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Cook, Elizabeth, James, Sophie, Laycock, Joanne et al. (2026) Effectiveness of polyhexanide, chlorhexidine with neomycin and mupirocin for nasal methicillin-resistant Staphylococcus aureus (MRSA) decolonisation:non-inferiority RCT (TIDE). Health technology assessment. ISSN: 2046-4924

https://doi.org/10.3310/GJMR0715

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Synopsis

Effectiveness of polyhexanide, chlorhexidine with neomycin and mupirocin for nasal methicillin-resistant Staphylococcus aureus (MRSA) decolonisation: non-inferiority RCT (TIDE)

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Published February 2026
DOI: 10.3310/GJMR0715

Abstract

Background: The bacterium *Staphylococcus aureus* is a leading cause of hospital-acquired infections. These infections are difficult to treat when there is increasing resistance to penicillin, known as methicillin-resistant *Staphylococcus aureus*. Patients who carry *Staphylococcus aureus* in the nose and skin are prone to developing infections and many patients admitted to hospital are routinely 'decolonised' to reduce this risk. The current standard treatment for nasal decolonisation is the antibiotic nasal mupirocin. There are concerns about over-reliance on a single treatment and the risk of mupirocin-resistant methicillin-resistant *Staphylococcus aureus*. Robust evidence for alternatives to mupirocin is required.

Objective: To investigate whether there are clinically and cost-effective alternatives to mupirocin for early nasal decolonisation of methicillin-resistant *Staphylococcus aureus* among adult hospital inpatients.

Design and methods: We designed a multicentre, three-arm parallel-group, non-inferiority, randomised controlled trial with economic and qualitative evaluations, to recruit 3000 participants.

Setting and participants: Adult hospital inpatients identified as being colonised with methicillin-resistant *Staphylococcus aureus* on routine hospital admission screening were eligible for inclusion.

Interventions: Participants were randomised (ratio 1 : 1 : 1) to receive one of the following decolonisation treatments: mupirocin (2%) nasal ointment (3 g), polyhexanide (0.1%) nasal gel (30 ml) or chlorhexidine (0.1%) with neomycin (0.5%) nasal cream (15 g).
Neither participants nor the investigators were blind to treatment allocation.

Main outcome measures: The primary outcome was successful early nasal decolonisation, defined as a negative trial specific nasal methicillin-resistant *Staphylococcus aureus* swab taken 48 hours following treatment completion. Secondary outcomes included successful early nasal decolonisation of methicillin-resistant *Staphylococcus aureus* not fully susceptible to mupirocin, successful late nasal decolonisation, acceptability of treatment to patients, methicillin-resistant *Staphylococcus aureus* infections, length of hospital inpatient stays and re-admissions, adverse events and mortality. Outcomes were collected up to 4 weeks following treatment completion.

This synopsis should be referenced as follows:
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Results: Recruitment and retention of participants were much lower than expected. In total, 297 patients were assessed for eligibility and 32 patients randomised. All participants received treatment as allocated. Seven participants withdrew from the study. The mean age was 73.8 years (standard deviation 16.6 years), with 62.5% (*n* = 20) of participants being male.
Semistructured interviews were undertaken with patients (*N* = 5), clinical teams (*N* = 19) and clinical trials unit staff (*N* = 5) to explore barriers and facilitators to recruitment and consent processes. Data from the qualitative evaluation contributed to progress discussions at trial management meetings and resulting remedial activities undertaken.
Limitations: The trial closed early after reaching < 2% of the recruitment target. The planned statistical and health economic analyses could not be conducted due to the limited data. The study objectives were not addressed due to poor recruitment.
Conclusions: It was not feasible to recruit to this trial in the current context, due to a reduced level of methicillin-resistant *Staphylococcus aureus* testing being undertaken in hospitals within the National Health Service.
Future work: To facilitate future research, further understanding of the routine decolonisation pathways in line with the revision to national guidance issued in 2021 is required. Validation of methicillin-resistant *Staphylococcus aureus* viability to increase processing time for nasal swabs could be undertaken and further exploration of the use of self-swabbing at home.
Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number NIHR132718.
A plain language summary of this synopsis is available on the NIHR Journals Library website https://doi.org/10.3310/GJMR0715.

Introduction

This report summarises the TIDE randomised controlled trial (RCT), as commissioned and undertaken, and the lessons learned. Due to challenges with recruitment and retention of participants, the trial was stopped earlier than originally planned.

Background

About methicillin-resistant Staphylococcus aureus

Staphylococcus aureus (S. *aureus)* is a bacterium. It is the leading cause of hospital-acquired infections[1] and the second 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.

Methicillin-resistant *Staphylococcus aureus* colonisation itself does not cause the patient any harm; however, colonised 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 found to be MRSA positive, 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 a 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]

Rationale

Some MRSA species have now also developed resistance to mupirocin, in addition to methicillin, and are known as mupirocin-resistant MRSA. Subsequently, there are concerns about over-reliance on a single antibiotic treatment in terms of potential shortages as well as antibiotic resistance. There are a number of other MRSA decolonisation treatment options that are available as alternatives to mupirocin. However, their relative effectiveness has not been tested in comparative RCTs.[4]

The TIDE trial was designed in response to a commissioning brief from the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme to investigate the clinical and cost-effectiveness of alternative treatments to mupirocin for nasal MRSA decolonisation. A nasal antiseptic alternative to mupirocin would be a preferable, long-term solution over another antibiotic, as the chances of MRSA developing resistance to an antiseptic is considered less likely than to another antibiotic. Options, where there were some suggestions of benefit, were povidone iodine, alcohol gel, octenidine and polyhexanide. At the early stages of

applying for the funding, two of these treatment options were available in the UK market as a nasal decolonisation preparation: octenidine and polyhexanide. Substantial changes to the formulation (concentration, viscosity and licensing) of octenidine were planned by the manufacturers during the study period; therefore, octenidine was not considered for inclusion.

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 was mixed and inconclusive, and largely consisted of observational studies.[4] One RCT 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% confidence interval (CI), −10.6% to 19.5%; $p = 0.56$]. However, 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] There was a lack of high-quality, randomised trials of polyhexanide, yet polyhexanide nasal gel was already being used in some NHS Trusts as part of their MRSA decolonisation protocols and was readily available via NHS procurement processes, making it an appropriate candidate for evaluation.

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

The 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 were already in use as part of many NHS Trust decolonisation policies and was used alongside each of the nasal decolonisation regimes in this study.

The eligible population for this trial was hospital inpatients, colonised with MRSA. Recruitment was intended to include recruitment from geographic populations with high disease burden. Our site identification and participant identification strategies are described in the Trial setting and Recruitment sections of the trial protocol (available at https://fundingawards.nihr.ac.uk/award/NIHR132718) and aim to include patients who have a greater risk of MRSA nasal colonisation, and particularly vulnerable and underserved populations.

Aims

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 among adult hospital inpatients.

Primary objective

To undertake a multicentre, 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 among adult hospital inpatients.

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 included 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.
- Undertake an analysis of secondary outcomes.

Methods

Trial design

TIDE was a multicentre, three-arm, parallel-group, non-inferiority, pragmatic RCT, designed to compare three treatments for MRSA decolonisation in adult inpatients.

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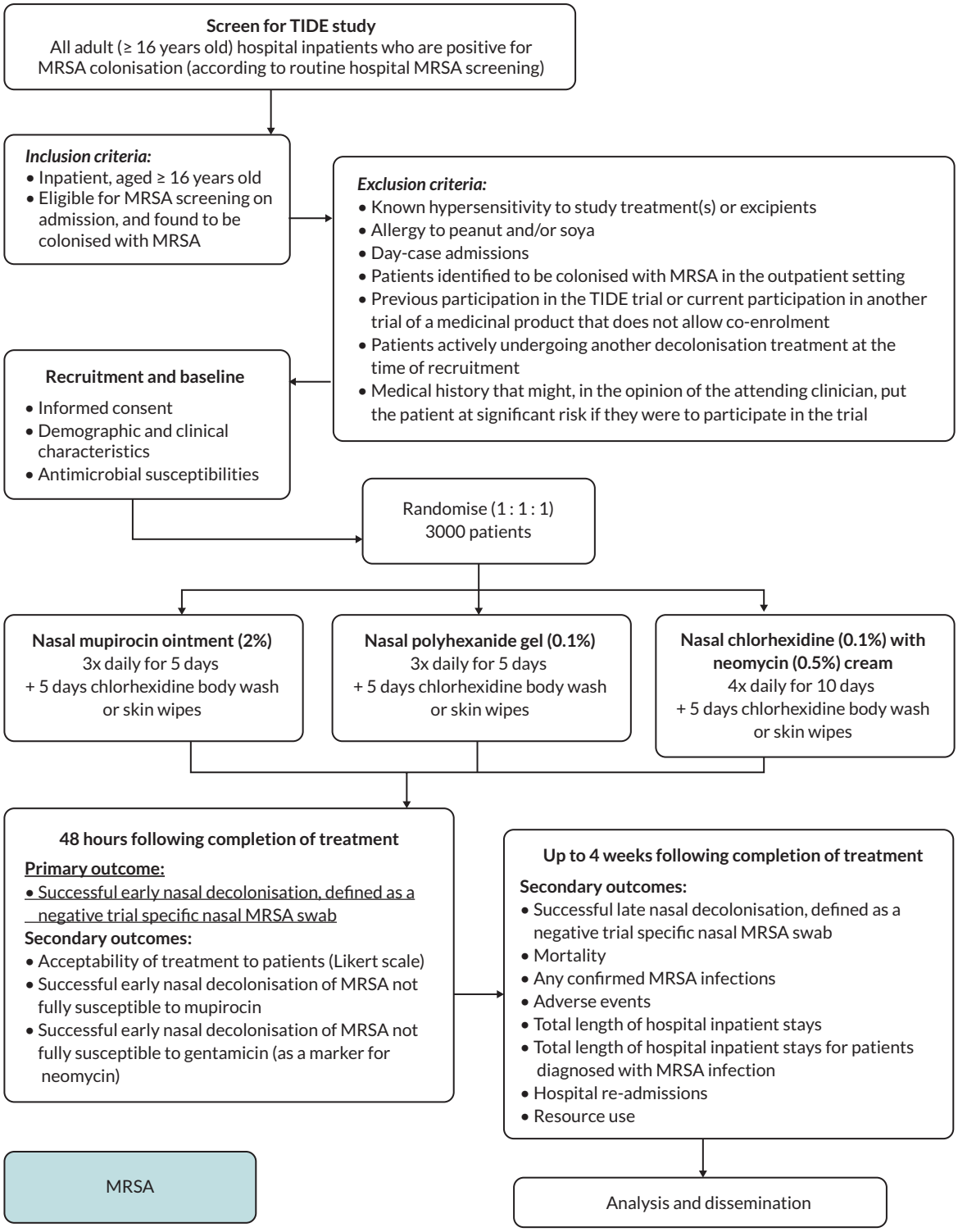

FIGURE 1 Trial flow chart.

As summarised in *Figure 1*, adult patients who were found to be colonised with MRSA and who met the eligibility criteria as set out in the protocol version 1.1 (available at https://fundingawards.nihr.ac.uk/award/NIHR132718) were randomised to receive one of the three study treatments and were followed up at 48 hours and at 1 month post completion of treatment. Randomisation was stratified by study centre and used randomly varying block sizes.

Demographics and clinical characteristics were collected at baseline, including comorbidities, smoking status and standard clinical swabs.

The outcome measures were mainly from laboratory-based analysis and were designed to have minimal impact on participants and research staff at sites. Patients were required to provide a nasal swab for the study at 48 hours and again at 4 weeks after treatment completion. Patients who were discharged prior to follow-up were asked to undertake a self-swab and post to the central processing laboratory. Research staff asked patients a limited number of questions on treatment acceptability and adherence to treatment at 48 hours after treatment completion. Research staff also collected some information from patient medical records at baseline, 48 hours and 4 weeks after treatment completion and adverse events (AEs), additional MRSA decolonisation treatments and hospital resource use at 4 weeks after treatment completion only.

