HEALTH ECONOMICS ANALYSIS PLAN FOR ALABAMA (HEAP)

JUNE 17, 2024

UNIVERSITY OF LEEDS

Contents

Section 1: Administrative Information

1.1 HEAP Administrative Information

Title	Penicillin allergy status and its effects on antibiotic prescribing, patient outcomes, and antimicrobial resistance
Trial registration number; registry	Ethics Ref: 19/LO/0176
Source of funding	National Institute for Health Research (NIHR)
Purpose of HEAP	The purpose of this HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan and it should be read in conjunction with them.
Trial protocol version; date	This document has been written based on information contained in the trial protocol version 12 dated 10/07/2023
Trial Statistical Analysis Plan (SAP) version, date	0.13, 22 March 2024
Trial HEAP version, date	1.0, 30/05/2024
HEAP revisions	Not applicable
Roles and responsibilities	This HEAP was prepared by Ruben Mujica-Mota, Miaoqing Yang, Dan Howdon and Rebecca Bestwick and approved by Jonathan Sandoe. The trial health economists Ruben Mujica-Mota, Miaoqing Yang, Dan Howdon and Rebecca Bestwick are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

APPROVALS

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

Role	Name	Signature	Date
Author	**Ruben Mujica-Mota, Miaoqing Yang, Dan Howdon, Rebecca Bestwick**		dd/mm/yyyy
Lead Health Economist	**Ruben Mujica-Mota**		dd/mm/yyyy
Chief Investigator	Jonathan Sandoe/Sue Pavitt		dd/mm/yyyy

Section 2: Trial Introduction & Background

2.1 Trial background and rationale

Penicillins, as the most commonly prescribed antibiotics, are first-line therapy for many infections. However, when a patient's medical records indicate a penicillin allergy, it significantly influences the selection of antibiotics for treatment. The prevalence of recorded penicillin allergies is about 6% in the general population, but records are often incorrect, for example because symptoms related to the underlying infection, rather than true allergic reactions, are mistakenly labelled as allergies. Consequently, a notable portion of people in the UK may unnecessarily miss out on effective penicillin treatments and receive broader-spectrum antibiotics instead. The presence of penicillin allergy records can result in less effective therapy, potentially poorer long-term outcomes and contribute to antibiotic resistance (AMR). The large discrepancy between reported and true allergy rates highlights the potential benefits of implementing a pre-emptive penicillin allergy assessment pathway (PAAP)

for patients likely to require antibiotics. While specialist clinics in the NHS offer allergy assessments, limited capacity restricts access. The PAAP presents a more accessible and efficient approach to testing as well as incorporating behaviour change materials, potentially leading to improved patient care, reduced healthcare-associated infections (HCAI), and cost savings within the NHS. Additionally, it may help limit AMR.

In January 2023 the NIHR decided recruitment into the ALABAMA trial should stop early, as COVID-19 had slowed recruitment. Approximately only one third of the target number of patients had been enrolled in the study. It instructed the research team that the economic study be correspondingly redesigned to address the research question of the value of information of conducting further research after ALABAMA.

2.2 Aim of the trial

The main aim of the ALABAMA trial is to examine if removal of "false positive" records of penicillin allergy using a complex intervention improves antibiotic prescribing and health outcomes, and is cost effective.

2.3 Objectives of the trial

The original primary objective of the ALABAMA trial was to investigate whether the PAAP intervention is clinically effective in improving the patient health outcome of treatment response failure. Following the early termination of recruitment, this is now a secondary outcome and the effect of PAAP on penicillin prescribing has become the primary outcome.

Secondary objectives of the trial include assessing the effects of PAAP on

- Treatment response failure
- symptom duration,
- total antibiotic prescribing,
- hospital admissions and length of hospital stays,
- mortality rates,
- Methicillin resistant *Staphylococcus aureus* (MRSA) infection/colonisation, and *Clostridioides difficile* infection.
- de-labelling at 3 months and up to 12 months post randomisation
- all outcomes for follow up post 12 months.

It also intends to explore patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use, as well as patient and clinician experiences of trial procedures. In addition, it intends to describe the influences on clinician and patient behaviour regarding prescribing and consuming penicillin following a negative test result. It will also assess the cost-effectiveness of the PAAP intervention compared to usual care; this document outlines the economic analysis plan.

