AmiTriptyline for the prevention of post-HErpetic NeuralgiA (ATHENA): multi-centre, individually randomised, pragmatic, placebo-controlled superiority trial with internal pilot, health economic analysis, study within a trial and nested qualitative study.

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This protocol has regard for the HRA guidance

FUNDED BY

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Contents

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BTC	Bristol Trials Collaboration
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
EC	European Commission
EU	European Union
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MHRA	Medicines and Healthcare Products Regulatory Agency
NIHR CRN	National Institute of Health Research Clinical Research Networks
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PDG	Portfolio Development Group
PIB	Participant Information Booklet
PPI	Patient and Public Involvement
QALY	Quality Adjusted Life Years
RCT	Randomised Control Trial
RDSF	Research Data Facility Storage
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics

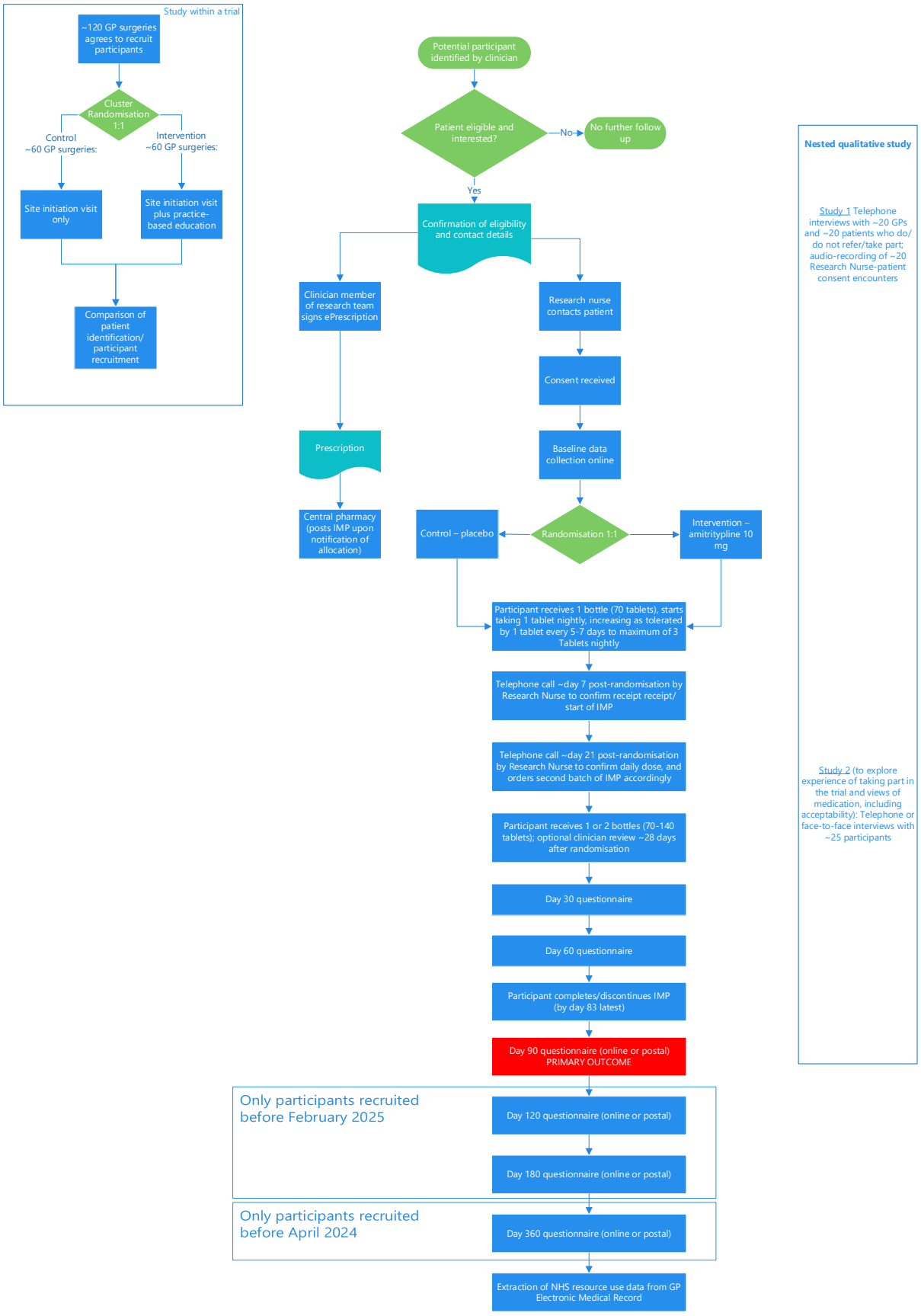
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	Amitrityline for the prevention of post-herpetic neuralgia
Short title	ATHENA
Chief Investigator	Professor Matthew Ridd
Sponsor	University of Bristol
Funder	NIHR Health Technology Assessment
Trial Design	Multi-centre, individually randomised, pragmatic, placebo-controlled superiority trial with internal pilot, health economic analysis, study within a trial and nested qualitative study.
Trial Participants	Adults ≥50 years, with a clinical diagnosis of herpes zoster presenting <144 hours of rash onset
Sample size	Minimum of 846
Number of study sites	~120
Intervention	Amitriptyline 10 mg (or matched placebo tablet), increasing in 10 mg steps over two weeks as tolerated, to 30mg maximum.
Treatment duration	≤70 days
Inclusion criteria	Adults ≥50 years, with a clinical diagnosis of herpes zoster, rash onset <144 hours, and immunocompetent
Exclusion criteria	Inability to give informed consent; known adverse reaction to amitriptyline or contraindications (monoamine oxidase inhibitors, current/recent (within previous two weeks) use of a tricyclic antidepressant, prolonged Q-T interval or concomitant drugs that prolong the QT interval, suicidal ideation, heart block, recent myocardial infarction, significant bradycardia, uncompensated heart failure, hyperthyroidism, severe liver disease, phaeochromocytoma or urinary retention. If female, pregnant or planning pregnancy in the next 3 months.
Primary objective	To compare the clinical effectiveness of low dose amitriptyline to placebo for the prevention of PHN at 90 days (primary outcome)
Primary outcome	Presence/absence of post-herpetic neuralgia at 90 days after rash onset

Secondary objectives	• To assess the safety, tolerability and acceptability of amitriptyline used for prevention of PHN • To compare shorter (<90 days) and longer-term (up to 12 months) outcomes of pain, quality of life and mental well-being (depression/anxiety) • To evaluate the cost effectiveness of low dose amitriptyline to placebo for the prevention of PHN at 90 days • To compare use of healthcare resources and analgesics
Internal pilot	Aim: To have recruited 225 patients across all centres by month nine of participant recruitment.
Nested qualitative study	Over two sub-studies, we will interview ~20 GPs and ~50 participants and audio-record a sample of recruitment conversations. Phase one will support and optimise the delivery of the trial with a focus on identifying modifiable barriers to recruitment. Phase two will seek to understand acceptability of the intervention and factors impacting retention, to aid interpretation, dissemination and implementation of the quantitative findings. Data will be audio-recorded, transcribed and analysed thematically, using both inductive and deductive coding
Study within a trial	Objective: To assess the effectiveness of a GP surgery-based education programme about shingles on participant recruitment Design: Cluster (GP surgery level) randomised controlled trial. Participants: Patient-facing staff at participating GP surgeries Intervention: "Whole practice" educational materials Outcome: Proportion of patients with shingles seen within 72 hours of onset of rash. Duration: First six months of participant recruitment.
Study duration	Funding start date: 1 July 2021 Study duration: 55 months (total) Study end date: 31 January 2026

TRIAL FLOWCHART



1. BACKGROUND AND RATIONALE

Herpes zoster (HZ) or "shingles" is characterized by a painful, blistering dermatomal rash, and is caused by reactivation of the varicella-zoster virus within a dorsal root, or cranial, sensory ganglion. The estimated lifetime risk of HZ in the general population is approximately 30%. Incidence rises with age, with estimates increasing from ~7/1000 per year at age 50 years increasing to ~10/1000 per year after 80 years of age.[1]

The diagnosis of HZ is usually made in general practice on clinical signs and symptoms alone. The typical clinical presentation is of a maculopapular rash that develops into vesicles with a unilateral dermatomal distribution accompanied by pain +/- allodynia (pain in response to a normally innocuous stimulus). Common prodromal symptoms (typically beginning several days before rash onset) include dermatomal pain, paraesthesia or dysaesthesia, itching, malaise, headache, and fever.[2]

Post-herpetic neuralgia (PHN) is the most common complication of HZ, where the pain is a direct consequence of the peripheral-nerve damage caused by virus reactivation in the ganglion.[2] This neuropathic pain is enduring and has a detrimental impact on the quality of life of affected patients.[3]

The incidence and prevalence of PHN varies with age and comorbidities. The risk of PHN is increased by prodromal pain, acute pain severity, rash severity, increasing age and ophthalmic involvement.[4] Researchers have used different durations of persistent pain (persisting for 30, 90 or 180 days) and severity of pain (clinically meaningful pain or any pain) to define PHN.[5] Consequently, the incidence of PHN in studies varies significantly, from 5-30%.[5]

1.1. Evidence explaining why this research is needed now

Existing treatments for PHN have poor efficacy leading to pain that can last unabated for years-to-decades.[6] Although HZ vaccination programmes have been shown to reduce the incidence of PHN, in the UK they are currently used only in the 70-79 year age group. The early administration of antivirals reduces the acute pain of HZ but has never been shown to reduce the incidence of PHN.[7] Other attempts to prevent PHN using either systemic or epidural steroid injections or administration of gabapentinoids have proved ineffective.[8 9]

There is a biological rationale for the use of amitriptyline early in HZ to reduce PHN, through its potential binding to nerve growth factor receptors to prevent nerve damage.[10] Bowsher[11] reported that amitriptyline 25 mg given to patients diagnosed within 48 hours of rash onset reduced the prevalence of PHN by 45% at 3 months. However, while conducted in primary care, this study was small (80 patients), methodologically limited, poorly reported and has never been repeated.

2. AIMS AND OBJECTIVES

2.1. Aim

To determine the clinical and cost effectiveness of prophylactic low-dose amitriptyline for the prevention of post-herpetic neuralgia (PHN) in patients diagnosed with herpes zoster (HZ).

