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

A study within a trial (SWAT) embedded within the ATHENA (AmiTriptyline for the prevention of post-HErpetic NeuralgiA) trial
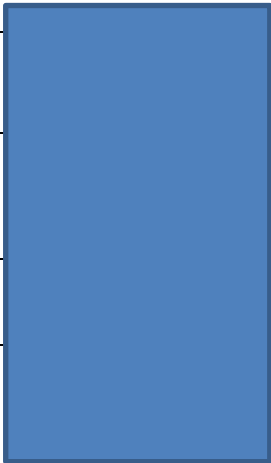
Statistical Analysis Plan

Version 0.1 (10/10/2022)
Based on Protocol version 3.0 (dated 5/7/2022)
ISRCTN 14490832

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents

	NAME	TITLE	SIGNATURE	DATE
Co-author and trial statistician	Yumeng Liu	Research associate in medical statistics		18 Oct 2022
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SWAT Chief Investigator	Dr Elizabeth Lovegrove	SWAT Chief investigator		19 Oct 2022
Host trial Chief Investigator	Dr Matthew Ridd	Chief investigator		18 Oct 22

Effective Date:	19/10/22

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List of abbreviations

Acronym	Details
ATHENA	AmiTriptyline for the prevention of post-HErpetic NeuralgiA
BTC	Bristol Trials Centre
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
GP	General Practitioner
IMD	Index of Multiple Deprivation
IQR	Inter-Quartile Range
ITT	Intention to Treat
PHN	Post-hepatic neuralgia
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SD	Standard Deviation
SWAT	Study Within a Trial
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Bristol

1. INTRODUCTION AND PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the SWAT embedded within the ATHENA trial.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with this analysis plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. BACKGROUND AND RATIONALE

2.1 Background of ATHENA host trial

Herpes zoster (shingles) is characterized by a unique painful, blistering, dermatomal rash which is most commonly diagnosed in General Practice (GP) on symptoms and signs alone. It is often preceded by a prodromal phase, including fever, malaise, dermatomal pain and dysesthesia. Antiviral treatment is recommended as soon as possible after rash onset (but up to 1 week), to treat the rash and reduce acute pain. However, there are currently no preventative treatments for post-herpetic neuralgia (PHN); the most common complication of shingles.

The ATHENA trial aims to determine the clinical and cost-effectiveness of prophylactic low-dose amitriptyline for the prevention of PHN at 90 days post-randomisation. It is the host trial of the SWAT described here.

2.1.1 ATHENA setting and eligibility criteria

ATHENA is a multi-centre, individually randomised, pragmatic placebo controlled superiority trial with internal pilot, health economic analysis, study within a trial (SWAT) and nested qualitative study. It is set in primary care practices in the United Kingdom (UK). Practices were recruited via NIHR (National Institute of Healthcare Research) Clinical Research Networks.

Eligible participants are adults aged 50 years and older with a clinical diagnosis of herpes zoster with rash onset within 144 hours. The number of potentially eligible patients seen and reasons for referral/non-referral is monitored by the trial team and feedback is provided to participating GP surgeries on a regular basis.

2.1.2 ATHENA intervention

The intervention treatment is Amitriptyline initially prescribed as a 10 mg dose, increasing in 10 mg steps over two weeks as tolerated, to 30mg maximum.

2.1.3 ATHENA comparator

The comparator is a placebo tablet formulated and manufactured according to a standard placebo composition to match the appearance of the active tablet. As with the intervention tablets, those prescribed the placebo will be allowed to increase the number of tablets in one tablet steps over two weeks as tolerated to a maximum of three.

2.1.4 ATHENA primary outcome

The primary outcome of the host trial is a binary variable indicating the presence/absence of PHN at 90 days after rash onset, using a cut-off of ≥3/10 on a numerical rating scale of average pain in the last 24 hours.

2.1.5 ATHENA screening and identification of patients

Patients are 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. To support practices in identifying and referring potential participants electronic medical record "pop ups" are offered to be installed on practice computers. They appear when patients with shingles who are 50 years or over are seen and will remind clinicians about the eligibility criteria and prompt the clinician to ask their patient about the study. In addition, or for practices that do not wish to have the pop-up, they will be asked 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.

