Statistical Analysis Plan

SAPPHIRE: Safe Antimicrobial ProPhylaxis for surgery study: a multi-centre observational cohort study

Version 1.0

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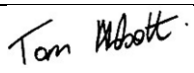
Signature	
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Version History

SAP Version	Protocol Version	Date	Reason for revision	Summary of changes made
0.1	**2.0**	**03/12/2024**	Statistician input	Sample size, added subgroup and sensitivity analysis sections.
0.2	**2.0**	**15/01/20205**	Revised sample size	Revised allergy label percentage and sample size
1.0	**2.0**	**26/01/20205**	Agreed on all changes	

1. Introduction

Background and rationale

Surgical site infection (SSI) is an important and preventable cause of postoperative morbidity which affects 250,000 of the five million NHS patients who undergo surgery every year.[1 2] Patients who develop SSIs stay longer in hospital, have an increased mortality, and can experience poorer quality of life. Treatment of SSIs is also associated with significant healthcare costs to healthcare providers.[3-5]

Antimicrobial prophylaxis is an important method for preventing SSI and is a widely used practice in surgical care. However, advances in surgical techniques (e.g. laparoscopic and robotic), operative theatre design (e.g. laminar flow air conditioning) and perioperative care (e.g. pre-operative patient showers) have reduced the inherent risk of SSI.[6-9] The evidence supporting the use of antimicrobial prophylaxis has significant limitations, with many trials conducted more than 20 years ago and potentially less relevant to contemporary practice.[7 9 10] A recent extensive systematic review and meta-analysis found that while antimicrobial prophylaxis is associated with a 1% absolute risk reduction for SSI, the evidence quality was poor. In several surgical groups, patients receiving prolonged courses of prophylaxis experienced a small benefit in terms of infection risk, compared to those receiving short-duration courses (Risk Difference -0.01 [-0.02 to -0.01]; I2=52%). A similar result was seen when comparing no prophylaxis to ≥1 dose (Risk Difference -0.02 [-0.03 to -0.02]; I2=62%). This suggests that antimicrobial prophylaxis might not be required in the doses currently prescribed or, in some cases, not required at all.

The side effects and harms caused by antimicrobial drugs can be substantial, with 1 in 50 surgical patients suffering complications directly attributable to antimicrobial use including acute kidney injury, hearing loss and anaphylaxis.[11] [12] A recent national audit identified antimicrobials as the single commonest cause of life-threatening allergic reactions during surgery.[13] The scale of this problem is unknown because there is no system to report antimicrobial use and its associated harms, and the frequency of side-effects of antimicrobial drugs are poorly reported in trials supporting their use.[11] At a societal level, the use of antimicrobial drugs is the principal cause of antimicrobial resistance and represents a fundamental threat to our society and to contemporary and future healthcare.[6] [11]

Antimicrobial prophylaxis may be associated with a small reduction in the risk of surgical site infection, but the evidence quality is poor. Limited reporting of harm makes it difficult to balance risks and benefits of this widely used intervention. We undertook an observational study to report both the benefits and harms of routine antimicrobial prophylaxis for common surgical procedures.

Objectives

- To identify any associations between the type and number of doses of antimicrobial drugs administered during the perioperative period and the incidence of surgical site infection within 30 days after surgery.
- To describe any associations between number of doses of antimicrobial prophylaxis and the following:
    - Antimicrobial side effects
    - Postoperative infections
    - Other complications (listed in appendix)
    - Hospital readmissions
    - Mortality at 30 days after surgery

2. Sample size calculation

Overview

The sample size for the SAPPHIRE observational cohort study was calculated using the “simsam” package in STATA (version 17.0), which employs a simulation-based approach. The study's primary objective is to detect an association between antimicrobial prophylaxis and the risk of surgical site infection (SSI). Additionally, the study seeks to evaluate

secondary outcomes, including antibiotic-related complications, mortality, and the impact of allergy labels on postoperative complications.