2.2. Primary objective

To compare the clinical effectiveness of low dose amitriptyline to placebo for the prevention of PHN at 90 days (primary outcome)

2.3. Secondary objectives

- To assess the safety, tolerability and acceptability of amitriptyline used for prevention of PHN
- To assess masking
- To compare shorter (<90 days) and longer-term (up to 12 months) outcomes of pain, quality of life, mental well-being and frailty
- To evaluate the cost effectiveness of low dose amitriptyline to placebo for the prevention of PHN at 90 days
- To compare use of health care resources and analgesics

2.4. Primary outcome

Presence/absence of PHN at 90 days after rash onset, using a cut-off of ≥3/10 on numerical rating scale worst pain in last 24 hours.[12]

- The presence of significant pain (≥3/10) in the affected dermatome from 90 days following HZ rash onset is the most commonly used definition of PHN.[4]
- The ZBPI has good reliability and validity[23] and as recommended by IMMPACT,[13] measures the severity of current, least, worst and average pain and discomfort within the past 24 hours.

2.5. Secondary outcomes

Secondary outcomes and their associated objectives are listed in Table 1.

Table 1: Secondary outcomes

Objective	Measure	Source
To assess the safety, tolerability and acceptability of amitriptyline	Side-effects and adverse events	● Participant-completed medication use and problems questionnaire ● Hospitalisation section of participant questionnaire or by direct report by participant or clinician
	Nested qualitative study	Interviews with ~30 participants
To assess masking of participants	Bang Blinding index[14]	Participant-reported assessment of whether taking amitriptyline or placebo
To compare shorter and longer-term outcomes of pain, quality of life, mental well-being and frailty	Average and least pain in last 24 hours, and current pain	Relevant pain questions of ZBPI[12]
	Shingles pain interference with activity, mood, walking, work, relationships, sleep and enjoyment of life	Quality of life questions of ZBPI[15]
	Mental well-being	9-item Patient Health Questionnaire (PHQ9)[16] and 7-item General Anxiety Disorder (GAD7)
	Frailty	Tilburg Frailty Indicator[17]
To evaluate the cost effectiveness of low dose amitriptyline to placebo for the prevention of PHN	Quality of life	EQ-5D-5L[18]
	GP appointments, prescriptions and referrals; out-patient attendance and hospital treatment	● Participant-completed healthcare resource use questions ● GP electronic medical records
To compare use of healthcare resources and analgesics	Medication use, including trial medicine and analgesia	● Participant-completed medication and healthcare resource use questions ● GP electronic medical records

3. TRIAL DESIGN and SETTING

Multi-centre, individually randomised, pragmatic placebo controlled (participants, clinicians and research team masked to allocation) superiority trial with internal pilot, health economic analysis, study within a trial and nested qualitative study.

3.1. Clinical Trial of an Investigational Medicinal Product

As the risks to participants are no higher than that of standard medical care, ATHENA is a type A Clinical Trial of an Investigational Medicinal Product (CTIMP).

To minimise performance bias (a placebo response of 15-16% in trials of PHN has been reported),[19] we have opted for a masked, placebo-controlled two arm trial. Because of concerns about side-effects, we will adopt a pragmatic design, with participants able to up-titrate to maximum tolerated dose (10, 20 or 30 mg of amitriptyline or matched placebo nightly), as advised by members of the Patient and Patient Involvement (PPI) group.

3.2. Internal pilot

Participants will be recruited over a nine-month period and trial viability assessed against the participant recruitment. By month nine of participant recruitment, we aim to have recruited 225 patients across all centres. If we achieve ≥80 to 99% of this, we will explore any modifications to recruitment processes based on the emerging recruitment rate trajectory. If we achieve ≥50 to <80%, we will discuss with the TSC reasons for this and make appropriate changes (such as recruiting more practices). If <50%, we will review the viability of the trial with the HTA.

We will also monitor adherence, contamination and unmasking.

3.3. Study Within A Trial

We will also conduct a Study Within A Trial (SWAT) to evaluate a practice-level education package, designed to facilitate early assessment of possible shingles and recruitment into the study (see Appendix 1).

3.4. Trial setting

Primary care, UK.

4. ELIGIBILITY CRITERIA

4.1. Subject population

Adults ≥50 years with a clinical diagnosis of herpes zoster presenting <144 hours of rash onset.

4.2. Inclusion criteria

Adults ≥50 years, with a clinical diagnosis of herpes zoster, rash onset <144 hours

4.3. Exclusion criteria

There are limited data available to quantify terms such as prolonged, recent, significant or severe; so it is within the prescriber's clinical judgement

a. Third or more episode of herpes zoster
b. Known adverse reaction to amitriptyline or contraindications (monoamine oxidase inhibitors)
c. Current/recent (within previous two weeks) use of a tricyclic antidepressant
d. Known prolonged Q-T interval or concomitant drugs that prolong the QT interval
e. Suicidal ideation
f. Known heart block
g. Recent (within 4 weeks) myocardial infarction
h. Immunosuppression[a]
i. Known significant bradycardia
j. Uncompensated heart failure
k. Hyperthyroidism
l. Severe liver disease
m. Phaeochromocytoma
n. Urinary retention
o. If female, current or planned (in the next 3 months) pregnancy or breast-feeding
p. Currently (or recently, within the previous 4 months) enrolled in another CTIMP
q. Inability to provide informed consent and complete study assessments/questionnaires

[a] Immunosuppression defined as:

Due to disease or treatment, including:

- patients undergoing chemotherapy leading to immunosuppression
- patients undergoing radical radiotherapy
- recipient of solid organ, bone marrow or stem cell transplants
- HIV infection
- haematological malignancy, including leukaemia, lymphoma, and myeloma
- genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement disorder, SCID).

Individuals receiving immunosuppressive or immunomodulating biological therapy, including:

- anti-TNF, alemtuzumab, ofatumumab, rituximab
- protein kinase inhibitors or PARP inhibitors
- sparing agents such as cyclophosphamide and mycophenolate mofetil
- systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day for adults.

4.4. Operationalisation of criteria

Clinical diagnosis of HZ by clinicians is accurate, so face-to-face baseline assessment to undertake objective assessment of the rash (such as photographs or swabs) is not warranted.

4.5. Potential participants who are at higher risk of adverse effects

The following conditions are NOT exclusion criteria and no additional monitoring is required but the patient's GP should consider these aspect during the eligibility assessment process:

- Frailty
- Other drugs with antimuscarinic properties

The Patient Information Leaflet explains this to potential participants.

4.6. Co-enrolment in other research studies

If potential participants are enrolled in other clinical trials, due care will be paid as to the burdens of co-enrolment in this trial. Enrolment will be considered on a case-by-case basis taking into consideration other factors such as comorbidities, social support and distances necessary to travel. Participants taking part in another CTIMP cannot be enrolled in this trial.

4.7. Prior and concomitant therapies

Concurrent use of another tricyclic antidepressant is not permitted.

4.8. Emergency contact procedure for participants

Details of what a participant should do if they experience any problems or side effects whilst taking part in the trial is detailed in a Patient Information Leaflet.

If a participant experiences symptoms that are troublesome or serious, they are advised to seek medical help in the normal way e.g. via 111, their GP, or in an emergency phoning 999 or via an Emergency Department. The trial team will only advise a participant on action to take with respect to the IMP and will not provide any other medical advice.

Participants will be given a card to carry with them to show to any medical professionals they encounter that they are taking part in the trial and potentially taking amitriptyline. In the event of a medical emergency the participant's treating clinician can contact the central pharmacy (Eramol) who will hold the treatment allocation and will be available 24 hours per day, 7 days a week:

- Eramol Ltd, Emergency contact on-call number: 07440 551967. Eramol will check with call maker that the unblinding is necessary and for medical reason, before disclosing the allocation.

5. TRIAL PROCEDURES

5.1. Recruitment of GP surgeries

GP surgeries will be recruited via NIHR Clinical Research Networks, primarily targeting but not limited to, West of England, Wessex and Thames Valley/South Midlands.

5.2. Trial advertising

The study will be advertised via local media and with the use of flyers and posters in local pharmacies. Participating GP surgeries will display posters in waiting rooms and put information about the study on practice websites. They may also introduce the study opportunistically, e.g. by text messages and when attending for procedures such as vaccinations. These will direct potentially eligible patients to their GP, the study website, or to contact the study team directly.

The study website will contain the patient information documentation for the study and contact details. A short animation, based on the Patient summary, will also be produced. Social Media (e.g. Twitter/X) will raise awareness of the study and will be for information purposes only.

The effect of additional educational materials on participant recruitment at the practice level will be evaluated through the study within a trial (see Appendix 1).

5.3. Screening and identification of patients

Patients will be recruited via GP surgeries when they present with a new onset herpes zoster rash.

Recruiting patients with incident, as opposed to prevalent, conditions into a clinical trial in primary care is challenging. We will support the practices in identifying and referring potential participants by:

- installing electronic medical record "pop ups" that appear when patients with shingles who are 50 years or over are seen. They will remind clinicians about the eligibility criteria and prompt the clinician to ask their patient about the study; and/or
- asking practices to run regular (twice or thrice weekly) electronic medical record searches for potentially eligible patients. Anyone not already invited can then be introduced to the study.

We will adopt a "deferred recruitment" approach, [20] which is a two-step process, distinct from delayed consent. The clinician's role will be to introduce the study, confirm interest and eligibility and pass on the patient's contact details to the research team.

Clinicians who are able to screen and refer patients into the study are "first contact" health care professionals who diagnose shingles and prescribe amitriptyline to patients as part of their normal practice. This includes, but is not limited to, GPs, Advanced Nurse Practitioners, and Clinical Pharmacists.

The number of potentially eligible patients seen and reasons for referral/non-referral will be monitored and feedback to participating GP surgeries on a regular basis.

5.4. Consent

On receiving the referral from the GP surgery, potential participants will be sent a Participant Information Leaflet (available by email, the study website or post, as suits individual patient) and given time to read it. A trained research nurse (or clinical studies officer, hereafter referred to as research nurse) will then speak with the patient, confirm understanding about the study and answer any questions, before receiving informed consent.