Trial participants were randomised (1 : 1 : 1) to receive one of three trial treatments being investigated:

- mupirocin (2%) nasal ointment (3 g) – applied to the inner surface of each nostril three times a day for 5 days
- polyhexanide (0.1%) nasal gel (30 ml) – applied to the inner surface of each nostril three times a day for 5 days
- chlorhexidine (0.1%) with neomycin (0.5%) nasal cream (15 g) – applied to the inner surface of each nostril four times a day for 10 days.

Any brand/manufacturer of each of the investigational medicinal products with a marketing authorisation in the UK could be used. All study medication was being used within the terms of licensing and sourced from routine stock.

Chlorohexidine body wash (4%) or wipes (2%) were used in conjunction with each of the trial treatments for bathing, showering or washing for 5 days.

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

From the study outset, comprehensive materials and guidance were in place for the inclusion of patients who lacked capacity or had fluctuating levels of capacity due to health-related delirium.

The trial design incorporated a 9-month internal pilot phase to assess the assumptions about site set-up, participant recruitment and follow-up and to provide guidance on optimisation of trial processes. The internal pilot phase was assessed against the pre-agreed criteria set out in *Table 1*.

Before the study commenced recruitment the required regulatory approvals were sought: Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Health Research Authority (HRA) approvals were obtained on 1 June 2022. REC reference: 22/EM/0096.

A summary of amendments can be found in *Appendix 2*, *Table 17*.

Information on public involvement activity undertaken can be found in the *Additional information* section and *Appendix 3*.

Planned statistical methods and data analysis

Sample size, randomisation

For 90% statistical power, 2697 participants (899 per group) were 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 CI (equivalent to a one-sided 97.5% CI) assuming the rate of early nasal decolonisation in each group is 81%.[9] Assuming 10% attrition at follow-up 48 hours following completion of treatment, the total target sample size was 3000 (1000 per group).

TABLE 1 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)

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.

The allocation sequence was independently generated by the trial statistician and was implemented using REDCap, a centralised secure internet interface managed by the University of York.

Statistical analysis plan

Full analyses were detailed in TIDE statistical analysis plan (SAP), which was reviewed and approved by the trial steering and Data Monitoring Committees (DMCs) and finalised before recruitment started.

The primary analysis model was to be on an intention-to-treat basis, analysing patients in the groups to which they were randomised. A mixed-effects logistic regression model was planned to compare chlorhexidine with neomycin cream and polyhexanide to mupirocin, adjusting for relevant baseline covariates as fixed effects and centre as a random effect. An odds ratio and associated CI were to be estimated from the model. Non-inferiority accepted if the lower bound of the two-sided 95% CI (equivalent to a one-sided 97.5% CI) lay within the non-inferiority margin of 6 percentage points (equivalent to a lower bound odds ratio CI of 0.70). Complier average causal effect analysis was planned as a sensitivity analysis. Other binary secondary outcomes were to be analysed using similar mixed-effects logistic regression models as specified for the primary analysis model.

Changes from planned statistical analyses

While a comprehensive analysis to investigate the effectiveness and cost-effectiveness of the TIDE interventions was planned, due to the trial's early closure prior to attaining the required recruitment target, the limited data are only summarised descriptively [Stata v18 (StataCorp LP, College Station, TX, USA)]. No formal hypothesis testing was undertaken.

For patients who at baseline had a chronic wound infected with MRSA, the type of wound colonised has not been presented and neither has the number of patients infected with MRSA before 48 hours post completion of treatment as this information was not collected. The global rating of assigned treatment has not been reported, as this question was not asked. The Index of Multiple Deprivation has been reported in place of the Index of Health Deprivation and Income Deprivation Affecting Older People Index for those eligible and randomised compared to those eligible and not randomised.

Health economic aspects

We planned to conduct a cost-effectiveness analysis of the three treatments using existing evidence in addition to evidence generated in this trial.

Resource use data were collected from participating sites using bespoke data collection tools. Data were sourced directly from patients (e.g. resource use) or healthcare staff (i.e. hospital costs such as drug costs, additional therapeutic treatments, laboratory testing, length of stay, outpatient visits and re-admissions). Unit costs were to be sourced from the NHS Reference Costs databases, the Personal Social Services Research Unit and other appropriate national sources.

Given the trial closed earlier than planned the cost-effectiveness analysis was not undertaken.

Planned qualitative review

The internal pilot phase included an embedded qualitative study, which was focussed on understanding recruitment and consent processes ahead of the main trial recruitment phase.

Semistructured interviews were undertaken via telephone or video conferencing with patients, clinical teams and trials unit staff. A flexible interview schedule specific to each group of participants was developed in consultation with the research team, patient/public advisory group (PAG) and health professionals and used to guide the interviews.

Interviews with patients and carers explored their 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. Due to the challenges encountered with delivery of the main trial, adaptations were made to the patient interview scheduled to focus on the barriers experienced in providing a nasal swab (which provided the primary outcome data).

Interviews with clinical staff involved with recruitment at participating sites and the trials unit also focussed on their experience of recruiting and consenting patients.

Informed consent was gained from each interviewee before the interview began. Following transcription, the interviews were analysed thematically.

Study Within a Trial

The TIDE trial was planned to act as a host trial for an embedded study which aimed to assess the impact of the use of a pictorial aid in conjunction with the patient information sheet (PIS) on recruitment. This Study Within a Trial (SWAT) was registered on the Medical Research Council (MRC) SWAT Repository (SWAT reference 187). Given the trial closed earlier than planned, the SWAT analysis was not undertaken.

Results

Nine sites in England and Scotland were opened to recruitment during the internal pilot (see *Appendix 1*, *Table 16*). The nine sites were open for a combined total of 72 months. A further seven sites were in various stages of set-up prior to study closure.

Recruitment took place between October 2022 and July 2023 and the flow of participants is reported in the Consolidated Standards of Reporting Trials diagram in *Figure 2*.

In total, 297 patients were screened, of which 146 (49.2%) patients were eligible and 151 (50.8%) were ineligible. The most common reason for ineligibility was actively undergoing MRSA decolonisation treatment (*n* = 76, 50%) or identified as colonised in the outpatient setting (*n* = 31, 21%) (*Table 2*).

Of the 146 eligible patients, 57 (39.0%) were approached for participation with 48 (84.2%) attempted directly with the participant, and 9 (15.8%) for whom consent was attempted via a legal representative. The main reason for non-approach was that the patient was discharged before they could be reached by the study team (*n* = 55, 62%; *Table 3*).

Of the 57 approached patients, 32 (56.1%) were consented and randomised. It was unclear why most participants declined participation (*n* = 18, 72%; *Table 4*).

Of the 146 eligible patients, 32 were randomised, corresponding to a recruitment rate of 21.9% (proportion of eligible patients randomised). The combined total of site recruitment months was 72, which gives an overall average recruitment rate of 0.44 participants per month per site.

The mean and median Index of Multiple Deprivation scores were slightly higher for those patients eligible and randomised (*n* = 32, mean= 5.2, median = 5) compared to those eligible but not randomised (*n* = 114, mean= 4.4, median= 4) with similar variation in scores [standard deviation (SD) = 3.1 vs. SD = 3.0] (*Table 5*). Scores indicate that those randomised were resident in slightly less deprived areas than those not randomised.

Baseline characteristics

Of the 32 participants randomised, 13 were randomised to mupirocin, 11 to polyhexanide and 8 to chlorhexidine. *Table 6* gives information on baseline characteristics. The mean age was 74 years (SD 16.6), with 63% (*n* = 20) of participants being male. One patient withdrew on the day of randomisation and as a result a date of birth was not obtained; however, when assessed for eligibility, it was stated they were between 66 and 75 years.

Treatment delivery

One participant in the polyhexanide group withdrew on the day of randomisation and therefore had no data on treatment confirmation. All other patients received their allocated treatment.

Of the data received, those randomised to mupirocin and polyhexanide all reported applying the nasal treatment for 4–5 days and the average number of times per day the patients applied the treatment was three for the Mupirocin group and 2 (1, 12.5%) or 3 (7, 87.5%) times for the polyhexanide group (*Table 7*). For the chlorhexidine with neomycin group, 5 (83.3%) reported applying the nasal treatment for 9–10 days and 1 (16.7%) for 3–5 days. The average number of times per day the patients applied chlorhexidine with neomycin was 2 (1, 16.7%), 3 (1, 16.7%) or 4 (4, 66.7%) times. Most people received the chlorhexidine body wash rather than wipes across the three groups (mupirocin *n* = 11, 91.6%; polyhexanide *n* = 8, 88.9%; chlorhexidine with neomycin *n* = 6, 100%) and the majority used it for 4 or 5 days (mupirocin *n* = 10, 83.3%; polyhexanide *n* = 8, 88.9%; chlorhexidine with neomycin *n* = 5, 83.3%) (*Table 8*).

Primary outcome

There were limited data returned for the 48 hours post completion of treatment swabs (10, 77% mupirocin; 6, 55% polyhexanide; and 2, 25% in the chlorhexidine with neomycin). Early decolonisation occurred in 1 (10%) person in the mupirocin group, 4 (66.7%) people in the polyhexanide group and 2 (100%) in the chlorhexidine with neomycin group.

Methicillin-resistant Staphylococcus aureus decolonisation

There were also limited data returned for the 4 weeks post completion of treatment swabs (8, 62% mupirocin; 4,

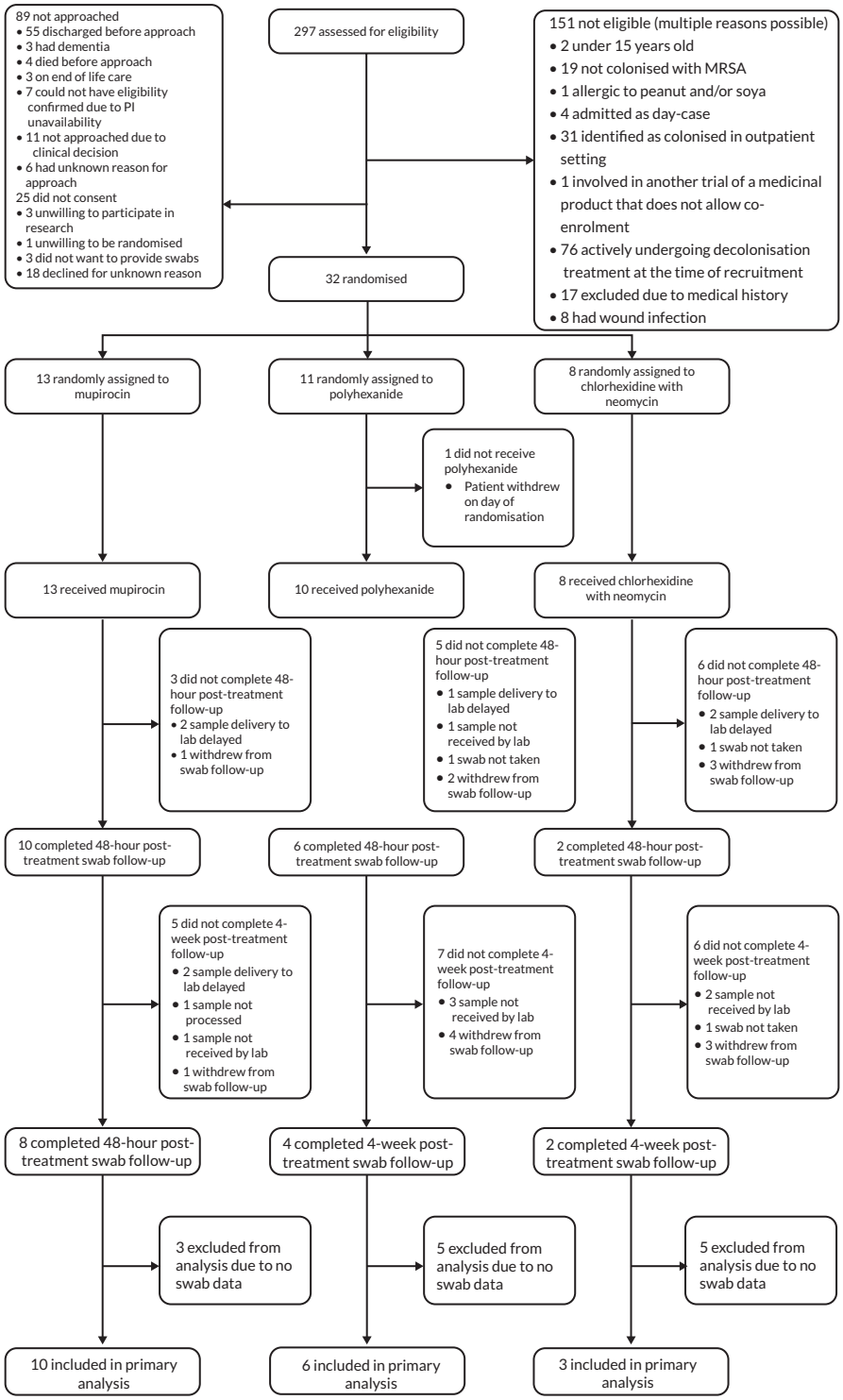

FIGURE 2 Consolidated Standards of Reporting Trials diagram. PI, principal investigator.