2.4 Trial population

Participants over 18 years of age with a record of a penicillin allergy. Inclusion and exclusion criteria for the trial population can be found in the Study Protocol (Armitage et al. 2023).

2.5 Intervention and comparator

Intervention: PAAP intervention. Those randomised to the PAAP intervention arm are booked into a half-a-day appointment at the hospital clinic where they receive penicillin allergy testing (PAT), either a skin test followed by oral challenge test (OCT), if negative, or straight to the OCT. If there is no reaction to the OCT, patients are asked to take penicillin at home for 3 days.

Comparator: Usual care, which consists of antibiotics prescribed by their general practitioner according to routine clinical practice. Referral for outpatient specialist allergy assessment may still take place, typically in a small minority of cases due to limited service capacity and restricted referral criteria (NICE drug allergy guideline), as part of routine clinical practice.

2.6 Trial design

This is a multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested pilot study. After a first appointment with the GP (or delegate) to confirm their eligibility to participate and consent them to take part in the study, participants will receive a phone call from a member of the trial team who will complete the baseline case report form (CRF), and randomise them to usual care or the PAAP intervention arm.

2.7 Trial start and end dates

Recruitment started in 05/2019 and finished in 10/2023. The follow-up period consists of at least 12 months, up until 04/2024.

Section 3: Economic overview

3.1 Aim of economic evaluation

The aim of the economic evaluation is to determine whether the PAAP intervention is cost-effective from the perspective of the NHS and Personal Social Services (PSS), compared to usual care in patients with a record of a penicillin allergy. In addition, the aim is to determine the value of conducting further research using Value of Information Analysis.

3.2 Objective of economic evaluation

The primary objective of the health economic evaluation is to estimate the incremental cost and incremental cost per QALY gained of the PAAP intervention compared to usual care over a period of 12 months, corresponding to the trial's follow-up period. The secondary objective is to estimate the cost per QALY gained of PAAP over 5 years relative to usual care. Due to the ALABAMA early termination, a third objective is to conduct Value of Information (VoI) Analysis of future research. Reflecting these priorities and the shortened timescale for analysis, the following sections focus on describing the within-trial analysis, leaving the description of the 5-year and VoI analyses to sections 6 and 7 respectively.

3.3 Overview of economic analysis

The within-trial analysis will be conducted using individual patient level data from the ALABAMA trial and linked Hospital Episode Statistics (Admitted Patient Care, Outpatient, Critical Care, Emergency Care Data Set) and Civil Registrations of Death data. Primary care consultations data (date of appointment and health care professional delivering care) will be identified from OpenClinica and SystmOne, and information on antibiotic prescriptions in primary care will be identified from SystmOne and 12-month case note review. In addition, for trial participants admitted to hospital within the 12-month follow-up, inpatient antibiotic prescription data will be collected from review of hospital notes and, where available, inpatient prescription data.

The analytical approaches will take the form of cost-utility and cost-effectiveness analyses. Based on trial evidence, incremental cost-effectiveness ratios (ICERs) will be calculated by taking a ratio of the difference in the mean costs and mean QALYs. Separately, similar ratios will also be produced in terms of the cost per de-labelled patient.

The team undertaking health economic analysis were not involved in trial delivery.

3.4 Jurisdiction

The trial is conducted in the UK (England), which has a national health service (NHS), providing publicly funded healthcare primarily free of charge at the point of use.

3.5 Perspective

The perspective adopted will be that of the NHS and PSS.

3.6 Time Horizon

Costs and health effects associated with the intervention and comparator will be estimated for the follow-up period of 12 months for within-trial analysis. Extrapolation analyses beyond 12 months are described in sections 6 and 7.

Section 4: Economic data collection & management

4.1 Statistical software

The latest available version of both R and Stata at the time of analysis will be used for exploratory analysis and for the main economic analysis.