We will use a mixed research nurse model, whereby the trained research nurse can be employed by one of the partner universities or working for the CRN. Interested, and eligible patients will be contacted by telephone (or video call, according to patient preference) as soon as possible after receipt of the referral. Any video calls will be conducted using a platform approved for this purpose by University of Bristol, Information Governance.

We anticipate that most patients will be willing and able to give consent online (e-consent).[21] "E-consent" will maximise recruitment efficiency, reduce travel-associated costs and carbon footprint. In cases where

participants do not have access to email, but are happy to consent remotely, postal paper consent will be offered. A copy of the consent form will be posted with the participant information leaflet and a freepost envelope, and will be completed by the participant and returned to the research team to countersign. The participant will then be sent a copy of the fully signed form for their records. In both types of remote consent, research nurses will be available by telephone/video call to provide any additional trial information and answer queries from potential participants to ensure fully informed consent.

A face-to-face consent appointment will be offered where possible when requested.

Consent for integrated qualitative research is discussed separately in section 13.2.

5.5. Prescription of IMP

The delegated prescriber will be a clinician on the research team. After reviewing the eligibility criteria on the GP screening form to satisfy that they have been met, they will prescribe study medication using a study-specific prescription to initiate the study medication dispensing process.

Alternatively, if the prescriber believes that eligibility criteria has not been met and that prescriptions cannot commence, the researcher will notify the individual that it is not suitable for them to take part in the trial and update records, as required.

5.6. Randomisation

Participants will only be randomised after eligibility, consent and the acceptability to prescribe have been confirmed. Trial participants will be allocated in a 1:1 ratio to receive amitriptyline (intervention) or placebo (control). Randomisation will be stratified by recruiting centre and minimised on age deciles (50-59, 60-69, etc), gender at birth (male or female), pain (cut off ≥3 on numerical rating scale average pain in last 24 hours) and shingles vaccination history (Yes or No/Don't Know as binary).

The randomisation sequence will be generated by the company Sealed Envelope™ using their online randomisation system,[22] which will allocate the participant to a treatment pack. The person undertaking the randomisation and the participant will remain masked as to which treatment group this code refers.

The study research nurse (or authorised delegate) will sign into the secure online randomisation system, enter the individual's (patient's) unique study identifier and necessary minimisation variables; they will then receive the code that allocates the participant to the study treatment, and this code will be recorded on the study-specific prescription.

The trial pharmacy will be directly informed of the randomisation code. The unblinded randomisation code will be held by the study pharmacy and selected members of the Bristol Randomised Trials Collaboration (BRTC)

The participant's GP will be informed that they are taking part in the ATHENA study, and a request will be made that their patient's participation is noted on their electronic medical record and that they may be taking amitriptyline during the intervention period.

5.7. Dispensing timepoints

At the time of randomisation participants will be sent one bottle of IMP (70 tablets of either amitriptyline, intervention, or placebo, control), and depending on tolerability up to two further bottles (of 70 tablets each) will be sent after three weeks of being randomised. The number of bottles sent will depend on the dose the participant has reached during the initial titration phase (see section 6.9)

5.8. Schedule of assessments

Table 2 specifies what outcomes are collected when. All days are counted from date of rash onset, except for research team contact at days 7 and 21 post-randomisation.

Participants will be asked to complete questionnaires (online or paper, according to preference) at baseline, 30, 60, and 90days, with text, email or telephone reminders. Participants recruited before April 2024 will also be sent a questionnaire at 120, 180 and 360 days. Participants recruited between 1st April 2024 and 31st January 2025 will also be sent a questionnaire at 120 and 180 days.

Participants will be contacted by the Research Nurse around 7 and 21 days post-randomisation for data on medication use and adverse events, and if necessary at day 90 for the primary outcome.

Completion of core data over the telephone or by videocall will be offered if necessary. With permission, we will extract data from the patient electronic medical records at 12 months (or 6 months for those recruited after March 2024 and 3 months for those recruited on or after 1st February 2025) for data on use of healthcare resources.

Table 2: Schedule of assessments

	Days after rash onset									
Outcome	B	R+7	R+21	30	60	90	120*	180*	360†	> 364
Demographics	●									
ZBPI	●			●	●	●	●	●	●	
EQ-5D-5L	●					●		●	●	
PHQ-9	●					●		●	●	
GAD-7	●					●		●	●	
Tilburg Frailty Indicator	●					●		●	●	
Medication use		●	●	●	●	●				
Adverse events		●	●	●	●	●	●	●	●	
Bang Blinding index				●	●	●				
NHS resource use						●		●	●	
EMR review										●

B = baseline; R = randomisation; † Only participants recruited before April 2024,* Only participants recruited before February 2025.

5.9. Masking and unmasking

The central research team, investigator site staff and participants will be masked to the allocation of treatment group, except for the Junior Trial Statistician and dispensing pharmacists.

Treatment codes will only be released to the investigative team once written confirmation has been received that the trial database has been locked. The central pharmacy will then send a list of all participants and their treatment allocation. Participants and their GPs will be informed of their allocation at the time of publication of the study's findings.

5.10. Emergency unmasking

The safety profile of the IMP is well established, therefore emergency unmasking should not be expected unless clear clinical need or other emergency dictates this. In this event, the participant's treating clinician will contact the central pharmacy (Eramol) who will provide a 24-hours unmasking service. Contact details for emergency unmasking will be on the Participant's information leaflet and card. Sites will follow the trial specific instructions for unmasking.

5.11. Discontinuation of study treatment

Participants can choose to discontinue study medication at any time. If a participant wishes to discontinue from taking study medication (receiving the allocated trial treatment), efforts will be made to continue to

obtain follow up data and they may also be invited to participate in interviews as part of the qualitative sub study.

Following discontinuation of IMP subsequent patient care will be decided by their GP according to usual practice.

5.12. Withdrawal from the trial

Participants can choose to withdraw for any reason at any time during their involvement in the trial. The Chief or Principal Investigators can also decide to withdraw participants based on clinical opinion at any time during the trial. Although it is the participant's right to withdrawal without giving a reason, it is a Good Clinical Practice requirement that a reason be sought and recorded if given. Participants may be asked to be interviewed as part of the nested qualitative study (see 13 NESTED QUALITATIVE STUDY).

In the event of any form of withdrawal and unless participants indicate otherwise, data obtained up to this point will be retained for analysis, as advised in the Patient information leaflet. We would also like to have the option to collect data from their electronic records, in the future, unless they request otherwise.

Following withdrawal from the study patient care will be decided by their GP according to usual practice.

5.13. Participant payments and communication

In recompense for their time and as a thank you, participants will be offered a £10 voucher and a modest study aide memoire (e.g. fridge magnet) at baseline; and a £10 voucher at 90 days and after their last questionnaire (180 or 360 days). Participants recruited on or after 1st February 2025 will be offered a £10 voucher and a modest study aide memoire (e.g. fridge magnet) at baseline and a £10 voucher at 90 days.

Participants will be sent a newsletter (around three times a year) with updates about the study progress and, at the end, a summary of the trial findings.

5.14. End of Trial

Participants end their involvement with the trial when their last follow up questionnaire is completed (or efforts to obtain final questionnaire have been unsuccessful), or they have withdrawn from the study

The end of trial will be when the last patient has completed their last follow-up questionnaire, data extracted from the medical records, all data queries have been resolved and the database has been locked, with subsequent data analysis completed.

5.15. Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator (CI), Regulatory Authority or Funder based on new safety information or for other reasons given by the Data Monitoring Committee (DMC)/Trial Steering Committee (TSC), regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder. If the trial is prematurely discontinued, no new participants will be recruited, and a decision on data collection on active participants will be made in discussion with the TSC/DMC and Sponsor.

6. INTERVENTION/IMP

6.1. General information

Within the trial, the following are classed are as IMPs:

- Amitriptyline: one tablet contains 10mg of amitriptyline
- Placebo: formulated and manufactured according to a standard placebo composition to match the appearance (shape, dimension, colour and taste) of the active tablet.

All participants will be offered antiviral medication (usually, aciclovir 800 mg five times a day for seven days, or locally recommended equivalent/alternative if there are any contraindications to aciclovir) by their clinician, as per usual clinical practice.

6.2. Amitriptyline

Amitriptyline is a tricyclic antidepressant and an analgesic, with anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation, of noradrenaline and serotonin at nerve terminals. Preventing reuptake of these monoamine neurotransmitters potentiates their actions in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium, and N-methyl-D-aspartate (NMDA) channels at both central and spinal cord level. The noradrenaline, sodium, and NMDA effects are mechanisms known to be involved in the treatment of neuropathic pain, chronic tension type headache prophylaxis, and migraine prophylaxis. The pain-reducing effect of amitriptyline is therefore not linked to its anti-depressive properties. TCAs also possess affinity for muscarinic and histamine-1 receptors to varying degrees, which are associated with their side effect profile.

Amitriptyline is licensed for the treatment of depression (dosages in the range of 150 mg to 200 mg) and has been widely used for this purpose since the 1960s. However, tricyclic antidepressants have since been replaced by selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors as first line treatments for depression. Nowadays, amitriptyline is most prescribed at low doses (10mg to 30mg) to treat pain and insomnia.[23-25]

The biological rationale for the use of amitriptyline early in HZ to reduce PHN is through its potential binding to nerve growth factor receptors to prevent nerve damage. [11 12]

6.3. Assessment and management of risk

This trial is categorised as 'Type A' according to the MHRA. Amitriptyline is licensed for the treatment of neuropathic pain and while this study seeks to establishes whether it can prevent (rather than treat) persistent neuropathic pain, the demarcation between its use in treatment and prevention current clinical practice is unclear. In addition, the ATLANTIS study (ISRCTN48075063), which is a placebo-controlled trial investigating amitriptyline at the same low doses (10-30 mg) as a second-line treatment for irritable bowel syndrome, has been classed as a type A CTIMP (when amitriptyline has an unlicensed indication for "abdominal pain or discomfort in patients who have not responded to laxatives, loperamide, or antispasmodics").

Common side effects of amitriptyline include dizziness, dry mouth, sedation, constipation, and weight gain. Side effects are more common with higher dosages. Amitriptyline is potentially lethal if taken as an overdose.

Therefore, we will screen for suicidal ideation at baseline, and people with active suicidal ideas or intent will be excluded. The very low daily dose proposed in this trial, and the sequential dispensing, means that participants will only have a very limited total amount of drug that they can access.