The primary analysis will use logistic regression models to test the association between antimicrobial prophylaxis and SSI.

Primary Outcome Sample Size Calculation

To detect an association between SSI risk and the number of antimicrobial doses administered, the dose was modelled as a Poisson random variable with a mean and variance of 2. A linear relationship was assumed between the log-odds of SSI and the antimicrobial dose, with the following parameters:

- **Risk of SSI at the mean dose**: 10%.
- **Risk of SSI at dose 0**: 12%.

Based on this relationship, the corresponding regression coefficients were derived. Using logistic regression to test the association between antimicrobial dose and SSI risk, the following assumptions were made:

- **Power** (β): 90% (1-β = 0.90),
- **Significance level** (α): 5% (two-sided test),
- **Test type**: Two-sided hypothesis test.

Under these assumptions, a total sample size of **6,000 patients** is required to detect the desired association.

Assumptions

- The baseline incidence of SSI is assumed to be 10%.
- The antimicrobial dose follows a Poisson distribution with a mean and variance of 2.

3. Methods

Study design and setting

The multicentre observational cohort study was conducted at 23 NHS hospitals. Data were collected over a 30-day period for patients undergoing a pre-defined list of surgical procedures. Only routinely collected data was used to answer our objectives. There was no additional patient or primary care contact.

Participants and data collection

Patients were aged 18 years and over at participating centres undergoing one of the below surgical procedures:

- Colorectal resection
- Elective Caesarean section
- Abdominal hysterectomy
- Vaginal hysterectomy
- Primary hip replacement
- Primary knee replacement
- Transurethral resection of prostate
- Transurethral resection of bladder tumour
- Open surgery for closed long bone fracture (leg or arm)

Open, robotic, laparoscopic, laparoscopically assisted and laparoscopic procedures converted to open are all eligible versions of the above procedures.

A thorough data cleaning procedure will be implemented as follows:

- The database has been designed to minimise data entry errors by having various validations measures in place. The e-CRF provides a warning message and asks the user to confirm the value of any data entered which lie outside the pre-determined validity range (hard and soft ranges), e.g. if haemoglobin is less than 30 g/L or age greater than 100 years.
- Data will be verified for duplicates and removed.

4. Exposures and outcomes

Exposures

- Number of doses of antimicrobial drugs administered as prophylaxis before, during or after surgery to prevent an infection
- Type of antimicrobial drug administered as prophylaxis before, during or after surgery to prevent an infection

Primary outcome

The primary outcome is surgical site infection (bacteriuria for urological surgery) within 30 days after surgery (US Centre for Disease Control Criteria).[19] This includes any of:

- Superficial surgical site infection
- Deep surgical site infection
- Organ space surgical site infection
- Urinary tract infection or bacteriuria

Secondary outcomes

- Number of antimicrobials to treat an infection
- Incidence of antimicrobial side effects within 30 days after surgery:
  - Acute kidney injury of any cause
  - Diarrhoeal illness of any cause
  - Hearing loss, tinnitus or vertigo of any cause
  - Suspected allergic reaction to antimicrobials
- Incidence of postoperative infection within 30 days after surgery
- Incidence of all postoperative complications within 30 days after surgery
- Mortality at 30 days after surgery

5. Statistical analysis

Characteristics of the cohort

The following characteristics will be presented overall.

- Age, mean (SD) and median (IQR)
- Gender, n (%)
- ASA grade (I, II, III, IV), n (%)
- Documented drug allergies – n (%)
- Risk factors (obesity, antibiotics for pre-existing infection, immunosuppressant disease, active malignancy, current smoker, diabetes mellitus, poor nutritional state, immunosuppressant drugs, know carrier of resistant organism, chemo or radiotherapy), n (%)
- Anaesthetic technique (general, spinal, epidural, other regional), n (%)
- Surgical procedure (colorectal resection, elective Caesarean section, abdominal hysterectomy, vaginal hysterectomy, primary hip replacement, primary knee replacement, transurethral resection of prostate, transurethral resection of bladder tumour, open surgery for closed long bone fracture), n (%)
- Wound contamination, n (%)
- Duration of surgery (<2, 2-<4, 4-<6, >6 hours), n (%)

