NHS
Health Research Authority

# TRIAL PROTOCOL

**Full Title:** A multi-centre, randomised controlled, non-inferiority and cost effectiveness trial comparing Polyhexanide and Chlorhexidine with Neomycin to Mupirocin for nasal methicillin-resistant Staphylococcus aureus (MRSA) decolonisation amongst adult hospital in-patients

**Short title:** TIDE (Trial of Decolonisation)

**Protocol version:** Version 1.1 dated 19.05.2022

**IRAS ID:** 1004425

**Eudract number:** 2021-006732-96

**Trial registration:** ISRCTN12184897

**Funder:** NIHR HTA programme (Reference NIHR132718)

**Sponsor:** South Tees Hospitals NHS Foundation Trust

**Sponsor Reference:** TIDE

South Tees Hospitals NHS
NHS Foundation Trust

York Trials Unit
Department of Health Sciences

Northumbria Healthcare NHS
NHS Foundation Trust

MRSA Action UK

University of York

This protocol has regard for the HRA guidance and is based on Template Version 1.2 March 2020

FUNDED BY
NIHR | National Institute for Health and Care Research

## 1.1 Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Co-Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

**For and on behalf of the Trial Sponsor:**

Signature:  Date: 07/06/2022

Name: Joe Millar

Position: Research Governance Manager

**Co-Chief Investigators:**

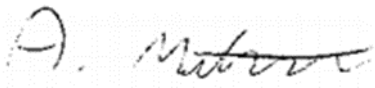
Signature:  Date: 24/06/2022

Name: Mike Reed

Signature:  Date: 07/06/2022

Name: Catherine Hewitt

**Statistician:**

Signature:  Date: 07/06/2022

Name: Alex Mitchell

Position: Trial Statistician

## 1.2 Key Trial Contacts:

| | |
|---|---|
| Co-Chief Investigators | Professor Mike Reed (MR), Consultant Orthopedic Surgeon, Northumbria Healthcare NHS Foundation Trust.<br>Email: mike.reed@nhs.net; Phone: 01670 529191<br><br>Professor Catherine Hewitt (CH), Professor of Trials and Statistics and Deputy Director, York Trials Unit.<br>Email: catherine.hewitt@york.ac.uk; Phone: 01904 321374 |
| Trial Manager | Mrs Elizabeth Cook, York Trials Unit.<br>Email: liz.cook@york.ac.uk; Phone: 01904 321522 |
| Sponsor | South Tees Hospitals NHS Foundation Trust<br>Mr Joe Millar, Research Governance Manager, Durham Tees Valley Research Alliance.<br>Email: stees.dtvra@nhs.net / joe.millar@nhs.net;<br>Phone: 07773 740784 |
| Joint-sponsor(s)/co-sponsor(s) | Not Applicable |
| Funder(s) | National Institute for Health Research (NIHR) Health Technology Assessment Programme.<br>Charlie Dukes, Research Manager<br>Email: charlie.dukes@nihr.ac.uk;<br>Phone: 02380 595653 |
| Clinical Trials Unit | York Trials Unit (University of York)<br>Email: ytu-tide-study@york.ac.uk<br>Phone: 01904 321726 |
| Statistician | Mr Alex Mitchell, York Trials Unit.<br>Email: alex.mitchell@york.ac.uk;<br>Phone: 01904 321756 |
| Trials Pharmacist | Vicky Hanlon, Specialist Lead Clinical Trials Pharmacist, The James Cook University Hospital.<br>Email: vicky.hanlon@nhs.net; Phone: 01642 854297 |
| Committees | **Trial Steering Group Chair**<br>Mrs Natalie Rowlands, Reader in Clinical Trials, Statistics Team Leader, University of Birmingham.<br>Email: n.j.ives@bham.ac.uk; Phone: 0121 415 9113<br><br>**Data Monitoring Committee Chair**<br>Dr Louise Stanton, Head of Statistics, Southampton Clinical Trials Unit, University of Southampton.<br>Email: L.Stanton@soton.ac.uk; Phone: 023 8120 3777 |

## 1.3 Amendment History/Changes from previous version

| **Amendment Number** | **Revised Protocol Version Number and date** | **Details of key changes made (including justification if required)** |
|---|---|---|
| NA (Changes requested during REC review) | 1.1 (19.05.2022) | Correction of typographical errors. |
| NA (Change from Detailed Project Description) | 1.0 (26Jan2022) | <u>Section 6.2: Secondary Outcomes</u><br>Additional outcome added relating to successful early nasal decolonisation of MRSA not fully susceptible to gentamicin (used as a marker for neomycin).<br><br><u>Section 6.3 Outcome measure definitions</u><br>Patient rated severity of key known side effects will be assessed using a 3-point Likert scale (severe, moderate, mild), rather than a 5-point Likert scale.<br><br><u>Section 8.1: Inclusion Criteria</u><br>Age amended from ≥18 to ≥16.<br><br><u>Section 8.2: Exclusion Criteria</u><br>Rewording of criteria relating to contra-indications and allergies.<br><br>Additional criteria added to exclude patients with medical history that would put them at risk from participation.<br><br><u>Section 9.5.1: Microbiology Evaluation</u><br>Recruiting sites will be requested to send a nutrient agar slope of the baseline sample, rather than a slope or the original swab, to Northumbria for the antimicrobial sensitivity analysis conducted at baseline.<br><br>Recruiting sites will be instructed to save the original admission swabs for 2 weeks. If the slope does not grow, or is not MRSA, the processing laboratory may request a repeat slope.<br><br>If another bacterium of concern is identified by the processing laboratory, this will be reported back to the participating site who have sent it as a duty of care.<br><br><u>Section 9.6: Trial assessments and data collection</u><br>To mitigate against the potential impact of the COVID-19 pandemic (e.g. increased restrictions, research staff capacity), participants may be asked to perform a self- |

| Amendment Number | Revised Protocol Version Number and date | Details of key changes made (including justification if required) |
|---|---|---|
| | | swab. Where practically possible the 48 hour post treatment swab for the primary outcome should be undertaken by a research nurse. |

## 1.4 List of Contents

## 1.5 List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| API | Associate Principal Investigator |
| AR | Adverse reaction |
| CACE | Complier Average Causal Effect |
| CI | Chief Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| CT | Clinical Trials |
| CTA | Clinical Trials Authorisation |
| CTIMP | Clinical Trial of an Investigational Medicinal Product |
| DMC | Data Monitoring Committee |
| DTVRA | Durham Tees Valley Research Alliance |
| ECG | Electrocardiogram |
| EQ-5D-5L | EuroQol Quality of Life Measure |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| FT | Foundation Trust |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment Programme |
| ICF | Informed Consent Form |
| ICT | Infection Control Team |
| IMP | Investigational Medicinal Product |
| ISF | Investigator Site File |
| ITT | Intention to Treat |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MIC | Minimum Inhibitory Concentration |
| MRSA | Methicillin Resistant Staphylococcus Aureus |
| MSSA | Methicillin Sensitive Staphylococcus Aureus |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| NRES | National Research Ethics Service |
| PAG | Patient/public Advisory Group |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| PPI | Patient and Public Involvement |

| | |
|---|---|
| R&D or R&I | NHS Trust Research & Development / Innovation Department |
| RCT | Randomised Controlled Trial |
| RDMS | Research Data Management System |
| REC | Research Ethics Committee |
| S. Aureus | Staphylococcus Aureus |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SD | Standard Deviation |
| SmPC/SPC | Summary of Products Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| SWAT | Study within a Trial |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UKCRC | UK Clinical Research Collaboration |
| USM | Urgent Safety Measure |
| YTU | York Trials Unit |

## 1.6 Trial Summary

| | |
|---|---|
| **Study Title** | Trial of De-colonisation (TIDE) |
| **Internal ref. no.**<br>**IRAS**<br>**Eudract** | Sponsor Reference Number: TIDE<br>IRAS: 1004425<br>Eudract: 2021-006732-96 |
| **Trial Design** | Multi-centre, randomised controlled, non-inferiority, pragmatic trial |
| **Trial Participants** | Patients on admission who are MRSA positive for colonisation and meeting the following inclusion/exclusion criteria:<br><u>Inclusion Criteria</u><br>• Adult in-patient (aged 16 years old or over)<br>• Eligible for MRSA screening on admission, based on the local hospital infection control policy, who are found to be colonised with MRSA<br><u>Exclusion Criteria</u><br>• Known hypersensitivity to study treatment(s) or excipients<br>• Allergy to peanut and/or soya<br>• Day-case admissions<br>• Patients identified to be colonised with MRSA in the out-patient setting<br>• Previous participation in this trial or current participation in another trial of a medicinal product(s) that excludes participants from taking part in other trials of medicinal products<br>• Patients actively undergoing another decolonisation treatment at the time of recruitment<br>• Medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial |
| Planned Sample Size | 3,000 |
| Follow-up duration | Up to 4 weeks *after* completion of study treatment |
| Planned Trial Periods: | The study will be 39 months duration with a proposed time frame of August 2021 to October 2024.<br>Study set up: 8 months, August 2021 to March 2022<br>Recruitment to pilot phase: 9 months, April 2022 to December 2022<br>Recruitment to main trial: 15 months, January 2023 to March 2024<br>Final follow up period: 1 month, April 2024<br>Analysis and reporting: 6 months, May 2024 to October 2024 |

| | |
|---|---|
| Primary Objective | To undertake a multi-centre, three-arm parallel group, non-inferiority RCT to determine whether nasal polyhexanide gel or nasal chlorhexidine with neomycin cream is not inferior to nasal mupirocin ointment, when each is accompanied with chlorhexidine body wash or wipes, for early nasal decolonisation of MRSA amongst adult hospital in-patients |
| Secondary Objectives | • Undertake a 9-month internal pilot to confirm the feasibility of the study, in particular recruitment rate and completeness of follow-up.<br>• Undertake an embedded qualitative study during the internal pilot study to optimise recruitment and consent processes with a particular focus on underserved and vulnerable populations.<br>• Undertake a cost-effectiveness analysis of the three interventions from the NHS perspective to identify the most efficient provision of future NHS care.<br>• Undertake an analysis of secondary outcomes. |
| Primary Outcomes | • Successful early nasal decolonisation, defined as a negative trial specific nasal MRSA swab taken 48 hours following treatment completion. |
| Secondary Outcomes | • Successful early nasal decolonisation of MRSA not fully susceptible to mupirocin.<br>• Successful early nasal decolonisation of MRSA not fully susceptible to gentamicin (used as a marker of neomycin).<br>• Successful late nasal decolonisation, defined as a negative trial specific nasal MRSA swab taken 4 weeks following treatment completion.<br>• Acceptability of treatment to patients (Likert scale).<br>• MRSA infections: any confirmed MRSA infections (e.g., skin and wound infections, joint infections, endocarditis, pneumonia and bacteraemia) up to 4 weeks following completion of treatment.<br>• Total length of hospital in-patient stays (obtained from patients' medical records) up to 4 weeks following completion of treatment.<br>• Total length of hospital in-patient stays for patients diagnosed with an MRSA infection (obtained from patients' medical records) up to 4 weeks following completion of treatment.<br>• Hospital readmissions (obtained from patients' medical records) up to 4 weeks following completion of treatment.<br>• Adverse events up to 4 weeks following completion of treatment.<br>• Mortality up to 4 weeks following completion of treatment |
| Investigational Medicinal Products (IMPs) | The IMPs in this study will be provided via routine hospital stocks.<br>Mupirocin 2% Nasal Ointment (3g)<br>Chlorhexidine 0.1% with Neomycin 0.5% Nasal Cream (15g) |
| Device | Polyhexanide 0.1% Nasal Gel (30ml) |

| | |
|---|---|
| Non-Investigational Medicinal Products | Chlorhexidine 4% body wash (250ml)<br>Chlorhexidine 2% skin wipes |
| Route | All Topical |

## 1.7 Funding

This study is funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) reference number NIHR132718.

