised if concurrent use of these types of medications becomes necessary during the trial intervention period.

Concomitant medications known to strongly or moderately inhibit or induce CYP2C19 or CYP3A4 will be recorded in the CRF. Over the counter medications are permitted during the trial, if required.

#### 7.1.9. Assessment of adherence with treatment

Parents/caregivers of participating infants will be asked to report how much of the trial medicine their infant took during the 4 week treatment period. The question will be included in the 4-week questionnaire. Adherence will be measured using the following categories:

- All medicine given
- Most medicine given
- More than half but less than three quarters of medicine given
- Some medicine given but less than half
- No medicine given

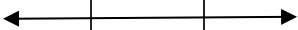
Reasons for not giving the full course of medicine will be collected as part of the 4 week questionnaire.

Parents of infants who are randomised as outpatients or in primary care will be asked to return unused and empty medicine bottles to their recruiting clinic to be disposed of safely, however return of these will not be mandated or tracked.

## 8. Trial procedures and assessments

### 8.1. Summary of assessments

**Table 8: Summary of assessments**

| TIMEPOINT                     | Trial period |                                                                                     |         |         |                                  |                                    |          |
|-------------------------------|--------------|-------------------------------------------------------------------------------------|---------|---------|----------------------------------|------------------------------------|----------|
|                               | Baseline     | Post randomisation                                                                  |         |         | Follow-up                        |                                    |          |
|                               | 0            | Day 0-3*                                                                            | 2 weeks | 4 weeks | Hospital discharge <sup>e1</sup> | Fortnightly text 6-week to 6-month | 6 months |
| <b>ENROLMENT:</b>             |              |                                                                                     |         |         |                                  |                                    |          |
| Eligibility screen            | X            |                                                                                     |         |         |                                  |                                    |          |
| Informed consent              | X            |                                                                                     |         |         |                                  |                                    |          |
| Randomisation                 | X            |                                                                                     |         |         |                                  |                                    |          |
| <b>INTERVENTIONS:</b>         |              |                                                                                     |         |         |                                  |                                    |          |
| Omeprazole or matched placebo |              |  |         |         |                                  |                                    |          |
| <b>ASSESSMENTS:</b>           |              |                                                                                     |         |         |                                  |                                    |          |
| Demographics & baseline data  | X            |                                                                                     |         |         |                                  |                                    |          |
| I-GERQ-R                      | X            |                                                                                     | X       | X       |                                  |                                    |          |
| Growth (Weight) <sup>2</sup>  | X            |                                                                                     |         | X       |                                  |                                    | X        |
| Treatment escalation          |              |                                                                                     |         | X       |                                  | X                                  | X        |

|                                                                             |              |                    |         |           |                                  |                                    |          |
|-----------------------------------------------------------------------------|--------------|--------------------|---------|-----------|----------------------------------|------------------------------------|----------|
| Oesophagitis /<br>Haematemesis                                              |              |                    |         | X         |                                  | X                                  | X        |
| NEC <sup>3</sup>                                                            |              |                    |         |           | X                                |                                    | X        |
| TIMEPOINT                                                                   | Trial period |                    |         |           |                                  |                                    |          |
|                                                                             | Baseline     | Post randomisation |         | Follow-up |                                  |                                    |          |
|                                                                             | 0            | Day 0-3*           | 2 weeks | 4 weeks   | Hospital discharge <sup>e1</sup> | Fortnightly text 6-week to 6-month | 6 months |
| Length of stay <sup>1</sup>                                                 |              |                    |         |           | X                                |                                    |          |
| Health-related quality of life (IQI and EQ-5D-5L)                           | X            |                    |         | X         |                                  |                                    | X        |
| Hospital admissions and length of stay                                      |              |                    |         | X         |                                  | X                                  | X        |
| Further GOR treatment                                                       |              |                    |         | X         |                                  | X                                  | X        |
| Infections                                                                  |              |                    |         | X         |                                  | X                                  | X        |
| Fractures                                                                   |              |                    |         |           |                                  | X                                  | X        |
| Feeding                                                                     |              |                    |         |           |                                  |                                    | X        |
| Healthcare use (primary care visits, secondary care visits, and medication) | X            |                    |         | X         |                                  |                                    | X        |

\* approximate IMP delivery window for infants recruited via secondary care outpatient clinics or GPs

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**Version Date:** 05 Jun 2026

<sup>1</sup>only preterm and term-born infants where treatment was started as an in-patient.

<sup>2</sup>weight measurement to be taken within 1 week of the timepoint

<sup>3</sup>in preterm and term-born infants where treatment was started as an in-patient, or at 6 weeks where treatment was started as an outpatient and NEC is recorded as an SAE.

## 8.2. Trial Procedures and schedule of assessments

The following assessments will be performed at each timepoint as outlined in Table 8 Summary of assessments.

### 8.2.1. Screening

Screening data for infants entering the trial will be collected by each site and recorded within the trial database.

### 8.2.2. Informed consent

Informed consent will be obtained as described in Section 5.8.

### 8.2.3. Routine assessments and eligibility

A GOR diagnosis in an infant is often made by clinical assessment and infant medical history. Therefore no formal diagnostic testing or additional investigations are required for inclusion in the trial. Eligibility will be assessed in line with Section 4. Infants who do not meet eligibility criteria will have the reason explained to their parent/caregiver and that not participating in the trial will not impact on their infant's medical care. They will then continue to have routine care as per usual practice.

### 8.2.4. Baseline appointment

After informed consent and eligibility assessments are complete, baseline appointment data will be collected. This will include:

- Demographic data
- Infant weight
- I-GERQ-R questionnaire
- Infant quality of life (IQI)
- Parent quality of life (EQ-5D-5L)
- Healthcare use (primary care visits, secondary care visits, emergency visits and medication)
- Feeding mode
- Previous GOR treatments

The full list of baseline data collected for this trial is detailed in the current version of the trial CRF.

### 8.2.5. Randomisation

Infants will be randomised to receive either omeprazole or matched placebo using the trial database. A member of the recruiting site research team will perform randomisation (as per the site delegation log). As the trial intervention is blinded, neither the parent/caregiver nor the recruiting

site staff will know which of the two treatments the infant has been allocated (see Section 6.1 for more information).

#### 8.2.6. IMP dispensing

Infants recruited to trial via a hospital inpatient setting will be dispensed the trial medication by the recruiting hospital pharmacy. Infants recruited to the trial via a hospital outpatient setting, or their GP will have their trial medication dispensed by a IPS pharma and delivered to their home address as a ready to use medicine, using a 24-hour delivery service. Parents/caregivers having the trial medication delivered to their home address will receive a text message 2 days post randomisation to ask them to confirm that the medication has been received. Details on the dispensing process for each site will be detailed in the current version of the Pharmacy Manual.