The clinician's role is 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 is monitored and feedback is provided to participating GP surgeries on a regular basis.

2.1.6 ATHENA 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, 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.

2.2 Rationale of SWAT

It is recommended that antiviral treatment for 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 also increase the pool of patients who are potentially eligible for the host trial.

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.

2.3 Primary objective of SWAT

To determine if a "whole practice" educational intervention improves the assessment of patients with shingles within 72 hours of onset of rash.

2.4 SWAT design

GP practices recruiting patients to the ATHENA trial are randomised 1:1 to intervention or control with outcomes analysed at the practice level.

2.5 Trial centres

ATHENA was originally set up with centres in West of England, Wessex and Thames Valley/South Midlands. GP surgeries approached to participate in the SWAT were among those recruiting to the main ATHENA trial from these centres.

2.6 SWAT eligibility criteria

All GP surgeries participating in the ATHENA host trial were eligible to participate in the SWAT. The intervention targeted patient-facing staff (receptionists, nursing and medical staff) at these surgeries. To maximise the number of eligible surgeries, where surgeries are comprised of multiple smaller practices the individual practices are randomised. Only when the practices share computer systems or administrative staff are they randomised as a whole.

Practices are recruited from early April 2022 to early August 2022

2.7 SWAT intervention

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

- Posters and desktop backgrounds to display in staff areas/install on practice computers

- Links to brief (1 minute) online training/video, which all staff with patient-contact will be asked to view.

This information will highlight the importance of 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.

2.8 SWAT control

Control practices will not receive special education interventions aimed at staff. They will, however, receive ATHENA trial posters designed for patients to be displayed in waiting rooms and on practice websites only.

2.9 SWAT randomisation

Practices are randomised 1:1 to intervention or control stratified by recruiting centre (West of England, Wessex or Thames Valley/South Midlands) and minimised on list size and deprivation based on the postcode of the practice using the index of multiple deprivation (IMD).

2.10 SWAT sample size justification

The sample size of the SWAT is dictated by the recruitment of practices to the ATHENA study during its internal pilot phase (first six months) and all practices were approached to participate in this period. There was also little information on which to inform the sample size calculation of the expected proportions of patients seen within 72hours of rash onset.

Assuming that, on average, 60% of patients at a GP practice are seen within 72 hours of rash onset in usual care and a standard deviation of 25, recruiting 60 practices in total would allow the study to detect an absolute increase of 20% (thus, 80% of patients at intervention practices being seen within 72 hours) with 86% power.

2.11 Blinding

Due to the nature of the intervention, practices, the statistician performing the randomisations and SWAT chief investigator communicating with practices cannot be blinded. The ATHENA chief investigator and senior statistician leading the writing of the analysis plan, however, are blinded to allocation group.

2.12 Interim analyses

No interim analyses are planned.

2.13 ATHENA and SWAT oversight

2.13.1 Trial management group (TMG)

The TMG have responsibility for the day-to-day management of ATHENA and report to the Trial Steering Committee. The TMG meet on a regular basis with a core working group of staff having frequent progress meetings. Progress of the SWAT is a point of discussion at each of the TMGs.

2.13.2 Trial steering committee (TSC)

The role of the TSC is to provide the overall supervision of ATHENA, monitor progress and conduct and advise on scientific credibility. They have not advised on the SWAT

2.13.3 Data monitoring committee (DMC)

The Data Monitoring Committee (DMC) has an independent chair and monitors accumulating ATHENA data during the trial and makes recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial.

2.14 SWAT outcome measures

The primary outcome is the proportion of patients seen within 72 hours since their rash onset among those with shingles screened for ATHENA at each SWAT practice. The secondary outcome is the proportion of patients seen within 144 hours since their rash onset among those with shingles screened for ATHENA at each SWAT practice. In order to inform recruitment to the larger ATHENA trial, follow-up data will be collected from practices until the end of the pilot stage of the main ATHENA trial (first nine months of recruitment)

3. GENERAL ANALYSIS CONSIDERATIONS OF THE SWAT

3.1 Analysis populations

The Full Analysis set includes all randomised practices. A modified primary intention-to-treat (ITT) analysis will be conducted using this dataset without imputing missing data.