The financial arrangements for the study will be as contractually agreed between the funder (NIHR HTA), and the Sponsor (South Tees Hospitals NHS Foundation Trust). A collaboration agreement will be put in place between the Sponsor and each of the collaborating organisations.

## 1.8 Role of Trial Sponsor

South Tees Hospitals NHS Foundation Trust will act as trial sponsor and have overall responsibility for the initiation and management of the trial. The primary responsibility for monitoring the safety of participants in clinical trials lies with the trial Sponsor.

## 1.9 Roles and Responsibilities of Trial Management Committees, Groups and Individuals

### 1.9.1 Co-Chief Investigators

This study has Co-Chief Investigators (Co-CIs), with clearly defined responsibilities:

Catherine Hewitt (CH) will lead on the methodological aspects of trial design and be responsible for the York Trials Unit's (YTU's) delivery of the trial, leading the team there. Mike Reed (MR), the clinical CI will be responsible for all regulatory aspects and work closely with CH across all clinical aspects of protocol development and trial activity, both liaising closely with the patient/public advisory group (PAG).

### 1.9.2 Trial Management Group (TMG)

A TMG has been established to oversee the day-to-day management of the TIDE study and is chaired by one of the Co-CIs. Other members include the trial statisticians, trial manager, trial-coordinators, infection control specialists, qualitative researcher, health economist, patient/public representative and other co-applicants. The role of the TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial. The TMG will meet by teleconference/video conference, with face-to-face meetings where feasible and required.

### 1.9.3 Trial Steering Committee (TSC)

An independent TSC has been established to provide overall independent oversight for TIDE on behalf of the Sponsor and Project Funder (NIHR HTA) and to ensure that the project is conducted to the rigorous standards set out in the UK Clinical Trials Regulations, the

Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice (GCP). The TSC will work to an agreed charter, meet at least annually and will report to the Funder. This committee comprises of an Independent Chair and independent members and the Co-CIs.

The trial manager, trial co-ordinator, a representative from the sponsor and other study collaborators may also attend the meeting with the agreement of the Chair.

### 1.9.4 Data Monitoring Committee (DMC)

The role of the DMC is to review accumulating safety and efficacy data arising from TIDE and advise the sponsor (directly or indirectly) on the future management of the trial. The DMC comprises independent members with an independent chair.

The DMC will work to an agreed Charter and make recommendations to the funder on whether there are any ethical or safety reasons as to why the trial should not continue.

### 1.9.5 York Trials Unit (YTU)

The trial will be managed and coordinated by YTU, a UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Unit based in the Department of Health Sciences at The University of York. YTU will oversee and manage the trial on a day-to-day basis, with oversight from the Co-CIs, sponsor and TMG, as well as the TSC and DMC.

## 1.10 Protocol contributors

*Table 1: Protocol Contributors*

| | |
|---|---|
| Prof Mike Reed (MR) | Co-Chief Investigator, Consultant Orthopaedic Surgeon, Northumbria Healthcare NHS FT |
| Prof Catherine Hewitt (CH) | Co-Chief Investigator, Deputy Director, York Trials Unit |
| Dr Catriona McDaid | Reader in Trials, York Trials Unit |
| Dr Alison Booth | Senior Research Fellow, York Trials Unit |
| Mr Ashley Scrimshire | Specialist Registrar, Northumbria Healthcare NHS FT |
| Belen Corbacho | Health Economist, York Trials Unit |
| Liz Cook | Trial Manager, York Trials Unit |
| Dr Arabella Scantlebury | Qualitative Researcher, York Trials Unit |
| Mr Paul Baker | Consultant Orthopaedic Surgeon, South Tees Hospitals NHS FT |
| Mr Martin Kiernan | Infection Control Lead, University of West London |
| Prof David Torgerson | Director, York Trials Unit |
| Karen Glerum-Brooks | Patient and Public Involvement (PPI) and Stakeholder Engagement Manager, York Trials Unit |
| Vicky Hanlon | Clinical Trials Pharmacist, South Tees Hospitals NHS FT |
| Maria Cann | Patient and Public Involvement (PPI) Representative, MRSA Action UK |
| Joe Miller | Sponsor Representative, South Tees Hospitals NHS FT |
| Dr David Tate | Director of Infection Prevention and Control, Northumbria Healthcare NHS FT |
| Dr Joanne Laycock | Trial Co-ordinator, York Trials Unit |
| Ann Cochrane | Trial Co-ordinator, York Trials Unit |
| Joanne Newman | Trial Support Officer, York Trials Unit |

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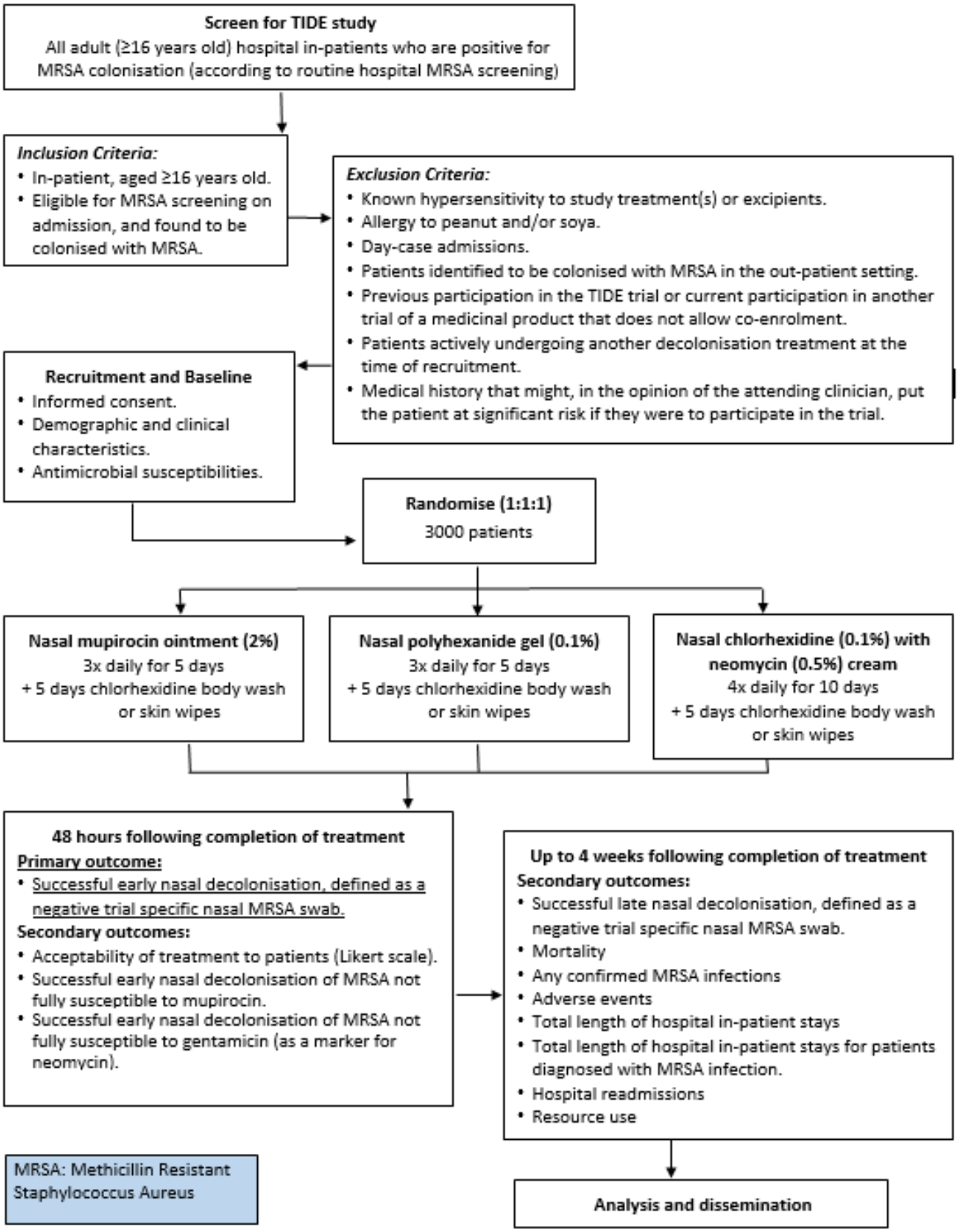
|---|---|
| Alex Mitchell | Statistician, York Trials Unit |
| Luke Strachan | Trainee Statistician, York Trials Unit |
| Val Wadsworth | Data Manager, York Trials Unit |
| Matthew Bailey | Software Development Team Lead, York Trials Unit |

## 1.11 Key Words

MRSA, Staphylococcus aureus, antibiotic resistance, nasal decolonisation

## 1.12 Trial Flow Chart



# 2 Background

## 2.1 About Methicillin Resistant Staphylococcus Aureus (MRSA)

*Staphylococcus aureus (S. aureus)* is a bacterium, it is the leading cause of hospital-acquired infections [1], and the 2nd highest cause of bloodstream infections [2]. These bacteria are difficult to treat when they have evolved resistance to the penicillin group of antibiotics and are known as methicillin-resistant Staphylococcus aureus (MRSA). Patients who carry MRSA in the nose or on their skin are said to be colonised with MRSA.

MRSA colonisation does not cause the patient any harm, however these patients are at increased risk of developing infections following hospital procedures. There is also a risk of passing MRSA on from an asymptomatic colonised carrier to another vulnerable patient in whom the bacteria may cause an infection. Many patients admitted to hospital are routinely screened for MRSA colonisation and if they are MRSA positive, they are treated to remove the MRSA from the nose and skin, this is known as being decolonised and reduces the risk of the patient developing an MRSA infection or passing MRSA on to a vulnerable patient.

The current standard treatment in the NHS for nasal MRSA decolonisation is the antibiotic nasal ointment mupirocin, which is approved and recommended by the National Institute for Health and Care Excellence (NICE)[3].