36% polyhexanide; and 2, 25% in the chlorhexidine with neomycin). Late decolonisation occurred in 4 (50%) people in the mupirocin group, 2 (50%) in the polyhexanide group and 1 (50%) in the chlorhexidine with neomycin group (*Table 9*).

Analysis of secondary outcomes

Overall, from the data returned (12/13 mupirocin, 8/11 polyhexanide and 6/8 chlorhexidine with neomycin) there were no deaths at 48 hours or at 4 weeks post completion of treatment. There were two participants who were

TABLE 2 Reasons for ineligibility

	Ineligible (*n* = 151)
Reasons for ineligibility (multiple reasons possible), n (%)	
Under 16 years old	2 (1.3)
Negative for MRSA colonisation on admission	19 (12.6)
Allergic to peanut/soya	1 (0.7)
Admitted as day case	4 (2.6)
Identified as colonised with MRSA in the outpatient setting	31 (20.5)
Currently participating in another trial of a medical product	1 (0.7)
Actively undergoing MRSA decolonisation treatment	76 (50.3)
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	17 (11.3)
Wound infection	8 (5.3)

TABLE 3 Reasons for non-approach

	Non-approach (*n* = 89)
Reasons for non-approach (multiple reasons possible), n (%)	
Discharged before could be reached by study team	55 (61.8)
Clinician decision	11 (12.4)
PI unavailable to confirm availability	7 (7.9)
Patient died before consent could be taken	4 (4.5)
Patient had dementia	3 (3.4)
Patient on end-of-life care	3 (3.4)
Missing	6 (6.7)

PI, principal investigator.

TABLE 4 Reasons for non-consent

	Not consented (*n* = 25)
Reasons for non-consent (multiple reasons possible), n (%)	
Unwilling to participate in research	3 (12.0)
Unwilling to be randomised to a treatment	1 (4.0)
Concerned/did not want to provide swabs	3 (12.0)
Participant declined (reason unknown)	18 (72.0)

TABLE 5 Index of Multiple Deprivation for non-randomised and randomised eligible patients

	Eligible but not randomised (*n* = 114)	Eligible and randomised (*n* = 32)
Index of Multiple Deprivation decile (1 = most deprived, 10 = least deprived)		
Number with data (%)	98 (86.0)	*31 (96.9)*
Mean (SD)	4.4 (3.0)	5.2 (3.1)
Median (IQR)	4 (2–7)	5 (3–7)
Minimum, maximum	1–10	1–10

IQR, interquartile range.

TABLE 6 Baseline characteristics for randomised participants

	Randomised (*n* = 32)			
	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine (*n* = 8)	Overall (*n* = 32)
Age at randomisation				
Number with data (%)	*13 (100)*	10 (90.9)	8 (100)	31 (96.9)
Mean (SD)	74.6 (16.8)	77.4 (9.3)	68.1 (22.9)	73.8 (16.6)
Median (IQR)	77 (69–86)	76 (68–84)	72.5 (54.5–86.5)	77 (67–86)
Minimum, maximum	28–93	67–93	26–92	26–93
Sex, n (%)				
Number with data (%)	*13 (100)*	*11 (100)*	*8 (100)*	*32 (100)*
Male	9 (69.2)	6 (54.5)	5 (62.5)	20 (62.5)
Female	4 (30.8)	5 (45.5)	3 (37.5)	12 (37.5)
Body mass index				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Mean (SD)	28.1 (15.1)	28.4 (8.9)	25.5 (6.6)	27.5 (11.2)
Median (IQR)	23.9 (20.9–25.9)	27.9 (26.4–30.3)	25.6 (20.4–28.3)	25.9 (20.9–30.3)
Minimum, maximum	18.7–76.5	15.2–49.3	17.1–37.9	15.2–76.5
Ethnicity, n (%)				
Number with data (%)	*12 (92.3)*	*11 (100)*	*8 (100)*	*31 (96.9)*
White British	12 (100)	11 (100)	8 (100)	31 (100)
Working status, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Working full time	2 (15.4)	0 (0)	2 (25.0)	4 (12.9)
Retired	9 (69.2)	9 (90.0)	6 (75.0)	24 (77.4)
Currently unable to work due to poor health	2 (15.4)	1 (10.0)	0 (0)	3 (9.7)
Highest level of education, n (%)				
Number with data (%)	*12 (92.3)*	*10 (90.9)*	*8 (100)*	*30 (93.8)*
No formal qualifications	2 (16.7)	3 (30.0)	0 (0)	5 (16.7)

TABLE 6 Baseline characteristics for randomised participants (*continued*)

	Randomised (*n* = 32)			
	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine (*n* = 8)	Overall (*n* = 32)
Some qualifications	8 (66.7)	5 (50.0)	5 (62.5)	18 (60.0)
Degree or higher	2 (16.7)	2 (20.0)	3 (37.5)	7 (23.3)
Living arrangements, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Live alone	2 (15.4)	1 (10.0)	2 (25.0)	5 (16.1)
Live alone with support from friends/relatives	2 (15.4)	0 (0)	0 (0)	2 (6.5)
Live alone with support from carer	2 (15.4)	0 (0)	1 (12.5)	3 (9.7)
Live with spouse or partner	5 (38.5)	7 (70.0)	5 (62.5)	17 (54.8)
Residential home with care support	1 (7.7)	0 (0)	0 (0)	1 (3.2)
Nursing home	1 (7.7)	1 (10.0)	0 (0)	2 (6.5)
Other	0 (0)	1 (10.0)	0 (0)	1 (3.2)
Initial admission specialty, n (%)				
Number with data (%)	*13 (100)*	*11 (100)*	*8 (100)*	*32 (100)*
Emergency medicine	1 (7.7)	1 (9.1)	0 (0)	2 (6.3)
Acute medicine	1 (7.7)	0 (0)	0 (0)	1 (3.2)
General medicine	2 (15.4)	1 (9.1)	0 (0)	3 (9.4)
Intensive care	0 (0)	0 (0)	1 (12.5)	1 (3.1)
Cardiology	3 (23.1)	0 (0)	1 (12.5)	4 (12.5)
Gastroenterology	1 (7.7)	0 (0)	1 (12.5)	2 (6.3)
Geriatric medicine	0 (0)	2 (18.2)	1 (12.5)	3 (9.4)
Respiratory medicine	1 (7.7)	2 (18.2)	0 (0)	3 (9.4)
General surgery	2 (15.4)	2 (18.2)	1 (12.5)	5 (15.6)
Trauma surgery	2 (15.4)	0 (0)	0 (0)	2 (6.3)
Orthopaedic surgery	0 (0)	0 (0)	1 (12.5)	1 (3.1)
Urology	0 (0)	2 (18.2)	1 (12.5)	3 (9.4)
Vascular surgery	0 (0)	1 (9.1)	0 (0)	1 (3.1)
Other	0 (0)	0 (0)	1 (12.5)	1 (3.1)
Reason for initial admission, n (%)				
Number with data (%)	*13 (100)*	*11 (100)*	*8 (100)*	*32 (100)*
Environmental/social	1 (7.7)	0 (0)	0 (0)	1 (3.1)
Fracture/dislocation	1 (7.7)	0 (0)	1 (12.5)	2 (6.3)
Medical	5 (38.5)	6 (54.5)	4 (50.0)	15 (46.9)
Musculoskeletal	0 (0)	1 (9.1)	0 (0	1 (3.1)
Surgical	2 (15.4)	4 (36.4)	0 (0)	6 (18.8)
Trauma	1 (7.7)	0 (0)	0 (0)	1 (3.1)
Other	3 (23.1)	0 (0)	3 (37.5)	6 (18.8)

continued

This synopsis should be referenced as follows:
Cook E, James S, Laycock J, Scrimshire A, Mitchell A, Leggett H, et al. Effectiveness of polyhexanide, chlorhexidine with neomycin and mupirocin for nasal methicillin-resistant Staphylococcus aureus (MRSA) decolonisation: non-inferiority RCT (TIDE) [published online ahead of print February 25 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJMR0715

TABLE 6 Baseline characteristics for randomised participants (*continued*)

	Randomised (*n* = 32)			
	Mupirocin (*n* = 13)	**Polyhexanide (*n* = 11)**	**Chlorhexidine (*n* = 8)**	**Overall (*n* = 32)**
Time between hospital admission and randomisation (days)				
Number with data (%)	*13 (100)*	*11 (100)*	*8 (100)*	*32 (100)*
Mean (SD)	8.5 (7.6)	14.4 (30.8)	6.6 (7.1)	10.1 (18.7)
Median (IQR)	6 (4–8)	5 (3–7)	4 (3.5–5.5)	5 (4–7)
Minimum, maximum	3–30	2–107	3–24	2–107
Time between MRSA swab and randomisation (days)				
Number with data (%)	*13 (100)*	*11 (100)*	*8 (100)*	*32 (100)*
Mean (SD)	4.0 (4.1)	2.0 (2.3)	2.1 (2.1)	2.8 (3.2)
Median (IQR)	3 (0–6)	1 (0–4)	2.5 (0–3)	2.5 (0–4.5)
Minimum, maximum	0–14	0–7	0–6	0–14
Swab location (multiple locations possible), n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Nose	13 (100)	10 (100)	8 (100)	31 (100)
Groin	10 (76.9)	8 (72.7)	5 (62.5)	23 (71.9)
Throat	2 (15.4)	3 (27.3)	2 (25.0)	7 (21.9)
Chronic wound colonised with MRSA, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Yes	1 (7.7)	0 (0)	0 (0)	1 (3.2)
No	12 (92.3)	10(100)	8 (100)	30 (96.8)
Patient currently prescribed medication, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Yes	12 (92.3)	10 (100)	6 (75.0)	28 (90.3)
No	1 (7.7)	0 (0)	2 (25.0)	3 (9.7)
Patient independently mobile outside home n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Yes	10 (76.9)	7 (70.0)	6 (75.0)	23 (74.2)
No	3 (23.1)	3 (30.0)	2 (25.0)	8 (25.8)
Colonised with MRSA in year prior to randomisation, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Yes	1 (7.7)	3 (30.0)	2 (25.0)	6 (19.4)
No	12 (92.3)	7 (70.0)	6 (75.0)	25 (80.6)
Infected with MRSA in year prior to randomisation, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Yes	0 (0)	0 (0)	0 (0)	0 (0)
No	13 (100)	10(100)	8 (100)	31 (100)

TABLE 6 Baseline characteristics for randomised participants (*continued*)

	Randomised (*n* = 32)			
	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine (*n* = 8)	Overall (*n* = 32)
Index of Multiple Deprivation decile (1 = most deprived, 10 = least deprived)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Mean (SD)	5.3 (3.1)	4.6 (3.2)	5.8 (3.4)	5.2 (3.1)
Median (IQR)	5 (3–7)	3 (2–7)	6 (3–8.5)	5 (3–7)
Minimum, maximum	1–10	1–10	1–10	1–10
Comorbidities present, n (%)				
Number with data (%)	*13 (100)*	*10 (90.9)*	*8 (100)*	*31 (96.9)*
Yes	12 (92.3)	10 (100)	7 (87.5)	29 (93.5)
No	1 (7.7)	0 (0)	1 (12.5)	2 (6.5)
Comorbidities (multiple comorbidities possible), n (%)				
Number with data (%)	*12 (100)*	*10 (100)*	*7 (100)*	*29 (100)*
Circulatory/blood related	10 (83.3)	6 (60.0)	6 (85.7)	22 (75.9)
Respiratory	4 (33.3)	4 (40.0)	2 (28.6)	10 (34.5)
Gastrointestinal	1 (8.3)	3 (30.0)	1 (14.3)	5 (17.2)
Endocrine/rheumatological	4 (33.3)	5 (50.0)	1 (14.3)	10 (34.5)
Renal/urological	2 (16.7)	2 (20.0)	2 (28.6)	6 (20.7)
Neurological	1 (8.3)	2 (20.0)	2 (28.6)	5 (17.2)
Psychiatric/psychological	2 (16.7)	1 (10.0)	2 (28.6)	5 (17.2)
Sensory/age related	3 (25.0)	2 (20.0)	2 (28.6)	7 (24.1)
Social/drug/alcohol	0 (0)	2 (20.0)	1 (14.3)	3 (10.3)

IQR, interquartile range.

