**Spray application of skin antisepsis in head and neck surgery**

Research protocol

Version 1

2nd November 2021



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# Project Team Roles and Responsibilities

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# Abbreviations/Acronyms

CHG – chlorhexidine gluconate

DSMB – Data safety and monitoring board

PICF – Patient information and consent form

PVI – Povidone iodine

SSI – Surgical site infection

WHO – World health organisation

# Background Information/Rationale

Skin antisepsis before surgery was first introduced by Joseph Lister in the nineteenth century [1] and has since become a standard step in almost all operations in order to reduce the risk of surgical site infection (SSI). SSI is defined by the Centres for Disease Control and Prevention (CDC) as infection at or near a surgical site within 30 days of surgery. Head and neck surgery encompasses any operation performed on the craniomaxillofacial regions or neck. Due to the frequent opening of the upper aerodigestive tract, the use of free tissue transfer, and the relatively high proportion of patients having undergone previous radiotherapy, SSI is a particular problem for these patients, with reported rates of 3-41% [2]. Global guidelines from the World Health Organisation (WHO) recommend alcohol-based chlorhexidine (CHG) or povidone iodine (PVI) unless contraindicated [3] as skin antisepsis for surgical site. Because of the proximity of the surgical site to the eyes and ears in head and neck surgery which are particularly susceptible to the toxic effects of alcohol, aqueous skin antisepsis agents are usually used in this region. Whilst much research has focussed on the efficacy of various antiseptic agents for the purpose of pre-operative skin preparation, there is very little evidence to guide the method of application. Indeed, an expert panel convened in 2016 to discuss skin antisepsis conclude that the method of application may be as important as the agent used, and that more research is required in this field [4].

Surgical site skin antisepsis is usually applied by painting on using a sponge or swab soaked in the antiseptic agent. The advantage of this technique is that it allows the use of friction which may help to penetrate the deeper layers of the epidermis, where up to 20% of skin flora reside [5]. However, painting the surgical site may risk colony transfer from peripheral skin to incision site, especially if the agent is not used correctly e.g. insufficient drying time prior to incision [6]. Furthermore, waiting until the surgical and scrub teams are sterile and ready to begin operating risks not only inadvertent desterilisation of gowns and gloves during the skin preparation process, but also rushing of the process in order to commence the operation. Spray-on skin preparation on the other hand, can be performed by a non-sterile member of the theatre team whilst the surgical and scrub team prepare for surgery, allowing the solution to dry properly before the skin incision is made.

Spray-on skin antisepsis was first studied in 1959, with a report on spray-on PVI in 100 cases demonstrating effective elimination of skin pathogens and no post-operative SSI [7]. *In vitro* studies have confirmed the bactericidal efficacy of aerosolised PVI [8], and Moen *et al.* demonstrated that spray-on PVI (with 3-minute drying time) is as effective as the traditional painted application at reducing skin bacterial colony counts in patients undergoing abdominal surgery [9].

The only existing randomised controlled trial on the use of spray-on skin antisepsis compared spray-on CHG with painted PVI in 737 patients undergoing gynaecological surgery. The authors found no statistically significant difference in SSI between the two groups, although there was a slightly lower SSI rate in the spray-on group [10]. There is no published evidence on the use of spray-on skin antisepsis in head and neck surgery and no randomised controlled trial comparing spray-on and paint-on application of the same agent with SSI as the primary outcome measure. The current study will build on previous authors’ work demonstrating the bactericidal efficacy of spray-on PVI by investigating its efficacy in terms of reducing post-operative SSI when compared with traditional paint-on application of the same agent in head and neck surgery.

# 

# Aims/Objectives/Hypothesis

## Primary Objective

## 

To assess the 30-day post-operative SSI rates in patients undergoing head and neck surgery using two methods of PVI skin antisepsis preparation.

## 

## Hypothesis

Spray-on PVI skin preparation is as effective as paint-on application at preventing surgical site infections (SSI).