# 3 Rationale

Some MRSA species have now also developed resistance to mupirocin as well as methicillin, they are known as mupirocin resistant MRSA. There are concerns about over-reliance on a single antibiotic treatment in terms of potential shortages as well as antibiotic resistance.

A trial is required to investigate the clinical and cost effectiveness of alternative treatment regimens for nasal MRSA decolonisation. This trial has been designed in response to a commissioning brief from the National Institute for Health Research Health Technology Assessment programme.

Sakr et al (2019) identify 17 different decolonisation treatments, many in very early stages of investigation and without the necessary approvals and are therefore not suitable for this study [4]. This trial will evaluate two options as this increases the likelihood of finding an alternative to mupirocin and is a more efficient design than a two-arm trial. A nasal antiseptic alternative to mupirocin is a preferable, long-term solution over another antibiotic, as the chances of MRSA developing resistance to an antiseptic is less likely than to another antibiotic. Options where there are some suggestions of benefit are povidone iodine, alcohol gel, octenidine, and polyhexanide. Two of these options are currently available in the UK market as a nasal decolonisation preparation; octenidine and polyhexanide. Substantial changes to the formulation (concentration, viscosity and licencing) of octenidine are planned by the manufacturers during the study period, therefore it will not be included.

This study will use polyhexanide nasal gel as the antiseptic that is an alternative to mupirocin. Polyhexanide has been shown to be effective in vitro against a wide range of antibiotic resistant S. aureus strains, including a vancomycin-intermediate strain and multiple mupirocin resistant strains, including strains exhibiting high-level mupirocin resistance [5, 6].

However, the existing evidence for the clinical effectiveness of polyhexanide for nasal MRSA decolonisation is mixed and inconclusive, and largely consists of observational studies [4]. There is one randomised controlled trial (RCT) which did not show a statistically significant benefit for nasal decolonisation at 28 days after the end of treatment with polyhexanide compared to placebo (risk difference, 4.5%; 95% CI, -10.6% to 19.5%; P = 0.56). This trial had several limitations, such as a small sample size and a lack of treatment adherence reporting. In addition, the authors later found their 'placebo' was also an active bactericidal compound against MRSA, limiting the usefulness of these results [5]. High quality, randomised trials of polyhexanide are currently lacking. Yet, polyhexanide nasal gel is already used in some NHS Trusts as part of MRSA decolonisation protocols and is readily available via NHS procurement processes.

The second intervention in this trial will be nasal chlorhexidine with neomycin cream [7], this is an antibiotic combined with an antiseptic. Although this still involves an antibiotic and cases of resistance have been reported [8], if it was shown to be a viable alternative to mupirocin, the options available for MRSA decolonisation would be widened. In addition, chlorhexidine with neomycin is already used in many NHS Trust MRSA pathways, often as an alternative to mupirocin or as a second line treatment, though high-quality randomised trials are lacking [3]. It is also readily available through NHS procurement processes.

NICE recommends that chlorhexidine body wash in combination with nasal mupirocin is considered, though notes the lack of comparative evidence of mupirocin with and without chlorhexidine body wash [3]. The potential advantage of this combined approach is to decolonise MRSA on the skin as well as in the nose, reducing the chances of early nasal re-colonisation that may occur if only the nose was decolonised. Chlorhexidine body wash and body wipes are already used as part of many NHS Trust decolonisation policies and one will be used alongside each of the nasal decolonisation regimes in this study.

The eligible population for this trial will be hospital in-patients, colonised with MRSA including recruitment from geographic populations with high disease burden. Our site identification and participant identification strategies are described in the 'Trial Setting' and 'Recruitment' sections and aim to include patients who have a greater risk of MRSA nasal colonisation, and particularly vulnerable and underserved populations.

## 3.1 Assessment and management of risk

All treatments used in this trial are routinely used across the NHS and are approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for use as MRSA decolonisation treatments.

In the context of a lack of robust evidence to determine the best intervention for patients with MRSA colonisation, the risks are not increased through trial participation. However, there are risks associated with this study, which are associated with all study treatments.

Patients will be screened for MRSA upon admission, in line with routine hospital policy. There will be no additional baseline swab, however, patients will be required to have two additional follow up nasal swabs for the study.

Measures taken such as emphasis on GCP and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits. We will adhere to the Research Governance Framework/ UK Policy Framework for Health and Social Care

Research and as this study falls under the legislation as a Clinical Trial of an Investigational Medicinal Product (CTIMP) we will work towards compliance with UK Statutory Regulations for The Medicines for Human Use (Clinical Trials) Regulations (2004) as amended.

The participant information sheets (PISs) will be developed with the involvement of our Patient Advisory Group (PAG) and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the individual decides a) not to enter the trial or b) to withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants as described in section 9.2 after sufficient time to read the study information materials and ask questions. The timeframe for consideration to take part may be restricted to less than 24 hrs in order for decolonisation treatment to commence quickly.

The trial will be subject to TMG, DMEC and TSC oversight. The study will also be monitored by the sponsor according to a monitoring plan.

This trial is categorised by the sponsor as:

- **Type A = No higher than the risk of standard medical care**

A risk assessment has been performed by the sponsor and will continue to be reviewed in accordance with the Durham Tees Valley Research Alliance SOPs (SOP DTVRA) - SOP 014. The risks from the study interventions and study treatments are not increased through trial participation and are similar to those of routine standard care for MRSA decolonisation management. Mitigation plans, such as emphasis on protocol and GCP compliance, study monitoring, and site training are expected to reduce these risks.

# 4 Objectives

We aim to investigate whether nasal polyhexanide gel (an antiseptic) or nasal chlorhexidine with neomycin cream (an antiseptic with antibiotic) are suitable alternatives to nasal mupirocin ointment (an antibiotic), when each nasal treatment is given with chlorhexidine (antiseptic) body wash or body wipes, for early nasal decolonisation of MRSA amongst adult hospital in-patients.

## 4.1 Primary Hypothesis

Polyhexanide or chlorhexidine with neomycin are not inferior to mupirocin for early nasal MRSA decolonisation in adult hospital in-patients.

## 4.2 Primary objective

To undertake a multi-centre, three-arm parallel group, non-inferiority RCT to determine whether nasal polyhexanide gel or nasal chlorhexidine with neomycin cream is not inferior to nasal mupirocin ointment, when each is accompanied with chlorhexidine body wash or wipes, for early nasal decolonisation of MRSA amongst adult hospital in-patients.

## 4.3 Secondary objectives

- Undertake a 9-month internal pilot to confirm the feasibility of the study, in particular recruitment rate and completeness of follow-up. This will include an embedded

qualitative study to optimise recruitment and consent processes with a particular focus on underserved and vulnerable populations.
- Undertake a cost-effectiveness analysis of the three interventions from the NHS perspective to identify the most efficient provision of future NHS care.
- Undertake an analysis of secondary outcomes.

# 5 Trial Design

TIDE is a multi-centre, three-arm, parallel group, non-inferiority, pragmatic RCT to compare three treatments for MRSA decolonisation in 3000 adult in-patients.

Following baseline assessments, and randomisation, participants will receive one of the three MRSA decolonisation treatments, and will complete follow-up assessments at 48-hours and 4-weeks post-completion of treatment.

The success of early nasal decolonisation of the three treatments will be compared along with the cost-effectiveness and other secondary outcomes. The trial design incorporates a 9-month internal pilot phase, which will assess the assumptions about recruitment and provide guidance on optimising the trial processes.

# 6 Outcome Measures

The outcome measures for this study are largely from laboratory-based analysis and have been designed to have minimal impact on participants and research staff at sites. Baseline assessments will utilise standard clinical swabs taken. Patients will be required to provide a nasal swab for the study at 48 hours and again at 4 weeks after treatment completion. Research staff will ask patients a limited number of questions on acceptability and adherence 48 hours after treatment completion. Research staff will also collect some patient information from patient medical records at baseline, 48 hours and 4 weeks after treatment completion. Patients will be asked further questions at 4 weeks after treatment completion (adverse events, additional MRSA decolonisation treatments and hospital resource use).

Further details about assessments and data collection can be found in section 9.6. Outcomes for the internal pilot phase and qualitative sub study can be found in section 9.7 and assessment of adherence details can be found in section 0.

## 6.1 Primary outcome

- Successful early nasal decolonisation of MRSA.

## 6.2 Secondary outcomes

- Successful early nasal decolonisation of MRSA not fully susceptible to mupirocin.
- Successful early nasal decolonisation of MRSA not fully susceptible to gentamicin (used as a marker for neomycin).
- Successful late nasal decolonisation.
- Acceptability of treatment to patients (global rating of assigned treatment and patient rating of severity of known side effects).
- MRSA infections up to 4 weeks following treatment completion.
- Total length of hospital in-patient stays up to 4 weeks following treatment completion.

- Total length of hospital in-patient stays for patients diagnosed with a MRSA infection up to 4 weeks following treatment completion.
- Hospital readmissions up to 4 weeks following treatment completion.
- Adverse events (AEs) up to 4 weeks following treatment completion.
- Mortality up to 4 weeks following treatment completion.
- Resource use.

## 6.3 Outcome Measure Definitions

- **Early/Late nasal decolonisation:** Defined as MRSA not detected on a trial specific nasal swab taken 48 hours (early) or 4 weeks (late) following treatment completion.

  A patient will be defined as being successfully decolonised of MRSA if MRSA is not detected in either the direct culture or the enrichment broth culture. If MRSA is detected on either the direct culture or the enrichment broth culture, they will be defined as not having been successfully decolonised (refer to section 9.5.1).

- **Susceptible/ resistant to mupirocin or gentamicin (used as a marker for neomycin)**:
  Antimicrobial sensitivities will be interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints[9] and MRSA colonies will be reported as susceptible or resistant to mupirocin and susceptible or resistant to gentamicin.

  MRSA colonies with some resistance to mupirocin are classified as having either low-level or high-level resistance using EUCAST breakpoints[9], to determine this the minimum inhibitory concentration (MIC) of resistant colonies will also be reported.

  In addition, the following antimicrobial sensitivities will be analysed: cefoxitin (used as a marker of flucloxacillin resistance), oxacillin, ciprofloxacin, erythromycin, clindamycin, trimethoprim, teicoplanin, vancomycin, fusidic acid, tetracycline, rifampicin, chloramphenicol, linezolid, daptomycin and tigecycline.

- **Acceptability of treatment to patients**: Collected from patients 48 hours after treatment completion. Acceptability will be assessed by;
  - a) A global question about whether the participant would be happy to use the nasal treatment if they were in the same position again using a 5-point Likert scale (agree strongly to disagree strongly);
  - b) Questions on the severity of key known side effects (adverse events of special interest (AESI)) related to use of the nasal products (which are mainly related to an itching or burning sensation) and whether they have experienced these during use, up to 48 hours after treatment completion. Severity will be assessed using a 3-point Likert scale (severe, moderate, mild).