TABLE 7 Treatment delivery presented descriptively by received treatment

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 10)	Chlorhexidine with neomycin (*n* = 8)
Number of days patient applied nasal treatment for, n (% of those who received mupirocin or polyhexanide)			
Number with data (%)	*12 (92.3)*	*8 (80.0)*	N/A
0–1	0 (0)	0 (0)	N/A
2–3	0 (0)	0 (0)	N/A
4–5	12 (100)	8 (100)	N/A
Average number of times per day patient took treatment, n (% of those who received mupirocin or polyhexanide)			
Number with data (%)	*12 (92.3)*	*8 (80.0)*	N/A
0	0 (0)	0 (0)	N/A
1	0 (0)	0 (0)	N/A
2	0 (0)	1 (12.5)	N/A
3	12 (100)	7 (87.5)	N/A

continued

TABLE 7 Treatment delivery presented descriptively by received treatment (*continued*)

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 10)	Chlorhexidine with neomycin (*n* = 8)
Number of days patient applied nasal treatment for, n (% of those who received chlorhexidine)			
Number with data (%)	N/A	N/A	*6 (75.0)*
0–2	N/A	N/A	0 (0)
3–5	N/A	N/A	1 (16.7)
6–8	N/A	N/A	0 (0)
9–10	N/A	N/A	5 (83.3)
Average number of times per day patient took treatment, n (% of those who received chlorhexidine)			
Number with data (%)	N/A	N/A	*6 (75.0)*
0	N/A	N/A	0 (0)
1	N/A	N/A	0 (0)
2	N/A	N/A	1 (16.7)
3	N/A	N/A	1 (16.7)
4	N/A	N/A	4 (66.7)

N/A, not applicable.

TABLE 8 Chlorhexidine body wash and skin wipe use presented descriptively by treatment received

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 10)	Chlorhexidine with neomycin (*n* = 8)
Received chlorhexidine body wash/skin wipes, n (%)			
Number with data (%)	*12 (92.3)*	*9 (90.0)*	*6 (75.0)*
Body wash	11 (91.7)	8 (88.9)	6 (100)
Skin wipes	1 (8.3)	1 (11.1)	0 (0)
Number of days the patient used the body wash/skin wipes for, n (%)			
Number with data (%)	*12 (92.3)*	*9 (90.0)*	*6 (75.0)*
0–1	0 (0)	1 (11.1)	0 (0)
2–3	2 (16.7)	0 (0)	1 (16.7)
4–5	10 (83.3)	8 (88.9)	5 (83.3)

TABLE 9 Methicillin-resistant *Staphylococcus aureus* decolonisation presented descriptively by treatment group

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine with neomycin (*n* = 8)
Successfully decolonised at 48 hours post completion of treatment (early decolonisation)[a], n (%)			
Number with data (%)	*10 (76.9)*	*6 (54.5)*	*2 (25.0)*
Yes	1 (10.0)	4 (66.7)	2 (100)
No	9 (90.0)	2 (33.3)	0 (0)
Successfully decolonised at 4 weeks post completion of treatment (late decolonisation), n (%)			
Number with data (%)	*8 (61.5)*	*4 (36.4)*	*2 (25.0)*
Yes	4 (50.0)	2 (50.0)	1 (50.0)
No	4 (50.0)	2 (50.0)	1 (50.0)

a Primary outcome.

found to be infected with MRSA before the 4 weeks post completion of treatment and they were both in the Mupirocin group (*Table 10*).

There was no experience of itching or burning sensation around the nose recorded across any of the three groups (*Table 11*). The median total length of hospital inpatient stay up to 48 hours and 4 weeks post completion of treatment was 7 [interquartile range (IQR) 1–7] and 8 (IQR 1–13) for the mupirocin group, 7 (IQR 3–7) and 10.5 (IQR 2–26) for the polyhexanide group, and 10 (IQR 7–12) and 10 (IQR 7–24) for the chlorhexidine with neomycin group (*Table 12*). Given that only two participants were diagnosed with a MRSA infection during the course of the study, these data have not been summarised. There was one participant in the chlorhexidine with neomycin group who was re-admitted to hospital before 48 hours post completion of treatment. At 4 weeks post completion of treatment, there were 2 (25%) patients in the chlorhexidine with neomycin group and 1 (11%) patient in the polyhexanide group who were re-admitted into hospital (*Table 13*). There were no AEs related to treatment during the study.

TABLE 10 Methicillin-resistant *Staphylococcus aureus* infections presented descriptively by treatment group

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine with neomycin (*n* = 8)
Infected with MRSA before 4 weeks post completion of treatment, n (%)			
Number with data (%)	*12 (92.3)*	*8 (72.7)*	*6 (75.0)*
Yes	2 (16.7)	0 (0)	0 (0)
No	10 (83.3)	8 (100)	6 (100)

TABLE 11 Patient rating of severity of known side effects presented descriptively by treatment group

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine with neomycin (*n* = 8)
Experienced itching sensation around nose, n (%)			
Number with data (%)	*12 (92.3)*	*9 (81.8)*	*5 (62.5)*
Yes	0 (0)	0 (0)	0 (0)
No	12 (100)	9 (100)	5 (100)
Experienced burning sensation around nose, n (%)			
Number with data (%)	*12 (92.3)*	*9 (81.8)*	*5 (62.5)*
Yes	0 (0)	0 (0)	0 (0)
No	12 (100)	9 (100)	5 (100)

TABLE 12 Total length of hospital stay presented descriptively by treatment group

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine with neomycin (*n* = 8)
Total length of hospital inpatient stay up to 48 hours post completion of treatment, days			
n (%)	*12 (92.3)*	*9 (81.8)*	*7 (87.5)*
Mean (SD)	4.5 (3.1)	5.4 (3.3)	8.7 (4.3)
Median (IQR)	7 (1–7)	7 (3–7)	10 (7–12)
Minimum, maximum	0–7	0–10	0–12
Total length of hospital inpatient stay up to 4 weeks post completion of treatment, days			
n (%)	*12 (92.3)*	*8 (72.7)*	*7 (87.5)*
Mean (SD)	10.3 (11.7)	13.8 (13.5)	13.7 (9.9)
Median (IQR)	8 (1–13)	10.5 (2–26)	10 (7–24)
Minimum, maximum	0–33	0–33	0–26

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Cook E, James S, Laycock J, Scrimshire A, Mitchell A, Leggett H, et al. Effectiveness of polyhexanide, chlorhexidine with neomycin and mupirocin for nasal methicillin-resistant Staphylococcus aureus (MRSA) decolonisation: non-inferiority RCT (TIDE) [published online ahead of print February 25 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GJMR0715

TABLE 13 Hospital re-admissions presented descriptively by randomised group

	Mupirocin (*n* = 13)	Polyhexanide (*n* = 11)	Chlorhexidine with neomycin (*n* = 8)
Re-admitted to hospital as an inpatient before 48 hours post completion of treatment, n (%)			
Number with data (%)	*12 (92.3)*	*10 (90.1)*	*8 (100)*
Yes	0 (0)	0 (0)	1 (12.5)
No	12 (100)	10 (100)	7 (87.5)
Re-admitted to hospital as an inpatient before 4 weeks post completion of treatment, n (%)			
Number with data (%)	*12 (92.3)*	*9 (81.8)*	*8 (100)*
Yes	0 (0)	1 (11.1)	2 (25.0)
No	12 (100)	8 (88.9)	6 (75.0)

Qualitative aspects

Between March and August 2023, 29 participants were interviewed including 5 trial participants, 19 clinical team members (research nurses = 10, infection control = 2, PIs = 4, microbiology = 2) and five trials unit staff. The participants interviewed consisted of two males and three females aged between 48 and 90 years (*Table 14*). We were unable to interview any patients who declined to participate in the trial. Interviews lasted between 10 and 60 minutes.

Patient acceptability of the treatment

Overall, the five patients interviewed found the treatment mostly acceptable. Participants found the nasal cream/gel/ointment acceptable and easy to administer. However, one participant who had previously tested positive for MRSA and been given a shampoo to use for 5 days said that they preferred this type of treatment to the cream and body wipe combination as it was quicker and easier to apply. They also felt that using a nasal cream in conjunction with nasal cannulas irritated their nose.

> *No, nothing. It [treatment] didn't bother me at all, no.*
>
> *P2*

> *Me nose a little because me nose was sore because I'm using nasal cannulas as well.*
>
> *P3*

> *I mean obviously putting the cream up inside your nose, first couple of times it was an odd sensation but not unpleasant. It didn't make us sneeze. It didn't have any, like side, well no side-effects at all.*
>
> *P4*

Those using the body wipes felt that more were needed to be supplied to ensure full coverage of the body; they also felt that it was often hard to know which bits of their body they had covered. The body wash was also seen as a 'pain' by one patient due to the length of time it took, but others did not find this an issue.

> *It's just all the faffing about with the wipes.*
>
> *P3*

> *The only thing is obviously they come in packs [unclear 8.45] and there's not a lot to cover your entire body if you like thoroughly clean yourself … The other thing is they weren't that moist, so it was really quite hard sometimes to tell whether you'd actually done a bit of your body.*
>
> *P4*

> *It was just the body wash was a bit of a pain. The one with the nose was over in a few minutes, you know. The one with the body wash apparently you had to stand there for three minutes and then do it again like twice over. That was the other thing but no, I'd done it.*
>
> *P5*

> *So I had the shower. You use it on your body. Leave it for 3 minutes, let it dried. Then have your shower after the 3 minutes. No it was fine, I'd got me own shower.*
>
> *P1*

In terms of frequency, patients did not report any issues with remembering to administer the treatments. Although, those that were in hospital during administration found that the hospital routine helped them remember to do it.

TABLE 14 Characteristics of patients who agreed to take part in the TIDE qualitative interviews

Patient ID	Age	Sex	Treatment received
1	72	Male	Nasal polyhexanide gel
2	68	Female	Nasal polyhexanide gel
3	69	Female	Nasal polyhexanide gel
4	48	Male	Nasal chlorhexidine (0.1%) with neomycin (0.5%) cream
5	90	Female	Nasal mupirocin ointment

> *Well it was only sort of once a day. It was just five days in a row, so that wasn't too bad. I used to do it in the morning when I got up. The same time every day thing.*
>
> *P5*

> *I mean the only thing that I had and to be fair, I think if I hadn't have been in hospital it would have been harder initially because to remember to do it four times a day but because I was in a place with a set routine for like a week and a half, I got into like a routine of when I was doing it. I would do it when I got up in the morning, then I would do it when I had lunch. Then I would do it when I had my evening meal and then I would do it before bed. Maybe if I wasn't in hospital and I was working, it would have been harder for us to remember to keep to that schedule.*
>
> *P4*

Challenges to trial delivery

Site-set-up: research infrastructure

The trial opened to recruitment in 2022, and the aftereffects of the COVID pandemic were still apparent at this time. Importantly the COVID pandemic resulted in many NHS trusts stopping MRSA swabbing on admission in order to divert materials (swabs) and PPE to COVID testing and all laboratory capacity to the analysis of COVID tests.