4.2 Identification of resources

The following items of health care resource use that may differ between arms will be measured:

1. Cost of PAAP intervention, including staff time, space and consumables
    a. Booking appointment
    b. Risk stratification
    c. Testing by Skin prick test (SPT) if and Intra-dermal Test (IDT), if conducted, and Oral Challenge Test (OCT).
2. Cost of usual care (SPT, IDT and OCT in specialised outpatient unit)
3. Costs of downstream health care use, including primary care visits, outpatient appointments, hospital admissions and A&E attendances
4. Costs of antibiotic medication use in primary care
5. Costs of antibiotic medication use in secondary care

4.3 Measurement of resource-use data

Resource use data related to the delivery of the PAAP intervention and downstream health care use and medication use will be collected as part of the trial. Resource inputs into PAAP will be collected both prospectively (the amount of time taken to carry out the test(s) and grade and title of staff involved) and retrospectively (resources required to train staff, employed tests reagents and consumables, and amount of clinician and immunologist supervision, as estimated by staff that delivered PAAP testing using a standardised proforma). A 12-month follow up period post-randomisation will be utilized based on data collected through (i) SystmOne and OpenClinica for primary care records and antibiotic medication use in primary/community care and (ii) Hospital Episode Statistics (HES) for secondary care. Antibiotic prescription information from primary care will be combined with medication usage data extracted from the 12-month case notes review.

4.4 Valuation of resource-use data

All resource use will be valued in monetary terms. Intervention delivery will be costed using NHS staff salaries, with tests, consumables and other materials costed at prices paid at the Leeds Teaching Hospitals Trust, the main study site at the time of trial (2023-2024). Antibiotic use will be valued in line with appropriate costing sources as per NICE guidelines (NHS Drugs Tariff prices in primary care). Primary care services will be valued using routinely published unit costs (PSSRU 2023). Secondary care service use will be valued using published costs from NHS reference costs and NHS Cost collection, and within our analysis we will give specific consideration for length of stays of admissions. Adjustments will be made for inflation using NHS price indices (PSSRU 2023).

4.5 Identification of outcomes

The primary outcome measure of the economic analysis will be QALYs derived from utility scores, with the EQ-5D-5L instrument as well as individual level survival data used for this purpose. To calculate QALYs, the utility values at baseline and 12 months as well as any utility values recorded due to an episode of antibiotic use will be used, as well as any record of the patient's death during this 12-month period.

4.6 Measurement of outcomes

Research staff will collect quality of life (QoL) from all randomised patients at different time points. Responses to the EQ-5D-5L will be collected at baseline, 2-4 days post antibiotic treatment (if applicable), 28-30 days post antibiotic treatment (if applicable), and 12 months post PAAP (+/- 2 weeks).

Research staff will provide the participant with the questionnaire pack after consent into the study has been obtained, but before randomisation. Participants will be asked to complete the questionnaire in clinic.

Participants will seal the completed questionnaire in an envelope and hand it to the research staff. Research staff will then post the sealed envelope to the CTRU. At the post-antimicrobial time point, unless the participant is being seen in clinic, and 12-month time point, the research team at site will contact the participant via phone in order for the patient to complete the questionnaire.

4.7 Valuation of outcomes

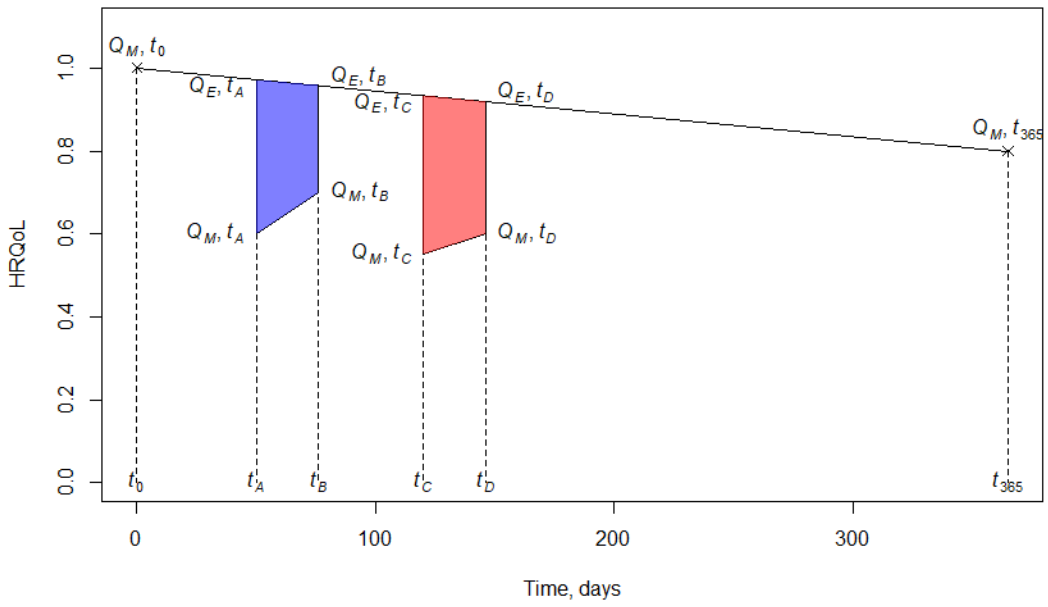
Utility scores will be derived from responses to the EQ-5D-5L. UK utility values will be derived using the current approach recommended by NICE, which is using the validated mapping function to convert EQ-5D-5L responses to the existing EQ-5D-3L index scores used in NICE appraisals (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l).