Analysis

Descriptive analysis

We will report a summary of descriptive data stratified by the presence or absence of antimicrobial prophylaxis. Continuous data will be presented as mean (SD) or median (IQR) and categorical data will be presented as number (%). Hypothesis testing will not be conducted on baseline data (table 1). We will summarise clinical care received, including the surgical procedure category and mode of anaesthesia (table 2)

Inferential analysis

Binary outcomes:

1. Surgical site infection within 30 days after surgery
2. Antimicrobial side-effects within 30 days after surgery
3. Suspected allergic reaction within 30 days after surgery
4. Postoperative infection within 30 days after surgery
5. Postoperative complications (Clavien-Dindo grade 2 or higher) within 30 days after surgery
6. Mortality within 30 days after surgery

Count outcomes:

1. Total number of doses to treat an infection

For each of the above binary outcomes, a mixed effects logistic regression model will be used. A random intercept for the trial site will be included to account for clustering of patients within centres. The models will be adjusted for baseline covariates, including age, gender, type of surgery, smoking status, diabetes status, ASA grades, wound contamination status, duration of surgery, active cancer, liver cirrhosis and obesity. These covariates are selected based on clinical plausibility and will be entered into the model using forced simultaneous entry rather than a variable selection procedure.

For the analysis of mortality, additional covariates such as hypertension, heart failure, coronary artery disease, peripheral vascular disease, and asthma/COPD will be included.

The count outcome of total number of antimicrobial doses administered to treat an infection will be analysed using a mixed effects negative binomial regression model to assess the association between antimicrobial exposure and the total number of doses required to treat an infection. This model will also include a random intercept for the trial site to account for clustering and will be adjusted for the same covariates as in the logistic regression model.

To investigate the association between the baseline risk factors and outcomes, as well as the main exposure of interest (antimicrobial prophylaxis), we will

1. Fit a mixed effect logistic regression model for binary outcomes and a mixed effects negative binomial regression model for count outcomes.
2. Adjust for covariates (age, gender, surgery type, smoking status, diabetes status, ASA grade, wound contamination status, duration of surgery, active cancer, liver cirrhosis, and obesity).
3. Compare the adjusted effect estimates with the crude effect estimates for the main exposure.

Subgroup analysis

The following subgroup analyses will be performed

By type of antimicrobial prophylaxis

- Single-dose prophylaxis
- Multiple-dose prophylaxis

Sensitivity analysis

Two main sensitivity analyses will be conducted:

- **Prophylaxis Timing**: We will stratify patients based on whether the first dose of antimicrobials was administered according to guidelines (i.e., before the induction of anaesthesia and within 60 minutes of surgical incision). The exposure variable will be re-categorized based on these criteria, and the primary analysis will be repeated to assess whether the timing of prophylaxis affects the outcomes.
- **Primary Care Initiation**: Not all centres have access to primary care data. To assess the robustness of the findings, we will stratify the analysis by whether the treatment was initiated by a General Practitioner (GP**)** and repeat the analysis accordingly.

All the analyses will be conducted using STATA version 17.0 or R 4.4.1. The results will be reported with 95% confidence intervals (CI) and p-values. A significance level of $p < 0.05$ will be considered statistically significant.

Handling of missing data

Missing data will be handled according to a pre-specified strategy. Depending on the extent and nature of missing data:

- **Complete case analysis**: The primary analysis will use only participants with complete data.
- **Multiple imputation**: If missing data are substantial and assumed to be missing at random (MAR), multiple imputation techniques will be employed using the R package mice 3.16.0.

- Sensitivity analyses will be conducted to assess the robustness of results when different methods for handling missing data are applied.