#### 8.2.7. Follow-up procedures

In accordance with standard clinical practice, parents/caregivers will not be required to revisit the hospital or GP as part of their participation in this trial. Following randomisation, follow-up information will be obtained directly from the parents/caregivers (e.g. electronic/paper questionnaires, SMS message or telephone call and coordinated by the NCTU with involvement from the recruiting site limited to support with follow-up completion when the NCTU have been unsuccessful.

##### 8.2.7.1. Hospital discharge

For preterm and term-born infants where treatment was started as an inpatient, the following data will be recorded in the trial database at the point of, or shortly after infant's hospital discharge:

- Necrotising enterocolitis
- Length of hospital stay

##### 8.2.7.2. Two week follow-up telephone call and questionnaire

Research staff will call the parent/caregiver of the participating infant to check on the family's wellbeing and provide support on the collection of the initial questionnaire (if not completed).

- I-GERQ questionnaire

If during the phone call, a parent/caregiver becomes distressed and is seeking support that cannot be provided as part of the OTTER trial or a safeguarding issue is noted, the research nurse conducting the call will pass the details of the parent/caregiver onto the local PI to follow-up and provide support in line with standard NHS care.

Unblinding parents/caregivers to their infant's treatment allocation will not happen during this call.

##### 8.2.7.3. Four week questionnaire

Parents/caregivers will complete a questionnaire (online, postal, SMS message or telephone) 4 weeks after randomisation which will collect information on the following:

- I-GERQ questionnaire (primary outcome)
- Growth (weight)
- Need for treatment escalation (including additional investigations, referrals and treatment)

- Any bacterial infections (either antibiotic prescriptions or admissions for infections)
- Suspected/confirmed bacterial respiratory infections (prescription of antibiotics for a respiratory illness)
- Any gastrointestinal infections (vomiting or diarrhoea which required medical attention)
- Infant quality of life (IQI)
- Parent quality of life (EQ-5D-5L)
- Healthcare use (primary care visits, secondary care visits, emergency visits and medication)
- Evidence of oesophagitis, haematemesis
- Further treatment with medication for GOR

Parents/caregivers will be asked to complete the 4 week questionnaire within one week of receipt. Questionnaire completion reminders will be sent to parents/caregivers who have not completed the questionnaire within the week following receipt. There will be a 2 week window for the return of the questionnaire. Primary outcome data may be collected by telephone where the 4 week questionnaire pack has not been completed. Questionnaires will no longer be available for completion once outside of the specified completion window; therefore, no protocol deviations will be required for completion of data outside of the specified data collection windows.

#### 8.2.7.4. Fortnightly questionnaire

Parents/caregivers will receive a fortnightly questionnaire, consisting of one question, from 6 weeks post randomisation to 24 weeks post randomisation (5 months of fortnightly questionnaires). The questionnaire will ask whether they have used any health services for their infant in the previous week. If they respond yes, they will be required to complete a longer survey asking further information such as whether their infant has received any further GOR treatment or been admitted to hospital.

Where a parent/caregiver answers yes, we will collect information on the following:

- Hospital admissions (and length of stay)
- Further treatment with medication for GOR
- Need for treatment escalation (including additional investigations, referrals and treatment)
- Any bacterial infections (either antibiotic prescriptions or admissions for infections)
- Suspected/confirmed bacterial respiratory infections (prescription of antibiotics for a respiratory illness)
- Any gastrointestinal infections (vomiting or diarrhoea which required medical attention)
- Evidence of oesophagitis, haematemesis

#### 8.2.7.5. Six month questionnaire

Parents/caregivers will complete a questionnaire (online, postal or telephone) 6 months after randomisation which will collect information on the following:

- Healthcare use (primary care visits, secondary care visits (i.e. hospital admission, A&E, inpatient appointments), medication)
- Infant quality of life (IQI)
- Parent quality of life (EQ-5D-5L)
- Fractures
- Growth (weight)
- Feeding

Any additional occurrences of the following will also be collected as part of the 6 month questionnaire, where not already report via the fortnightly questions:

- Hospital admissions (and length of stay)
- Further treatment with medication for GOR
- Need for treatment escalation (including additional investigations, referrals and treatment)
- Any bacterial infections (either antibiotic prescriptions or admissions for infections)
- Suspected/confirmed bacterial respiratory infections (prescription of antibiotics for a respiratory illness)
- Any gastrointestinal infections (vomiting or diarrhoea which required medical attention)
- Evidence of oesophagitis, haematemesis

In cases where parents/caregivers do not respond or where data provided by them is unclear or conflicting, the relevant primary and/or secondary care clinical records will be reviewed for information on health care resource use including hospital admission, infections, fractures oesophagitis and haematemesis. Clinical records will be reviewed, and relevant information entered into the trial database by a member of the site research team on completion of the individual infant's participation in the trial.

Completion windows for the 6-month questionnaire will be 4 weeks. Questionnaire completion reminders will be sent to parents/caregivers who have not completed the questionnaire within the four weeks following receipt. Towards the end of this 4 week completion window if parents have not completed the questionnaire they may be called by the trial team and the relevant data collected via telephone and recorded directly into the trial database.

Questionnaires will no longer be available for completion once outside of the specified completion window; therefore, no protocol deviations will be required for completion of data outside of the specified data collection windows.

### 8.3. Discontinuation and withdrawal procedures

The parent/caregiver must remain free to withdraw the participating infant at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Parent/caregiver

withdrawal of consent from the trial must be explicitly documented in the trial REDCap database and infant medical record.

### 8.3.1 Withdrawal prior to randomisation

Any parents/caregivers that request to withdraw consent for their infant's participation **prior to randomisation** will be withdrawn completely from the trial; they will not be randomised, and follow-up questionnaires will not be issued.

### 8.3.2 Discontinuation and withdrawal post-randomisation

Parents/caregivers may withdraw their consent for follow-up and/or other trial-related activities including receiving trial-related communications. The NCTU must be informed of all requests by parents/caregivers to stop their infant's involvement in the trial; appropriate action will be taken to ensure that the parent's wishes are followed.

Sites will be trained to determine which activities parents may wish to withdraw from if they don't want to completely withdraw from the trial.