- **Clinical data to be collected up to 4 weeks following treatment completion:** Details will be obtained from patients' medical records and from discussions with patients. This will be reported by research nurses to YTU. Clinical data collected at 48 hours and 4 weeks following treatment completion will include:
  - Details of any confirmed MRSA infections (e.g. skin and wound infections, joint infections, endocarditis, pneumonia and bacteraemia).
  - Total length of hospital in-patient stay.

- Adverse events.
- Mortality (to be notified to YTU as soon as known).
- Hospital readmissions.
- Resource use: Data on resource use (i.e. hospital costs) will be collected to inform the economic evaluation.

# 7 Trial Setting

Patients will be recruited from up to 25 NHS secondary care hospital sites in the UK that support research activity. There is no restriction on the type of NHS hospital (e.g. Teaching or District General Hospital) as long as they currently perform screening for MRSA on admission and have the infrastructure and capacity to participate in a research study. We will also specifically target sites in areas of the UK that have a higher burden of MRSA infections[10]. A list of all study sites will be maintained by the trial management team and held in the trial master file (TMF).

There are some groups in hospital who are at more risk of having MRSA nasal colonisation or are considered particularly vulnerable to infection, such as those admitted to hospital from nursing homes, people with chronic leg ulcers or pressure sores, surgical patients, patients in intensive care or dialysis units. A systematic review identified multiple risk factors of MRSA colonisation, several of which are associated with an elderly population including hospitalisation within the last 24 hrs and previous admission to a long-term care facility in the past 18 months [11]. Some variation in colonisation rates and MRSA infection is expected across hospitals depending, amongst other factors, on local population (such as elderly population and number of elderly care homes) and presence of specialist units such as renal units.

Our site recruitment strategy aims to include vulnerable and underserved populations. This will include elderly patients living in a long-term care facility, those who lack capacity, patients from deprived areas and ethnic minorities. In order to achieve this, we have already collated regional level data from multiple national sources on the number of nursing and care home beds per 100 people aged over 75 [12, 13], the index of multiple deprivation [14], the index of health deprivation [14], the Income Deprivation Affecting Older People Index [14] and ethnicity [15]. In addition, we will use regional level data to target populations at higher risk of MRSA colonisation, based on known risk factors [11]. These include patients in a long-term care facility [12, 13], areas reporting a higher rate of antibiotic prescribing [16] and higher rates of MRSA bacteraemia [17]. These measures have been combined and regions ranked nationally to identify those that have a higher proportion of vulnerable and underserved populations, as outlined above, and/or are at a higher risk of MRSA colonisation.

Through our previous work on methicillin-sensitive Staphylococcus aureus (MSSA) decolonisation we have built an extensive network of 50 NHS Trusts, including clinicians, microbiologists and infection prevention teams [18].

The trial team will work closely with hospital research associates and infection prevention teams to optimise the identification, screening and recruitment processes to local circumstances. We will also encourage the appointment of a junior doctor or other relevant healthcare professional as an Associate Principal Investigator (API) at each recruitment site to support the Principal Investigator (PI) with study delivery and recruitment.

# 8 Participant Eligibility Criteria

Adult in-patients (aged 16 years old or over) who test positive for MRSA colonisation as part of routine screening on admission and who meet the eligibility criteria detailed in Sections 8.1 and 8.2 will be invited to take part in the study.

Any questions raised about eligibility will be addressed prior to entering the patient into the study. There will be no exceptions (waivers) to eligibility criteria prior to inclusion into the study. To be included in the study patients must meet all of the inclusion criteria and none of the exclusion criteria.

Further details of the methods for eligibility screening and patient approach are given in Section 9.

## 8.1 Inclusion Criteria

- Adult in-patient (aged 16 years old or over).
- Eligible for MRSA screening on admission, based on the local hospital infection control policy, who are found to be colonised with MRSA.

## 8.2 Exclusion Criteria

- Known hypersensitivity to study treatment(s) or excipients.
- Allergy to peanut and/or soya.
- Day-case admissions.
- Patients identified to be colonised with MRSA in the out-patient setting.
- Previous participation in the TIDE trial or current participation in another trial of a medicinal product that does not allow co-enrolment.
- Patients actively undergoing another decolonisation treatment at the time of recruitment.
- Medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.

# 9 Trial procedures

## 9.1 Recruitment

### 9.1.1 Participant identification

Timely identification of patients who are found to be colonised with MRSA will be important as decolonisation treatment is generally implemented quickly. The fact that eligible patients may be admitted to multiple different wards across the hospital means that a centralised identification process will be crucial for successful recruitment.

Generally, hospital infection control policies require screening of high risk patients for MRSA colonisation such as emergency admissions, patients attending regularly for treatments such as dialysis or chemotherapy and as part of the pre-admissions process for elective surgical procedures [19, 20].

Typically, on routine screening for MRSA, swabs from the nose are pooled with those from the throat, axilla and/or groin for analysis. Therefore, where a positive MRSA diagnosis

shows that a patient is colonised with MRSA in their nose and/or on their skin, they do not explicitly have a nasal MRSA colonisation. This will be the same for all three randomised groups and reflects current practice, and therefore is a pragmatic approach.

To allow for the practicalities of screening and recruitment prior to treatment starting we will exclude day-case patients and others who are screened and treated pre-admission.

### 9.1.2 Screening for the study

All hospital in-patients aged 16 years old and over who undergo MRSA screening on admission and test positive for MRSA colonisation, will be assessed for eligibility to take part in the study.

Screening against the study eligibility criteria can be undertaken by any staff trained in the trial protocol, GCP and delegated to do so on the trial site delegation log. Eligibility must be confirmed by a clinician and documented in the patient's medical notes.

Screening data will be reported by participating centres throughout the trial. We will collect data on the number of eligible patients; eligible patients approached for consent (including through personal and professional legal representative); eligible patients not approached and reasons why; patients approached who provide consent; patients approached who do not provide consent and reasons why; patients providing consent who are randomised (all metrics will be collected, including patients approached through personal and professional legal representative). We will also collect data on the number of patients randomised who do not receive the randomly allocated treatment and the reasons why.

### 9.1.3 Payment

Patients will not receive payment for their participation in this study. There will be no additional clinic visits and the follow-up aims to be of minimal burden to patients and staff.

## 9.2 Informed Consent

The study will be introduced and the consent conversation take place with a member of staff who is trained in the trial protocol, GCP and delegated to take consent by the site PI on the delegation log.

Potential participants will be provided with information about the trial which will be made available in different formats as required (e.g., electronic or paper participant information sheets, narrated, and animation) and invited to participate in the study. For patients unable to read, narrated versions or voice-assisted software will be used as available through the NHS given that patients will be recruited in hospital settings. For patients unable to speak English, sites will use either a translator or telephone translation service depending on local availability.

All information required by the UK Health Research Authority (HRA) template guides will be included in the trial participant information materials. Information about the trial will be developed in conjunction with the trial specific PAG. We have been advised by our co-applicant from MRSA Action UK that it can be a confusing and frightening experience as a patient to be told that you are colonised with MRSA as this can be confused with MRSA infection. We will be mindful of this when developing any patient-facing materials for the trial.

In addition, it was brought to our attention that existing resources for patients about MRSA and decolonisation are available, from which we will also draw on.

Consent is voluntary and patients will have the opportunity to ask questions of the clinical care team or local research team before giving consent for the study. Participants will have the right to withdraw from the study at any time without giving a reason, see section 9.8.

Consent for participation in the qualitative element of the study will be sought separately.

### 9.2.1 Inclusion of patients who lack the capacity to consent

A significant number of patients in this population may lack capacity to provide informed consent for themselves, this could be long term, for example due to dementia or learning disabilities, or it could be short term such as delirium due to chest or urinary infection related to the reason for their hospital admission. Patients who are deemed unable to consent for themselves, and who are MRSA positive are still at increased risk of acquiring an infection and have as much to gain from inclusion in the study as those with full capacity. In line with the Medicines for Human Use (Clinical Trials) Regulations (2004), consent in these patients will be obtained via a personal legal representative wherever possible. However, because of the need to start decolonisation treatment as soon as possible after a positive MRSA swab is confirmed, where a personal legal representative is not available a professional legal representative will be identified and asked to legally consent for the patient to participate. The professional legal representative will be a healthcare professional who is independent of the trial. Processes and information material for including people who lack capacity to consent for themselves, will be developed in conjunction with the trial PAG.

Patients who have capacity to consent for themselves at baseline and give their consent to participate, but then lose capacity during the study period should remain in the trial under the original consent. This is appropriate as any personal or professional legal representative, under the legislation for CTIMPs can consent for the patient and should act on the patient's wishes if known. Due to the short duration that patients are in the trial (4 weeks after treatment completion), and the minimal input required from patients during follow up, we do not envisage that a patient's wishes regarding trial participation are likely to change during the trial.

Participants who regain capacity following initial consent by a Legal Representative: In the event a patient regains capacity within 4 weeks after treatment completion, where they did not initially consent for themself, they will be informed of their involvement in the trial by the PI or other delegated person and updated on where they are in the study conduct. They will be asked for their consent to continue in the study and sign a specific informed consent form. Participants will be given the opportunity to consider their ongoing participation and provided with written information about the trial. Participants may decline to continue their participation without prejudice  If they do wish to remain in the study up to the week 4 post-treatment timeline they will be able to provide written consent for them self. This must all be fully documented in the medical notes and the PI made aware.

### 9.2.2 Additional consent provisions for collection and use of participant data in ancillary studies

Participants will be asked to consent for the information collected about them to be used to support other research in the future and shared anonymously with other researchers and third parties.

### 9.2.3 Study within a trial (SWAT)

Randomised controlled trials are the keystone of evidence-based healthcare. However, recruitment and retention are major challenges to the success of a trial, particularly when trying to include participants from underserved groups.

The TIDE trial will act as a host trial for an embedded study which aims to look at the use of a pictorial aid with the patient information sheet (PIS) to improve recruitment. We plan to undertake a study within the trial (SWAT) to assess the impact of a pictorial aid on recruitment to the TIDE trial. Patients with low health literacy are less likely to participate in decisions about their own health [21, 22] and there is evidence that just under one in six adults in the UK have the literacy of an 11-year-old [23]. There is systematic review evidence that the use of pictures with text can improve health communication [24] and that patients with low health literacy may gain a better understanding when being asked to consent to taking part in a trial if diagrams and pictures are used [25].

This will be a cluster randomised controlled trial, sites will be randomised to issue potential participants or their Legal Representatives with either the standard PIS alone or the standard PIS with a pictorial aid. The primary outcome will be the recruitment rate measured as the proportion of participants randomised in each group to the main trial.

To ensure there is no negative impact on overall recruitment to the TIDE trial, both the standard PIS and the pictorial aid will be developed in conjunction with our PAG. The PIS and the pictorial aid will be reviewed at a roundtable meeting following the pilot phase, which will also consider the findings of the qualitative study.