3.2 Procedures for missing data

In all tables, missing data will be indicated using footnotes.

4. DESCRIPTION OF PRACTICE CHARACTERISTICS

4.1 Disposition

The flow of practices through the SWAT will be summarised in a CONSORT-style diagram.

4.2 Baseline characteristics

Baseline characteristics of practices will be compared between the two arms by reporting relevant summary statistics to determine whether any potentially influential imbalance occurred by chance. Baseline characteristics will be summarised using means (SD), medians (Inter-quartile-range; IQR) or number (%) depending on the nature of the data and its respective distribution. If the baseline characteristics of the groups differ by more than 10%, or 0.5SD, then the effect of this variable on the outcome will be investigated in sensitivity analyses.

5. ASSESSMENT OF STUDY QUALITY

5.1 Data validation

Once the data are downloaded by the trial statistician, internal consistency checks will be performed by them in preparing the data for analysis in Stata. They will aim to identify spurious values or inconsistencies. When inconsistencies are identified, these will be reported to the ATHENA trial manager who verifies available records.

5.2 Study completion

Follow-up for the SWAT will finish on 10 October, 2022, which covers the period pre-specified in the ATHENA protocol. Analysis will begin once the final version of the current SAP has been approved.

5.3 Protocol deviations

There will be no prospective, planned deviations or waivers to the protocol.

6. ANALYSIS OF EFFECTIVENESS

Stata version 17 (or higher) will be used for all SWAT analyses. Two-tailed tests will be used with effect estimates, 95% confidence intervals (CI) and p-values presented. A significance level of 5% will be used and no adjustment will be used for multiple testing. Analyses using regression models will adjust for stratification and minimisation variables. The primary approach for analysis will be on an intention-to-treat (ITT) basis defined as analysing participants according to the arm to which they were randomised.

6.1 Mis-randomised practices

Practices will be analysed according to the arm to which they were randomised.

6.2 Summary of primary and secondary endpoints

The primary and secondary endpoints are summarised below:

Outcome	Timepoints	Interpretation	Range
Primary			
Proportion of patients seen within 72 hours since their rash onset among those with shingles screened for ATHENA at each SWAT practice	Assessed at the end of follow-up as of 10/10/22	Higher proportions indicate a greater proportion of patients seen within 72 hours of rash onset	0-1
Secondary			
Proportion of patients seen within 144 hours since their rash onset among those with shingles screened for ATHENA at each SWAT practice	Assessed at the end of follow-up as of 10/10/22	Higher proportions indicate a greater proportion of patients seen within 144 hours of rash onset	0-1

6.3 Primary analysis

The practice level proportion of patients seen by their GP within 72 hours of rash onset will be analysed using a linear regression model with treatment arm and all variables used in the randomisation as covariates. The coefficient effect comparing the intervention and control group with corresponding 95% confidence interval and P-values will be reported.

6.4 Secondary outcomes analyses

The secondary outcome will be analysed in the same manner as the primary outcome.

6.5 Sensitivity analyses

To account for differing durations of follow-up a sensitivity analysis will be run adjusting for the duration of follow-up at the individual practice. Duration of follow-up will be calculated as the number of days between communication of practice allocation and 10/10/22.

Should there be evidence of imbalance between treatment groups on important baseline characteristics as described in **section 4.2**, sensitivity analyses will be conducted where the primary analysis is repeated, adjusting for variables showing an imbalance. This sensitivity analysis will be performed for both the primary and secondary outcomes.

6.6 Further analysis

Further exploratory analyses are planned, which are not part of the main SWAT analysis presented here. These will be done after the results from this analysis are shared.