**Table 9: Discontinuations**

| Type of discontinuation                                              | Procedure                                                                                                                                                                                                                                                                                                                                                  | Use of data                                                                                                     |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Discontinuation of the intervention due to parental/caregiver choice | Parents/caregivers that request to stop treatment, will be asked to continue to complete questionnaires and complete the outcomes. Information on reason for stopping trial treatment will be recorded by the site if given and will not affect ongoing care. These infants will be marked as stopped treatment on the trial database.                     | Data collected prior to or after discontinuation of the intervention will be retained and used in the analysis. |
| Discontinuation of the intervention by investigator/clinical team    | Investigator/clinical team that requests to discontinue the trial treatment if the infant has a significant adverse event due to treatment will be asked to continue to collect data and complete the outcomes. Parents of such infants will be asked to complete questionnaires. These infants will be marked as stopped treatment in the trial database. | Data collected prior to or after discontinuation of the intervention will be retained and used in the analysis. |

|                                                                           |                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Withdrawal from follow up questionnaires due to parental/caregiver choice | Parents/caregivers that request to discontinue from trial questionnaires will be marked as withdrawn from questionnaire collection on the trial database and no further contact relating to questionnaires will be made.                                                                       | Follow-up questionnaire data collected prior to parent/caregiver discontinuation of follow-up questionnaires will be retained and used in the analysis.<br><br>Clinical follow-up data can still be collected should a parent/caregiver withdraw from questionnaire completion activities.                               |
| Complete withdrawal from the trial as per parental/caregiver choice       | Parents/caregivers that request to fully withdraw from the trial will be marked as complete withdrawal on the trial database. Information on reason for complete withdrawal will be recorded if given and will not affect ongoing care. No further contact relating to the trial will be made. | Data collected prior to infant withdrawal will be retained and used but all parent/caregiver information will be redacted and no further contact will be made.<br><br>Clinical follow-up data cannot be obtained for infants whose parent/caregiver has withdrawn from the trial prior to the data collection timepoint. |

#### 8.4. Post-trial care

Usual clinical care will continue after completion of the trial IMP dosing (4 weeks post randomisation). Treatment outside of the trial will not be funded by the trial Sponsor. Infants with a continuing need for GOR treatment will be treated in accordance with standard NHS care.

Data collection will continue until 6 months post randomisation.

## 9. Adverse Event reporting

### 9.1. Reporting requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 (and subsequent amendments). Definitions of the different types of AEs are listed in Table 10 below.

**Table 10: Standard Adverse Event Definitions**

|                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Adverse Event (AE)</b>                | Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.<br>Comment:<br>An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Adverse Reaction (AR)</b>             | All untoward and unintended responses to an IMP related to any dose administered.<br>Comment:<br>An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Serious Adverse Event (SAE)</b>       | Any untoward medical occurrence or effect that: <ul style="list-style-type: none"> <li>• Results in death</li> <li>• Is life threatening*</li> <li>• Requires hospitalisation or prolongation of existing hospitalisation</li> <li>• Results in persistent or significant disability or incapacity</li> <li>• Is a congenital anomaly/birth defect</li> <li>• Or is otherwise considered medically significant by the Investigator***</li> </ul> <p><u>The term severe is often used to describe the intensity (severity) of a specific event. This is different from serious, which is based on participants/event outcome or action criteria.</u></p> <p>* Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.</p> <p>** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.</p> |
| <b>Serious Adverse Reaction (SAR)</b>    | An Adverse Reaction which also meets the definition of a Serious Adverse Event                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Unexpected Adverse Reaction (UAR)</b> | An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SmPC) for a licensed product).<br>When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|                                                              |                                                                                                                                                                                            |
|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Suspected Unexpected Serious Adverse Reaction (SUSAR)</b> | A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.<br>A SUSAR should meet the definition of an AR, UAR and SAR. |
|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 9.2. Adverse Events and reporting requirements/procedures

AEs are commonly encountered in infants receiving omeprazole. As the safety profiles of the IMP used in this trial is well characterised, only selected ARs experienced during treatment will be collected from parents/caregivers, although all Adverse Events will be recorded in the source data.

The following are secondary outcomes and will therefore be collected on the follow-up questionnaires, completed by the parent/caregiver:

- Necrotising enterocolitis at hospital discharge (for infants' diagnoses where treatment started as an inpatient) or at 6 weeks post randomisation (for infants' diagnoses where treatment was outpatient, reported as an SAE.)
- Any bacterial Infections (prescription of antibiotics, admission where infection was admission or discharge diagnosis, 6 months from randomisation)
- Suspected/confirmed bacterial respiratory infections (defined by prescription of antibiotics for a respiratory illness, 6 months from randomisation)
- Any gastrointestinal infections (vomiting or diarrhoea which required medical attention, 6 months from randomisation)
- Fractures (defined as a fracture diagnosed on x-ray following a consultation with a medical professional, 6 months from randomisation)

Only the presence or absence (and severity where appropriate) of the above ARs will be routinely collected for this trial. ARs will be reported by the parent/caregiver of the infant, directly to the NCTU on the follow-up questionnaires.

## 9.3. Serious Adverse Events and reporting requirements/procedures

SAEs that meet the SAE criteria will be reportable throughout the 4 week treatment period plus the two weeks following the end of the IMP treatment period (total 6 week reporting period). All events meeting the SAE criteria should be reported during this period, other than those relating to birth defects as these are not reportable as part of the trial. The 4 week questionnaires, along with the first fortnightly survey (week 6) will include questions to ascertain whether an infant has experienced an SAE since they were randomised to their trial specific treatment.

Where a parent/caregiver has responded with information that suggests a reportable SAE e.g., infant unplanned hospital admission, a review of the questionnaire data will occur, and the recruiting site will be contacted by the NCTU and asked to obtain further information to determine whether an event has occurred that fulfils the SAE criteria. Where the criteria for an SAE has been met, the Principal Investigator (or delegate) must report the SAE on an SAE form to the NCTU. The reporting procedure for this is outlined later in this section.

In instances where a suspected SAE has been reported in a questionnaire response, but the recruiting site has been unsuccessful in contacting the parent/caregiver to obtain further details

about the infant's event, the PI will assess the event based on the information obtained by the site research team using medical records and the information within the questionnaire. Where the PI deems the event meets the trial SAE criteria, the recruiting site will be required to report the SAE to the NCTU via an SAE report within 24 hours of assessment.

AR and potential SAE information will be primarily collected from parents/caregivers via trial questionnaires however, infants may experience SAEs as an inpatient or the parents/caregivers may contact the site directly to report a potential SAE that has occurred whilst participating in the trial or may report an SAE. Where a suspected SAE has been observed by the site or reported by a parent/caregiver, an SAE form must be completed and submitted in line with the trial SAE reporting procedure.

Investigators will report AEs that meet the definition of an SAE. AEs defined as serious require expedited and should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE.

Causality of an event will be categorised as one of the following:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Unrelated

On becoming aware that an infant has experienced an SAE, the Investigator (or delegate) must complete the electronic SAE form within the trial database. The form should be completed as soon as possible and no later than 24 hours after first becoming aware of the event. The site investigator will define the causality of the SAE and sign the form electronically.

Completion of the electronic SAE form will generate a unique SAE reference number and will trigger an alert, via email, to NCTU. The SAE reference number will be quoted on all correspondence regarding the SAE. NCTU will request Medical Monitor assessment via the trial database.