The TIDE SWAT protocol will be registered on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry.

## 9.3 The randomisation scheme

For the main trial, randomisation to one of the three treatment arms will use a computer-generated pseudo-random allocation schedule with random permuted blocks of randomly-varying size. The randomisation will be stratified by recruiting centre.

The allocation schedule will be generated by a statistician at YTU not involved in recruitment.

### 9.3.1 Method of implementing the randomisation / allocation sequence

When patients have consented and any required baseline forms have been completed, the recruiting research associate/clinical staff at each site will access a secure web-based randomisation service, hosted by YTU, ensuring allocation concealment. The randomisation service will require the recording of information and a check of patient eligibility to avoid

inappropriate entry of patients into the trial. The randomisation system will provide an immediate allocation and a confirmation email.

The email confirming randomised allocation will be sent to the PI and all authorised users of the randomisation system at the recruiting site, this will include pharmacy where required. The Co-CIs and the trial team at YTU will also receive a confirmation of randomisation email.

An appropriate clinician will be informed of the allocation by the recruiting research associate to allow prescribing of the allocated intervention.

The prescribed medication will be recorded in the patient's medical notes so that clinical teams have access and can refer to the information, it will also be recorded in the study data capture system.

To support treatment adherence and compliance, patients will be provided with written instructions for the application of their allocated treatment.

## 9.4 Blinding

This is not a blinded trial. To be pragmatic, patients, treating clinicians and the site recruitment teams will be informed of the allocation and the intervention received.

The primary outcome of early nasal decolonisation is based on laboratory analysis of a sample, the laboratory staff will be blind to allocation therefore the outcome should not be subject to patient or clinician bias. Many of the secondary outcome data will also be obtained from laboratory results therefore limiting the risk of introducing patient or clinician bias.

## 9.5 Baseline data

Baseline demographic and clinical data will be collected on the ward by the research nurse/associate both from reviewing patients' medical records and from discussion with the patient.

### 9.5.1 Microbiology evaluation

The routine clinical swab used to identify the patient as MRSA positive upon admission will be used to analyse the antimicrobial sensitivity of baseline MRSA colonies. A nutrient agar slope plated from the original swab will be sent to the central laboratory (Northumbria Healthcare NHS Foundation Trust) by the participating site. MRSA colonies will be processed in accordance with the laboratory trial manual.

Antimicrobial sensitivities will be interpreted using EUCAST breakpoints [9] and MRSA colonies will be reported as susceptible or resistant to the following antimicrobials: mupirocin, cefoxitin (used as a marker of flucloxacillin resistance), oxacillin, ciprofloxacin, erythromycin, clindamycin, trimethoprim, teicoplanin, vancomycin, gentamicin (used as a marker for neomycin), fusidic acid, tetracycline, rifampicin, chloramphenicol, linezolid, daptomycin and tigecycline.

For MRSA colonies with some resistance to mupirocin, their minimum inhibitory concentration (MIC) will also be reported.

Sites will be asked to retain the original clinical baseline swabs for 2 weeks. If the slope does not grow, or does not contain MRSA, a repeat slope will be requested.

If another bacterium of concern is identified by the central laboratory this will be reported back to the participating site where the sample was collected, as a duty of care.

Study nasal MRSA swabs (48 hours and 4 weeks post treatment completion) will be analysed for the detection of MRSA by the central laboratory and processed in accordance with the laboratory trial manual. Swabs will be analysed by direct culture and by culture of an enrichment broth to give the highest possibility of detecting MRSA by laboratory methods. The results of these study swabs will not be shared with participants routinely.

## 9.6 Trial assessments and data collection

A schedule of trial assessments is presented in Table 2.

Nasal swabs and study data will be collected, 48-hours and 4-weeks following completion of treatment. For patients randomised to mupirocin or polyhexanide, treatment is for 5 days, for patients randomised to chlorhexidine with neomycin, treatment is for 10 days. Assessments will be scheduled using the planned duration of treatment.

Our survey indicates that there is variation in clinical practice as to whether a swab is routinely taken 48 hours following completion of MRSA decolonisation treatment. Some hospitals do not retest at any stage to establish whether decolonisation has successfully occurred. At hospitals where a 48 hour swab is collected, this is usually a combined nasal, throat, axilla and/or groin swab. For this study this is insufficient, we will therefore implement a 48 hour post treatment nasal only swab to address the primary outcome for TIDE.

Both the 48 hour and 4 week post treatment nasal swab will be undertaken either by a research nurse or with a self-swab. Where practically possible the 48 hour swab for the primary outcome should be undertaken by a research nurse. Swabs should be taken at the place convenient for the patient, for example the patient's place of residence, their place of discharge or on the ward if they are still in hospital. Swabs will be for research purposes only and results will not be reported clinically therefore will not impact on patient care.

Outcome data will be collected from participants 48 hours and 4 weeks after treatment completion, this will either be in person by a research nurse or by telephone. At 48 hours this includes; acceptability, adherence and severity of AESI. At 4 weeks this includes collecting adverse event data and resource use data. All other outcome data will be gathered directly from patients' medical records by the research nurses.

A web-based system for electronic data collection will be used (see section 13).

*Table 2: Trial Assessment Schedule*

| | Baseline | Treatment | 48 hrs post treatment completion | 4 weeks post treatment completion |
|---|---|---|---|---|
| Eligibility Assessment | X | | | |
| Informed Consent | X | | | |
| Demographics | X | | | |
| Clinical Characteristics | X | | | |
| Randomisation | X | | | |
| Intervention Delivered | | X | | |
| Routine MRSA screening swab | X | | | |
| Nasal only MRSA Swab | | | X | X |
| MRSA antimicrobial susceptibility testing | X | | | |
| Acceptability | | | X | |

| | | | | |
|---|---|---|---|---|
| MRSA /other Infections | | | X | X |
| Adverse Events | | | X | X |
| Mortality | | | X | X |
| Length of hospital stay | | | X | X |
| Readmissions | | | X | X |
| Resource Use | | | X | X |

## 9.7 Internal pilot phase

A 9-month internal pilot phase will confirm feasibility of the trial and test our assumptions about rate of site set up, participant recruitment rate and completeness of primary outcome follow up data. These outcomes will be assessed against the progression criteria described below. Screening data will be maintained by all participating centres throughout the trial as described in 9.1.2 'screening for the study'.

Using 2019 data from Northumbria Healthcare NHS Foundation Trust (500,000 population) we estimate 300 people testing positive for MRSA colonisation per year per Trust. Estimating that a minimum of 50% of eligible patients will be recruited to the trial would provide an average of 12 recruits per site per month. We aim to achieve 90% follow-up for the primary endpoint.

The internal pilot will be reviewed by the DMC, the TSC and the funder to determine whether the study progresses to the full trial. Green, amber and red thresholds for progression have been set and Table 3 provides details of these internal pilot progression criteria.

*Table 3: Proposed progression criteria to be assessed at end of 9-month internal pilot*

| **Domain** | **Target at end of internal pilot** | **Green** | **Amber** | **Red** |
|---|---|---|---|---|
| Site setup | 10 sites set-up and recruiting first participant | 100% (10) | 60 to 99% (6 to <10) | <60% (<6) |
| Participant recruitment | Average of 12 participants recruited per site, per month | 100% (12) | 60 to 99% (7 to <12) | <60% (<7) |
| Primary outcome follow-up data | 90% of expected data collected for the primary outcome | 100% (540) | 70 to 99% (420 to <540) | <70% (<420) |

### 9.7.1 Qualitative study

The 9-month internal pilot phase will include an embedded qualitative study, which will be focussed on understanding recruitment and consent processes ahead of the main trial recruitment phase. We know from our preparatory PPI work and previous evidence that certain vulnerable groups such as those admitted from nursing homes and people with dementia are more at risk of MRSA colonisation [11]. Considering this and the recently published INCLUDE Ethnicity Framework which aims to improve trial delivery for groups that are typically underrepresented in medical research [26], a key focus of the qualitative study will be to ensure our trial includes a diverse sample of patients that is reflective of those who are most likely to require treatment for MRSA nasal colonisation in routine practice.

The qualitative study will consist of: i) interviews with patients and/or carers who agree to take part in the trial (n=15-20); ii) interviews with patients who decline to take part in the trial (n= 10-15); iii) interviews with clinical teams involved in recruitment to the trial (e.g. doctors, infection control teams, research nurses) (n=15-20); iv) interviews with the CTU research team who are involved in recruitment (e.g.: trial support officer, trial coordinator and trial manager) (n=3-5). The qualitative research team will work closely with the trial team and site staff to purposively sample patients and carers to ensure maximum variation according to age, gender, ethnicity, treatment received, residential status and comorbidities. Trial recruiters from all participating centres will be invited to participate in the qualitative study and will be sampled purposively to ensure a mix of professional groups and grades are represented. Given that patients may be recruited to our RCT from a range of clinical specialties, we anticipate that this will be a challenge for the proposed study. We will therefore aim to interview staff from a range of wards and clinical specialties at study sites and will discuss the potential implications of the patient pathway on recruitment during interviews with trial recruiters and CTU staff. Following recent guidance, we will not aim to interview until saturation, but instead will focus on ensuring that a varied sample is represented [27]. However, our proposed sample size is consistent with recommendations [28].

All interviews will be semi-structured and will be conducted face-to-face or via telephone/video conferencing depending on the preferences of each interviewee. A flexible interview schedule will be developed following discussions with the research team, PAG and health professionals with expertise in the area. Emphasis will be placed on ensuring that the interview schedule is appropriate and where necessary adapted for use with vulnerable groups, such as those for whom English is not their first language. Interviews with patients and carers will explore reasons for participation and non-participation, experiences of being approached and consented to take part in the trial and how this could be improved, particularly for vulnerable groups. Interviews with trial recruiters from study sites and the CTU will also focus on experiences of recruiting and consenting patients and ascertaining who is being recruited and which populations we are ‘missing’ and why.

Informed consent will be obtained from all participants prior to the start of each interview. For those who are unable to consent for themselves, interviews will be undertaken with carers or professional representatives. With permission from participants, all interviews will be audio-recorded, transcribed verbatim with data organisation facilitated using NVIVO. To achieve a systematic approach to data analysis, all interviews will be analysed thematically following the stages outlined by Braun and Clarke [29, 30]: detailed familiarisation; generating initial codes; searching for themes; reviewing themes; defining and naming themes and data reporting. Findings from the qualitative study will be combined with pilot RCT data pertaining to recruitment and will form the basis of a roundtable discussion between the PAG, research team and clinical co-applicants. The aim of the consultation will be to inform any necessary changes to the way that patients are recruited and consented to the main trial and develop strategies for ensuring they are implemented at trial sites. This will include reviewing the patient materials being developed for the SWAT.