The total Quality Adjusted Life Years (QALYs) accrued over the 12-month period is calculated, at an individual level, in two steps. We detail these steps with reference to the graph below. *Q* is used to indicate Health Related Quality of Life (HRQoL) at a given time period; a subscript *M* is used to indicate that this is based on a measured value from a patient questionnaire, and a subscript *E* is used to indicate that this is a counterfactual estimate. *t* with its associated subscript indicates the time point at which this measure was taken or for which this estimate applies.

Firstly, we calculate the overall QALYs that would have been accrued in the absence of any antibiotic event by computing the area under the curve for the 12-month period, with HRQoL linearly interpolated between measured HRQoL at the beginning (t_0) and end (t_{365}) of the period. This is represented in Figure 1 by the average of HRQoL at t_0 and t_{365}, denoted as Q_M, t_0 and Q_M, t_{365}, respectively.

Secondly, for patients who had primary events, we gather HRQoL measures at 2-4 days and 28-30 days post-prescription (time points t_A and t_B, respectively). These measured HRQoL values at t_A and t_B are denoted as Q_M, t_A and Q_M, t_B, respectively. To estimate the disutility during this time period, we first use the interpolation method described above to obtain estimates of HRQoL at these points in the absence of prescription (Q_E, t_A and Q_E, t_B, respectively). We then use actual HRQoL measures (Q_M, t_A and Q_M, t_B) between which we linearly interpolate and thus derive a disutility trapezium under the assumption that utility falls immediately from its counterfactual estimated level to its measured level at time t_A and rises immediately from its measured level to its counterfactual estimated level at time t_B. This overall method can be generalised to two or more prescription episodes.

Figure 1. Estimating QALYs by the area under the curve method (example with two prescription episodes)



Section 5: Economic data analysis

5.1 Analysis population

The full analysis set will include all randomised participants, which is in accordance with the intention to treat (ITT) principle.

5.2 Timing of analyses

The primary analysis will be conducted at the time of trial data lock, expected at the end of April 2024. By this time access to the linked NHS England data on secondary care service use, civil registration of death and medications in secondary care will have been received and processed by the health economics team. No interim analysis will be conducted. The primary analysis will consist of a within-trial 12-month analysis.

5.3 Discount rates for costs and benefits

Costs and health effects will not be discounted in the primary analysis due to the single year timeframe of the primary analysis.

5.4 Cost-effectiveness threshold

The primary analysis will use the cost-effectiveness threshold of £20,000 per QALY.

5.5 Statistical decision rules

Mean differences in costs, QALYs and net benefits between the treatment groups will be estimated with associated 95% Confidence Intervals.

5.6 Analysis of costs and outcomes

Resource use related to primary care visits, outpatient attendances, hospital admissions and A&E visits will be compared between the treatment group and control groups. Absolute means and mean differences in service use will be presented with confidence intervals based on appropriate distributions (Poisson for counts, logit for proportions).

Mean differences in costs and outcomes will be analysed using ordinary least squares (OLS), adjusting for all minimisation factors (GP practice, age, number of antibiotic prescriptions in the 24 months prior to randomisation, and number of Quality and Outcomes Framework registered diseases), except for GP practice which will be treated as a random effect (to align our methods with those described in the Statistical Analysis Plan). Generalised linear models will be used to explore the effect on results of using alternative regression methods. Censoring due to any withdrawal from trial follow-up and failure to complete the 12-month follow-up questionnaire will be accounted for in analysis.