All non-COVID research that was taking place in the NHS had been paused for a period in 2020. When other research was allowed to resume, there was an issue with research capacity to complete existing research studies and undertake new studies. Studies were subject to an intensified local governance process within each potential participating Trust and the set-up process for the trial was protracted as a result.

Admissions avoidance schemes had been active during the COVID pandemic, with additional resources made available to them to prevent hospital admission or to discharge patients in a timely manner as possible, which could happen before the results of the MRSA admission swab were known. Anecdotally, it was noted that the population of patients being admitted to hospital and staying there were older and sicker than admissions prior to the pandemic. This resulted in challenges to recruitment and retention. The primary focus of many patients at admission was the health condition for which they had been admitted and not about participating in a trial on a topic that was less important to them.

Policy change

Trusts perform MRSA screening in line with national guidance and that was updated in 2021 allowing for targeted rather than universal screening to be adopted.[10] As a result, MRSA screening numbers reduced significantly from those initially projected which were based on pre-pandemic universal screening figures.

At the time of study closure, our collaborator at the Health and Safety Authority was not aware of any plans to prioritise MRSA screening moving forwards with current national focus on *Clostridium difficile* (particularly hospital acquired). It was noted that there was no expectation that screening would increase in the near future and that at best MRSA testing would stay at the same level but may reduce further given financial constraints post pandemic. The patients most likely to be swabbed for MRSA were those admitted to ICU or surgical assessment units and those who have previously tested positive for MRSA colonisation.

Assessing barriers to recruitment and actions taken to increase enrolment

The barriers and facilitators to recruitment were monitored through discussions between recruiting sites and the trial team that took place during the set-up processes, at Site Initiation Visits (SIVs), qualitative interviews, cross-site research team meetings, and through regular contact via e-mail and phone call. The pictorial representations displayed in *Figures 3–5* were generated.

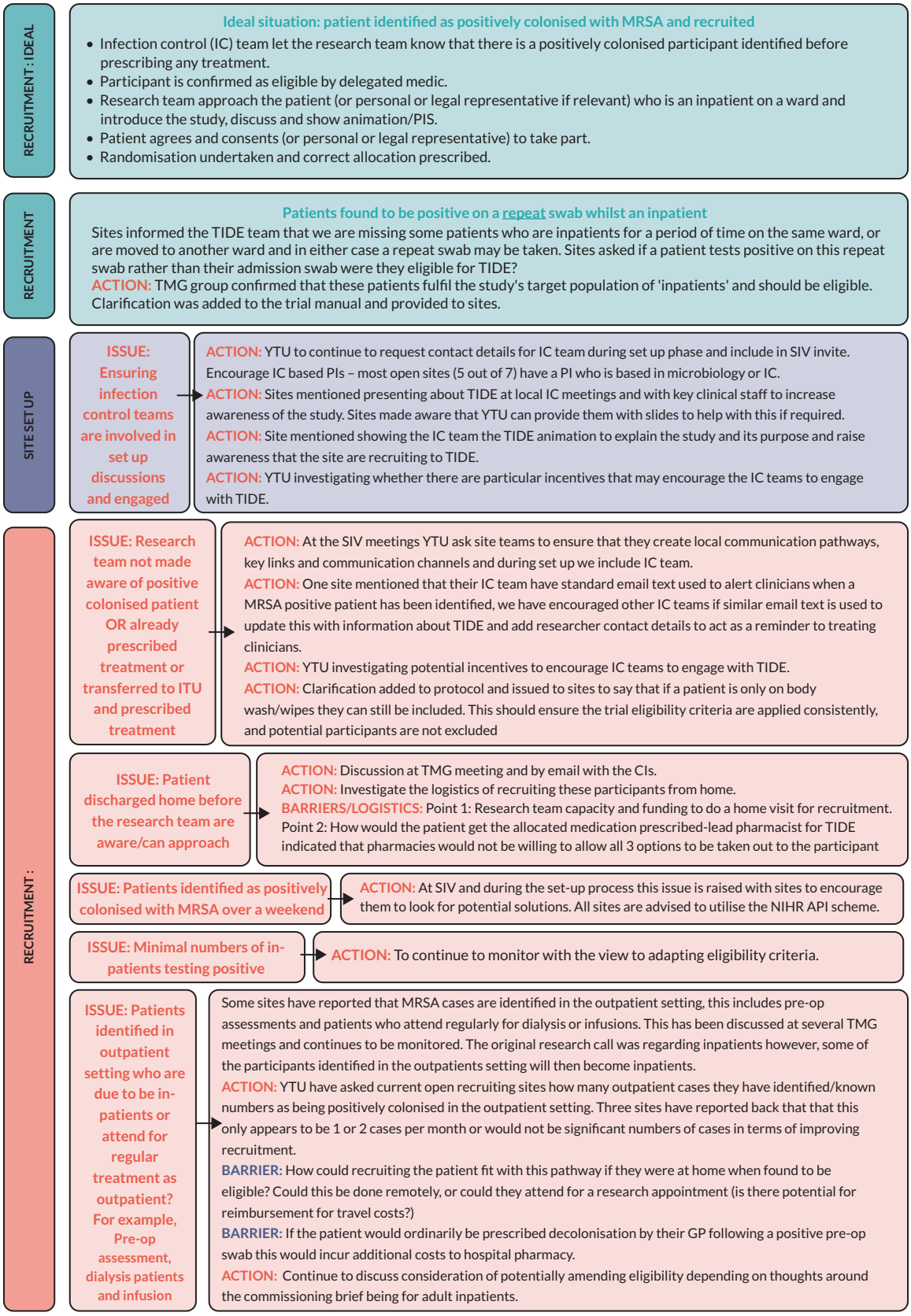

FIGURE 3 TIDE issues, actions, barriers relating to recruitment. API, Associate Principal Investigator; GP, general practitioner; SIV, Site Initiation Visit; TMG, Trial Management Group; YTU, York Trials Unit.

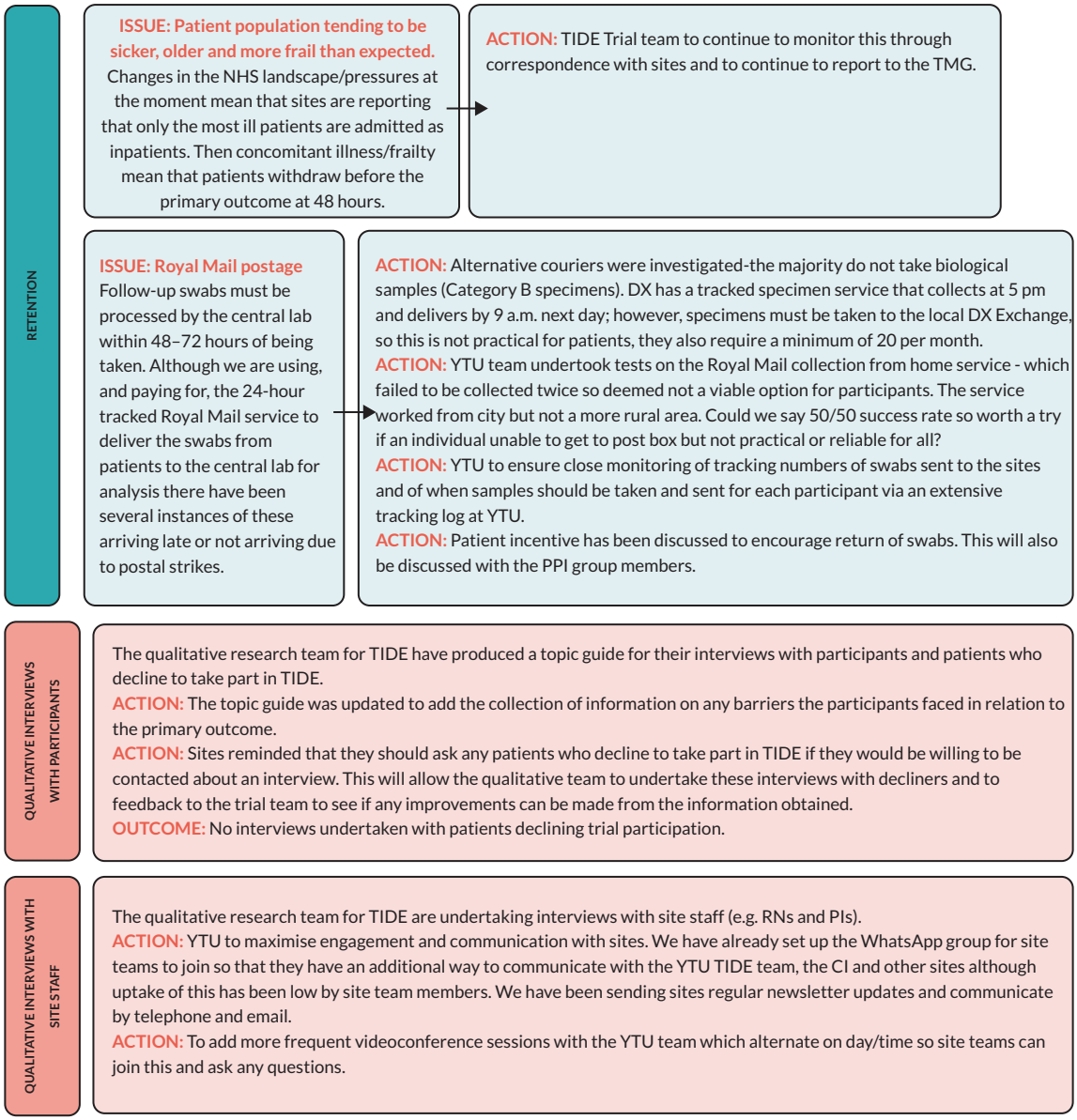

FIGURE 4 TIDE issues, actions, barriers relating to retention. PPI, patient and public involvement; RN, registered nurses; TMG, Trial Management Group; YTU, York Trials Unit.

Ensuring infection control teams were involved in set up discussions and engaged with TIDE

Patients could be recruited from any clinical specialty upon admission and therefore a centralised identification process was considered crucial for successful recruitment. At the start of the study, infection control teams were identified as being key to the identification of patients. It was those teams that were initially approached (where contacts were known) about joining the study as a site.

Additionally, infection control leads were required to approve the study taking place within their Trusts because the decolonisation treatments being used in the trial may be different to those in the Trust policy.

Timely identification of patients who are found to be colonised with MRSA was important as decolonisation treatment is generally implemented quickly, and the trial team did not want the trial recruitment to add unnecessary delays to treatment. To encourage the necessary engagement from infection control teams to deliver the study, the infection control or microbiology leads were encouraged to take on the role of PI and this was achieved in seven of the nine sites opened. However, awareness of the trial needed to be maintained in all specialties and wards across the participating site.

FIGURE 5 TIDE issues, actions, barriers relating to retention – end of pilot information. TMG, Trial Management Group; TSC, Trial Steering Committee.

Minimal numbers of inpatients testing positive for methicillin-resistant Staphylococcus aureus *colonisation on admission*

The low number of patients testing positive for MRSA colonisation was a consequence of reduced testing being performed as previously described. One suggested strategy to increase the numbers of patients available to recruit was to include patients on an elective pathway. This would have the additional benefit of allowing research staff more time to complete all the processes required at the point of recruitment.

> *We haven't really got very far. We've only recruited one patient and in the end that patient had to be withdrawn from the study and I think the study is probably looking at the wrong patient group because over the years we've got very good, because of policies and procedures that can very quickly identifying these patients and provide them with decolonisation treatment and that was part of our MRSA reduction journey. So, you know, the education and training that the clinical staff have got, you know, as soon as somebody is diagnosed on MRSA then we put them on decolonisation treatment. If somebody comes into hospital that's had a previous MRSA history, we put them straight on to decolonisation treatment to reduce the risk of anything further occurring, any infection. So I think the difficulties, you know, because I think quite often by the time the research colleagues get to the patient, the patient has already commenced on decolonisation treatment. Whereas if we looked at the elective pathway, they'd probably have a bit more time.*
>
> *S12 Infection Control*

> *At the moment it's just that throughput of positive patients that we're lacking … the ones that come through we have a relatively slick process to get patients consented, confirmed, prescribed, supplied what they need. It's just that throughput of patients I think.*
>
> *S02 PI*

The lack of positive patients was seen to hinder the research team's recruitment processes with regard to getting into a routine and finding eligibility easier to get signed off.

