Joint Research Management Office (JRMO) Research Protocol for Research Studies

Full Title	**Safe Antimicrobial ProPhylaxis for surgery study**
Short Title	SAPPHIRE
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1. Contents

2. Glossary

CI	Chief Investigator
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
IRAS	Integrated Research Application System
ISF	Investigator Site File
Participant	An individual who takes part in a clinical study
PI	Principal Investigator
QMUL	Queen Mary University of London
REC	Research Ethics Committee
TMF	Trial Master File

3. Signature Page

CI Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of GCP, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

CI name: **Dr Tom Abbott**

Signature: 

Date: **29/04/2024**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for the statistical work in this protocol is accurate and take responsibility for statistical analysis and oversight in this study.

Statistician's name: **Mr Akshaykumar Patel**

Signature: 

Date: **29/04/2024**

4. Summary and Synopsis

Short title	SAPPHIRE study
Methodology	National, multi-centre prospective observational cohort study collecting only anonymised data
Research sites	NHS hospitals undertaking elective surgery as listed above
Objectives	1. To identify association between the use of perioperative antimicrobial drugs and the incidence of postoperative surgical site infection. 2. To identify association between the use of perioperative antimicrobial drugs and other perioperative complications. 3. To identify association between antimicrobial allergy labels and perioperative complications.
Number of participants	13,720 patients data sets
Inclusion criteria	Adult patients (aged ≥18 years) undergoing one of the following surgical procedures: • Primary hip or knee replacement • Internal fixation of a closed long bone fracture (upper or lower limb) • Colorectal resection • Trans-urethral resection of prostate or bladder tumour • Caesarean section • Hysterectomy (vaginal or abdominal)
Exclusion criteria	• Use of antibiotics in the two weeks prior to surgery • Previous participation in the study
Statistical methodology and analysis	Continuous variables will be reported as a mean with standard deviation or median with interquartile range. Multivariable regression analysis will be used to test associations between exposure and outcome measures, adjusting for pre-specified covariates that are plausibly associated with both exposure and outcome. Logistic regression models will be used for binary outcomes and linear regression models for continuous outcomes. The threshold for statistical significance will be 5%. A single final analysis is planned at the end of the study.

Study duration	31 months

5. Study Team

Name	Role
Dr Tom Abbott	CI NIHR Clinical Lecturer
Dr Louise Savic	Site PI - Consultant Anaesthetist and NIHR Doctoral Fellow
Dr Vikas Kaura	NIHR Clinical Lecturer
Professor Rupert Pearse	Professor of Intensive Care Medicine
Dr Priyanthi Dias	Senior Trials Coordinator
Ms Salma Begum	Trials Coordinator
Mr Akshaykumar Patel	Statistician
Dr Alexander Fowler	NIHR Doctoral Research Fellow
Mr John Hitchman	Patient and Public Involvement Researcher

6. Introduction

6.1. Background

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] We conducted an extensive systematic review and meta-analysis and found that while antimicrobial prophylaxis is associated with a 1% absolute risk reduction for SSI, the evidence quality was poor. In a number of surgical groups, patients receiving prolonged course 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] In addition, self-reported antimicrobial allergy can lead to harm from the use of alternative antimicrobial drugs that are less effective and more toxic.[11] Up to 1 in 7 patients carries such a label, although a diagnosis of allergy has rarely been proven through specialist allergy investigation. Previous work has demonstrated that the most common antibiotic allergy is to penicillin, with this label carried by 12% (2624/21,224) of elective surgical patients in the UK.[14] Of such patients, half received second-line antimicrobial drugs and 40% received either no prophylaxis,

or a drug not recommended by local guidelines. Based on these findings, an estimated 100,000 patients every year may be unnecessarily denied penicillin-based antibiotics. Avoidance of penicillin is a recognised cause of harm in a variety of patient groups, associated with increased nosocomial infections,[15] increased wound infections,[16] and higher mortality.[17] Other research has demonstrated increased length of stay for mixed populations of hospital in-patients.[18] The scale of this problem is unknown because there is no system to report antimicrobial use and its associated harms.[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. One third of hospital in-patients receive antimicrobial drugs but as many as two thirds of these prescriptions may be inappropriate in terms of indication, duration or dose.[6 11] Antimicrobial prophylaxis represents a major driver of antimicrobial resistance and may increase the number of untreatable surgical infections. 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. The over-arching aim of our research is to provide contemporary evidence for perioperative antimicrobial prophylaxis and find safe ways to minimise the use of these drugs.