6.4. Manufacture of IMP

Amitriptyline 10mg tablets will be purchased by Eramol (Eramol Unit 11, Gatwick Metro Centre, Horley, RH6 9GA, UK and Unit 9, North Downs Business Park, Lime Pit Lane, Sevenoaks, TN13 2TL, UK), an MHRA-licensed wholesale distributer of human medicinal products. They will also supply a matching pressed tablet placebo, whose composition will be approved by the MHRA. This will be formulated and manufactured according to standard placebo composition to match the appearance of the active amitriptyline tablets.

6.5. Packaging, labelling, storage and shipping of IMP

Eramol, Unit 11, Gatwick Metro Centre, Horley, RH6 9GA (UK) and Unit 9, North Downs Business Park, Lime Pit Lane, Sevenoaks, TN13 2TL (UK) will package, label, store and QP release the trial IMPs, providing identical treatment bottles of amitriptyline and placebo, each containing 70 identical tablets for oral administration. To maintain the masking of the trial, the tablets and bottles will be identical and labelled with the same study-specific label. The label texts for all packaging will comply with the requirements of Annex 13 of the Rules Governing Medicinal Products in the European Union. Containers will be identified only by a unique kit code.

Eramol will perform Qualified Person (QP) release prior to IMP being ready for dispensing via their in house central pharmacy. IMP will be posted to participant's preferred address using a tracked delivery service (e.g. Royal Mail tracked).

Storage requirements will be detailed in a trial specific working instruction.

6.6. Kit allocation

Each bottle will be allocated a unique kit code during production. Management of kit codes will be conducted by the senior study statistician. Any information that could unmask members of the trial team will be stored electronically in folders accessible only to the senior statistician and authorised unmasked individuals, or physically in a locked cupboard.

6.7. Dispensing of IMP to participants

The signed trial prescription, which covers the whole of the treatment period, will be sent to the central pharmacy. Following randomisation, the dispensing pharmacy will be notified of the participant's name, trial identification number and allocation, by Sealed Envelope (randomisation system). They will pick the next bottle from the allocation list and record the kit number against the patient's ID in their records. They will dispense the trial specific supply of IMP and post it to participants, free of charge.

Initially, one bottle (70 tablet per bottle) will then be sent, which will cover approximately 28 days, including the titration period. Around three weeks post-randomisation, where required the central pharmacy will be notified to send the participant one or two further bottles for the remaining 42 days. The number of bottles sent will consider their titrated dose with a small excess, to cover wastage.

Trial IMP packs will be sent directly to the participant by tracked delivery to their home address. Alternatively, trial IMP packs will be sent to the patient's GP practice when preferred by the patient, and if acceptable to the GP practice.

6.8. Dosage and duration of IMP

Between one and three tablets will be taken daily for a maximum of 70 days, to allow for: delay between rash onset and starting medication; and a "wash out" period before collection of primary outcome at 90 days from rash onset (the half-life of amitriptyline after single dose is ~24 hours).[26] Dosage will be determined by self-titration (see 6.9 Self-titration).

6.9. Self-titration

Because of concerns raised by PPI and clinicians about side-effects deterring recruitment or affecting retention, we have adopted an escalating dose from one to three tablets nightly (amitriptyline 10mg or

matched placebo) over two weeks. This approach follows usual clinical practice and reduces the risk of participants stopping the medication or withdrawing due to side-effects.

Participants will be instructed to start their treatment as one tablet daily (usually around bedtime). Participants will be asked to increase their daily dose by one tablet every five to seven days up to a maximum dose of three tablets daily, if there are no intolerable side effects. Therefore, after two weeks participants will be taking up to three tablets daily.

After the initial two-week titration period, it is anticipated that most participants will then remain on a steady dose of study medication. We expect most participants to be able to tolerate at least one tablet daily, but participants will be allowed to reduce their dose further, to one tablet every other day, if they continue to experience troublesome side effects at one daily.

To facilitate the titration (and study processes), participants will be contacted by a member of the research team around one week after randomisation, to deal with any queries, and to provide standardised advice about dose titration. Participants will be contacted again around three weeks after randomisation to confirm the dose reached during titration.

Participants will be offered a review with their clinician at approximately one month, for safety purposes, if the research nurse or participant have any queries or concerns. Clinicians who are able to conduct safety reviews for the study are "first contact" health care professionals who diagnose shingles and prescribe amitriptyline to patients as part of their normal practice. This includes, but is not limited to, GPs, Advanced Nurse Practitioners, and Clinical Pharmacists.

6.10. Return and destruction of IMP

Participants will be asked to safely dispose of unused trial medication by returning them to a local pharmacy for destruction. Any unused IMP held by the trial pharmacy at the end of the study, will be destroyed (when authorised by the Sponsor) in line with the central pharmacy trial specific instructions on the disposal of IMP.

If the study medication bottle is lost or damaged between randomisation and the end of the participant's treatment period, the study medication will be replaced by using the kit allocation system, which will allocate new bottle(s) with new kit codes.

6.11. Common side-effects

Reference Safety Information (RSI) defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to subjects participating in a clinical trial. The RSI will be one single definitive list or document that determines which Serious Adverse Reactions (SARs) require expedited reporting to the MHRA as Suspected Unexpected Serious Adverse Reactions (SUSARs). The term 'expectedness' from a regulatory perspective (in relation to safety reports and SUSARs) means whether or not the reaction is an expected side effect of the IMP, thus establishing whether it does or does not need reporting in an expedited fashion.

Surprisingly given the length of time in use, data on the incidence of side-effects for amitriptyline is sparse, especially in relation to dose (most literature does not distinguish between use at low (10-30 mg) or high "depression treatment" (75-150 mg) doses) and age/comorbidity – the expectation being that side-effects will be more common at high dose/in older people and those taking other antimuscarinic drugs.

Common side effects include sedation, dizziness, nasal congestion, hyperhidrosis, dry mouth, constipation, weight gain and blurred vision. Amitriptyline is potentially lethal if taken as an overdose. Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic.

The RSI for this trial is section 4.8 of the Summary of Product Characteristics (Amitriptyline).

6.12. Post-trial

Continuation of the treatment following the end of the intervention phase is the responsibility of the participant's normal clinician, but can only occur after collection of the primary outcome at 90 days post-shingles rash onset.

6.13. Drug accountability

As the study is a pragmatic trial/class A CTIMP, a full reconciliation (tablet count) is unnecessary and would be difficult to undertake. Drug accountability records will be maintained throughout the course of the study by the in house-Eramol central pharmacy. Designated pharmacy staff will document the date and quantity of IMP as it is received and dispensed to study participants.

Table 3: Drug accountability activity and who is responsible

Activity	Responsibility
Supply of IMP (active and matched placebo)	Eramol
Provision and QP of IMP	Eramol
Package and labelling of IMP	Eramol
QP release IMP to trial pharmacy	Eramol
Dispense IMP in line with prescription to participant	Eramol
Maintain dispensing log	Eramol
Report stock levels at site	Eramol
Return of unused trial medicines (where applicable)	Eramol
Destruction of unused trial medicines	Eramol/Sponsor
Unblinding	Eramol

6.14. Intervention and IMP COVID-19 considerations

At time of writing, the COVID19 immunisation programme had invited everyone in the "at risk" groups for their first vaccination, and was on target to vaccinate all adults in the UK by the end of July 2021. While some "social distancing" measures may still be in place by the time the first participant is randomised, no implications from the pandemic have been identified for this study.

7. TRIAL DATA

Recognising the value of sharing trial data, and the requirement for data sharing of some journals,[27] we will observe the principles of data sharing during trial set-up, conduct and closure.[28] No later than 3 years after the completion of the study, we will deposit a completely deidentified data set in an appropriate data archive for sharing purposes.

8. PHARMACOVIGILANCE

8.1. Operational definitions

Pharmacovigilance will be carried out in accordance with the guidance set out by the European Commission Detailed Guidance CT-3 2011, and the requirements of the Medicines for Human Use (Clinical Trials) Regulations, including the terminology of adverse events and reactions and the assessment of seriousness, causality, and expectedness of an event.

Table 4: Definitions of adverse events and reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product "means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the Summary of medical Product Characteristics (SmPC). It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening[a] • requires inpatient hospitalisation or prolongation of existing hospitalisation[b] • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. [a] *"Life-threatening" in the definition of "serious" 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 which hypothetically might have caused death if it were more severe.* [b] *"Hospitalisation" is defined as an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Emergency Department would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.*

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question
Suspected serious adverse reaction (SSAR)	A suspected serious adverse reaction (SSAR), is any serious adverse reaction that is suspected (possibly or probably) to be related to the investigational medicinal product/medical device/intervention.

Table 5: Classification of Severity

Mild event:	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event:	An event that prevents normal everyday activities.

Table 6: Classification of Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

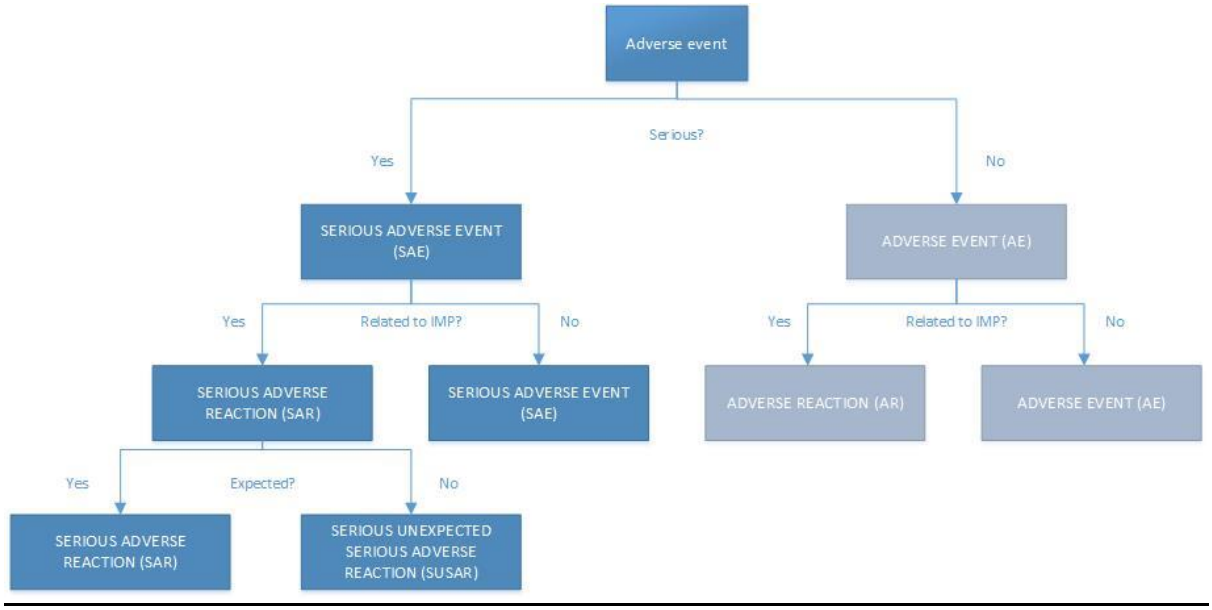
Table 7: Classification of Expectedness

Expected	Reaction previously identified and described in the Summary of medicinal Product Characteristics (SmPC).
Unexpected	Reaction not previously described in the Summary of medicinal Product Characteristics (SmPC).