> *The more times that you do it, you kind of know what to do. So each time now, and I kind of think, oh there's a TIDE patient, oh my god what do I need to do? Then I have to go into my study pack and write all my notes and think about what it is that I need to find.*
>
> *S19 Research Nurse*

There were further discussions at the TMG meetings around the potential for inclusion of patients that tested positive for MRSA colonisation within the outpatient setting (e.g. those patients that attend regularly for treatment). MRSA swabs in this scenario were taken in an outpatient clinic several days before the patient attended hospital for their treatment.

> *It's probably better to look at patients on the primary care pathway because those patients will get screened in preparation of coming in for their planned care activity and they'll be at home but they're delayed a bit longer so there's time for other people to get involved. Whereas in hospital they're there on hand, so that timeliness is keen.*
>
> *S12 Infection Control*

Participating sites were asked to identify numbers of patients testing positive for MRSA in the outpatient setting in order to explore the feasibility of widening the inclusion criteria for the trial. Sites that were able to provide this detail reported that one or two cases per month were identified. The Trial Management Group (TMG) also investigated the capacity of research teams to conduct home visits to recruit patients from or deliver the allocated trial treatments to the home setting. Two separate visits by staff would be required, one for consent and baseline and one for treatment, as the Trust pharmacies were unlikely to allow the dispensing of three treatments, only for one to be used. Given that most of the trial patients were elderly and often with illness it was not considered feasible for them to have to collect medication. Patients would also likely incur a prescription fee which would have to be reimbursed.

Communication channels at site level

Despite attempts during set-up and conduct of the study at each participating site, research teams reported not being made aware of MRSA-colonised patients. Additionally, by the time that research teams were informed, some patients had already been prescribed or started treatment or had been transferred to an Intensive Therapy Unit where it was usual policy for decolonisation treatment to be started immediately. In further cases patients had been discharged from hospital prior to the MRSA swab result being known.

> *The rest [of missed patients] have just been like lack of staff or we've found out about them but they've already started treatment which has been a really big issue that I've found. So we get to know 3 or 4 days later. So what I've done to overcome that is I've been in touch with IPC*

and they've just appointed a new nurse over there who deals with MRSA and MSSA and I'm working with him.

S10 Research Nurse

I would say over 50% that come through and [name] will respond and they would have already been started on treatment.

S05 Research Nurse

We have a system called [name]but what we find in that, they document [name] really late, you know, by the time if we just stick to looking at the [system] we will miss the patient by the time they're already on de-colonisation, so that's why we requested microbiology to cc us when they cc the infection control team.

S20 Research Nurse

They're certainly not getting there before the patient is started on the treatment and what I don't want to do is send out a message in the organisation is to wait for the research nurse because that could build in a patient's safety issue, you know, with those patients. In the last ten years we've been saying act quickly, act quickly, you've got the result, this is what you most do, you know, so it's about that research nurse getting there quickly and promptly before that occurs and I don't know what that delay is or what that timeliness is.

S12 Infection Control

Methicillin-resistant *Staphylococcus aureus* test results could be received at any time including in the late afternoon or at the weekend. At most of the participating sites, the research team staff did not work evenings or during weekends; therefore, any patients who tested positive during this time were unable to be invited to participate in the trial. Test results which arrived in the late afternoon were often deemed to be too late for the research staff to have time to go through the process of getting eligibility signed off and approaching the patient before their shift ended. At one site where there was a good relationship between the research nurse and infection control team, there was a discussion regarding one patient whose results came back in the early evening. The infection control team did allow the team the opportunity to speak to the patient the following morning.

So we don't work weekends and we normally don't work after 4 o'clock. So if a patient comes up positive on the ward, say Friday at 7 o'clock, the ward staff would be able to prescribe that treatment rather than infection control because infection control don't really work the weekends either. So there's been a couple of times when we've come in on the Monday, and they've already had treatment prescribed on the Saturday. So there's nothing we can really do about that.

S01 Research Nurse

We agreed at that point that the patient is not going to be getting any nasal ointment before 8 o'clock, 9 o'clock in the morning and they're probably not going to be washed until … so we agreed that we would wait until you'd had a chance to talk to them.

S04 Infection Control

During site set-up, we tried to work with the site teams to establish bespoke and workable lines of communication to facilitate effective recruitment. Missed opportunities to recruit eligible patients occurred when sites first opened. The facilitation of discussion between research and infection control teams continued. In interviews, staff reported cases where they worked together to smooth out their process of notifying the research team of positive patients and they felt that fewer patients were missed due to this as time went on.

Eligibility process

Recruiting staff fed back that the recruitment process could be lengthy and suggested that it could take on average 2 hours from identification to randomisation. This was thought to be due to the number of steps involved and having to wait for the patient's clinician to agree to their participation and then for another delegated clinician to sign off the patient's eligibility; this could take between 30 minutes and 3 hours. Site teams tried to resolve this by adding more clinicians to the delegation log. The eligibility process was time pressured since the patient needed to start decolonisation treatment as soon as possible. There were instances where patients were unable to be recruited as recruitment could not be completed within a reasonable time frame. Research staff believed this would be mitigated if nurses or pharmacists could sign off on patient eligibility.

So we get an email through off infection control. It doesn't just go to me. It goes to all of the people in our department or research department because it's not just me who works on the study. I've got everybody on the delegation log. So say if I'm off, there's always going to be somebody there to pick that patient up. So I get that email through. As soon as I get that email through, it comes in on a spreadsheet …. Then from there I send it through to the medics on the delegation log via email just asking if anyone can confirm eligibility for this patient. I then send an email to infection control saying please can you hold off just for now, just getting eligibility confirmed and then we're going to approach

this patient. So say the patient is at this hospital where I am, I would get eligibility confirmed. I would go and see the patient and assess if they've got capacity to make that decision. Discuss the study with them. Give them a patient information leaflet and leave them for about half an hour just to read through it and get an informed decision on that. Go back and just say, do you want to take part and then from there take consent. Then I take consent, and I come back to the office and I put all of it into the computer. Randomise the patient. Go back to the patient and then inform them of what the outcome is, if it's going to be the sort of one where it's only 5 days treatment or if it's 10 days treatment.

S01 Research Nurse

It's chasing these people because the medics we've got on the delegation log, we don't necessarily know where they're going to be, so especially the junior doctors, they're sort of across wards. They might not be on the same ward every day. The more senior doctors, especially [name] he's in surgery most of the time. So it's just finding somebody who is around who can confirm that eligibility. So we are in the middle of trying to get more people on the delegation log to make that a little bit easier. But yeah, it can range from half an hour to about three hours by that point infection control are emailing saying what are you doing, what's going on? Just give us another half an hour, it'll be fine! So it can be quite stressful, I'm not going to lie.

S01 Research Nurse

A good few hours isn't it…. it's coordinating all the different people rather than the actual process.

S08 Research Nurse

I think last week we identified a patient and I went down with another nurse, it literally took us from about half past nine to half past three, two of us to go backwards and forwards just trying to find the medics, go to the patient, then go back and getting the swabs and then getting the prescription, telling them what the prescription is.

S19 Research Nurse

Sometimes the clinicians will be around and sometimes we have to wait and know they come for ward rounds and stuff, so we check with them whether they have any objections for the patients participating. If you look at the screening log, that's another issue that I will come to, yeah. So we will check with the treating clinician. Then we look for the doctor who can sign eligibility who has knowledge of the study. I think if we have some doctors on the delegation log but it still takes a lot of time to find them.

S20 Research Nurse

Patients found to be positive on a repeat swab while an inpatient

Early feedback from sites indicated that some potentially eligible patients were being missed. Patients who had tested negative on admission but had been inpatients for a period of time on the same ward, or were being moved to another ward often had repeat MRSA swabs taken. Clarification was sought from the TMG who provided confirmation that if an inpatient tests positive on this repeat swab rather than their admission swab, that they were eligible for inclusion. Clarification was issued to all participating sites via direct e-mail and also through update of the trial manual (instructions).

Retention

Taking of swabs

There was a higher-than-expected withdrawal rate from the trial. Information gathered from sites was that recruited patients were generally frail and/or very unwell and their focus was on the primary reason for their admission, especially when this condition deteriorated, as opposed to continuation with the trial.

Qualitative interviews with patients corroborated this view. Participants felt that doing the swab at home was just too much for them at that moment in time.

He literally said, oh didn't they tell you, I'm not going to be doing any swabs. Apparently he left his medication and everything at the hospital, so he then wanted to withdraw from the study … I think it was quite a lot that he was having to deal with at the moment. It was a very short conversation and I think having to worry about doing an extra thing for him to think about, I think that's what it was.

S19 Research Nurse

One site was able to offer a staff visit to perform the follow-up swab (in hospital or at home). One patient stated that they would not have taken part if this was not possible. Despite this, the remaining four patients interviewed did not find taking the swab and sending the sample back to be problematic.

I wouldn't have done it [without the at home visit]…. Added task. I wouldn't do it, no. I ain't go and try and find a post-box, no way. Too old!

P1

The TMG discussed whether a monetary incentive should be offered to participants to complete and return the swabs. This was to be raised with the patient advisory

group, but it was the opinion of the trial team that an incentive would not overcome the barrier of patients being unwell or too frail to complete this activity.

Transfer and processing of swab samples

Transfer of the 48-hour and 4-week swabs to the central laboratory for processing experienced several issues, which compounded the issues with participant retention. These swabs were posted via the Royal Mail 24 hours tracked service to the central laboratory from the hospital or from patients at home. Swab samples were subject to loss or delay in transit due to the Royal mail strikes taking place at the time of the study and resultant backlogs. If the samples did not reach the lab within 72 hours of being taken, they were not processed as the swabs were deemed no longer viable.

Alternative means of transferring samples from hospital or patient's home to the central laboratory were investigated. Some couriers did not take biological samples (Category B specimens). One supplier had a tracked specimen service that collected at 5 p.m. and delivered by 9 a.m. next day; however, specimens had to be taken to a specific drop-off point, and therefore this was not a practical solution for participants. The central trial team undertook test collections via the Royal Mail collect from home service as a possible alternative. The test items were not collected on half of the test occasions and therefore this service was also not considered suitable for wider use within the trial.

A potential way to improve the number of analysable samples was to extend the 72 hours viability window so that if the postage of the swab was delayed in transit the swab could potentially still be tested to obtain an outcome. A published study noted survivability of MRSA and vancomycin-resistant enterococci (VRE) for extended periods of time and temperatures using a standard swab for assessment which showed that transportation in Liquid Amies medium could be performed at room temperature or 4 °C for up to 14 days without a decrease in recovery of MRSA or VRE.[11] Hence, this was investigated with the central laboratory and they confirmed that their protocol was to reject any swabs which are > 3 days old on receipt. The swabs were only verified in-house for culture up to 72 hours post sampling and therefore the laboratory procedures could not be changed without negative impact on the reliability of the analysis. It may be possible to extend sample viability in future to for up to 14 days if validation testing was performed that showed that MRSA was still viable at this time point.

Decision to close the trial early

Given the challenges with recruitment, discussion with the funder was initiated on 16 June 2023 in order to take a proactive approach to trial next steps. At that time, study progress against the progression criteria was that the progress was in the amber region for site setup and the red region for participant recruitment and collection of the primary outcome (*Table 15*).

The DMC met in June 2023 and the Trial Steering Committee met in July 2023. The recommendation of both groups was that the study was not feasible to deliver in the current landscape, and that the study should close. The TMG met on 20 July 2023 to confirm the decision on early closure of the trial. Sites were informed that recruitment should stop on 31 July 2023 and access to the randomisation system was revoked for all staff on that date to prevent further randomisations (and therefore further prescribing) taking place.

Patient and public involvement

The aim of patient and public involvement (PPI) in this trial was to learn from the experiences and views of people who had been inpatients, who were at a higher risk of hospital admissions, or who cared for a vulnerable person.