In the unlikely event that the electronic SAE reporting system is unavailable, a paper SAE form must be completed by the site investigator (or delegate). For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments.

Paper SAE forms (only in the unlikely event that the electronic SAE reporting system is unavailable) must be emailed to [NCTU-SAE@nottingham.ac.uk](mailto:NCTU-SAE@nottingham.ac.uk) as soon as possible and no later than 24 hours after becoming aware of the event. NCTU will request Medical Monitor assessment via email.

\*reasonable equates to possible, probable or definitely related in the opinion of either the Investigator or Chief Investigator

The MedDRA medical coding dictionary will be used for the coding of serious adverse events documented in this protocol.

### 9.3.1. Sites

For SAE Forms completed by someone other than the PI, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The original form should be retained at site in the Site File and a copy returned to the NCTU. Investigators must also report SAEs to their own Trust in accordance with local practice.

### 9.3.2. NCTU

On receipt of an SAE form (either electronic or paper), seriousness and causality will be reviewed independently by the Medical Monitor (Chief Investigator or delegate) responsible for determining causality assessments. An SAE judged by the Investigator to have a reasonable\* causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Chief Investigator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e., is not defined in the current version of the Reference Safety Information (RSI)) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR). Any events classified as a SUSAR will trigger a notification to the trial management team. The trial Sponsor office will be notified of the SUSAR as required.

\*reasonable equates to possible, probable or definitely related in the opinion of either the Investigator or Chief Investigator

### 9.3.3. Provision of follow-up information

Parents/caregivers should be followed up until resolution or stabilisation of the infant's event. Follow-up information should ideally be provided directly within the trial database or a new paper SAE form if the REDCap system is unavailable.

## 9.4. Reporting period

Details of potential SAEs will be documented and reported via parent/caregiver reported questionnaires at 4 weeks and 6 months. SAEs that are judged to be at least possibly related to the IMP must be reported in an expedited manner, if occurring within or up to 2 weeks after the IMP administration period.

## 9.5. Reporting by the NCTU

### Regulatory Agency

The MHRA will be notified immediately if a significant safety issue is identified during the trial.

In the event of a SUSAR, the NCTU (reviewed by trial Sponsor) will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) within 7 calendar days beginning with the date that they became aware. Detailed follow-up information will be provided within a further 8 calendar days. Non-life-threatening or non-fatal SUSARs will be reported to the licensing authority within 15 calendar days beginning with the date they became aware.

The NCTU (reviewed by trial sponsor) will report details of all SAEs and SARs (including SUSARs) to the MHRA annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Details of all AEs will be reported to the MHRA upon request.

### Research Ethics Committee

The REC will be notified immediately if a significant safety issue is identified during the trial.

### Trial Investigators

Details of all SUSARs and any other safety issue which arises during the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

### Data Monitoring Committee

The independent Data Monitoring Committee will review all SAEs.

### Reporting to third parties

No reporting of adverse events to third parties is expected. Any safety issues identified during the trial will be notified to the MHRA

## 10. Data Handling and Record Keeping

### 10.1. Source Data

To allow for the accurate reconstruction of the trial and clinical management of the infant, source data will be accessible and maintained.

Source data is kept as part of the infant's medical notes generated and maintained at site. Each site will record the location of source data at their site using a source data location log prior to commencing recruitment. Data that are not routinely collected elsewhere may be entered directly onto the eCRF; in such instances the CRF will act as source data, and this will be clearly defined in the source data location log and recorded.

For this trial, source data refers to, though is not limited to, the infant's medical notes, data recorded by site staff directly into the eCRF, and parent/caregiver reported follow-up data (follow-up questionnaires).

All data collected directly from parents/caregiver will be considered as source data within the eCRF. Where paper questionnaires are issued to parents/caregivers these will be returned to the NCTU for data entry and will be considered source data. Where questionnaire data is obtained via telephone, this data will be entered directly into the CRF by site research staff or a member of the NCTU trial team, and will be considered source data.

### 10.2. Electronic Case Record Form (eCRF) completion

Data for the trial will be captured directly into a REDCap eCRF. Data reported on each eCRF will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete eCRFs will be GCP trained and receive trial-specific training from the NCTU team on how to complete these correctly.

In all cases it remains the responsibility of the site PI to ensure that the eCRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site's Principal Investigator on the eCRF. It is the responsibility of the Principal

Investigator to ensure there are site staff in place locally to complete data entry into the eCRF in a timely manner.

Site staff are only required to complete the eCRF for the baseline appointment, 2 week follow-up phone call and at 6 month follow-up. This must be done within 7 days of the visit date. Where a suspected SAE has been reported sites will be required to investigate the event and complete the SAE form as required. Site staff may also be asked to review clinical records at 6 months and enter any relevant information onto the eCRF.

Questionnaire data will be captured directly into the eCRF where possible using the electronic responses (e.g., email containing link to questionnaire). Where information is completed by the parent/caregiver on paper, questionnaires will be sent to the NCTU for data entry by a member of the trial team.

### 10.3. Data management

All trial data will be entered into REDCap with each infant assigned a participant ID number for use on eCRFs and other trial documents. The documents and trial database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth.

Parent/caregiver contact details will be logged separately to the trial eCRF data, to ensure their identifiable data is separate to data used for analysis. The trial team may also use parent/caregiver contact details to send out trial related questionnaires and correspondence limited to the duration of the infant's participation in the trial or to share the trial results once the trial has been published.

The trial database will have in-built validation to ensure that all the identifiers used match with the allocated infant participant ID number. eCRFs will be treated as confidential documents and held securely in accordance with regulations. Access to REDCap will be restricted and secure and eCRFs will be restricted to those personnel approved by the CI or local PI and recorded on the trial delegation log. Missing or ambiguous data will be queried with the site via the REDCap eCRF and sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. Errors will be corrected and recorded on the eCRFs on the audit log. The CI or local PI (or their designee) will sign a declaration ensuring accuracy of data recorded in the eCRF.

The CRF will only collect the minimum required information for the purposes of the trial. Access to the information will be limited to the trial staff, investigators, authorised sponsor representatives and relevant regulatory authorities (see above). Electronic data including the trial database will be held securely and password protected restricted to those approved requiring access for the trial. For questionnaire data collected electronically (2 week, 4 week and 6 month questionnaires and after a positive response to fortnightly questionnaire), a secure link to an online questionnaire will be sent. Where paper copies of questionnaires are used, a paper version of the questionnaire will be sent by NCTU to the contact address provided by the parent/caregiver at their baseline appointment, with a pre-paid return envelope. If questionnaire data is collected by telephone, the data will be entered directly into the trial database by site research staff or a member of the NCTU trial team with the same restricted access as described above.