8.2.Adverse events classification flowchart

For each adverse event the seriousness, relatedness and expectedness will be determined (as per the definitions above) in order to appropriately classify the episode as per figure 1.

Figure 1: Classification of adverse events flowchart



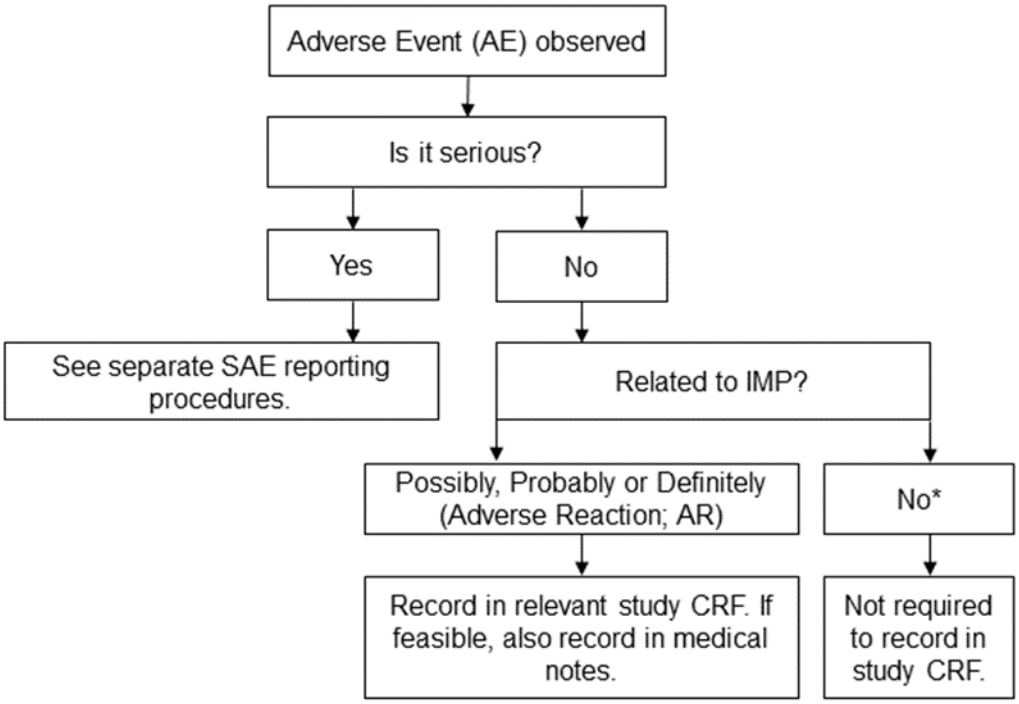
8.3.Adverse Events (AEs)

Only non-serious adverse events that are assessed as being possibly, probably or definitely related to the IMP (adverse reaction AR), will be recorded in the relevant study documentation from the time a signed and dated informed consent form is obtained until completion of the last trial-related procedure. Non-serious adverse events that are unrelated to the IMP will not be recorded (figure 2).

It is anticipated that the majority of AEs will be detected via the follow-up questionnaires. The lead centre will communicate with the local PI and site team if additional information is required e.g. determine causality. If a patient attends a routine (i.e. non-trial related appointment) and an AE is reported, the site research teams will assess and log this according to the same working instructions. AEs will be reviewed by the DMC at the next booked meeting.

The PI of each participating site (or appropriate delegate, e.g. clinician, or CI if required) is responsible for assessing and categorising AEs. For each AE the seriousness, relatedness to IMP and expectedness will be determined (as per the definitions above) in order to appropriately classify and record and report (where applicable) the episode; see also Figure 3, above.

Figure 2: Recording framework for non-serious Adverse Events (AEs).



8.4.Serious Adverse Events

The reporting framework for serious adverse events is presented in figure 2.

Local research teams will record all SAEs (SAE/SAR/SUSARs) in the ATHENA SAE Log, which should be retained in the ISF. The SAE log will be sent to UHBW on a regular basis for review, and will be sent within 24 hours in the case of an unrelated, unanticipated SAE (for SUSAR reporting see below). The central research team will review the SAE Log monthly for monitoring and reporting purposes and will prepare regular summary reports of all SAEs for discussion at relevant oversight meetings, including the DMC as per their written charter. The SAE log will have as a minimum the following details for each event:

- Event number
- Brief description of the event;
- Date (and time where known) that it started and stopped;
- Reason event was an SAE
- Classification of severity
- PI (/delegated clinician's) assessment of whether the event was related to study drug
- For events related to the study drug, an assessment of whether the event was expected (as per Reference Safety Information for IMP).
- For events not related to the study drug, an assessment of whether the event was anticipated (Refer to list of unrelated anticipated events below)
- Whether the event resulted in death
- Outcome of the event (including details about sequelae, where relevant)
- Details of any actions taken in response to the event.

Hospitalisation for an elective procedure or for a pre-existing condition (prior to study entry) which has not worsened, does not constitute a serious adverse event. All SAEs will be followed until resolution.

8.5. Expectedness of events

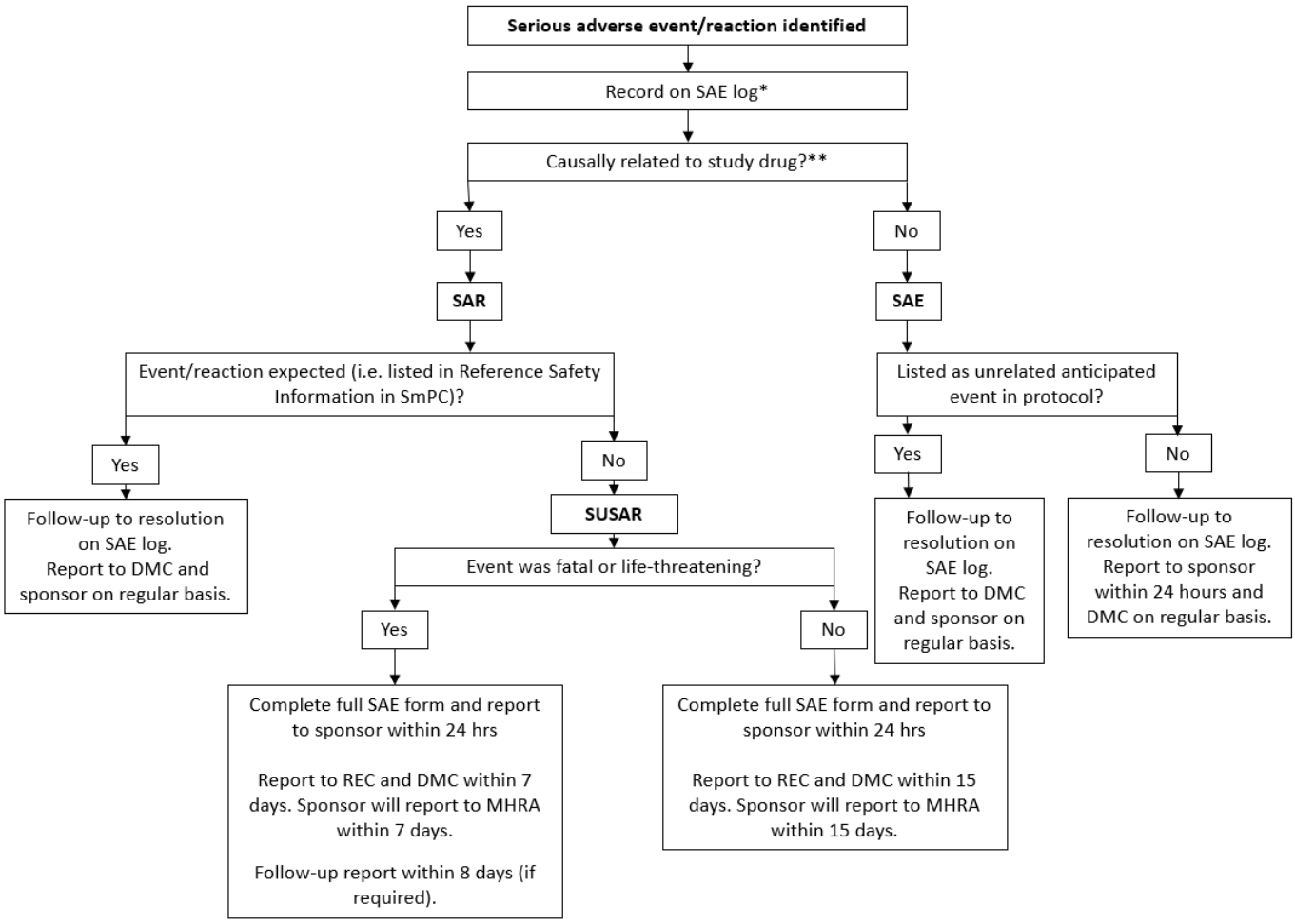
The expectedness of a serious adverse reaction shall be determined according to the current approved reference safety information (see Summary of Product Characteristics - Amitriptyline).