TABLE 15 Progression criteria

Domain	Target at end of internal pilot	Green	Amber	Red	Criteria as of 9 months
Site setup	10 sites set-up and recruiting first participant	100% (10)	60% to 99% (6 to < 10)	< 60% (< 6)	9
Participant recruitment	Average of 12 participants recruited per site, per month	100% (12)	60% to 99% (7 to < 12)	< 60% (< 7)	0.44 participants per site per month
Primary outcome follow-up data	90% of expected data collected for the primary outcome	100% (540)	70% to 99% (420 to < 540)	< 70% (< 420)	56%

Potential participants would be in hospital with an injury or illness completely unrelated to MRSA and it is likely that some would struggle to understand what it means to participate (e.g. patients with dementia or learning disabilities). Experience with MRSA treatment or infection was not required. We wanted to discuss with public contributors what information patients (and those who care for them) would need to help them decide whether to take part, and how this information should be presented. We also needed their views on how to best carry out interviews with participants and paid or unpaid carers, and on the best ways to share the findings.

Public involvement method

Our PPI lead and public co-applicant developed a role description for the public co-applicant and our PAG. In addition, they worked together to develop a plain English recruitment advert on the NIHR People in Research platform website. For insurance purposes, our public co-applicant was appointed as a Visiting Research Fellow in the Department of Health Sciences at the University of York for 3 years.

The recruitment and selection process for the PAG described:

- roles of team members involved in the process
- information the team needed from applicants
- selection criteria
- information provided to successful candidates
- information provided to unsuccessful candidates.

Thirteen people responded to the advert and after a short (video) call with each of the applicants eight people formed the final PAG for the study. The members included different ethnic/minority backgrounds, experience of different (chronic) health conditions and neurodiversity.

The PAG members received a TIDE Trial Welcome Pack containing a:

- plain language summary of the trial
- trial timeline (diagram)
- patient journey (diagram)
- TIDE organigram
- description of the role of the PPI group in the trial
- description of the expected time commitment
- provisional code of conduct (to be confirmed during the first meeting)
- information on training and support
- information on (claiming) payments and expenses
- glossary of terms.

Meetings

The PPI group met four times with each meeting lasted 2 hours. Before each meeting, members received an agenda and documents for review. Members who could not attend, were invited to meet with the PPI lead on an individual basis or to contribute via e-mail. All PPI input was recorded in a PPI log. During every meeting, we informed the PAG about the trial's progress and what had been done with their previous input. The specific content of the meetings is provided in *Appendix 3*.

We developed a feedback form to give PAG members the chance to rate and suggest improvements on meeting content and structure, how comfortable they felt in the meeting and the overall meeting. In addition, the form provided the opportunity for PAG members to further comment on the study. For example, to add comments they may not have voiced during the meeting. We also encouraged them to indicate if they needed any training or support to help them fulfil their role.

The feedback form was anonymous, but PAG members could leave their name if they wanted to speak with the team about any of their answers. The feedback form was sent out within 2 days after the meeting, along with the payment claim forms.

The PAG members received newsletters to inform them about trial progress and developments. With these newsletters the team aimed to bridge the gaps between meetings due to delays in recruitment (more details on the Newsletter content available in *Appendix 3*).

Informing of the closure of the study

Patient/public advisory group members received an e-mail on 17 November 2023 to inform them about the decision to close the study. This also meant that there would be no further opportunity for involvement of this group in the trial. This was followed up in December with a feedback form in which PAG members were invited to reflect on their involvement in the trial. Unfortunately, none of the PAG members responded to this.

Results

Having early, very open discussions with PPI contributors on their views and feelings about the trial provided us with valuable initial input for public facing recruitment materials. For example, PPI contributors were concerned about practicalities (e.g. stains on clothing), side effects (e.g. skin

reactions) and long-term effects (e.g. fertility problems) of treatments used in the trial. They also provided valuable information on different formats that could be helpful, such as availability of information in British Sign Language, other languages and easy read versions.

Changes to the PIS were made after discussion with the PAG. For example, we:

- removed the full name of the trial in the title, as PPI contributors found it too complex
- introduced antibiotic resistance on page 1
- clarified the difference between carrying MRSA and having an infection
- shortened and simplified many sentences to improve readability
- clarified why the trial would not share SWAB results directly with patients
- prioritised allergy information
- clarified what happens if a participant decides to withdraw from the study.

We also built on the insights the PAG had provided when preparing drafts of the Infographic, the Qualitative study PIS and Topic Guide, and Animation Script. These materials were then discussed with the PAG members, when we learned the following.

Infographic:

- The infographic should represent what is going to happen to the patient.
- Photographs in limited colour palette were preferred.
- Two pages should be the maximum length.
- A testimonial from a patient should be included. (A PAG member who had had MRSA later provided the quote.)

Qualitative PIS:

- PAG members were happy with the layout and length.
- It should include information on withdrawal from the qualitative study.
- Treatment and the taking part in the study are the same to patients.

Qualitative topic guide:

- PAG members wanted to add a question about the timing of being invited to take part in the trial.
- They felt the 'about you' questions were a bit nosey.
- They were concerned about jargon such as randomisation and equipoise.

Animation:

- PAG members highlighted the need to show not just white skin.
- They did not want to see any representations of MRSA, as MRSA cannot be seen with the naked eye.
- They preferred a voice over with a neutral accent, clearly spoken.

The follow-up consultation, during which PAG members viewed the draft animation, revealed they were very positive about it. They said that explaining that the treatments were not experimental was key. Some suggested slowing down the pace and/or adding subtitles to aid understanding. They praised the diversity of the people shown in the animation. Although one person felt that non-White people were overrepresented, which could have the unintended consequence of stigmatisation. Our public co-applicant suggested adding a link to the TIDE website.

We received between two and four feedback forms after every meeting; although response waned as the trial progressed. The meetings received praise from the start, as a more experienced PPI contributor in the group wrote: '*What I have to say is this is the best organised of the PPI opportunities I have been involved with so far and I really appreciated being provided with an agenda'*. Our final meeting received top marks across the board.

Open questions were sometimes used to give more specific feedback. Such as a desire to spend more time in the breakout rooms or being taken aback by the fact that some of the PAG members knew each other (which was a surprise to us as well). PAG members also used the opportunity to comment further on the trial, for example, providing suggestions for video content and accessibility. One person expressed a particular desire to learn more about study design and statistics, so we sent them a copy of the book: *'Designing and running randomised trials in health, education and the social sciences: An introduction'*.

End of pilot phase

The PAG members regarded it as an unfortunate set of circumstances that the TIDE trial had not reached its goals during the pilot phase. They voiced strong support for a continuation of research into MRSA. They were concerned about antibiotic resistance and the chance of outbreaks in the future at greater social and economic costs.

Discussion

Impact of patient and public involvement on the TIDE trial

The TIDE trial succeeded in its aim to learn from the experiences and views from a diverse group of people who had been inpatients, who were at a higher risk of hospital admissions, or who cared for a vulnerable person. The TIDE team did everything it could to incorporate suggestions on the conduct of the study from the PAG members. Recruitment materials were much improved, and the team had a better understanding of how some of the qualitative questions would be received. However, PAG members' concerns about closing the TIDE trial did not change the trial team's view that continuation of the TIDE trial could no longer be justified.

Impact on future trials and studies

The following tools have been reused (and further refined) many times since they were developed for this study:

- recruitment and selection process
- welcome pack
- agenda and detail, internal agenda
- PPI log
- meeting feedback form.

In addition, an online PPI Toolkit was developed to share PPI resources across the trials unit.

Intangible impacts

Beyond the tangible impact, there were considerable intangible impacts. PAG members brought support, energy and enthusiasm to the trial. Many of their remarks have made us see the world differently. For example, we will be forever aware of the cultural differences in how some diseases and the role of doctors are perceived, and how that can impact on a trial. Moreover, other University of York trials and studies have benefitted from the networks the PAG members brought with them and some members have gone on to become involved in our other studies.

Reflections

Public involvement plays an important role in helping to break down barriers between researchers and those who stand to benefit from their work. We are proud that our public involvement approach was successful in doing this. We were thrilled with the wealth of information and perspectives we gathered through vibrant conversations with our generous public contributors.

The start of the TIDE trial provided an example of what has been recently referred to as *incommensurability between the temporal demands of research and those of meaningful PPI practice*.[12] While the trial officially started on 1 August 2021, PPI preparations began three months earlier, with the recruitment advertisement being placed in July 2021. Timely and meaningful PPI with diverse voices, could not have been achieved if we had not brought the PPI timeline forward and started working on it before the funding came in.

Similarly, when the trial and its funding ended, PPI funding, and therefore PPI, ended abruptly as well. This posed the question: How do we now manage the carefully built relationship with our public contributors? Should we carry on nurturing the relationships and support these volunteers in their PPI journey for the benefit of the entire research community? And if so, how? These questions do not have definite answers yet.

Equality, diversity and inclusion

Our approach

Ensuring the trial included vulnerable and underserved populations was a key element of our recruitment strategy from the initial planning stage. We considered our approach during both site and participant recruitment.

Our site recruitment strategy aimed to include vulnerable and underserved populations, including elderly patients living in a long-term care facility, those who lack capacity, patients from deprived areas and ethnic minorities.[13] In order to achieve this, we collated regional-level data from multiple national sources such as Public Health England, the Ministry of Housing, Communities and Local Government and the Office for National Statistics. We collated up to date, regional-level data on the number of nursing and care home beds per 100 people aged over 75,[14] the Index of Multiple Deprivation, the Index of Health Deprivation, the Income Deprivation Affecting Older People Index[15] and ethnicity.[16]

In addition, we utilised regional-level data to target populations at higher risk of MRSA carriage, based on known risk factors.[17] These include patients in a long-term care facility,[14] areas reporting a higher rate of antibiotic prescribing[18,19] and higher rates of MRSA bacteraemia.[20,21]

These measures were then combined, and regions ranked nationally to identify those that had a higher proportion of vulnerable and underserved populations, as outlined above, and/or are at a higher risk of MRSA carriage. These data were used along with the trials team's existing network of NHS Trusts to identify potential recruitment sites. These data highlighted that our existing network

included one in three of the top 10% of regions with the most vulnerable and underserved populations, and half of the top 10% of regions at the highest risk for MRSA carriage. Furthermore, we used these data to target recruitment at regions outside of our network, but in the highest risk or most underserved areas.

At a participant level, efforts were made to ensure that potential participants were not unduly excluded from the trial. Examples include, providing participant information in multiple formats, ensuring PPI involvement with developing patient facing materials and having procedures in place to include participants who lack capacity.

Equality, diversity and inclusion outcomes

While we followed the plan laid out above, as recruitment of sites and participants became increasingly challenging, we found we were able to be less selective with our selection criteria. Due to the low level of recruitment, the data available and any conclusions are limited.

Of the 26 target sites identified at the outset, only 4 opened to recruitment. The remaining five sites were recruited from other sources. Of the 144 eligible participants, the majority (89, 62%) were not approached about the trial. Of those that were approached, 25 of 57 did not consent to the trial. Unfortunately, for the majority of these (18 of 25) no reason was recorded. This makes it impossible to understand the factors that contributed to this.

The limited data that we do have demonstrates that the average Index of Multiple Deprivation scores were slightly higher for eligible participants who were randomised (mean = 5.2, median = 5) compared to those who were not randomised (mean = 4.4, median = 4). Indicating that on average those randomised were from slightly less deprived areas than those not. However, our data also show that we were able to recruit participants from across the full range of deprivation backgrounds, including the most and least deprived deciles, suggesting our strategy of inclusivity was effective to some degree in this regard. We were also able to demonstrate inclusion of participants with a variety of levels of education and work categories (*Table 6*). All included participants were of a White British ethnicity; however, we have no data on the ethnicity of those who were not approached or declined to participate, so we cannot draw any conclusions from these limited data.

Equality, diversity and inclusion summary

Overall, we had a considered approach to equality, diversity and inclusivity in planning and delivering this trial. Difficulties in recruitment meant that we had to be less selective when selecting sites, and small participant numbers make it unreliable to draw meaningful conclusions from much of this work in this instance.

Impact and learning

For some of the barriers to recruitment, it is difficult to see how they could have been addressed as they were national policies. The viability of a trial such as TIDE is closely dependent upon hospital screening policies which changed between the research being prioritised and commissioned and the trial being set-up.