Paper questionnaires returned to NCTU will be entered by a member of NCTU and a sample will be reviewed by a separate member of the NCTU. Further details will be documented in the current version of the DMP. Data obtained from parent/caregiver reported outcomes will not be subject to data queries. Decisions on how to treat anomalous data will be made by members of the TMG blinded to allocations and documented in the current version of the DMP and/or Statistical Analysis Plan.

#### 10.4. Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Location and duration of record retention for:

- Source records: Infant medical records will be stored and maintained according to any applicable regulatory or local requirements.
- Essential documents and study data will be held for minimum of 25 years

Destruction of essential documents will require authorisation from the Sponsor.

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g., signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participating infants' medical records, copies of CRFs etc.) at their site are securely retained for 25 years, in accordance with Clinical Trial Regulation EU 356/2014.

#### 10.5. Data sharing

Individual participating infant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Parent/caregivers' contact details, including name, address, telephone/mobile number and email will be shared between participating sites, NCTU and third parties (where required) for the purposes of issuing questionnaires and electronic reminders (text/email) for the trial.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU trial team will have access to these data.

Utilising identification code numbers will further ensure parent/caregiver and participating infant confidentiality to correspond to treatment data in computer files.

Data generated as a result of this trial will be available for inspection on request by University Hospital Southampton NHS Foundation Trust, NCTU, the REC, local R&D departments and the regulatory authorities.

De-identified parent/caregiver and infant data may be shared with researchers external to the trial team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the Nottingham Clinical Trials Unit.

## 11. Study Within A Trial (SWAT)

### 11.1. SWAT background

An embedded Study Within a Trial (SWAT) is included in the trial, to evaluate whether providing real-time training, via a virtual site initiation visit with key members of the trial team, or modular-video based training, which can be accessed at the site members' convenience, is more effective. The SWAT addresses Priority 1, question 15: approaches to make workloads more manageable for clinical and research staff. This is one of the research priorities to improve recruitment and retention in clinical trials, identified by the PRioRiTy study [22].

### 11.2. SWAT interventions

**Intervention:** Pre-recorded modular SIV training followed by a 30-minute meeting to meet members of the team and to discuss any aspect of the trial that requires clarification. The pre-recorded material can also be used to train new members to the team.

The modular-based training will include a series of animations/ graphics, interviews and voice overs. The modular-based training will be developed by the joint lead applicants, trial management team and key co-investigators, as needed.

**Comparator:** Real-time SIV training. All sites randomised to the comparator group will be trained on a per-site basis by the Trial Manager and a clinical member of the investigator team.

### 11.3. SWAT method of allocation

Sites will be randomised (1:1 allocation ratio) to either the intervention (modular training) or control (real-time training) using a probabilistic minimisation algorithm balancing on site type (primary or secondary care). Sites will be randomised by the trial management team using a web-based randomisation system developed and maintained by the NCTU and hosted on a secure server.

### 11.4. SWAT outcome measures

We will use outcome measures developed through a Delphi-consensus building on site performance metrics in an NIHR funded project.[23] The same outcome measures are used in the FEED1 SWAT, which similarly aims to evaluate site performance based on mode of SIV training delivery [24].

Primary outcome: Actual recruitment (number of participants recruited to the trial) vs target recruitment (number of participants planned to be recruited to the trial), presented as percentage of target recruitment achieved.

Secondary outcomes:

- percentage of eligible babies whose parents/caregiver give consent
- percentage of randomised infants with complete data for the primary outcome
- percentage of infants with at least one protocol violation
- associated costs (direct and in-direct) of delivering the training

### 11.5. SWAT sample size

The sample size for the SWAT will be predicated by the number of sites in the OTTER trial who agree to have their training delivery method randomised. We anticipate including at least 30 sites in the SWAT.

### 11.6. SWAT analysis

The analysis of the SWAT will be specified in the OTTER SWAT statistical analysis plan. Analyses will include appropriate descriptive statistics and between-group comparisons will use appropriate regression models with analysis at the site level.

### 11.7. SWAT dissemination

The SWAT will be registered on the Northern Ireland Medical Research Council (MRC) Trials Hub for Methodology Research SWAT registry. The findings will be made publicly available as soon as possible after the end of the SWAT and will be made available to researchers conducting meta-analysis in this field.

## 12. Quality control and quality assurance

### 12.1. Site set-up and initiation

#### Recruiting centres (primary and secondary care)

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to NCTU – this should be signed within the last 2 years. All members of the site research team will also be required to sign a site delegation and training log. Prior to commencing recruitment, all sites will undergo a process of initiation (format of training to be determined by the SWAT described in section 11) and will have completed any necessary training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with access to an online Investigator Site File, as part of the Florence electronic TMF system, and a Pharmacy File containing essential documents, instructions, and other documentation required for the conduct and reconstruction of the trial. NCTU must be informed immediately of any change in the site research team.

#### GP PIC

Prior to commencing participant identification activities, participating PICs will undergo training appropriate to their trial role to cover the protocol, screening searches and initial conversations with parents/caregivers. Documentation and support to complete the identification of eligible infants will be provided as required.

### 12.2. Monitoring

This study will be monitored and may be participant to monitoring and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor and other regulatory bodies to ensure adherence to ICH GCP, UK Policy Framework for Health and Social Care Research, applicable contracts/agreements and national regulations. All study related documents will be made available on request for monitoring and audit by UHS, the relevant REC or other licensing bodies.

Site monitoring will be conducted as required following a risk assessment and as documented in the monitoring plan, stored in the Trial Master File. NCTU will be in regular contact with the site research teams to check on progress and address any queries that they may have. The trial team will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and

timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, lower than expected SAE reporting rates, excessive number of parent/caregiver withdrawal of infants or deviations. If a monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU trial staff access to source documents as requested.

Sites will be requested to upload copies of signed Informed Consent Forms for in-house review for all parents/caregivers providing explicit consent. This will be detailed in the monitoring plan and the Participant Information Sheet.

### 12.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify NCTU of any MHRA inspections. The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

### 12.4. Notification of Serious Breaches

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be reported to the NCTU for review and escalated to the sponsor where necessary.

Frequent non-compliances will be investigated by the NCTU in line with the trial monitoring plan. Where appropriate, identified issues will be escalated to the Sponsor with frequent non-compliances potentially classified as a serious breach.

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and its amendments) the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where NCTU is investigating whether a serious breach has occurred sites are also requested to cooperate with NCTU in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment could potentially meet the criteria of a Serious Breach and sites may be suspended from further recruitment. Any major problems identified during monitoring may be reported to specify trial specific committees and/or stakeholders e.g., Trial Management Group, Trial

Steering Committee, the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

### 13. End of trial definition

The study end will be defined by the completion of all data collection. The Chief Investigator will inform the relevant Research Ethics Committee giving favourable opinion within 90 days of the study ending using the appropriate form.