8.6. Anticipated Events

The following events are anticipated for this patient population. Events of this nature will be recorded in the SAE log but not immediately reported to the Sponsor, unless deemed to be related to the study drug:

- Myocardial infarction/acute coronary syndrome
- Stroke/cerebrovascular accident/TIA
- Aortic dissection
- Limb ischaemia/ arterial thrombosis
- Thromboembolic disease (DVT/PE)
- Cancer (of any type)
- Acute liver failure
- Gall bladder disease, including biliary colic and cholecystitis
- Acute renal failure/kidney disease, including renal stones
- Heart failure
- Gastrointestinal haemorrhage, including ulcers
- Gastrointestinal infection
- Dementia
- Acute confusion/delirium secondary to infection
- Exacerbation of COPD or asthma
- Respiratory tract infections, including bronchitis or pneumonia
- Acute depression, anxiety or psychosis
- Urinary tract infections
- Sepsis
- Superficial skin infections, including cellulitis
- Complications of procedures, devices or implants
- Fractures
- Trips and/or falls

Figure 3: Reporting framework for all Serious Adverse Events (SAEs)



*All SAE/SAR/SUSARs will be recorded in an SAE log

**causality should have been assessed prior to reporting to UHBW, however as part of their assessment on behalf of the Sponsor, UHBW will also review causality

8.7.Suspected Unexpected Serious Adverse Reactions (SUSARS)

A full written report to the Sponsor of all SUSARs will be notified in writing to the sponsor within 24 hours of the investigator(s) becoming aware of the event. Expedited reporting will carried out within 7 days of the initial sponsor notification to the MHRA and REC if fatal or life-threatening or 15 days otherwise.

The local research team will provide information missing from the initial report within 5-working days of the initial report to the necessary bodies. Any change of condition or other follow up information relating to a previously reported SAE will be reported on a separate trial SAE/SUSAR Follow Up Report Form. All SAEs will be followed up until the event has resolved, or a final outcome has been reached.

Occurrences meeting the definition of unexpected serious adverse event (SUSAR) will be reported using the Serious Adverse Event Form, including any SUSARS spontaneously reported to the Investigator within 30 days after the participant has completed the intervention phase of the trial. University Hospitals Bristol and Weston NHS Foundation Trust (UHBW), on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by the CI beyond the time frame specified in the protocol.

8.8. Urgent safety measures

In line with UHBW's Research Safety Reporting procedures, the Sponsor and investigator may take appropriate urgent safety measures to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (i.e. the MHRA) and ethics committee.

The first action is to protect patient safety/health. Following that, the CI/Sponsor should discuss the USM by telephone as soon as it has been put in place with an MHRA safety scientist in the first instance. This should be followed-up with written notification within 3-days to the MHRA. Notification should be in the form of a substantial amendment and describe the event, the measures taken and justification for the measures taken.

8.9. Notification of deaths

All deaths occurring during the intervention phase of the trial or within 28 days after the last dose of trial medication will be reported immediately as soon as the central research team become aware.

8.10. Safety reporting period

The Sponsor Adverse Events Reporting Policy incorporates the requirements of the Medicine for Human Use (Clinical Trials) Regulations 2004. UHBW, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. For each participant the end of safety reporting will be within 30 days of the participant having completed intervention phase.

8.11. Development Safety Update Reports (DSURs)

The sponsor will submit DSURs once a year throughout the clinical trial, or as necessary to the MHRA and where relevant the Research Ethics Committee. Trials authorised under the MHRA Notification Scheme as 'Type A', will utilise a short format DSUR. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

9. STATISTICS AND HEALTH ECONOMICS ANALYSIS

9.1. Sample size calculation

846 participants will be required to detect a clinically relevant proportionate reduction of at least 45% in PHN (present/absent) at 90 days with 90% power, assuming 20% PHN in the control group and a 20% loss to follow-up. However, because of the uncertainty in the estimates used to calculate this sample size (see Table 8) in the event that it is possible to recruit more than 846, recruitment will continue until either 900 participants are randomised or 30 April 2025, whichever happens first.

Table 8: Study power exceeding the target sample size with different prevalence of PHN and loss to follow-up

	Power		
Number recruited	Assuming PHN prevalence of 20% in the placebo group and 10% loss to follow-up	Assuming PHN prevalence of 15% in the placebo group and 10% loss to follow-up	Assuming PHN prevalence of 10% in the placebo group and 10% loss to follow-up
846	93%	83%	64%
900	93%	85%	67%

9.2. Statistical analysis

A full analysis plan will be completed and approved by the TSC prior to the end of patient recruitment.

Analysis and presentation of the trial data will be in accordance with CONSORT[29] and CONSORT PRO[30] guidelines. Baseline characteristics of patients will be compared by reporting descriptive statistics; numeric variables will be summarised using means, medians, standard deviations and ranges as appropriate and categorical variables will be summarised using frequencies and proportions. These will be used to determine whether there are meaningful differences between the treatment groups at baseline and inform any subsequent sensitivity analyses adjusting for such imbalances.

The primary statistical analyses will be conducted on an intention-to-treat (ITT) principle, analysing patients in the groups to which they were randomised. The primary analysis of effectiveness of the primary outcome will use logistic regression to estimate the odds ratio of PHN comparing the intervention and control group after adjusting for variables used in the randomisation.

Repeated measures analyses will be conducted of the secondary outcomes measured at multiple follow-up time points to examine the effect of the intervention over time. For binary outcomes these will involve logistic regression models and for continuous outcomes linear regression models will be used. Descriptive analysis of safety endpoints will be presented according to randomised group.

This is a pragmatic study, where participants can upwardly and downwardly self-titrate the dose of amitriptyline from 10 mg to 30 mg as tolerated. We will ask patients to report how regularly they are taking their prescribed tablets and these data will be described by arm. Based on the data collected we will classify individuals as “adherent” and “not adherent”, as defined in the statistical analysis plan. This will allow us to perform a Complier Average Causal Effect (CACE) analysis to investigate the efficacy of the intervention for comparison with the primary intention to treat effect estimate as well as explore if there are patient and illness characteristics associated with adherence. A per protocol analysis will also be conducted based on pre-defined criteria associated with intervention adherence.

Sensitivity analyses will assess the robustness of the primary analysis to:

- the impact of missing data on the primary analysis. The approach taken to handling missing primary outcome data will depend on the patterns and nature of the missingness.
- adjustment for variables demonstrating a marked imbalance at baseline
- adjustment for whether or not the participant was prescribed anti-viral treatment at point referral (assuming sufficient numbers of participants are/are not prescribed antivirals)

Sub-group analyses will examine whether the effect of the intervention difference according to:

- time from rash onset to starting treatment on pain outcomes
- effect of daily use and total dose of treatment on pain outcomes
- whether first or second episode of shingles on pain outcomes

Subgroup analyses will be performed by incorporating a treatment group-subgroup interaction term in the appropriate regression model. Testing will be done using the likelihood ratio test. As the study was not powered to detect subgroup effects these results will be interpreted with due caution.

9.3.Analysis of safety endpoints

We will use descriptive statistics to describe adverse events for participants who took one or more dose(s) of the drug.

9.4.Economic evaluation

The primary analysis will present both cost-effectiveness (in terms of cost per case of PHN prevented) and cost-utility analysis from an NHS/personal social services perspective at 90 days – the timepoint selected to coincide with the trial primary outcome. For the cost utility analysis, utilities will be measured by the EQ-5D-5L and valued by application of the 3L cross-walk value set unless the NICE position statement offers different guidance at the time of analysis. Secondary analysis will consider if the effect is sustained over 12 months.

Resource use data collection (from electronic medical records) will focus on relevant resource use relating to the complications of Herpes Zoster and side-effects of amitriptyline and analgesics. Information on side effects will also be identified from patients as part of the patient and public involvement activities. EMR review (carried out at 12 months (or 6 months for those recruited after March 2024 and 3 months for those recruited after January 2025) but with the data extraction and linkage approach tested within the internal pilot) will include frequency and detail relating to: GP appointments, prescriptions and referrals, out-patient attendance and hospital treatment. Further detail of the extraction and analysis will be pre-specified in the Health Economics Analysis Plan and articulated in the data specification template agreed with OneCare. Resources will be valued using nationally available sources of unit costs.

Incremental differences in both costs and quality-adjusted life years (QALYs) will be presented with cost-utility considered in terms of net benefit. Statistical methods selected shall deal with skew, baseline imbalance, missingness and sampling uncertainty as appropriate. Additionally, the construction of cost-effectiveness acceptability curves which show the probability that early prescribing of amitryptyline is the optimal choice over a range of possible values of the ceiling ratio will be constructed.

10. DATA MANAGEMENT

10.1. Source Data and documents

When a participant consents to enter the trial, they will have a unique participant identification number allocated. Personal data entered directly onto the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the EEA will be anonymised. Participants will be asked to consent to their name, date of birth, and contact details being stored on the secure database with the central research team.

Data obtained by paper will also be entered onto the password protected database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to trial staff. Information capable of identifying participants will not be removed from University of Bristol or clinical centres or made available in any form to those outside the trial, for the exception of NHS digital for linkage.

Consent forms and clinical letters with personal identifiable data will be stored separately in a locked filing cabinet. Participant details will be anonymised in any publications that result from the trial.

Source data for this trial will consist of certified scanned copies and/or paper copies of the consent form, participant completed questionnaires as well as the electronic case report forms designed specifically for the study.

10.2. Data collection

Clinical outcomes will be assessed by participant-completed questionnaires at baseline and during follow-up. Case report forms will be completed at the time of the baseline assessment and treatment phase up to 12 months. We are using standardised outcome instruments. The components and timing of follow-up measures are shown in Table 2.

The database will be set up to prompt the central research team when participant questionnaires are due.

10.3. Case Report Forms (CRFs)

Case report forms at study centres will be completed using the secure trial database. Questionnaires from participants will be identifiable only by participant trial number and will be returned by the participant by post or via electronic means to the central research team. Any paper copies will be stored in a secure locked cabinet in an access-controlled area.

10.4. Data handling and record keeping

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

For this trial, research data will be kept for at least 5 years. Personal data (e.g. name and address, or any data from which a participant might be identified) will not be kept for longer than is required for the purpose for which it has been acquired. Documents will be reviewed by the CI before being destroyed.