6. References

1. Abbott TEF, Fowler AJ, Dobbs T, et al. Frequency of surgical treatment and related hospital procedures in the United Kingdom: A national ecological study using hospital episode statistics. British Journal of Anaesthesia 2017; 119(2): 249-57.
2. ISOS study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle and high-income countries. Br J Anaesth 2016; 117(5): 601-09.
3. GlobalSurg Collaborative. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. The Lancet. Infectious diseases 2018; **18**(5): 516-25.
4. A summary of selected new evidence relevant to NICE clinical guideline 74 “Prevention and treatment of surgical site infection” (2008). Evidence update 43. June 2013. Manchester: National Institute for Health and Care Excellence; 2013. (http://www.nice.org.uk/guidance/cg74/evidence, accessed 21 July 2016).
5. Scottish Intercollegiate Guidelines Network. Antibiotic prophylaxis in surgery. July 2008, updated April 2014. Edinburgh:

7. Appendix 1: Dummy tables

Table 1: Patient baseline and operative characteristics

Patient baseline and operative characteristics	Number of patients with available data – no. (%)	Summary measure
Gender – no. (%)		
Male		
Female		
Age (years)		
Mean (SD)		
Median (IQR)		
[a] American Society of Anaesthesiology grade – no. (%)		
I		
II		
III		
IV		
Documented drug allergies – no. (%)		
Yes		
No		
[b] Risk factors – no. (%)		
Obesity (BMI ≥ 30)		
Liver cirrhosis		
Heart failure		
Hypertension		
Asthma/COPD		
Diabetes mellitus		
Active cancer		
Coronary artery disease		
Stroke		
Peripheral vascular disease		
Current smoker		
Anaesthetic technique – no. (%)		
General		
Spinal		
Epidural		
Other regional		

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] American Society of Anaesthesiology grades are defined as follows (grade 5 patients were not eligible for inclusion): 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; and 4, a patient with severe systemic disease that is a constant threat to life.

b Patient may have more than one risk factor.

Table 2: Clinical care

Clinical characteristics	Number of patients with available data – no. (%)	Summary measure
Anaesthetic technique – no. (%)		
General		
Spinal		
Epidural		
Other regional		
Surgical procedure category – no. (%)		
Colorectal resection		
Elective Caesarean section		
Abdominal hysterectomy		
Vaginal hysterectomy		
Primary hip replacement		
Transurethral resection of prostate		
Transurethral resection of bladder tumour		
Open surgery for closed long bone fracture (leg or arm)		
Wound contamination during surgery – no. (%)		
Yes		
No		
Operative time – no. (%)		
0-<2 hours		
2-<4 hours		
4-<6 hours		
> 6 hours		

Table 3: Antimicrobial administration during and after surgery

Antimicrobial administration	Number of patients with available data – no. (%)	Summary measure
Prophylactic antimicrobial use		
Start of surgery – no. (%)		
Number of doses		
Mean (SD)		
Median (IQR)		
Further antibiotics during surgery – no. (%)		
Number of doses		
Mean (SD)		
Median (IQR)		
After surgery – no. (%)		
Number of doses		
Mean (SD)		
Median (IQR)		
Therapeutic antimicrobial use to treat an infection - no. (%)		
Indication - no. (%)		
Route of antimicrobial administration - no. (%)		
Intra-venous		
Oral		
Patient discharged with an antimicrobial prescription - no. (%)		
Total duration of all therapeutic antimicrobials (days)		
Mean (SD)		
Median (IQR)		
Total number of antimicrobial doses administered		
Mean (SD)		
Median (IQR)		
Antibiotic class - no. (%)		
None		
Cefuroxime		
Co-Amoxiclav		
Metronidazole		
Gentamicin		
Teicoplanin		
Other		

Table 4: Primary analysis

Table 5: Secondary analysis

Table 6: Reintervention and hospital stay within 30 days of surgery

Figure 1: Patient flow chart