## 

## Aims

The overall aim of this study is to test the efficacy of spray-on PVI in preventing SSI as compared with standard practice of paint-on application.

# Participating Sites

This is a single site study, recruiting participants only at the head and neck surgery department of Chris O’Brien Lifehouse.

# Study Design

Prospective randomised controlled trial

Informed consent

Assessment for eligibility

Randomisation

Group B

Paint-on skin preparation

Group A

Spray-on skin preparation

Assessment and follow-up

Analysis

## Sample Size

Cases (Group A): N=50 Controls (Group B): N=50

## 

## Study duration

Start date: November 2021

End date: July 2022

Each participant’s involvement will last from the time of surgery to 30 days post-surgery

## 

## Inclusion Criteria

* Adult patients (18 years or older)
* Undergoing elective open head and neck surgery (involving a skin incision)

## Exclusion Criteria

* Patients undergoing emergency surgery
* Patients undergoing oral or transoral surgery where skin antisepsis would not usually be used
* Patients with active skin infection
* Patients with known allergy to any topical skin antisepsis agent
* Patients with known immunosuppression
* Patients taking systemic steroids
* Patients not consenting to randomisation

## 

## Study Plan

Table 1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **STUDY PERIOD** | | | |
|  | **Enrolment and allocation** | **Visit** | | **Final Visit** |
| **TIMEPOINT\*\*** | **0** | ***D1*** | ***D7 +/- 2 days*** | ***D30 +/- 5 days*** |
| **ENROLMENT:** |  |  |  |  |
| **Informed consent** | X |  |  |  |
| **Eligibility screen** | X |  |  |  |
| **Allocation** |  | X |  |  |
| **INTERVENTIONS:** |  |  |  |  |
| ***Spray-on group (A)*** |  | X |  |  |
| ***Paint-on group (B)*** |  | X |  |  |
| **ASSESSMENTS:** |  |  |  |  |
| ***7-day SSI*** |  |  | X |  |
| ***30-day SSI*** |  |  |  | X |

# Procedures/interventions:

## Intervention

Aqueous 10% PVI solution will be used in each group, and the area of skin surrounding the planned surgical incision will be prepared. This is a routine standard of care in these patients, and the only difference between groups will be the method of application of the solution.

Following induction of general anaesthesia participants in:

Group A will undergo surgical site skin antisepsis by spray-on application of aqueous PVI solution using a standard multipurpose spray applicator until all skin in the region of the planned surgical site is visibly coated with PVI, and allowing to dry as recommended by the manufacturer.

Group B will undergo skin antisepsis by application of the same solution by painting with a sterile gauze swab until all skin in the region of the planned surgical site is visibly coated with PVI, and allowing to dry as recommended by the manufacturer.

## Randomisation procedure

A random number generator will be used to allocate participants to treatment groups on the morning of surgery. Participants will be stratified according to prior radiotherapy at the surgical site, and type of surgery which will be classified as clean (involving a skin incision with no involvement of the upper aerodigestive tract) or clean-contaminated (involving the mucosa of the upper aerodigestive tract).

# Data Collection:

Basic demographic information including patient date of birth, gender, smoking status and relevant medical history (e.g. diabetes), as well as details of the operation being performed and the duration of surgery will be recorded at the time of surgery. Time from WHO checklist to skin incision will also be recorded. Data will be kept in a password protected encrypted datasheet using REDcap software. The same datasheet will be updated with outcome information consisting of SSI incidence at day 7 and day 30. SSI will be identified according to the CDC definitions of SSI (Table 2)