Implications for decision-makers

Due to poor recruitment and insufficient follow-up data, we are unable to determine the effectiveness or cost-effectiveness of the alternatives to mupirocin for nasal decolonisation in adult hospital inpatients.

Research recommendations

To facilitate future research, further understanding of the routine decolonisation pathways in line with the revision to national guidance issued in 2021 is required.

Consideration could be given to a hibernation design in future similar scenarios. This would involve progress to approvals and readiness to open but hibernating the study until MRSA testing or positive cases increase to a level where recruitment could be achieved.

Widening the scope of the study so that patients could be recruited from outpatient and elective settings could also be considered, though this would need to be balanced against the complexity of the trial in terms of any potential to increase recruitment.

Further investigation of feasibility and logistics required to achieve successful analysis of self-swabs taken by participants in their own residence. Further validation of MRSA viability to increase the time available for the processing of nasal swabs to reliably detect MRSA could be undertaken.

Evaluation of the MRSA decolonisation treatments investigated in TIDE and other treatments remains warranted.

Conclusions

The research question posed by TIDE is still valid and remains unanswered. The challenges around obtaining primary outcome data could potentially be overcome; however, at the reduced level of MRSA testing being undertaken in hospitals within the NHS, recruitment to the trial was significantly lower than predicted and the trial was not considered feasible to deliver.

Additional information

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Acknowledgements

The research team would like to thank the study participants who kindly agreed to take part in this study. We would also like to thank our patient and public involvement contributors whose input has been indispensable in providing patient insight to the study design and conduct.

We extend our thanks to the members of the Trial Steering Committee: Mrs Natalie Rowlands (Chair), Dr Jon Otter, Professor Lesley Price, Dr Julie Robotham, Dr Jennifer Bostock, Dr Sherena Nair, Dr Alison Cracknell and DMC: Dr Louise Stanton (Chair), Dr

Mark Garvey, Dr Jackie Prieto, for their support, oversight and input during the study. We thank our NIHR Associate Principal Investigator: Dr Katherine Hill (NHS Lothian) for their invaluable support of the study. We thank all clinical and research staff who supported the study at the participating sites and within the central laboratory. We would like to thank Sally Baker and Emma Toyne (York Trials Unit, University of York) for their administrative support for this study and also Ann Cochrane and Joanne Newman who were involved with trial coordination activities at York Trials Unit, University of York. We also gratefully acknowledge the data management support from Val Wadsworth, Sarah Gardner-Bailey and Matthew Bailey at York Trials Unit, University of York.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

The data sets generated during the study (fully anonymised) are available on request. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review by the chief investigators.

Ethics statement

Pharmacy technical assurance was received on 18 March 2022. The study was submitted for regulatory review via the combined review process on 8 April 2022. The study was reviewed by the East Midlands – Derby Research Ethics Committee (REC) at their meeting on 5 May 2022. MHRA, REC and HRA approvals were obtained on 1st June 2022. REC reference: 22/EM/0096. A summary of amendments can be found in *Appendix 2*, *Table 17*.

Information governance statement

South Tees Hospitals NHS Trust (Sponsor) and York Trials Unit, University of York (Clinical Trials Unit) are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation York Trials Unit, University of York is the Data Processor; South Tees Hospitals NHS Trust is the Data Controller, and personal data was processed in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for South Tees Hospitals NHS Trust Data Protection Officer here www.southtees.nhs.uk/freedom-of-information-foi/foi-contacts/.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJMR0715.

Primary conflicts of interest: Elizabeth Cook declares support for the current manuscript via payments made to employing institution.

Catriona McDaid was a member of the NIHR HTA and EME Editorial Board.

Paul Baker declares that he was a member of the HTA Prioritisation Committee 1 March 2020 to 31 March 2024.

Mike Reed declares grants or contracts with Stryker, Zimmer Biomet, Heraeus, Link, Depuy, Smith and Nephew, Implantcast; Biocomposites payments made to institution to support the Bone and Joint Infection Registry; Heraeus for payments made to institution in respect to chief investigator role on RCT; Zimmer Biomet for payments made to institution in respect to an educational grant in support of a fellow; Microsoft, payments made to institution for Machine Learning for risk prediction financial support via Microsoft Founders Programme; Heraeus Medical Consulting fees on unrelated medical device paid to a company that is part owned by author; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Zimmer biomet, Heraeus Medical, Stryker, Pharmacosmos, Ethicon sutures, Amotio.

Arabella Scantlebury declares support for the current manuscript via payments made to employing institution and support for the following NIHR grants; Identifying innovative models of urgent and emergency care in rural and coastal areas in England: a mixed methods study. NIHR HSDR. Surgery versus conservative osteoarthritis of Thumb Trial (SCOOTT) An RCT to determine clinical and cost-effectiveness of treating arthritis of the base of the thumb, with or without surgery, and to determine the clinical and cost-effectiveness of trapeziectomy versus base of thumb joint replacement. NIHR HTA Evaluating the High Volume Low Complexity (HVLC) surgical hubs model. NIHR HS&DR. Intensive Interaction for children and young people with profound and multiple learning disabilities. Do Safe and Well Visits delivered by the Fire and Rescue service reduce falls among older people? FIREFLI; Arabella Scantlebury declares membership of Trial Steering Committees: NIHR Perioperative medicine for older

people undergoing surgery scale up (POPS-Sup) (2024–present) and NIHR Comprehensive geriatric assessment (CGA) to sustain independence for older people living with heart failure with preserved ejection fraction (HFpEF) and frailty (2024–present).

David J Torgerson was a member of the CTUs funded by NIHR Committee 2021.

Catherine E Hewitt declares payments made to the academic institution for membership in the NIHR HTA Commissioning Committee (2015–22) and Deputy Chair (2019–22), NIHR Senior Investigator, Member of the NIHR HTA General Committee (2023–present) and Chair (2023–present), Member of the NIHR CTU SAC (2020–2), coDirector NIHR RSS (2023–present), Member of the HTA Commissioning Sub-Board (EOI), HTA Post-Funding Committee teleconference, HTA Funding Committee Policy Group (formerly CSG), HTA – Fast-Track Funding Committee, HTA Fast Track Committee – June 2021.

All other named authors declare no conflict of interest.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by the interviewees in this publication are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

The trial is prospectively registered as ISRCTN12184897.

Publications

Reed M, Hewitt C, Baker P, Booth A, Cann M, Cook L, *et al*. *Conference Poster TIDE: Trial of Decolonisation Infection Prevention Society*. 13th Annual Conference 2021, Liverpool, 27–29 September 2021.

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number NIHR132718.

This synopsis provided an overview of the research award *A multi-centre randomised controlled non-inferiority and cost effectiveness trial comparing Polyhexanide and Chlorhexidine with Neomycin to Mupiricon for nasal meticillin-resistant Staphylococcus aureus (MRSA) decolonisation among adult hospital in-patients*.

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR132718).

About this synopsis

The contractual start date for this research was in August 2021. This synopsis began editorial review in December 2024 and was accepted for publication in August 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' synopsis and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

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List of abbreviations

AE	adverse event
DMC	Data Monitoring Committee
HRA	Health Research Authority

HTA	Health Technology Assessment
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRSA	methicillin-resistant *Staphylococcus aureus*
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PAG	patient/public advisory group
PI	principal investigator
PIS	patient information sheet
PPI	patient and public involvement
RCT	randomised controlled trial
REC	Research Ethics Committee
SWAT	Study Within a Trial
TMG	Trial Management Group
VRE	vancomycin-resistant enterococci

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Appendix 1 Participating sites

TABLE 16 TIDE recruiting sites

TIDE recruiting NHS Trusts (or health board)	Principal investigator	
Northumbria Healthcare NHS Foundation Trust	Alastair Green	Lead Clinical Pharmacist for Research
South Tees Hospitals NHS Foundation Trust	Professor Paul Baker	Consultant Orthopaedic Surgeon
Sherwood Forest Hospitals NHS Foundation Trust	Dr Shrikant Ambalkar	Consultant Microbiologist
Somerset NHS Foundation Trust	Dr Susan Hardman	Consultant Microbiologist
NHS Lothian	Dr Simon Dewar	Clinical Infection Research Group
The Mid Yorkshire Hospitals NHS Trust	Dr Achyut Guleri	Consultant Infection/Clinical Microbiologist
Milton Keynes University Hospital NHS Foundation Trust	Dr Chakrabarti	Consultant Microbiologist
York Teaching Hospitals NHS Foundation Trust	Dr Damian Mawer	Consultant Microbiologist
Mid and South Essex NHS Trust	Dr John Day	Consultant in Infectious Disease and General Medicine

Appendix 2 Amendments

TABLE 17 Summary of amendments

Substantial amendments			
Amendment #	**Description**	**Date of amendment submission**	**Date(s) of final REC/ MHRA/HRA approval**
Substantial Amendment 1	To obtain approval for the trial website	10 November 2022	13 December 2022
Non-substantial amendments			
Amendment #	Description	Date of amendment submission	Date(s) of final REC/ MHRA/HRA approval
Non-substantial Amendment 1	Addition of participating sites	15 July 2022	15 July 2022
Non-substantial Amendment 2	Minor revisions to participant treatment instructions	20 July 2022	20 July 2022
Non-substantial Amendment 3	Addition of study documentation	18 August 2022	18 August 2022
Non-substantial Amendment 4	Change in PI at a participating site	21 September 2022	22 September 2022
Non-substantial Amendment 5	Addition of participating sites	19 April 2023	27 April 2023

Appendix 3 Further information on the patient/public advisory group

Further information on contents of patient/public advisory group meetings

For each meeting, the PPI Lead and the trial team developed a more detailed, internal agenda. This would not only describe the meeting topics, but also name the person leading on the topic, allocate time and list the questions that were to be discussed with the attendees.

To optimise attendance, we put forward two meeting dates for each meeting and selected the one that would have the highest attendance. Members who could not attend, were invited to meet with the PPI lead on an individual basis or to contribute via e-mail. All PPI input was recorded in a PPI log. During every meeting, we informed the PAG about the trial's progress and what had been done with their previous input. After each meeting, we send payment forms and an evaluation form.

Meeting 1 (27 September 2021)

- Icebreaker: we asked everyone to briefly state their motivation for joining the group
- Presentation/Q&A session on the content of the Welcome Pack
- Presentation on MRSA from a patient's perspective
- Presentation of TIDE and the patient's pathway
- Discussion to gather insight in the challenges around patient recruitment and consent. This was structured around the following questions:
  - If you (or the person you care for) were asked to take part in this trial, what questions would you have?
  - Would you have any worries about taking part? If so, what would they be?
  - How can we make sure that we encourage a wide variety of people to take part in the trial?

Meeting 2 (2 November 2021)

- Presentation/discussion of feedback received on the previous meeting
- Presentation/discussion of PIS and consent form

Meeting 3 (15 February 2022)

- Impact of PPI on the development of the PIS
- Presentation/discussion of a draft infographic to aid recruitment
- Presentation/discussion of the draft topic guide for qualitative research
- Looking ahead at the development of animation to aid recruitment and discussion of the script

E-mail consultation (27 September 2022)

As agreed with the PAG members, we sent them the draft animation for comment. We reminded them of the aim of the animation, explained that small changes could still be made, and invited them to give feedback (like the meetings, this was a paid activity).

Meeting 4 (29 June 2023)

- Presentation to update the PAG members on trial recruitment, trial recruitment challenges and participants' views on the trial
- Discussion in relation to the trial pilot report: thoughts on the pilot and process review findings and thoughts on progression beyond the pilot

Further information on content included in newsletters shared with the PAG

Newsletter 1 (July 2022)

patient/public advisory group members received an e-mail update on the trial that covered:

- Ethics approval
- Change of staff
- The trial Twitter account and website
- A blog that one of the PAG members had written

Newsletter 2 (December 2022)

Patient/public advisory group members received an update via e-mail on the trial that covered:

- Progress on site openings (as requested by PAG members)
- Patient recruitment
- The latest in the development of the patient recruitment animation
- Reasons why the planned autumn 2022 PAG meeting had not taken place and why it would now take place around June 2023 (end of pilot meeting)