6.2. Rationale

Our aims of the study are to provide detailed data describing the clinical effectiveness of antimicrobial prophylaxis and define the risks of harm during the perioperative period. This will include:

1. An understanding of the treatment effect of antimicrobial prophylaxis in preventing SSI
2. Description of clinically relevant harm associated with the use of antimicrobial prophylaxis
3. Details of any association between drug allergy labels and SSI

7. Study Objectives

7.1. Exposures of interest

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

7.2. Primary objective

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.

7.3. Primary outcome measure

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

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

7.4. Secondary objectives

To describe any associations between number of doses of antimicrobial prophylaxis or presence of an allergy label and the following:

- Antimicrobial side effects
- Postoperative infections
- Other complications (listed in appendix)
- Mortality at 30 days after surgery

7.5. Secondary outcome measures

- 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
- Suspected allergic reaction to any other drug
- Incidence of postoperative infection within 30 days after surgery
- Incidence of all postoperative complications within 30 days after surgery
- Mortality at 30 days

7.6. Process measures

- Duration of hospital stay (number of days from surgery until hospital discharge)
- Critical care admission (level two or level three)*
- Duration of critical care days (level two or level three)*

*A full list of definitions is available in the appendix A

7.7. Inclusion criteria

Adult patients aged 18 years and over undergoing one of the following surgical procedures:

- Primary hip or knee replacement
- Internal fixation of a closed long bone fracture (upper or lower limb)
- Colorectal resection
- Trans-urethral resection of prostate or bladder tumour
- Caesarean section
- Hysterectomy (vaginal or abdominal)

7.8. Exclusion criteria

- Use of antibiotics in the two weeks prior to surgery
- Previous participation in the study

8. Study Design

Multi-centre observational cohort study.

8.1. Recruitment and informed consent

Patient consent will not be required on the basis that the dataset will only include variables documented as part of routine clinical care and that identifiable patient data

will not leave the hospital where each individual patient is treated. Only anonymised or coded data will be provided to the SAPPHIRE study group.

8.2. Schedule of assessment

Event/ Visit	Screening	Before surgery	After surgery	Hospital discharge	30 days after surgery
Inclusion/ exclusion criteria	x				
Medical history		x			
Demographic information		x			
Review of medical notes		x	x	x	x
Preoperative information		x			
Intraoperative information			x		
Postoperative information			x		
Details of hospital stay				x	
End of study					

8.3. Study data

Data will be collected on all eligible patients who undergo surgery during the study recruitment period. Only routine clinical data will be included and where this is unavailable the domain will be left blank.

8.4. Data collection

A standardised data set will be collected for each patient recruited by the study investigator in all participating hospitals. The patient's medical records will be reviewed by a member of the research team, and identify significant events during the admission. The primary outcome assessment will occur at 30 days after the index surgical procedure. Data will be uploaded directly onto a bespoke and secure online database held by Barts London NHS Trust.

8.5. End of study definition

The end of the study is defined as the end of the 30-day follow-up for the last patient enrolled in the study.

9. Statistical Considerations

We will use a pre-specified statistical analysis plan. The sample size required to detect an association between SSI and dose was calculated using the 'simsam' package in STATA (Version 17.0), which uses simulation. We assumed that dose was a Poisson random variable with mean and variance 2, and that there was a linear relationship between log(p/(1-p)) and dose, where p is the risk of SSI. To specify the association we would like power to detect we specified the SSI risk at the mean dose (10%) and the SSI risk at dose 0 (12%), which then determines the coefficients in the linear relationship between log(p/(1-p)) and dose. To demonstrate an association between dose and SSI risk using logistic regression, with 90% power at the 5% significance level, we require 6000 patients. Also, to demonstrate an association between allergy label (binary exposure) and complications. The incidence of complications in exposed 15% and unexposed 10%, with 80% power at the 5% significance level we require 1372 patients. However, we expect only 10% of the sample to have an allergy label, so the total sample size would need to be 13720. Considering both sample size calculations for our primary and principal secondary outcomes we aim to recruit a total 13720 patients.