10.5. Access to data

For monitoring purposes, the CI will allow monitors from the sponsor (or delegate), persons responsible for the audit, representatives of the REC and other Regulatory Authorities to have direct access to source data/documents.

The Data Manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable meta-analyses (see section 15.9).

10.6. Archiving

This trial will be sponsored by the University of Bristol who are also the data custodian. All research data will be retained in a secure location during the conduct of the trial and for 5 years after the end of the trial, when all paper records will be destroyed by confidential means. An archiving plan will be developed for all trial materials in accordance with the University of Bristol archiving policy.

11. TRIAL MANAGEMENT

Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) will be established in conjunction with a Trial Management Group to provide oversight of the trial on behalf of the funder.

11.1. Trial Management Group (TMG)

The TMG will have responsibility for the day-to-day management of the trial and will report to the TSC. The TMG will meet on a regular basis with a core working group of staff having frequent progress meetings.

11.2. Trial Steering Committee (TSC)

Membership, responsibilities, and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial to the TMG and minutes will be sent to the funder. The TSC will comprise a Chairperson, Statistician, Health Economist, Qualitative Researcher and patient representative. The Chief Investigator and Lead Statistician will represent the TMG.

11.3. Data Monitoring Committee (DMC)

The Data Monitoring Committee will meet once prior to recruitment of the first participant and convene prior to the TSC meeting to review the adverse event data and any other ethical aspects that arise and report to the TSC. The DMC will comprise a Chairperson, Statistician and Clinician as independent members. The Chief Investigator and Lead Statistician (open session only) and tbc (Trial Statistician) (attending both open and closed sessions).

11.4. Patient and Public Involvement (PPI)

People with shingles will be involved in every phase of the research trial. This will involve group meetings, specific roles on the trial management group, review of the protocol, participant information, consent and data collection forms and informing dissemination of the research findings to participants.

We will observe the principles set out in the UK Standards for Public Involvement:[31]

- Use plain language for well-timed and relevant communications, including to a wider audience: For meetings involving PPI, we will try to avoid jargon and provide a glossary of definitions for commonly used terms. "PPI" will be a standing item in Trial Management Group meetings, and the meeting chair/PPI coordinator will specifically seek lay opinion on matters as they arise. Outside of meetings, we will aim to strike the right balance between keeping PPI contributors (co-applicant, TSC and group members) informed and involved, without over-burdening them. Our external communications will be targeted according to the intended audience, for example summary Plain English briefings via the study website; or brief updates on trial progress via social media.
- Value all contributions, building and sustaining relationships: The foundations for mutually respectful and productive working together has been laid in our work with PPI pre-grant. Terms of reference will be agreed during trial set-up and activities that support this will be reviewed in an on-going manner. We will also offer training opportunities, so members can build their skills and hence confidence to contribute.
- Involvement in research governance, management and decision making, identifying and sharing the difference this makes to our research: Our previous experience is that good PPI often heads-off problems and reassures the relevant regulatory authorities (Sponsor, ethics committee, etc.) about the design and acceptability of clinical trials. We will prospectively record how PPI influences decisions and actions and report these at the end, using the GRIPP2 checklist.[32]
- Communicate with a wider audience about public involvement and research, using a broad range of approaches that are accessible and appealing.

12. MONITORING, AUDIT & INSPECTION

12.1. Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All trial related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and for inspection by MHRA and other licensing bodies.

The University of Bristol holds a Service Level Agreement with University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). Under the Agreement UHBW undertakes to monitor and carry out pharmacovigilance for certain UoB sponsored studies. These activities should be carried out in accordance with the Service Level Agreement, the identified risks, subsequent proposed monitoring and the trial's specific Monitoring Plan.

A Trial Monitoring Plan will be developed by the Sponsor and agreed by the TMG and CI based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.

The sponsor usually delegates some of the monitoring to the central research team. Checks of the following would be typical:

- written informed consent has been properly documented
- data collected are consistent with adherence to the trial protocol
- CRFs are only being completed by authorised persons
- SAE recording and reporting procedures are being followed correctly
- no key data are missing
- data is valid
- of recruitment rates, withdrawals and losses to follow up.

On a regular basis we will monitor the percentage of patients that meet the eligibility criteria and report the percentage of participants who consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on adverse event and dropout rates observed in the trial population.

12.2. Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations will be documented and reported to the CI and Sponsor immediately. They will also be reported to the DMC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

Any potentially serious protocol breach will be reported to the Sponsor as soon as possible. The sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC and MHRA

12.3. Notification of Serious Breaches to GCP and/or the protocol

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

a. the safety or physical or mental integrity of the subjects of the trial; or
b. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate trial specific instructions.

13. NESTED QUALITATIVE STUDY

The aims of the nested qualitative study within ATHENA are to:

1. Support and optimise delivery of the trial with a focus on identifying modifiable barriers to recruitment during the pilot; and
2. Understand acceptability and perceived effectiveness of the intervention during the trial, to aid interpretation and implementation of the trial findings.

13.1. Phase 1: Support and optimise delivery of the trial

Qualitative work during the pilot will focus on identifying potentially modifiable barriers to recruitment (both recruiting and being recruited), along with exploring initial acceptability of the intervention. We will do this in two ways.

First, we will audio-record a sample of recruitment conversations undertaken by research nurses and other staff as part of the two-step "deferred consent" process. This will allow us to understand how the trial is introduced and explained to patients and help us to identify any areas that may be modified to improve understanding of the trial and recruitment. Given the "deferred" and "mixed research nurse model" of recruitment, we will ensure that we audio-record recruitment conversations with different types of staff that may be undertaking them with patients. Examples may include university, CRN and practice-based research nurses or GPs.

Summaries of the audio-recordings will be made by the qualitative researcher, using a pre-defined template to identify the key factors that may be hindering recruitment and how these could be modified. Findings will be fed-back to recruiting staff to enhance the recruitment process.

Second, we will conduct brief (5-20 minute) telephone interviews with up to 20 staff (GPs, Advanced Nurse Practitioners, Associate Physicians, research nurses, administrative/reception staff) who have been involved in identifying and recruiting patients, and up to 20 patients who have consented to participate, declined or withdrawn from the pilot. We will aim to conduct the patient interviews within one month of them presenting to their GP. We will use flexible topic guides, informed by relevant literature and developed in collaboration with the trial management group and public contributors. New and unanticipated topics will be added as interviews progress. In these interviews we will explore health care professional and patient understanding of the trial; factors that aid or hinder recruitment from the perspective of practice staff and patients; and initial views of acceptability of the intervention.

Interview participants will be identified by an unmasked member of the trials unit (e.g. the junior statistician), guided by sampling criteria provided by the qualitative research team. The qualitative research team will be masked to an individual participant's treatment allocation until the end of primary outcome data collection for that participant and unmasked thereafter to enable meaningful data analysis. The rest of the TMG will remain masked throughout the qualitative study, only viewing redacted transcripts or excerpts of data.

The interviews will be audio-recorded and transcribed verbatim by an approved transcription company. Analysis will be thematic, using a combination of inductive and deductive coding, led by the qualitative researcher. A sub-set of data independently coded by other members of the research team, to enhance trustworthiness of the analysis process and to contribute to theme development.

Collectively, the qualitative findings from the pilot will help us to identify modifiable barriers to recruitment and guide any necessary changes.

13.2. Phase 2: Acceptability and perceived effectiveness of the intervention

Qualitative work during the main trial will focus on the second aim, namely understanding acceptability and perceived effectiveness of the intervention, to aid interpretation and implementation of the trial findings.

We will do this by conducting semi-structured telephone interviews with up to 30 patients (to achieve sufficient information power),[34] across intervention and control arms. Including patients from the control arm will allow us to make between-group comparisons and to tease-out patients' understandings of the

trial process and the perceived impact of treatment. Patients will be purposefully sampled to ensure variation in age, pain (quality and severity) and adherence. We will include patients who stop treatment or drop out of the trial with exploration of reasons why.

We will use a flexible topic guide, informed by relevant literature and developed in collaboration with the trial management group and public contributors. New and unanticipated topics will be added as interviews progress. We will aim to conduct these interviews at around two months post-randomisation because by this time participants will have decided their daily dose (self-titration, including none), and clinicians on the trial team advise that amitriptyline is likely to have had meaningful effects for patients. In these interviews we will explore patients' understanding and experiences of the intervention focusing on perceptions of amitriptyline and how it works (e.g. whether preventing or treating pain), experiences of self-titration and alterations in dosage, experiences of side-effects, and impact on willingness to continue treatment and stay in the trial.

Interview participants will be identified by an unmasked member of the trials unit (e.g. the junior statistician), guided by sampling criteria provided by the qualitative research team. The qualitative research team will be masked to an individual participant's treatment allocation until the end of primary outcome data collection for that participant and unmasked thereafter to enable meaningful data analysis. Other members of the TMG will remain masked throughout the qualitative study, only viewing redacted transcripts or excerpts of data.

The interviews will be audio-recorded and transcribed verbatim by an approved transcription company. Analysis will be thematic, using a combination of inductive and deductive coding. Deductive coding will be informed by previous literature, the qualitative findings from the pilot and by domains from the Common Sense Model, which provides a framework for understanding how patients make sense of illness and treatment.[33] Analysis will be led by the qualitative researcher, with a sub-set of data independently coded by the other members of the research team, to enhance trustworthiness of the analysis process and to contribute to theme development.

13.3. Consent process for qualitative components

Research team and staff at participating GP surgeries will be given an information leaflet about the nested qualitative study and invited to ask questions. Consent for the audio recordings will be received in electronic or written form. This will be a one-off process to cover consent for future recording of study discussions with patients throughout the study. Verbal consent for the interviews will be confirmed/audio recorded at the time of interview. The process for taking verbal consent will be detailed in study instructions, which will be followed by the researcher.

Regarding patients/participants, consultations in which the ATHENA study is discussed may be recorded with verbal consent. It will be explained to patients that recordings are undertaken to explore how treatment and study information is conveyed to patients, and that the recording can be erased after the consultation if they decide they do not want it used. Information about the audio-recordings and interviews is in the patient information leaflet. Potential participants are free to decline to be audio-recorded and this does not affect their potential participation in the rest of the study. Written/electronic consent to approach participants for interview will be sought in the study consent form. Patients who decline to take part in the study at the pre-consent stage will be asked if their contact details can be passed to the qualitative research team.