7. CHANGES TO THE SAP

All changes made to the planned statistical analyses are described below:

Previous version	Previous date	New version	New date	Brief summary of changes

8.   FINAL REPORT TABLES AND FIGURES (SUBJECT TO CHANGE)
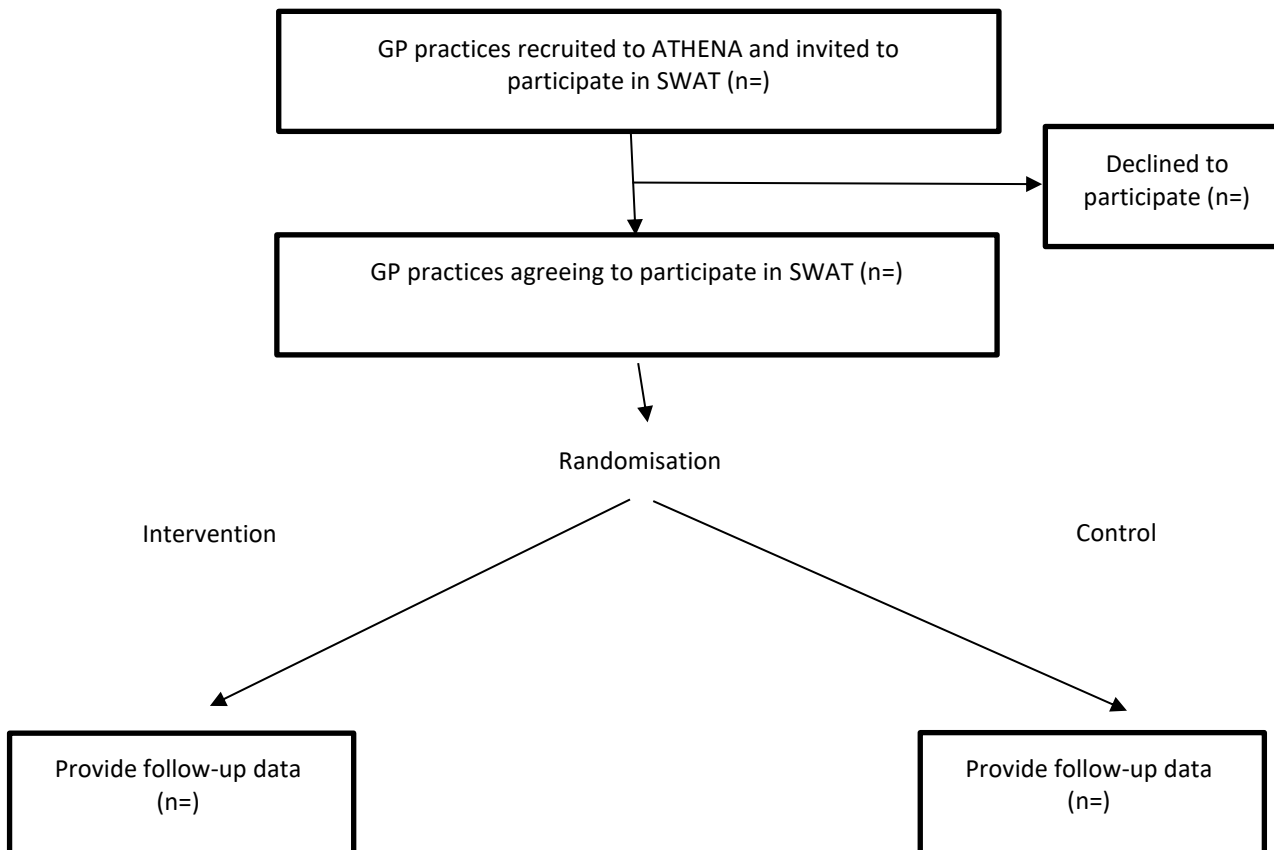
Figure 1: CONSORT

Figure 2: Recruitment of practices to the SWAT over time

(graph with the cumulative number of practices recruited on the vertical axis and date of randomisation on the horizontal axis)

Table 1: Baseline characteristics of participating practices

	Intervention	Control
List size; n(%) <10000 patients≥10000 patients		
Centre ; n(%) West of England Wessex Thames Valley/West Midlands		
IMD at practice level; Median (IQR)		

Table 2: Primary and secondary outcome analyses

	Intervention; mean (SD)	Control; mean (SD)	Difference (95% CI)*	p-value
Proportion of patients seen within 72hours of rash onset				
Proportion of patients seen within 144hours of rash onset				

Adjusted for variables used in the randomisation