The primary analysis will test associations between antimicrobial prophylaxis and surgical site infection. Secondary analyses will examine the association between the type and number of doses of antimicrobial prophylaxis and potential antibiotic-related harms (including allergic reactions, acute kidney injury, diarrhoeal illness within 30 days after surgery), as well as other postoperative infective complications within 30 days after surgery, and mortality at 30 days. In addition, we will examine any associations between the presence of drug allergy labels and SSI, other postoperative infections and antibiotic-related complications. We will report continuous variables as mean with standard deviation or median with interquartile range. We will use multivariable regression analysis to test associations between exposure and outcome measures, adjusting for pre-specified covariates that are plausibly associated with both exposure and outcome. We will use logistic regression models for binary outcomes and linear regression models for continuous outcomes. The threshold for statistical

significance will be 5%. We will handle missing data according to a pre-specified plan, based on the type and amount of missing data. Our main strategies will be list-wise deletion and multiple imputation. Data will be analysed using STATA version 14 or R. Analysis code will be published in a supplementary appendix to any manuscript.

10. Ethics

The Chief Investigators (CI) must ensure that the study is conducted in accordance with the guidelines of the International Conference on Harmonisation, Good Clinical Practice (GCP) and UK legislation. All study documentation will be reviewed and approved by the research ethics committee prior to start of recruitment. Research Ethics Committee (REC), Health Research Authority (HRA) and Sponsor approvals will be in place before patient recruitment commences. The study will be sponsored by QMUL. Additionally, each participating site will ensure that the approval of the relevant trust Research & Development (R&D) department and Ethics Committee is in place and a written confirmation is provided to the Sponsor.

10.1. Annual Safety Reporting

There is no risk of harm to either patients or investigators.

11. Public Involvement

The grant proposal for this study has been designed with the PPI members at The Patient, Carer & Public Involvement and Engagement (PCPIE) group at the Royal College of Anaesthetists. Furthermore, our PPI co-applicant have reviewed the protocol and will continue to advise us for the duration of the study including dissemination of the study results.

12. Data Handling and Record Keeping

12.1. Information governance

The study will be sponsored by Barts Health NHS Trust and will follow NHS and sponsor standard operating procedures for data storage and access and are consistent with the principles of the Data Protection Act and General Data Protection Regulation (GDPR).

12.2. Data management

Data will be transcribed onto the electronic CRF (eCRF) on the secure data entry web portal. Submitted data will be reviewed for completeness and consistency by authorised users within the trial coordinating team. Submitted data will be stored securely against unauthorised manipulation and accidental loss. Only authorised users at site, or at Barts Health NHS Trust will have access. Desktop security is maintained through usernames and passwords. Data back-up procedures are in place and a full audit trail will be kept. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK).

12.3. Source Data

For the purposes of this study, source data will be the information collected in the patient's medical notes.

12.4. Confidentiality

The PI has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and REC Approval. The CI and the study team will adhere to these parameters to ensure that the participant's identity is protected at every stage of their participation within the study. Patients will be anonymised with regards to any publications relating to this study.

12.5. Record retention and archiving

During the course of research, the CI has full responsibility of all study records which must be kept in secure conditions at all times. The UK Policy Framework for Health and Social Care Research requires that research records are kept for 5 years after the study has completed. Archiving will be authorised by the Sponsor following submission

of the end of study report. The Sponsor is responsible for maintaining and archiving the study TMF. The study database will be stored according to the Sponsor's policies. Electronic data sets will be stored indefinitely. The sites are responsible for maintaining and archiving all local records including the ISF and CRFs. These records should be archived together once authorisation has been given by the Sponsor. It is the responsibility of the PI to ensure a full set of records is collated and documented.

13. Monitoring and Auditing

The sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable. The SAPPHIRE study master documents will be audited by the sponsor to ensure study activities are conducted according to the protocol, the sponsor's standard operating procedures, GCP and the applicable regulatory requirements. In participating hospitals, local study documents may be selected for audit on a local basis. However, the SAPPHIRE study team will not routinely monitor data collection in individual hospitals or conduct source data verification.

14. Study Management

The SAPPHIRE study will be managed by the Critical Care and Perioperative Medicine Research Group (CCPMG) based at Queen Mary University of London. The day-to-day conduct of the study trial will be led by the trial management group, under the management of the Chief Investigator(s) or nominated deputy.

15. Finance and Funding

The SAPPHIRE study is funded by the British Journal of Anaesthesia/ Royal College of Anaesthetists project grant (WKR0-2020-0020), and by an NIHR Doctoral Fellowship (NIHR301454). The funders will play no role in study design, conduct, data collection, data analysis, reporting or interpretation of the results.