### 14. Statistical considerations

#### 14.1. Determination of sample size and statistical power

Published studies have reported a standard deviation for the primary outcome (I-GERQ-R) of between 5 and 6.5.[25-27]. Using a conservative standard deviation of 6.5, a total of 200 infants (100 per group) are required to detect a 3-point difference in mean I-GERQ-R between two groups (active intervention vs placebo comparator) with 90% power and a 5% two-sided significance level. Allowing for 20% loss to follow-up in the two infant populations, gives a total trial sample size of 500 infants (250 in each population, 125 per randomised group). Sample size calculations were conducted using PASS v22.0.3.

##### 14.1.1. Rationale for target treatment difference

A 3-point difference in I-GERQ-R score has been chosen as the target difference for the sample size calculation above, based on several studies. The original development study for the I-GERQ-R demonstrated that a change in I-GERQ-R score of 5 to 6 could be considered clinically meaningful, but that a change of 3 might represent a minimally important clinical difference (MCID)[28]. A later structured literature review and meta-analysis of interventional studies using the I-GERQ-R to assess GOR symptoms, reported a mean change of I-GERQ-R of 6.54 (95% confidence interval 4.35 to 8.74) across studies. The same meta-analysis also reported a standardised mean difference in I-GERQ-R scores of 2.9, with an upper limit of the 95% confidence interval of 4. This led the authors to conclude that the minimally important difference was between 3 and 4[25]. We have therefore chosen 3 as the target difference for this trial.

Of note, the same structured literature review and analysis included RCTs and observational studies, including both term and preterm infant populations. This included a study, Campanozzi *et al*, which reported no significant difference between the I-GERQ score of children who were preterm at birth and those children born at term [29]. In addition, Pados *et al*, reported similar I-GERQ scores for infants born between 32 and <37 weeks' gestation to infants born at ≥37 weeks' gestation with higher scores for infants born at <32 weeks' gestation[26]. These findings justify use of the same target difference for both the preterm and term-born populations. Furthermore, opting for this relatively small target mean difference could indicate that we are more likely to be able to detect a difference between treatments, if one exists.

#### 14.2. Statistical methods used to compare groups for primary and secondary outcomes, including harms

The analysis and reporting of the trial will be in accordance with CONSORT guidelines with all analyses specified in the Statistical Analysis Plan (SAP) [30], finalised prior to database lock [31]. The final analysis for all outcomes will be conducted after database lock. The trial is powered to detect treatment differences in the two populations (preterm/term born) separately, and data will be analysed and presented separately for each population.

The main approach to between-group comparative analysis will be according to randomised allocation, without imputation for missing outcome data. Descriptive statistics will be used to illustrate balance between the groups at baseline in each population.

All analysis, where technically possible, will include adjustment for minimisation factors, excluding prescribing site since this was included as a minimisation factor for logistical reasons only. Instead, recruiting site will be included in the analysis as a random effect to account for potential differences in practice between sites.

Analysis of the primary outcome will employ a mixed-effects model using all available longitudinal data up to 4 weeks, adjusting (if technically possible) for baseline I-GERQ-R score and minimisation factors (excluding prescribing site), with recruiting site as a random effect. A random effect for 'pregnancy' will be nested within site, to account for the correlation between outcomes for infants born from a multiple pregnancy. The model will include a treatment-by-time interaction to obtain the estimates of treatment effect at each follow-up time, with 4 weeks being the primary timepoint used for inference. The estimated between-group treatment effect will be presented as an adjusted difference in means, with corresponding 95% confidence interval.

Between-group comparisons of secondary outcomes will use a regression model appropriate to the outcome data type (e.g., binary, continuous, ordinal), with adjustment for minimisation factors (excluding prescribing site), where technically possible.

#### 14.3. Definition of who will be included in each analysis (e.g., all randomised participants), and in which group

| Outcome         | Analysis set                                                                                                                                                                                                                                                                                                                                    |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary outcome | <p>All participants will be analysed according to the treatment they are assigned, regardless of the treatment that they receive or adherence with allocation. (i.e. Intention to treat)</p> <p>Participants with some outcome data collected (i.e. two week or 4 week I-GERQ-R) will be included in the analysis using all available data.</p> |

| Outcome                                             | Analysis set                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Secondary outcomes                                  | <p>All participants will be analysed according to the treatment they are assigned, regardless of the treatment that they receive or adherence with allocation. (i.e. Intention to treat)</p> <p>The main analysis for each outcome will be for participants with available outcome data. (i.e. missing data will be considered non evaluable in the main analysis.)</p>                                                                                                                                    |
| Serious adverse events & secondary safety outcomes. | <p>All participants who have received at least one dose of trial medication according to:</p> <ol style="list-style-type: none"> <li>1. Randomised allocation</li> <li>2. Treatment (Omeprazole) received</li> </ol> <p>The main analysis for each outcome will be for participants with available outcome data. (i.e. missing data will be considered non evaluable in the main analysis.)</p> <p>More detail, including considerations for use of omeprazole after 4 weeks will be given in the SAP.</p> |

#### 14.4. How missing data will be handled in the analysis

The primary analysis using a mixed effects model assumes that missing data are missing at random (MAR) i.e. does not depend on the values of the missing data conditional on the observed data included in the analysis model.

As a sensitivity analysis to include all randomised participants, the primary analysis will be repeated using multiple imputation for missing data. Full details regarding the handling of missing data, including sensitivity analyses to explore the robustness of the results to departures from the MAR assumption, will be specified in the SAP.

The main analysis for each secondary outcome will be for participants with available outcome data.

#### 14.5. Planned Interim Analysis

No formal interim analyses are planned.

#### 14.6. Planned Subgroup Analyses

Pre-specified subgroup analyses will investigate the consistency of the treatment effect using the statistical test of interaction for the following factors: gestational age at birth (for preterm

population), age at randomisation (for term-born population) and setting (inpatient vs outpatient for both populations).

#### 14.7. Planned Sensitivity Analyses

Further details of sensitivity analysis in addition to those specified in 14.4 will be detailed in the SAP.

#### 14.8. Planned Exploratory Analyses

We will explore heterogeneity between sites in the effect of the intervention through the addition of a random effect for site and treatment in the mixed model.

We will also consider doing an exploratory subgroup analysis on 'infant feeding at trial entry' if numbers of infants exclusively breast or bottle feeding at randomisation are sufficient.

### 15. Economic evaluation

#### 15.1. Aim

A within trial cost-utility analysis will be undertaken to estimate the cost effectiveness of pharmacological treatment with omeprazole compared to standard care (where the cost of placebo medication is excluded) for the two patient populations, preterm and term-born infants with reflux, separately from an NHS perspective.