## 9.8 Withdrawal criteria

Participants have the right to withdraw from the study at any time without giving a reason. If given, the reason for withdrawal will be recorded in the electronic data capture system.

If a patient's treatment course is changed during the trial or during the follow-up period, the patient can remain in the study. Details of any alternative decolonisation treatments prescribed will be recorded.

### 9.9 Storage and analysis of clinical samples

This study will use a nutrient agar slope prepared from the routine clinical swab taken during MRSA screening prior to recruitment, as well as trial specific nasal swabs taken at 48 hours and 4 weeks post treatment completion.

All research swabs or slopes will be processed at Northumbria Healthcare NHS Foundation Trust as described in a trial specific laboratory manual.

Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with the trial laboratory manual to ensure compliance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

### 9.10 End of trial

The end of the trial will be defined as last patient, last visit (LPLV), the date that the last patient reaches the last follow up time point, 4 weeks post treatment completion.

The end of the trial will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The PIs will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial will be provided to the REC and Regulatory Authority within one year of the end of the trial. An end of trial report should also be issued to the funders at the end of funding.

## 10 Trial Treatments

### 10.1 Name and description of investigational medicinal product(s) / Device

- Mupirocin (2%) nasal ointment (3g)
- Polyhexanide (0.1%) nasal gel (30ml)
- Chlorhexidine (0.1%) with neomycin (0.5%) nasal cream (15g)

Any brand/manufacturer of each of the investigational medicinal products with a marketing authorisation in the UK can be used.

### 10.2 Regulatory status of the drug(s) / Device

Both mupirocin and chlorhexidine with neomycin are Investigational Medicinal Products (IMPs). Both have a UK marketing authorisation and are being used within the terms of their marketing authorisation.

Polyhexanide is licenced for use in the UK as a medical device and will be used within the terms of its product safety data sheet.

Each of the treatments in this trial will be accompanied by chlorohexidine body wash (4%) or wipes (2%). Chlorhexidine (body wash and wipes) are considered non-IMPs for the purposes of the trial.

## 10.3 Product Characteristics

The concentrations and doses to be used for nasal MRSA decolonisation in this trial are in keeping with the Summary of Product Characteristics (SmPC) for mupirocin [31] and chlorhexidine with neomycin[32], and manufacturer recommendations for polyhexanide[33].

Monthly checks for updates to SmPCs and product safety data sheet will be undertaken by Sponsor lead pharmacy personnel. Updates will be notified to trial coordination staff and cascaded to participating sites as required.

## 10.4 Drug storage and supply

All IMPs and non-IMPs are licensed treatments and will be sourced locally by the research site.

All aspects of treatment including receipt, storage, supply, administration and destruction will be in accordance with standard local policy for prescription medications and medical devices. Additional accountability records will not be required. Study treatments should be stored as per the manufacturers' storage instructions. They may be stored alongside other routine medications with no additional temperature monitoring.

Participants will not be required to return unused product as this represents an infection control risk and would add limited value in terms of estimating treatment adherence.

Participants will be prescribed all study treatments by an authorised healthcare professional. If the person who writes the prescription does so in accordance with standard clinical practice, and that person has no other protocol specific activities, then that person does not need to be on the study delegation log.

## 10.5 Labelling of Investigational Medicinal Product / Device

There is no specific trial labelling required. Treatments will not be labelled other than as required for routine dispensing for clinical use. Trial-specific labelling is not required as all the trial treatments have a marketing authorisation in the UK and are being used within the terms of their marketing authorisation.

## 10.6 Dosage schedules

Dosing regimens for all trial treatments are as detailed on the SmPC or safety data sheet.

- Mupirocin nasal ointment (2%) applied to the inner surface of each nostril three times a day for five days.
- Polyhexanide nasal gel (0.1%) applied to the inner surface of each nostril three times a day for five days.
- Chlorhexidine (0.1%) with neomycin (0.5%) nasal cream applied to the inner surface of each nostril four times a day for ten days.

All the nasal products will be provided in conjunction with chlorhexidine (4% body wash or 2% skin wipes dependant on existing recruiting Trust practices) for bathing/ showering/ washing for five days.

Patients will be shown how to use the decolonisation treatment and will also be provided with written study instructions on how to apply/use each decolonisation treatment, according to their allocated regimen.

## 10.7 Dosage modifications

There are no planned dose modifications in this trial.

## 10.8 Known drug reactions with other therapies

No medicinal product interactions have been identified for any of the trial treatments.

Contraindications and side effects detailed in the SmPC for the two IMPs and the safety data sheet for polyhexanide have been reviewed [31-33]. The main or most common side effects for all products when used as planned in this trial are skin or mucosa irritation. Data on these side effects will be collected as an AESI.

## 10.9 Concomitant medication

Concomitant medication is any drug given in addition to the study medication. Throughout the study, the clinical care team may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. There is no restriction on the use of concomitant medications as part of the trial. Details of concomitant medications will be recorded at baseline.

## 10.10 Trial restrictions

Contraindications are as listed in the SmPCs or safety data sheet.

There are no other trial restrictions.

Women of childbearing potential and pregnant women can be recruited. Pregnant women would receive MRSA decolonisation treatment as part of standard care.

## 10.11 Assessment of adherence with treatment

Treatment adherence will be assessed through a sequence of questions that are answered by a research nurse 48 hours after treatment completion and in discussion with the patient, if required. If the patient remains an inpatient for the full treatment duration these questions can be answered by referring to the patient's drug chart. If the patient is discharged during the treatment course these questions can be answered by discussing with the patient alongside referring to the patient's drug chart.

Levels of adherence to treatment will not influence the decision to continue or stop the trial. Noncompliant participants will continue in the trial and will be followed up and assessed in accordance with the protocol.

### 10.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

Chlorhexidine (4% body wash or 2% skin wipes dependant on existing recruiting Trust practices) for bathing/ showering/ hair washing for five days.

## 11 Pharmacovigilance

The PI at each participating site is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

### 11.1 Definitions

| Term | Definition |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| **Adverse Event of Special Interest (AESI)** | An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific, for which ongoing monitoring and communication could be appropriate. |
| **Adverse Reaction (AR)** | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.<br><br>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.<br><br>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event. |
| **Serious Adverse Event (SAE)** | A serious adverse event is any untoward medical occurrence that:<br>• results in death<br>• is life-threatening<br>• requires in-patient hospitalisation or prolongation of existing hospitalisation<br>• results in persistent or significant disability/incapacity<br>• consists of a congenital anomaly or birth defect<br>Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. |

| | |
|---|---|
| | NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |
| **Serious Adverse Reaction (SAR)** | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information:<br>• in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken.<br>• in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question |

**Causality**

Adverse reactions should be assessed for causality using the definitions below. This assessment must be made by a medically qualified doctor who is part of the research team.

*Relationship Description:*

- *Unrelated:* There is no evidence of any causal relationship
- *Unlikely:* There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
- *Possible*:* There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- *Probable*:* There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- *Definitely*:* There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- *Not assessable:* There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. This should be regarded as a temporary assessment and must be followed up within 24 hours and assessed by a medically qualified doctor.

* If the AE is serious and unexpected, the possible, probable and definitely related should be notified to the MHRA, the relevant REC and the Sponsor as SUSARs.

## 11.2 Operational definitions for SARs and SUSARs

In this trial, all the interventions are marketed products for which safety profiles are already known and all are being used in accordance with their licences. A modified procedure for pharmacovigilance will be used, based on a specific risk assessment and in line with the published guidance on Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products [34].

All adverse events observed for any of the interventions will be treated as per standard care, and fully documented in the patient's medical notes and only reported to YTU if considered to meet the criteria for an Adverse Reaction (AR) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR).

Expected Serious Adverse Events and Reactions for this trial will be taken from the reference safety material for the interventions (SmPCs or Product Safety Data Sheet).

SARs should be reported by site staff to YTU as soon as they are made aware of the event. SARs/SUSARs will be followed up to resolution. Fatal or life threatening SUSARs will be reported to the MHRA by the Sponsor within 7 calendar days and all other SUSARs will be reported within 15 calendar days after the Co-CI (MR) is first aware of the reaction.

All reported ARs, SARs and SUSARs will be summarised for presentation at Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) meetings and be provided to MHRA as part of the annual Development Safety Update Report (see also section 11.10).

For the purposes of this trial, the following events will <u>not</u> be reported as SAEs/SARs/SUSARs:

- Prolongation of hospitalisation for the condition that was the reason for initial hospital admission.
- Hospitalisation or prolongation of hospitalisation for a pre-existing condition that has not worsened.
- Deterioration of the existing condition or known side-effects recorded as primary or secondary endpoints.
- MRSA infections or extended hospital stays as a consequence of MRSA infection because they are secondary outcomes for the trial.

## 11.3 Recording and reporting of AESI, ARs, SARs AND SUSARs

Expected events and reactions for this trial will be taken from the reference safety material for the interventions (SmPC or product data safety sheet). All events deemed by the site PI to have a causal relationship with the trial treatment require recording or reporting as part of the trial.

Nasal itching or burning sensation are key known side effects related to use of the nasal products and each will be considered as an AESI. Patients will be asked whether they experience either side-effect during use of the trial treatment and up to 48 hours post treatment completion. Patients will assess severity using a 3-point Likert scale (severe, moderate, mild).

All adverse events observed for all of the interventions will be treated as per standard care, and fully documented in the patient's medical notes. Events considered to meet the criteria for an Adverse Reaction (AR) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) will be recorded and reported to YTU via the data collection system.

## 11.4 Responsibilities

All SARs, except those expected ones defined in section 11.2 that do not require immediate reporting, must be reported to YTU within 24 hours of discovery or notification of the event. York Trials Unit will perform an initial check of the information and ensure that it is reviewed by the Co-CI (MR) or another delegated medical doctor.

SUSARs will be reported to the sponsor for expedited reporting to the MHRA.

## 11.5 Notification of Deaths

Mortality is a secondary outcome. Deaths occurring during the 4-week post-treatment follow-up period will be recorded and added to the study data set but not be reported via the expedited pharmacovigilance process unless they are deemed to be SUSARs.

Deaths that are assessed having a causal relationship to any of the trial treatments will be reported to the sponsor immediately. These will be onward reported the MHRA by the Sponsor where required.

## 11.6 Pregnancy Reporting

Pregnancy is not a contraindication for any of the investigational products. There are no specific pregnancy reporting requirements. All study treatments are topically applied and systemic absorption of active ingredients is unlikely.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

## 11.7 Overdose

There is currently limited experience with overdosage of any of the investigational products.

There is no specific treatment for an overdose of mupirocin. In the unlikely event of overdose, the patient should be treated supportively with appropriate monitoring as necessary and the event reported as an SAE. Further management should be as clinically indicated or as recommended by the UK national Poisons Centre, where available (www.toxbase.org).