Table 2

|  |
| --- |
| **Criteria for diagnosis of superficial SSI** |
| Event within 30 days of procedure |
| AND |
| Involves only the skin and subcutaneous tissue of the incision site |
| AND |
| Patient has at least one of: |
| 1. purulent drainage from the superficial incision |
| 1. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or nonculture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment. |
| 1. superficial incision that is deliberately opened by a surgeon or physician and culture or non-culture-based testing of the superficial incision or subcutaneous tissue is not performed   AND  patient has at least one of the following signs or symptoms:  localized pain or tenderness; localized swelling; erythema; or  heat. |
| **Criteria for diagnosis of deep SSI** |
| Event within 30 days of procedure |
| AND |
| Involves deep soft tissues of the incision |
| AND |
| 1. purulent drainage from the deep incision. |
| 1. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon or physician   AND  organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment  AND  patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. |
| 1. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test. |

## Assessment of Efficacy:

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## SSI Assessment

Surgery will then proceed as usual, and the incidence of SSI will be recorded prospectively at 7 days and 30 days post operatively according to the CDC definition of SSI as outlined in table 2. In patients undergoing surgery at two anatomical sites (e.g. neck incision and separate incision for a free flap) SSI at both sites will be recorded separately. A telephone call will be made to patients who are no longer in hospital to ensure that all events are captured. It is assumed that any clinically significant SSI occurring after discharge from hospital will result in attendance to the general practitioner or hospital, and if there is any doubt following discussion with the patient, the general practitioner will be contacted for confirmation. Outcome data will be binary, with patients either meeting or not meeting the criteria for SSI outlined in table 2. At 30 days post-operatively the study period will end and the participants will no longer be actively enrolled in the trial.

## Recruitment and Screening

Patients will be identified by the treating surgical team at pre-operative clinic attendances, and informed consent will be taken following provision of verbal and written information on the study. Patient records will be accessed during the routine course of providing their surgical care.

# Ethical Considerations

## Informed Consent Process/Documentation

The study will be executed in accordance with the National Statement on Ethical Conduct in Human Research [11]. All participants will sign an HREC approved Participant Information Sheet and Consent Form (PISCF). Informed consent will be obtained in accordance with the Declaration of Helsinki, and local standard operating procedures/regulation. The written informed consent will be obtained by authorised study personnel. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations and will be approved by a Human Research Ethics Committee.

Initial contact will be made by a member of the study team as designated by the Principal Investigator, if not the Principal Investigator themselves. Information will be given in both verbal and written form. The patient will be informed of the study and if interested in taking part and appear they may be eligible, they will be given a copy of the current approved PICF to then take home and discuss with family/friend(s)/local doctor (GP). The authorised study staff will explain the study objectives, risks and benefits, and overview of the study procedures to all participants as part of the consent process. The participant will have as much time as they require to read all of the information available and ask as many questions as they require to obtain a clear understanding of all the requirements of participating in this study, and what the study involves. It will be made clear to the potential participant if they do not wish to voluntarily consent to the study or they withdraw, it would not affect their normal treatment or medical care at the institution.

This protocol and the PICF contained in Appendix 2 will be reviewed and approved by the sponsor and the applicable HREC with respect to scientific content and compliance with applicable research and human participant regulations.

The Investigator will make safety and progress reports to the HREC within three months of study termination or completion. These reports will include the total number of participants enrolled and summaries of each Data Safety and Monitoring Board (DSMB) review of safety and/or efficacy.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by Chris O’Brien Lifehouse and approved by the HREC prior to implementation and authorised as per local governance policies. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the study group and will be documented in a memorandum. The HREC may be notified of administrative changes at the discretion of the sponsor.

Randomisation Procedure

Patients previously identified as being eligible, and having provided informed consent, will be randomised using a computerised random number generator on the morning of surgery. There will be no blinding of clinicians, investigators or patients.

## Confidentiality and Privacy

A unique study number will be assigned to each participant in order to maintain their privacy. The trial number will only be linked to the patient's details at the institution and will not be sent offsite. The study data will be kept in coded form and will be stored in a computerised database located at Chris O’Brien Lifehouse. The investigator will maintain a confidential participant identification list that allows the unambiguous identification of each participant. Consent to transfer data is sought via the Patient Information and Consent Form. No identifying information will be published. It is also understood that the recipients will treat the data in accordance with all applicable privacy legislation and local policies and that recipients will not use of disclose the information outside the parameters of the agreement between them and the institution. All data (including personal data) obtained will be treated as confidential. The personal data will be stored at the study site in encrypted electronic form and will be password protected and secured in a locked room to ensure that only authorised study staff have access.