#### 15.2. Resource use measurement

The intervention resource use and that related to side effects will be collected via case report forms. Relevant NHS resource use data (primary care visits, secondary care outpatient appointments and inpatient admissions, emergency visits and medications) related to GOR will be collected using online or paper-based participant resource use (PRU) logs with the main parent/caregiver at baseline, 4-weeks and 6-months. The costs to families of GOR will also be captured in the PRU logs. Published unit costs in UK sterling for the most recent price year at time of analysis will be used to value resource use. Mean (SD) cost and the mean difference (95% CI) in costs between the omeprazole and standard care groups in the two populations separately will be estimated.

#### 15.3. Outcome measurement

Preference-based infant quality of life will be measured using the Infant health-related Quality of life Instrument (IQI)[32-34] at baseline, 4-weeks, and 6-months. This can be completed by parent/caregiver online or on paper and will be valued using the UK value set [34]. Quality-Adjusted Life Years (QALYs) will be estimated using linear interpolation and area under the curve with baseline adjustment. Health-related quality of life for the main parent/caregiver will also be elicited using EQ-5D-5L and reported separately. Mean (SD) QALYs and the mean difference (95% CI) in QALYs between the omeprazole and standard care groups in the two populations will be estimated and presented separately.

**Table 11: Health Economic outcomes**

| Health Economic Outcomes                                                                     | Timing                                            | Source                                                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intervention resource use and that related to side effects                                   | During the 6 months from randomisation            | Case report forms                                                                                                                                                                                                    |
| Healthcare use (primary care visits, secondary care visits, emergency visits and medication) | Baseline, 4-weeks and 6-months from randomisation | Parent or caregiver reported questionnaire completed online <sup>1</sup><br>Case note review and Case Report Form completion where appropriate <sup>2</sup>                                                          |
| Personal costs and time off work incurred by the family as a result of GOR                   | Baseline, 4 weeks and 6 months from randomisation | Parent or caregiver reported questionnaire completed online <sup>1</sup>                                                                                                                                             |
| Health-related Quality of life                                                               | Baseline, 4 weeks and 6 months from randomisation | Infant Health-related Quality of Life Instrument (IQI, a Parent proxy reported questionnaire) and<br>EQ-5D-5L (European Quality of life 5-Dimensional 5 level)<br>Questionnaire for self-completion of parental HRQL |

1 – a paper version will be provided if needed

2 – where there is partial or complete missing data from the parent or caregiver reported questionnaire

#### 15.4. Health economic evaluation

There has been little research on the economic impacts of GOR in infants and children, such that the evidence informing the NICE guidance on this topic [NG1] was unable to undertake any health economic evaluations using the NICE reference case [5]. This trial will therefore provide results that can feed into a revision of NICE guidance on this topic.

A detailed health economic analysis plan will be written and reviewed by the Trial Steering Committee. In brief, in each population, if the intervention is effective, a within-trial economic evaluation (6-month time horizon) will be undertaken using a cost-utility approach to estimate the cost-effectiveness of pharmacological treatment with omeprazole for 4 weeks compared to standard care (where the costs of the placebo are excluded) from an NHS-perspective, with a family perspective presented separately. This will utilise the resource use and outcome data specified in sections 15.2 and 15.3.

A regression-based approach including all infants on an intention to treat basis will be undertaken controlling for baseline and minimisation variables. If there is missing data, the pattern and nature of any missingness will be analysed to inform the appropriate method of handling missing data. Guidelines of best practice will be followed to decide on the imputation procedure [35, 36]. Sensitivity analyses to explore any assumptions or uncertainties will be undertaken, for instance this analysis could explore the impact of compliance on cost-effectiveness. [35, 36] Subgroup analyses

will be undertaken where results from the clinical analysis find important differences for the sub-groups specified in the SAP, this might include gestational age at birth (for preterm-born population), age at randomisation (for term-born population) and setting (inpatient vs outpatient for both populations). If there is sufficient variation in the number of infants breast vs bottle feeding at the start of the trial, then this may also be a subgroup analysis. If the intervention is not found to be clinically effective in either population then an incremental analysis will not be undertaken as it is unlikely that Omeprazole would be recommended for infants. In this case data on resource use, costs and outcomes would be reported using descriptive analysis.

## 16. Qualitative Process Evaluation

A qualitative process evaluation will be conducted by the qualitative research team at the University of Southampton, in line with MRC guidance to evaluate how the intervention was delivered, and to explore potential influences of behavioural and contextual factors on trial delivery and outcomes [37]. Qualitative interviews will provide insight into experiences of being in the trial, including acceptability of randomisation, acceptability and experiences of treatments, and adherence to protocol. An experienced qualitative researcher will recruit participants, conduct and analyse semi-structured interviews. We estimate interviewing 25–30 parents/caregivers taking part in the trial (up to 15 parents/caregivers of preterm infants and up to 15 parents/caregivers term-born infants) and 25–30 health professionals involved in trial delivery, but will remain flexible in terms of exact sample size to allow the topics to be adequately explored. It is possible that we may recruit as few as 20 HCPs and as many as 40 parents/caregivers depending on data saturation. Participants will be purposively sampled to ensure a range of demographics (gender, ethnicity, socioeconomic status, health professional role), recruitment site and treatment allocation and adherence.

Participants will be identified and invited via their participation in the trial. As part of the trial consent process all participants signing up will be asked if they are willing to be recontacted about later participation in a qualitative interview. Potential participants will then be contacted by phone, text message or email with further information about the interview study and the opportunity to ask questions. They will then be asked to give informed consent online prior to the interview, or if they do not manage to complete online consent but attend for an interview then verbal consent will be recorded at the start of the interview. Participants will be free to withdraw at any time by contacting the research team.

Interviews will be conducted via telephone or video call, and participants will be given a gift voucher for their time. Interviews will be recorded and transcribed verbatim. Interview recordings will be stored on a secure laptop and deleted once the interview has been transcribed, anonymised and transcripts have been checked. Anonymised transcripts will then be analysed using reflexive Thematic Analysis [38].

Process evaluation interviews will start during the internal pilot phase in order to inform the stop-go decision if needed, and will continue throughout the trial. Findings will be used to inform implementation of trial results.

## 17. Patient and Public involvement

Patient and public involvement (PPI) is critical to the development of the trial, and the views of parents/caregivers with experience of GOR across different settings have been included from the outset of the trial design and will continue through to the reporting of the trial results.

### 17.1. Design

The research question, trial design, selection of outcome measures, and overall feasibility have been shaped through early and ongoing engagement with parents who have lived experience of GOR in infants. The trial team includes two PPI co-applicants and their contributions, along with those of a wider group of parents, have led to meaningful refinements of the trial protocol.