## 11.8 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

### 11.9 The Type and Duration of the Follow-Up of Participants After Adverse Reactions

All unexpected SARs or SUSARs that result in a participant's withdrawal from the study or are present at the end of the study, will be followed up, if appropriate, until a satisfactory resolution occurs.

### 11.10 Development safety update reports

An annual Development Safety Update Report (DSUR) will be submitted to the MHRA and the main REC listing all SARs and SUSARs. The Chief Investigator is responsible for submitting annual DSURs to the MHRA and the main REC on the anniversary of the Clinical Trial Authorisation approval.

If applicable, a short format DSUR form will be submitted[35].

## 12 Statistics and Data Analysis

### 12.1 Sample size calculation

For 90% statistical power, 2,697 participants (899 per group) are required to establish non-inferiority of each intervention compared with mupirocin within a margin of 6% in successful early nasal decolonisation, based on the lower limit of a 95% two-sided confidence interval (equivalent to a one-sided 97.5% confidence interval) assuming the rate of early nasal decolonisation in each group is 81% [36].

Assuming 10% attrition at follow-up 48 hours following completion of treatment, the total target sample size is 3,000 (1,000 per group).

The non-inferiority margin was based on expert opinion and all respondents to a survey confirmed that this would be a clinically acceptable non-inferiority margin.

### 12.2 Planned Recruitment Rate

Using 2019 data from Northumbria Healthcare NHS Foundation Trust (500,000 population) we estimate 300 people testing positive for MRSA colonisation per year per Trust. Estimating that a minimum of 50% of eligible patients will be recruited to the trial would provide an average of 12 recruits per site per month.

The expected recruitment rate is 12 participants per site per month (with a 50% reduction for the first 3 months of sites opening and staggered opening of sites). Recruitment will be over 24 months and the internal pilot will be assessed at 9 months at which point we aim to have recruited one fifth of the participants over approximately one third of the recruitment window.

### 12.3 Pilot Phase Analysis

The recruitment rate and 95% confidence interval will be estimated from the data collected. A CONSORT diagram will be constructed to show the flow of participants through the study and the following outcomes calculated: number of eligible patients; proportion of eligible patients approached for consent; proportion of eligible patients not approached and reasons why; proportion of patients approached who provide consent; proportion of patients approached who do not provide consent; proportion of patients providing consent who are

randomised; proportion of patients randomised who do not receive the randomly allocated treatment; proportion of patients dropping out between randomisation and follow-up; proportion of patients for whom a primary outcome is recorded. Data will be summarised on the reasons why eligible patients were not approached, reasons for patients declining to participate in the study; reasons why randomised patients did not receive their allocated treatment and reasons for drop-out, if available.

Results will be compared against the study's recruitment assumptions and progression targets using a traffic light system. The recruitment data will also be combined with the qualitative data and will form the basis of a roundtable discussion between the PAG, research team and clinical co-applicants to identify any modifications required. The continuation of the trial or relevant modifications will be decided by the funding body.

## 12.4 Statistical Analysis Plan (SAP)

For the analysis of the full trial (assuming continuation) a CONSORT flow diagram will be provided to display the flow of participants through the study. The number of participants withdrawing from the trial will be summarised with reasons where available. Baseline characteristics will be presented descriptively by group. All outcomes will be reported descriptively at all collected time points. Continuous data will be presented using means and standard deviations or medians and ranges as appropriate, and categorical data will be presented using frequencies and percentages. The primary analysis will be on an intention-to-treat (ITT) basis, analysing patients in the groups to which they were randomised. A mixed-effects logistic regression model will be used to compare chlorhexidine with neomycin and polyhexanide to mupirocin, adjusting for relevant baseline covariates as fixed effects and centre as a random effect. An odds ratio and associated confidence interval will be estimated from the model. Non-inferiority will be accepted if the lower bound of the two-sided 95% confidence interval (equivalent to a one-sided 97.5% confidence interval) lies within the non-inferiority margin of 6 percentage points (equivalent to a lower bound odds ratio confidence interval of 0.70).

Completeness of data at follow-up will be reported by group. In non-inferiority comparisons the ITT analysis could bias towards the null, which may lead to false claims of non-inferiority, hence we will undertake both ITT and CACE (complier average causal effect) analyses. Other binary secondary outcomes will be analysed using similar mixed-effects logistic regression models as specified for the primary analysis model. Full analyses will be detailed in the trial's statistical analysis plan (SAP), which will be reviewed and approved by the trial steering and data monitoring committees and finalised before recruitment starts.

## 12.5 Interim Analysis and Criteria for the Premature Termination of the Trial

There are no plans to undertake interim analyses other than the pilot phase analysis described in section 12.3. Ad hoc interim analysis may be performed at the request of the DMC. There will be no formal stopping.

## 12.6 Participant Population

The primary analysis will be on an intention-to-treat (ITT) basis, analysing patients in the groups to which they were randomised. CACE analysis will be used to obtain unbiased estimates of treatment effects in patients who comply with their treatment allocation.

## 12.7 Procedure(s) to Account for Missing or Spurious Data

Every effort will be made to minimise loss to follow-up, however, it is anticipated that there will be some loss to follow-up and we have accounted for this in our sample size calculation. For each outcome measure the number of non-responders will be calculated for each treatment group and response rates compared. Appropriate sensitivity analyses will be used to examine the effects of missing data on outcomes.

## 12.8 Other Statistical Considerations

Deviations from the statistical analysis plan will be documented alongside reasons for the deviation in a statistical analysis plan departures log.

## 12.9 Economic Evaluation

We will conduct a cost-effectiveness analysis of mupirocin, polyhexanide and chlorhexidine with neomycin for MRSA decolonisation amongst adult hospital in-patients, using existing evidence in addition to evidence generated in this trial. There are other treatments that can be used in the NHS to reduce the risk of MRSA transmission and infection [4]. Decision makers are thus faced with a wide variety of strategies while considering the cost and effectiveness of each regime. Models are particularly useful in this context, where it is not feasible to fund and support multiple clinical trials to compare a range of strategies. For this reason, we will follow a modelling rather than within-trial approach for our analysis, developing a comprehensive model that brings together all available evidence to predict long term experience of patients receiving each treatment. The analysis will be undertaken from a National Health Service (NHS) and Personal Social Services (PSS) perspective. The methods will follow the reference case set out by NICE [37], and Decision Modelling for Health Economic Evaluation [38].

Resource use data will be collected from the participating sites using bespoke data collection tools. Data will be sourced from patients (e.g. resource use) or health care staff (i.e. hospital costs such as drug costs, additional therapeutic treatments, laboratory testing, length of stay, outpatient visits and readmissions), then managed centrally at YTU. Unit costs will be sourced from the NHS Reference Costs databases, the Personal Social Services Research Unit and other appropriate national sources. Other parameter estimates, including health related quality of life associated with MRSA infections, will be sourced from primary data sources, previous modelling studies and the best available evidence from the literature. Systematic searches will be undertaken to update the most comprehensive evidence in this area. A within trial analysis with total costs and QALYs will be presented for both intervention groups. This analysis will be conducted using regression methods and will assess the short-term effect on patients' health and costs to the NHS. We anticipate that there may be certain levels of missing data. The following approach will be used to impute missing data if necessary [39]. Missing baseline covariate data will be imputed using mean imputation. Multiple imputation with chained equations will be used to impute costs and HRQoL based on patient characteristics, this will be done separately for each trial arm [40].

The results of the trial will provide an unbiased estimate of the relative treatment effect of the three interventions. However, it is unlikely to provide all the evidence relevant to the decision on what is the most cost effective treatment for MRSA decolonisation amongst adult hospital inpatients within the NHS. Hence, a decision-analytic model will be developed to extrapolate

the effect on long term costs and QALYs combining the best available evidence. To capture the impact of any infection related mortality on health gains, we will apply age related life expectancy to surviving patients. A 3.5% annual discount rate will be applied for costs and outcomes. The model will generate long term predictions of costs, infection rates, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). The model will allow an estimate of the cost per QALY gained to be produced which would allow the cost-effectiveness of the strategies evaluated to be viewed within the context of published NICE cost-effectiveness thresholds (£20,000 and £30,000 per QALY gained; £13,000/QALY will be also used as per recent research [41, 42].

Decision uncertainty will be estimated as the probability that each intervention is considered the more cost effective for a given cost-effectiveness threshold. The structure of the decision analytic model will be developed in discussion with a group of clinical advisors, all experienced microbiologists, surgeons, physicians and infection control specialists from the UK.

A detailed health economics analysis plan (HEAP) will be drawn up in advance of the analysis. We do not anticipate any further analyses assessing the impact of the Covid-19 pandemic on the study results. However, work is currently being done in the trial's community on this topic, and should guidance relevant to our trial be published, the trial team will update the HEAP with the approval of the DMEC and TSC. All updates will be carried out before the end of data collection.

# 13 Data Management

## 13.1 Data Collection Tools and Source Document Identification

The data collected by sites will be entered onto a secure online REDCap interface. For data that are collected via participant report only the study data in REDCap will be the source data. Table 4 provides details of the data to be collected and source documents.

*Table 4: Source Data List*

| **Type of Data** | **Source Document** |
|---|---|
| Informed consent | Informed Consent Form / E-consent record |
| Relevant Medical History and Current Medical Conditions / medications | Patient Medical Records |
| Fulfilment of eligibility criteria | Patient Medical Records |
| Demographics and Baseline Data | Patient Medical Records / Patient Self-report |
| Laboratory Outcomes | Laboratory Worksheets / Laboratory Information Systems |
| Health Economic Data | Patient Medical Records |
| Acceptability / Adherence Data | Patient Self-report |
| Adverse Events | Patient Medical Records / Patient Self-report |

## 13.2 Data Handling and Record Keeping

The data collected by participating sites and generated in the central laboratory will be entered onto a secure online Research Electronic Data Capture (REDCap) interface specifically developed for this study[43, 44]. Computerised data cleaning and validation checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

Data will be checked according to procedures detailed in a trial specific Data Management Plan.

An electronic audit trail system will be maintained within the data management system to track all data changes in the database once the data has been saved initially into the system or electronically loaded.

## 13.3 Access to Data

Data will be held securely on the cloud-hosted REDCap server. Access to the study interface will be restricted to named authorised individuals granted user rights by a REDCap administrator at YTU.

The Department of Health Sciences, in which YTU is based at the University of York, has a backup procedure approved by auditors for disaster recovery. Full data backups are performed nightly using rotational tapes, to provide five years' worth of recoverable data. The tape backup sessions are encrypted, and password protected, with tapes stored in a locked fire-proof safe in a separate secured and alarmed location.

All study files will be stored in accordance with GCP guidelines. Study documents (paper and electronic) held at YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. All work will be conducted following the University of York's data protection policy which is publicly available (www.york.ac.uk/records-management/dp/policy).

## 13.4 Archiving

All essential study documents, including source documents, will be retained for a minimum period of five years after study completion, in line with the Sponsors' policy. The separate archival of electronic data will be performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory requirements.