If selected for an interview, the qualitative researcher will contact the patient to explain more about the interview, answer any questions and, if they agree, arrange a convenient time to conduct the interview. Verbal consent will be taken and recorded at the start of the interview following a standard procedure (statements from approved consent form read out and each verbally agreed to by participant).

13.4. Data protection and patient confidentiality in relation to the qualitative data

All audio-recordings (study discussions and interviews) will be made using an encrypted audio-recorder. Interview data captured on the encrypted audio-recorder will be transferred to a University of Bristol computer as soon as possible after each interview. If interviews are conducted through a video

conferencing platform, then only the audio-recording file will be transferred securely to the University of Bristol and both the audio and video files will be deleted from the video-conferencing platform. All data will be stored on password protected computers maintained by the University of Bristol.

Audio-recordings will be transcribed by University of Bristol employees or University approved transcription services. Transcripts will be labelled with a study-assigned participant number, edited to ensure anonymity of respondents and stored securely adhering to the University's data storage policies. Audio-recordings and transcripts will be retained by the University of Bristol where anonymised quotations and parts of voice modified recordings may be used by the University for training, teaching, research and publication purposes for this and future studies. Anonymised transcripts may be made available to other researchers (including those outside of the University) by controlled access if they secure the necessary approvals for purposes not related to this study, subject to individual written informed consent from participants.

14. ETHICAL AND REGULATORY CONSIDERATIONS

The acceptability of e-consent has been confirmed by our Sponsor and PPI and is in-line with HRA/MHRA guidance.[21]

14.1. Governance and legislation

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a greenlight letter.

For all amendments, the CI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

This research trial will be run in accordance with ICH GCP. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

14.2. Research Ethics Committee (REC) review and reports

Ethics review of the protocol for the trial and other trial related participant facing documents (e.g., consent form) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents will be approved by the Sponsor before being submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

ICH GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to ICH GCP guidelines.

14.3. MHRA review and reports

MHRA review of the protocol for the trial and other trial related documents relating to the IMP/placebo will be carried out by MHRA. Clinical Trial Authorisation (CTA) will be obtained. All correspondence with the MHRA will be retained in the Trial Master File (TMF).

After the initial CTA has been approved, any amendments which effect the safety (physical or mental integrity) of the participants, the scientific value of the study, the conduct or management of the study or the quality or safety of any IMP) will constitute a substantial amendment and a request to the MHRA for approval will be submitted.

In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (SUSARs), a Development Safety Update Report (DSUR) will be submitted to the MHRA, once a year

throughout the clinical trial or on request until the end of the trial is declared. The annual safety report should consider all new available safety information received during the reporting period and assess the safety of subjects included in the study.

The sponsor will submit an end of trial summary results on the appropriate reporting platform within one year of the end of study declaration being submitted.

14.4. Amendments

HRA approval will be sought alongside the REC and MHRA approval process.

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA (Clinical Trial Authorisation) or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) for consideration. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

14.5. Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA process, which includes independent expert and lay reviewers.

14.6. Regulatory compliance

The trial will comply with the necessary regulations (MHRA, CTA, etc.) and will gain sponsor and HRA approval. The trial will not commence until a CTA is obtained from the MHRA and Favourable REC opinion and HRA approval have been provided, and sponsorship is issued. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

14.7. Data quality

The quality of the trial data will be monitored throughout the trial (see 12.1) and data completeness will be reported to the DMC and TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

14.8. Financial and other competing interests

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

14.9. Indemnity

The necessary trial insurance is provided by the Sponsor. The patient information sheet provides a statement regarding indemnity.

14.10. Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with University of Bristol policy. Data will be kept anonymous on research data facility storage (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreements available from the RDSF website which will be confirmed by the CI (or appointed nominee).

The data sharing agreement should cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

15. DISSEMINATION POLICY

A plan for disseminating the trial results will be developed by the TMG.

The main results of the trial will be published in a high impact peer-reviewed journal. Initial findings will be submitted to relevant national and international meetings. Innovative methods of dissemination will be explored such as videos, YouTube clips and blogs to accompany scientific papers that are accessible to patients as well as providing a lay summary.

On completion of the trial a final report will be prepared for the Funder (NHR HTA) and once approved, made publicly available on their website.

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17. AMENDMENT HISTORY

Record of protocol version numbers and amendments:

Version		Notes
Number	**Date**	
1.0	03.09.2021	Original, approved protocol
2.0	05.11.2021	Minor amendments: addition of CPMS ID; correction of baseline participant vouchers (£10, not £5); consistency in references to intervention (removal of antivirals from "trial summary") and Patient information leaflet (not booklet); other minor corrections to titles/names (e.g. RenaClinical instead of Renaclinical), duplicated text or typing errors
3.0	05.07.2022	Added ISRCTN number Change of name from RenaClinical to Eramol due to company name change. 4.3 Clarification of wording for exclusion criteria 5.2 Changed wording to allow inclusion of other CRN areas. 5.3 Clarified alternative methods of patient identification (pop-up and search), and addition of other staff who routinely prescribe amitriptyline, now able to refer to study (not just GPs), to reflect current practice, e.g. advanced nurse practitioners. 5.9 Correction; the data manager is masked, not unmasked 6.10 Clarification of destruction of IMP in line with pharmacy manual. 13.3 Clarification of staff qualitative interview consent process. Appendix: Corrections and clarifications around SWAT analysis. Corrections of typos and cross referencing errors, including table numbers.
4.0	20.12.2022	3.2 Internal pilot, increased to 9 months from 6 months, in line with agreement from HTA. 5.4 Addition of postal remote consent 6.5 Addition of second approved address for Eramol ltd. 6.9 Clarification that 'clinicians' are able to conduct the 28 day safety review if required (previously 'GP') 8.6 List of anticipated events, added 'fractures' and 'Trips and/or falls' Correction of GP to Clinician in places previously missed, to bring in line with previous amendment.
5.0	05.07.2023	4.8 Update to Eramol (Pharmacy) emergency unmasking phone number.
6.0	15.09.2023	2.4 Change of definition of post-herpetic neuralgia from average to worst pain. 9.2 Error corrected: As the DMC have had sight of unmasked data, they will NOT be approving the analysis plan. Clarification that adherence will be defined in the statistical analysis plan. 10.4 Correction of duration records will be kept to 5 years (to be consistent with section 10.6 and patient information leaflet).

		13.1 Clarification of description of phase 1 qualitative work
7.0	01.12.2023	Changes following contract variation and 12 months recruitment extension: Participants recruited after March 2024 will be followed up for 6 months (vs 12 months).
8.0	15.05.2024	5.2 Use of flyers and posters to advertise the study via pharmacies.
9.0	01.10.2024	Changes following contract variation and 7 months recruitment extension: Participants recruited on or after 1st February 2025 will be followed up for 3 months only.
10.0	16.01.2025	Trial Summary and 9.1 Sample size calculation: Allowance for recruiting more than target sample size of 846 if time permits.

1. APPENDIX 1: Study Within A Trial (SWAT)

1.1. Research question

Does a practice-level educational intervention improve the timely assessment of adults with shingles?

1.2. Background

It is recommended that antiviral treatment for herpes zoster (shingles) in adults be commenced with 72 hours of rash onset, and most patients will be diagnosed and treated by their GP. Therefore, early recognition of the symptoms in primary care is important to ensure timely access to medication. Improving the number of patients seen within 72 hours of rash onset will increase the pool of patients who are potentially eligible for the main trial.

Shingles has several characteristic features that assist in its diagnosis: prodromal phase with abnormal skin sensations and pain in the affected dermatome; followed by a distinctive painful, itchy, and/or tingly maculopapular rash (that develops into clusters of vesicles), which unlike other rashes, does not cross the midline of the body.

Access to most GP appointments is facilitated by reception staff who will often ask what the reason for the appointment is. Highlighting to them, and reminding practice nurses and doctors, of the unique nature of shingles and the importance of early treatment, may help them identify and prioritise appointments for adults whose new onset of rash fits the description of shingles.

1.3. Trial Design

Cluster (GP surgery level) randomised controlled trial.

1.4. Objective

To determine if a "whole practice" educational intervention improves the assessment of patients with shingles within 72 hours of onset of rash, and hence recruitment for this trial.

1.5. Participants

Patient-facing staff (receptionists, nursing, and medical staff) at participating GP surgeries

1.6. Intervention

In addition to patient-facing materials, intervention surgeries will be sent the following:

- Posters and screensavers to display in staff areas/install on practice computers
- Links to brief (2-3 minute) online training/videos, which all staff with patient-contact will be asked to view.

This information will highlight the importance of the early recognition of patients who contact the surgery with possible shingles. It will cover the unique, characteristic features (prodromal symptoms, unilateral, maculopapular dermatomal rash) and importance of early (<72 hours from rash onset) antiviral treatment.

1.7. Comparator

All surgeries will be asked to display patient-facing materials on websites, waiting room noticeboards and TVs, and social media.

1.8. Outcome

Proportion of patients with shingles seen within 72 hours of onset of rash.

1.9. Consent

GP surgeries who take part in the trial will be asked to consent to being randomised to the educational intervention or control group.

1.10. Randomisation

Participating GP surgeries will be cluster randomised (1:1) to control or intervention, stratified by centre and minimised by practice list size and deprivation based on the postcode of the practice.

1.11. Trial population and size

With 60 GP surgeries and assuming a standard deviation of 30 and a mean of 60%in the control group, we would have: 97% power to detect a 50% proportionate increase in the proportion of potentially eligible patients seen; or 86% power to detect a 40% proportionate increase.

1.12. Data and analysis

Data which is being routinely collected during this time as part of GP screening and referral will be collated and compared in intervention and control surgeries: the proportion of potentially eligible patients seen within 72 hours; and number of potentially eligible patients referred. Comparisons between the two groups will be conducted using linear regression adjusting for randomisation variables.

1.13. Study duration

The first six months of participant recruitment.

1.14. Ethical considerations

Patients in control GP surgeries will not be disadvantaged because there is no evidence that this type of practice-level intervention improves the timeliness of diagnosis and treatment; and because diagnosis times may improve in all practices by virtue of agreeing to take part in the main trial. All control practices will be offered the intervention after the six-month evaluation period.