16. Sponsorship and Insurance

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

17. Dissemination of Research Findings

Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the SAPPHIRE study group. At least one of the lay members will contribute to the dissemination of protocol and final manuscripts. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the design, committee membership, accrual of eligible patients and statistical analysis. All authors will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. The funders, contributing centres (and participating investigators) will be acknowledged in the final manuscript. No investigator may present data from his/her centre separately from the rest of the study results unless approved by the study management team and the sponsor. The full study report will be submitted to the funder and will also be made accessible via ISRCTN.

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19. Appendices

19.1. Appendix A: Clavien-Dindo grading and complication definitions

Clavien-Dindo scale grading:

I. Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention. Anti-emetics, anti-pyretics, diruetics, electrolytes or physiotherapy are not considered a deviation from the normal postoperative course.
II. Requires pharmacological treatment with drugs (including blood transfusion or total parenteral nutrition) other than those excluded from grade I.
III. Requires surgical, endoscopic or radiological intervention.
IV. Life-threatening complication requiring critical care admission
V. Death

Definitions:

Infective complications

Surgical site infection (SSI) (superficial)

a) Involves only skin and sub-cutaneous tissue of the incision AND
b) the patient has at least one of the following:
   - purulent drainage from the superficial incision
   - organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
   - at least one of the following symptoms or signs of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.
   - diagnosis of an incisional surgical site infection by a surgeon or attending physician.

Surgical site infection (deep)

a) Involves deep soft tissues (e.g. fascial and muscle layers) of the incision AND
b) the patient has at least one of the following:
   - purulent drainage from the deep incision but not from the organ/space component of the surgical site
   - a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least

one of the following symptoms or signs: fever (>38^{o}C), or localized pain or tenderness. A culture-negative finding does not meet this criterion.

- an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination.
- diagnosis of an incisional surgical site infection by a surgeon or attending physician.

Surgical site infection (organ space)

An infection at the surgical incision site involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and the patient has at least one of the following:

- purulent drainage from a drain that is placed through a stab wound into the organ/space.
- organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space.
- an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- diagnosis of an organ/space surgical site infection by a surgeon or attending physician.

Pneumonia

This is defined as two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

- new or progressive and persistent infiltrates
- consolidation
- cavitation

And at least one of the following:

- fever (>38°C) with no other recognized cause
- leucopenia (<4x10^{9}/L) or leucocytosis (>12x10^{9}/L)
- for adults >70 years old, altered mental status with no other recognized cause

And at least two of the following:

- new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
- new onset or worsening cough, or dyspnoea, or tachypnoea
- rales or bronchial breath sounds
- worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand)

Urinary tract infection

A positive urine culture of ≥10^5 colony forming units/mL with no more than two species of micro-organisms with at least one of the following symptoms or signs:

- fever (>38°C)
- urgency
- frequency
- dysuria
- supra-pubic tenderness
- costo-vertebral angle pain or tenderness with no other recognised cause, identified within a 24-hour period.

Alternatively, the patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathologic examination with one of the following:

- purulent drainage from affected site
- radiographic evidence of infection
- physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space
- physician institutes antibiotic therapy for an infection of the kidney, ureter, bladder, urethra, or surrounding tissues

Laboratory confirmed bloodstream infection

An infection which meets at least one of the following criteria but is not related to infection at another site:

- Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site
- Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following:
    - common skin contaminant cultured from two or more blood cultures drawn on separate occasions
    - common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes antimicrobial therapy
    - positive blood antigen test

Intracranial infection

An infection must meet at least one of the following criteria:

- Patient has organisms cultured from brain tissue or dura.
- Patient has an abscess or evidence of intracranial infection seen during a surgical operation or histopathologic examination.
- Patient has at least two of the following signs or symptoms with no other recognized cause:
    - headache
    - dizziness
    - fever (>38°C)
    - localizing neurologic signs
    - changing level of consciousness, or confusion

  And at least one of the following:
    - organisms seen on microscopic examination of brain or abscess tissue obtained by needle aspiration or by biopsy during a surgical operation or autopsy
    - organisms seen on microscopic examination of brain or abscess tissue obtained by needle aspiration or by biopsy during a surgical operation or autopsy
    - positive antigen test on blood or urine
    - radiographic evidence of infection, (e.g., abnormal findings on ultrasound, CT scan, MRI, radionuclide brain scan, or arteriogram)

- diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen

And

- if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy

MEN – Meningitis or ventriculitis

An infection must meet at least one of the following criteria:

- Patient has organisms cultured from cerebrospinal fluid (CSF)
- Patient has at least one of the following signs or symptoms with no other recognized cause:
  - fever (>38°C)
  - headache
  - stiff neck
  - meningeal signs
  - cranial nerve signs,
  - irritability

And at least one of the following:

- increased white cells, elevated protein, and/ or decreased glucose in CSF
- organisms seen on Gram's stain of CSF
- organisms cultured from blood
- positive antigen test of CSF, blood, or urine
- diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

And

- if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

Infection, source uncertain

An infection which is considered likely to be one of the following but cannot be differentiated because clinical information suggests more than one possible site: superficial SSI, or deep SSI, or organ space SSI, or pneumonia, or urinary tract infection, or laboratory confirmed blood stream infection. There must be a strong clinical suspicion of infection meeting two or more of the following criteria:

- core temperature <36°C or >38°

- white cell count >12 x 10^9/L or <4 x 10^9/L
- respiratory rate >20 breaths per minute or $PaCO_2$ <35 mmHg
- pulse rate >90 beats per minute

Acute kidney injury: Please see KDIGO staging criteria below:

Staging	Serum Creatinine	Urine output
1	1.5-1.9 times baseline OR ≥ 0.3mg/dl (≥26.5µmol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0mg/dl (≥353.6 mcmol/l) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Anastomotic leak

Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localised area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a sub-clinical leak**.**

Acute Respiratory Distress Syndrome (ARDS)

According to the Berlin consensus criteria (2012):

- Within one week of a known clinical insult or new worsening respiratory symptoms
- AND bilateral opacities on chest imaging, not fully explained by effusions, lobar/lung collapse, or nodules

- AND respiratory failure not explained by cardiac failure or fluid overload (requires objective assessment e.g. echocardiogram to exclude hydrostatic oedema if no risk factors are present)
- AND supplemental oxygenation (requires correcting if altitude >1000m):
  - Mild: PaO2:FiO2 between 200 and 300 mmHg with PEEP or CPAP ≥5 cmH_2O
  - Moderate: PaO2:FiO2 between 100 and 200 mmHg with PEEP ≥5 cmH_2O
  - Severe: PaO2:FiO2 ≤100 mmHg with PEEP ≥5 cmH_2O

Diarrhoeal illness (any cause)[20]

Diarrhoea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Frequent passing of formed stools is not diarrhoea.

Hearing loss (any cause)

- Partial or total loss of hearing in one or both ears

Vertigo

- Sensation of moving or of surrounding objects moving when they are not

Tinnitus[21]

- Head or ear noises that are perceivable only to the specific patient, or perception of sound when no actual external sound is present

Myocardial infarction

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:

- Symptoms of ischemia
- New or presumed new significant ST-segment or T-wave ECG changes or new left bundle branch block
- Development of pathological Q-waves on ECG
- Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intra-coronary thrombus at angiography or autopsy

Postoperative bleed

Gastro-intestinal bleed

Unambiguous clinical evidence or endoscopy showing blood in gastro-intestinal tract.

Other postoperative haemorrhage

Overt blood loss, not from the gastro-intestinal tract, requiring transfusion of two or more units of blood in two hours

Pulmonary embolism

A new blood clot or thrombus within the pulmonary arterial system. Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery

Stroke

An embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

Other definitions:

Level of care after surgery

The level of care should be defined according to the care the patient received rather than the location. For example, a patient receiving level 2 care in a level 3 area should be recorded as receiving level 2 care.

i) Critical care level three: includes advanced organ support e.g. invasive ventilation, renal replacement therapy.
ii) Critical care level two: may include advanced cardiorespiratory monitoring (e.g. invasive arterial / central venous monitoring) and basic organ support (e.g. non-invasive ventilation, inotropic/vasoactive drug administration).
iii) Surgical ward (level 0/1): normal ward care without level 2 or 3 capabilities.

Elective surgery

Surgical procedure planned or booked in advance of routine admission to hospital

Urgent surgery

Acute onset or deterioration of conditions that threaten life, limb or organ survival; fixation of fractures; relief of distressing symptoms.