Participating Sites: The PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site Agreement.

YTU: The electronic data will be stored for a minimum of 20 years in electronic format in accordance with guidelines on Good Research Practice[45]. All electronic records will be stored on a password protected server. All paper records will be stored in a secure storage facility or off-site by York Trials Unit.

# 14 Monitoring, Audit and Inspection

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

Regular monitoring will be performed according to UK Regulations for Clinical Trials and the specific TIDE Monitoring Plan. A copy of the monitoring plan will be filed in the Trial Master File.

Data will be verified for compliance with the protocol and accuracy in relation to source documents. Following written standard operating and trial specific procedures, the trial monitor(s) will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

# 15 Ethical and Regulatory Considerations

## 15.1 Research Ethics Committee (REC) review and reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other patient facing documents and materials.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the Trial Master File (TMF).

An electronic copy of the annual progress report (APR) will be emailed to the REC by one of the Co-CIs or a designee, within 30 days of the anniversary date on which the favourable opinion was given, and annually until the end of trial declaration is submitted.

The REC will be notified of the end of the trial as described in Section 9.10.

A final report will be submitted to the REC within one year of the trial end.

## 15.2 Peer review

The TIDE trial protocol is based on the application for funding, including a detailed project description which was submitted to NIHR and subject to peer review as part of the funding process.

The TIDE trial protocol has been reviewed by the TMG and comments incorporated into the final version of the protocol prior to regulatory submission.

The TIDE trial protocol will be reviewed by the TSC and DMC prior to recruitment start.

All reports of work arising from the TIDE trial including conference abstracts should be peer reviewed by the TMG prior to submission.

## 15.3 Public and Patient Involvement

The TIDE trial team includes a public co-applicant who has contributed to the development of the funding application and plain English summary and will continue involvement throughout the trial.

Initial, pre-application discussions with the public co-applicant highlighted that it can be a confusing and frightening experience as a patient to be told you are colonised with MRSA as it can be confused with MRSA infection. This feedback will be borne in mind when developing any patient-facing materials for the trial. In addition, the public contributor has drawn to our attention existing resources for patients about MRSA and decolonisation that we will also draw on. She has also been involved in developing the PPI strategy for the trial. One of the challenges we face is that most people do not realise that they are colonised with MRSA and do not go on to develop a MRSA infection. Therefore, we think it is important to take a broad approach to public involvement in the trial beyond MRSA Action UK. In consultation with the public co-applicant, we have developed a broad study specific PAG with a view to capturing the lived experience of groups who are more likely to have an emergency admission. PAG input will be valuable in informing our approach to recruitment of patients who may still be trying to process the information about being diagnosed as positive for colonisation.

In collaboration with the project lead for PPI and the public co-applicant, we developed a role description for involvement in the PAG and sought participation through advertising the opportunity with NIHR People in Research. Our PPI contributors represent people at highest risk and carers of vulnerable groups including those who lack capacity. Any specific training or information needs identified by PAG members will be addressed. For example, we will run a series of short sessions related to evidence-based healthcare, randomised controlled trials, and an introduction to the roles of different team members. We have introduced PAG members to the project including discussion and agreement on expectations and how we will work together.

The PAG will advise on several aspects and activities throughout the trial. Design and planning for recruitment particularly from vulnerable groups such as those lacking capacity, will be informed by the PAG group. The group has been involved in writing, editing and commenting on patient facing documentation such as the patient information sheets. We will be undertaking a study within the trial (SWAT) assessing the effectiveness of adding a pictorial aid to the patient-facing information. We are taking a co-production approach with the PAG to develop the pictorial aid for the SWAT. Information on MRSA decolonisation will of course be provided by hospitals as part of standard practice, trial patients will be signposted to information on the MRSA Action website (http://mrsaactionuk.net/).We will also explore production of additional material such as a video to ensure that all participants and personal legal representatives are fully informed about what the diagnosis means.

The group will also provide valuable input into development of the topic guides for the qualitative study exploring recruitment to the trial, planning and implementing the dissemination strategy and producing and distributing outputs such as plain English summaries of the findings. We will have an event at the end of the trial to inform the group of the findings and to reflect on how the PAG and researchers worked together and identify any recommendations for how this could be improved and developed for the future.

An independent public member will also be invited onto the Trial Steering Committee.

## 15.4 Regulatory Compliance

This study will be conducted in line with the UK Medicines for Human Use (Clinical Trials) Regulations (2004) as amended, and any relevant local and national regulations.

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion is in place.

Before any site can enrol patients into the study, the CI/PI or designee will ensure that appropriate approvals from participating organisations are in place.

## 15.5 Protocol Compliance

Each PI will ensure the study is conducted in line with the protocol, GCP guidelines and applicable UK clinical trial legislation.

Accidental protocol deviations could happen at any time. Any deviations from the protocol or GCP must be reported to YTU who will notify the Co-CIs and Sponsor for their oversight.

## 15.6 Notification of Serious Breaches to GCP and/or the Protocol

A “serious breach” is defined as a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial

Any breaches of GCP or the protocol must be reported to the MHRA in line with the sponsor’s SOP DTVRA SOP 017 - Identifying, Recording and Reporting Potential Serious Breaches of GCP or Trial Protocol.

## 15.7 Data Protection and Patient Confidentiality

All Investigators and study site staff involved with this study must comply with the requirements of the General Data Protection Regulation (GDPR) (2016/679) (2018), the Data Protection Act (2018), and the Caldicott Principles with regard to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the regulation(s).

South Tees Hospitals NHS Foundation Trust will act as the Data Controller for this trial.

The researchers and clinical care teams must assure that patients’ anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a Unique Trial Identification Number, and this will be used on all data collection tools; patients will not be identified by their name in order to maintain confidentiality.

Access to collated participant data will be restricted to authorised staff. Computer systems used to collate the data will have access restrictions controlled via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

## 15.8 Financial and other Competing Interests for the Co-CIs, PIs at each site and committee members for the overall trial management

Independent members of the trial oversight committees will be required to declare conflicts and/or competing interests and this will be documented on the signed charters and meeting minutes.

## 15.9 Indemnity

This study will be sponsored by South Tees Hospitals NHS Foundation Trust. If there is negligent harm during the trial, when the NHS Trust owes a duty of care to the person harmed, NHS Indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the R&D department.

NHS indemnity does not offer no-fault compensation and the Sponsor is unable to agree in advance to pay compensation for non-negligent harm.

## 15.10 Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor.

For any amendment to the study protocol, the Co-CIs or designee, in agreement with the sponsor will submit information to the appropriate regulatory body in order for them to issue approval for the amendment. The Co-CI or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments to other documentation should not be implemented until appropriate approvals are in place.

## 15.11 Post-Trial Care

Individual participants will not be provided with further IMP once their study participation ends.

## 15.12 Access to the Final Trial Dataset

Once the analysis and reporting has been completed and all intended papers have been published in scientific journals, the anonymised data may be made available for other researchers.

In principle, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes.

Requests for access to data will be reviewed by the Co-CIs and study Sponsor.

# 16 Dissemination and Publication Policy

## 16.1 Dissemination Policy

Throughout the project we will engage with a range of stakeholders for whom the study will be of relevance and interest. The clinician group will include microbiologists, surgeons, physicians and infection control specialists, identified through the personal networks of the applicants, such as the QIST network, the British Society for Antimicrobial Chemotherapy, Healthcare Infection Society and the Infection Protection Society.

Awareness raising about the study will include promotional activities within the participating Trusts, for example through the provision of posters and leaflets personalised to the Trust. Engagement will be encouraged through regular feedback to participating Trusts and other stakeholders through newsletters and messages via a project specific Twitter feed.

Publications will include the trial protocol, the HTA report, main findings paper, health economics, qualitative and a SWAT paper (assessing the impact of a pictorial aid alongside the PIS on recruitment to the study).

A plain English summary bulletin will be sent to all participating Trusts and other stakeholders and made available on relevant websites. Participants will also be offered the opportunity to receive a plain English summary of the results of the trial.

The summary of the findings will be shared through the clinical applicants' existing extensive contacts with NHS England and NHS Improvement, Public Health England, Royal Colleges and other policy making bodies including NICE. The awareness raising work with Trusts should underpin the implementation of any revised guidance, providing the appropriate impact from the study.

## 16.2 Authorship eligibility guidelines and any intended use of professional writers

A dissemination and publication policy will be developed with an agreement between partners including ownership and exploitation of intellectual property, and publication rights. The publication policy and the agreement will ensure that any intellectual property generated during the project is protected and that the publication process is organised in a fair, balanced and transparent manner. The TMG will be responsible for overseeing these arrangements. The creation of the publication plan will be the responsibility of the TMG (via coordinating centre (YTU). It will be ensured that all partners have input into the document.

# 17 Department of Health disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

# 18 References

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# 19 Appendices

## 19.1 Appendix 1 – Risk

A risk assessment has been performed by the sponsor and will continue to be reviewed in accordance with the Durham Tees Valley Research Alliance SOPs (SOP DTVRA) - SOP 014 and maintained within the Trial Master File.

## 19.2 Appendix 2 - Principal Investigator (PI) responsibilities

The PI is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

A Delegation Log will be prepared for each site, detailing the delegated responsibilities of each member of staff working on the trial. This should be signed by those named on the list.

Informed Consent

The PI is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. Where this is not possible due to incapacity, a Legal Representative will be asked to consent on the participant's behalf.

Participants must receive adequate oral and written information, including the PIS and Consent Forms. The oral explanation to the participant should be performed by a designated person, and must cover all the elements specified in the Participant Information Sheet/Informed Consent.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided subject to the time constraints imposed by the need to begin decolonisation treatment in line with site policy. It should be emphasised that the participant may withdraw their consent to participate at any time without any effect on their current or future care.

The participant should be informed and agree to their medical records being inspected by regulatory authorities but understand that inspection is undertaken by authorised personnel and their data will remain confidential.

The PI or delegated member of the trial team and the participant or their Legal Representative should sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant should receive a copy of this document and a copy should be filed in the participant's medical records. Copies should also be filed in the Trial Master File (TMF) and the Investigator Site File (ISF).

Study Site Staff

The PI must be familiar with the study treatments, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMPs, protocol and their trial related duties as delegated.

Data Recording

The PI is responsible for the quality of the data recorded in the data collection tool.

Investigator Documentation

Prior to beginning the study, each PI will be asked to provide particular essential documents to the Sponsor, including but not limited to:

An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents)

The CI, with the agreement of the Sponsor, will ensure all other documents required for compliance with the principles of GCP are retained in the TMF and that appropriate documentation is available in local ISFs.

GCP Training

Study staff should be qualified, by education, training and experience, appropriate to their role in the project.

Confidentiality

All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC.

The PI and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

## 19.3 Appendix 3 – Safety Reporting Flow Chart