PPI members will also shape the qualitative process evaluation, including contributing to the design of the interview topic guide and interpretation of parent feedback.

### 17.2. Conduct

Both PPI co-applicants will be active members of the Trial Management Group (TMG), contributing equally alongside clinical and academic colleagues. A broader Patient Advisory Group (PAG) including mothers, fathers and caregivers from a diverse population will meet quarterly to review progress and advise on trial delivery. This group will provide feedback on participant materials, monitor recruitment and retention (particularly in underserved groups and across care settings), and support family engagement through parent-to-parent communication tools, including short videos.

Two additional parents (one with experience of a preterm infant and one with a term infant with GOR) will be recruited to the independent Trial Steering Committee (TSC).

Broader engagement will also be sought through social media, including the “Bump2Baby Parents’ Voices” closed Facebook group.

### 17.3. Reporting

The PPI group will play a central role in shaping the dissemination strategy, with a particular focus on communicating results to families affected by infant GOR. This will include input into Plain English summaries, digital and print materials, and communication plans tailored to parent communities.

PPI contributions will be clearly acknowledged in all reporting and dissemination activities. PPI members will be invited to co-author relevant publications, posters and other trial outputs and will be named where appropriate. Their involvement will be reported using the GRIPP2 (Guidance for Reporting Involvement of Patients and the Public) framework to ensure transparency and consistency.

## 18. Trial organisational structure

The roles and responsibilities for each organisation are documented in the Contractual Agreement and the specific responsibilities of the (Sponsor/CI/NCTU) are detailed in the Delegation of Responsibilities (DoR).

### 18.1. Sponsor

The Sponsor is University Hospital Southampton NHS Foundation Trust (UHS), which is the organisation that is taking legal responsibility for the trial.

### 18.2. Clinical Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU). The role and responsibilities of NCTU are outlined in the DoR.

### 18.3. Trial Management Group

The Trial Management Group (TMG) will include those individuals responsible for the day-to-day management of the trial, such as the CI, NCTU lead, Statistician, Trial Manager, Data Manager, with other members of the trial team attending as required. The role of the group is to: (i) ensure high quality trial conduct to time and within budget, (ii) to monitor all aspects of the conduct and progress of the trial, (iii) ensure that the protocol is adhered to, and (iv) take appropriate action to safeguard parents/caregivers and their infants and the quality of the trial itself. The TMG will report to the Independent Trial Steering Committee.

### 18.4. Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide overall oversight for the trial on behalf of the Sponsor and Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The TSC will monitor trial progress and conduct. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent, and ultimately carries the responsibility for deciding whether a trial needs to be modified or stopped on grounds of safety or efficacy.

The TSC includes members who are independent of the Investigators, their employing organisations, funder and Sponsor. The TSC will operate in accordance with a trial specific charter. It will meet annually at a minimum, but more frequently as requested by the committee, dependent on trial activity or phase.

### 18.5. Data Monitoring Committee

The role of the Data Monitoring Committee (DMC) is to monitor unblinded trial data and make recommendations to the TSC on whether there are any ethical or safety reasons which might require recommending ceasing recruitment into one or both of the trial populations, or aspects of the trial design be amended. This is to safeguard the interest of the parents/caregivers and their infants, investigators and Sponsor. Members of the Data Monitoring Committee (DMC) should be independent of the trial (i.e., should not be involved with the trial in any other way or have any competing interest that could impact on the trial).

Reports will be supplied in confidence to an independent DMC, which will be tasked with giving advice on whether the accumulated data from the trial, together with the results from other emerging research, justifies the continuing recruitment of parents/caregivers and their infants. The DMC will operate in accordance with a trial specific charter based upon the template created by the DAMOCLES Group [39]. The DMC will meet annually at a minimum but more frequently as requested by the committee, dependent on trial activity or phase.

## 18.6. Finance

The National Institute for Health and Care Research (NIHR) (funder reference number NIHR165206) funds this trial. No other funding has been secured for the trial.

## 18.7. Participant gratitude and stipends

Parents/caregivers of recruited infants will not receive payment to participate in the OTTER trial. Parents/caregivers will be receive a £20 shopping voucher with their 4 week questionnaire, as a token of our appreciation, to recognise their time and commitment to the outcome of the trial. Parents/caregivers and healthcare staff who are selected to participate in the process evaluation interviews will be offered a £20 shopping voucher as a token of appreciation for taking part.

## 19. Ethical considerations

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body, Health Research Authority (HRA), main research ethics committee (REC) and that local permission has been obtained prior to any infant recruitment.

All substantial modifications and non-substantial modifications (as determined by the sponsor) will not be implemented until HRA/REC have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial modifications and non-substantial modifications. Relevant approvals must be obtained before any substantial modifications and non-substantial modifications may be implemented at sites.

All correspondence with the HRA and the REC will be retained in the Trial Master File and the Investigator Site File (maintained by the site).

Within 90 days after the end of the trial (as defined in section 13), the NCTU will ensure that the HRA and the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The NCTU will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 12 months after the end of the trial.

All results will be published on a publicly accessible database.

The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

## 20. Confidentiality and data protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participating infants will always be identified using only their unique trial identification number, on the Case Report Form and correspondence between the Trials Office and the participating site. Parents/caregivers will give their explicit consent for the movement of their consent form, giving permission for the Trials Office to be shared a copy within REDCap. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to NCTU (e.g., Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that parent/caregiver and their infant confidentiality is protected.

NCTU will maintain the confidentiality of all parent/caregiver and participating infant's data and will not disclose information by which they may be identified to any third party other than those directly involved in the treatment of the infant and organisations for which the parent/caregiver has given explicit consent for data transfer (e.g., Registries, laboratory staff, competent authority, Sponsor). Representatives of the OTTER trial, NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

## 21. Insurance and indemnity

University Hospital Southampton NHS Foundation Trust will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS Trusts taking part, NCTU, Sharp clinical services, IPS pharma and Esendex.

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

The sponsor is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

## 22. Publication policy

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the CI and the members of the TMG, and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the Chief Investigator in a timely fashion and in advance of

being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the sponsor, NCTU, TSC, DMC and the Parent and public involvement (PPI) group.

During the trial, press releases may be issued by the Sponsor or NCTU. Presentations or other material prepared by local investigators to publicise the trial must be reviewed by the CI or delegate and NCTU. No party will be entitled to submit any publicity material without prior approval of the NCTU.

Trial results presented in a plain English summary will be shared with parents of randomised infants and members of the public. Results will be presented in different media (e.g., infographics or videos) and translated into the top 5 languages included in the trial to improve accessibility of the findings. The findings will be disseminated among people via our PPI groups, the trial website, sponsor and NCTU websites and social media.

A results presentation meeting for stakeholders (including sites and parents/caregivers of recruited infants) will be held prior to publication of results.

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