5.7 Data cleaning for analysis

Face validity tests will be conducted on data and checked against the source documents. Corrections identified will be documented and agreed with the trial management team.

5.8 Missing data

The impact of missing data will be examined using multiple imputation methods, using a number of imputations and model specification suitable for the observed prevalence of missing data and likely mechanism of missingness (Faria et al. 2014). The suitable imputation model specification will be agreed in consultation with clinical study leads and statisticians in the research team.

5.9 Analyses of cost-effectiveness

Cost and QALY data will be combined to calculate an Incremental Cost Effectiveness Ratio from the NHS perspective. We will also present incremental cost per de-labelled patients at 12 months.

5.10 Sampling uncertainty

Mean cost and QALY differences between trial arms will be presented alongside their bootstrap confidence intervals. A cost-effectiveness plane and Cost-effectiveness Acceptability Curve will be produced based on the 1,000 bootstrap samples using the percentile method.

5.11 Subgroup analyses or analyses of heterogeneity

Subgroup analysis will be presented by age (<65 years versus ≥65 years), gender (females), number of quality and outcomes framework conditions (<2 versus ≥2) and number of antibiotic prescriptions at baseline.

5.12 Sensitivity analyses

Sensitivity analyses will be undertaken to explore uncertainties surrounding key parameters in the economic evaluation. We will present analyses using alternative unit costs of PAAP to reflect hypothetical scenarios for service delivery, considering different personnel (nurses, pharmacists, doctors) conducting risk stratification and tests.

We will also conduct analysis following the As Treated (AT) principle and focus on participants who completed either the skin test or oral challenge test or both. In addition, we will limit the analysis to patients who had a 'primary event', in which an antibiotic was prescribed for a pre-defined list of infections (see Appendix II in Statistical Analysis Plan). Among patients who had 'primary events', healthcare resource use in both primary and secondary care will be limited to 56 days following the primary event.

The results for complete cases as well as those employing multiple imputation of data will be provided to identify the impact of missing data on the analysis.

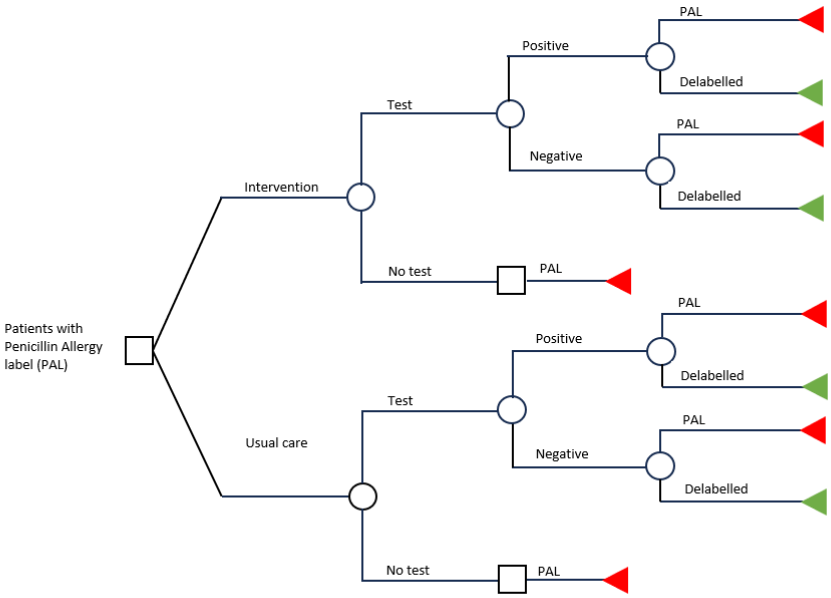
Section 6: Modelling

We will extrapolate costs and QALYs from observed results at 12-month to 5-year post PAAP. The analysis will extrapolate 12-month costs and QALYs derived from observed results to 5-year post PAAP predictions using fitted regression equations in Section 5 on all available data up to the maximum follow-up time in ALABAMA. The model will be populated with estimates from post-hoc analysis of the ALABAMA trial data, published study data and expert opinion from clinical investigators in ALABAMA. Costs and QALYs occurring after the first year will be discounted at an annual rate of 3.5% as stated by current NICE recommendations. The details of the model are described in the following section.

6.1 Decision analytic modelling

A conceptual model based on the test results of PAAP intervention will be built and populated with data from the literature and post-hoc statistical analysis of ALABAMA data. The decision tree represents the initial test pathways following different combinations of test results and de-labelling status. At the end of each pathway, extrapolation analyses will be conducted to calculate the associated costs and QALYs over 5 years, accounting for the impact of de-labelling on the likelihood of any antibiotic use and broad-spectrum antibiotic use, outpatient and hospital inpatient service use (Macy et al. 2019) as well as mortality (West et al. 2019) and quality of life.

Figure 2. Decision tree model



Key: PAL = Penicillin Allergy Label. TEST: the skin test or direct challenge test or both. Positive: positive test result indicating patient allergic to penicillin. Negative: negative test result indicating patient not allergic to penicillin.

Costs and utility pay-offs for each group (delabelled (green triangle Fig.2) or retained PAL (red triangle Fig 2.)) will be estimated using OLS regressions of individual patient data on total costs, including inpatient, outpatient, A&E services and primary care visits (Section 5.7). Each year of follow-up will constitute a unit of observation, clustered within patients and within GP practices (3-level model). The analysis will have de-labelled status as exposure and adjusting covariates will include the minimisation factor covariate set (see Statistical Analysis Plan). The probabilities of de-labelling will be informed by trial data and data from the literature. The analysis will adjust for incomplete or censored years of follow-up. Depending on the estimated coefficient on the randomised treatment allocation variable the analysis may or may not consider using trial arm specific pay-offs.

A tornado analysis will be produced to illustrate the most influential parameters in the results for the 5-year analysis. Univariate sensitivity analysis will be conducted on those parameters and assumption thus identified as key. In addition, two-way sensitivity analyses will be conducted to simultaneously vary assumptions regarding the cost of delivering PAAP and de-labelling state transitions probabilities. Other sensitivity analysis will include fitting alternative pay-off estimating questions with an additional exposure for the occurrence of treatment failure (See Statistical Analysis Plan) in order to derive predicted pay-offs conditional on the rate of this rare outcome. Results will be synthesised using the incremental cost per QALY gained and Net Monetary Benefit measures from the NHS perspective. Monte Carlo simulations will be used to estimate the probability that PAAP has a cost per QALY gained below £20,000.

Section 7: Value of Information Analysis

The Expected Value of Sample Information (EVSI) will be estimated. We will explore the value of conducting a new trial (ALABAMA2) to reduce uncertainty in key parameters, such as the probability of treatment failure; the number of outpatient and A&E attendances; number of days in hospital; number of primary care contacts (Macy and Shu 2017; Sousa-Pinto et al. 2021).

The EVSI will be compared with the costs of ALABAMA2 at study sizes being considered by the ALABAMA statistical team, as well as a range of alternative study sizes. The fixed and per patient costs of ALABAMA2 will be calculated used information provided and in collaboration with the ALABAMA management and financial team.

Section 8: Reporting/publishing

8.1 Reporting standards

Methods and results will be reported in adherence to the CHEERS checklist (Huserau et al. 2022) and Philips guidelines (Philips et al. 2006).

8.2 Deviations from the HEAP

Deviations from the HEAP will be described and justified in the final report.

Section 9: Data storing and archiving

All data, including clinical trial and linked NHS England data, will be stored in the University of Leeds LASER system. Data will be archived on 30/09/2024 and destroyed on 30/03/2025.

Section 10: References

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Section 11: Appendices

Table 1*: Measure and time point for data collection*

	Assessment						
Measure	**Baseline**	Day0	Day 4-6	2-4 days post Ab prescription	28-30 days post Ab prescription	**Month 12**	**Month 12+ up to 54 months**
Trial participant characteristics Minimisation factors							
PAAP Resources involved in testing for PAAP arm		✓					
Follow-up PAAP test Health care service use			✓				
Health care resource utilisation and survival Linked to HES (Admitted Patient Care, Outpatient, Critical Care), Emergency Care Data Set, Civil Registrations of Death, Medicines Dispensed in Primary Care data. Through HES APC, Ab prescriptions during hospital admissions collected from review of hospital notes.	Ongoing						
EQ-5D-5L Measures utility scores.	✓			✓	✓	✓	

Notes: EQ-5D data is also available beyond 12 months following antibiotic treatments.