## 

## Data Storage and Record Retention

1. Data will be collected from medical records
2. Data will be stored as outlined above, in re-identifiable form
3. Data will be held for 2 years following study completion, then destroyed by deleting the master datasheet
4. During the study and for two years after completion, the data will be stored on a password protected computer at the study site, in a locked office
5. Data containing participant identifying information (including MRN, patient names) will not leave the site.

# Safety and Adverse Events

Safety reporting will be in line with research governance policy at the study institution, and National Health and Medical Research Council Guidance [12]. An adverse event will be defined as any untoward medical occurrence in a participant without regard to the possibility of a causal relationship. Adverse events will be collected after the participant has provided consent and enrolled in the study. If a participant experiences an adverse event after the informed consent document is signed (entry) but the participant has not yet undergone skin preparation with aqueous PVI, the event will be reported as not related to the study intervention. All adverse events occurring after entry into the study and until hospital discharge will be recorded. An adverse event that meets the criteria for a serious adverse event (SAE) between study enrolment and hospital discharge will be reported to the HREC as an SAE. A serious adverse event for this study is any untoward medical occurrence that is believed by the investigators to be causally related to the study intervention and results in any of the following: Life-threatening condition (that is, immediate risk of death); severe or permanent disability, prolonged hospitalisation, or a significant hazard as determined by the researchers. Serious adverse events occurring after a participant is discontinued from the study will NOT be reported unless the investigators feel that the event may have been caused by the study intervention or a protocol procedure. Investigators will determine relatedness of an event to the study intervention based on a temporal relationship to the intervention, as well as whether the event is unexpected or unexplained given the participant’s clinical course, previous medical conditions, and concomitant medications. The study will monitor for the following adverse effects daily through patient examination and chart review:

* Local skin reactions
* Allergic reactions

This will be assessed by clinical review of the surgical site on the day of surgery and then on a daily basis until discharge from hospital. Clinical evidence of allergic reaction including localised erythema, blistering and rash, or systemic features such as tachycardia, dyspnoea and anaphylaxis will be recorded in the data capture file and designated as adverse effects of the intervention if deemed to be temporally related by the clinical team (within 12 hours of application of aqueous PVI) and not attributable to another cause e.g. infection.

Participants will receive topical application of the same solution in the same preparation regardless of which arm they are randomised to, and the safety profile of aqueous PVI has been well established having been used on a daily basis around the world for many years, so it is not anticipated that adverse events will be encountered at differing frequencies in the study and control groups.

## Assessment and Documentation of Adverse Events

Following an adverse event, the participant will be followed up until complete resolution of all symptoms. The frequency of follow up following an adverse event will depend upon the severity of the adverse event and may range from daily to monthly, and take the form of clinical assessment or telephone consultations. All adverse events will be documented both in the participant’s medical record and the study data file.

## Monitoring

The research will be conducted in compliance with the approved protocol;

(a) Safety Reports will be reported to the HREC and Lifehouse Research Governance Manager (RGM) in line with the *National Health and Medical Research Council (2016). Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods [12]*.

(b) Annual Progress Reports and any other reports as requested by the HREC or RGM, will be submitted annually or as otherwise requested by the HREC and RGM;

(c) All amendments to the HREC approved study documentation will be submitted for approval, including but not limited to amendments that:

(i) are proposed or undertaken in order to eliminate immediate risks to participants;

(ii) may increase the risks to participants; or

(iii) significantly affect the conduct of the research;

(d) The HREC will be informed as soon as possible of any new safety information from other published or unpublished research that may have an impact on the continued ethical acceptability of the research or that may indicate the need for modification of the project.

## Early Termination/Withdrawal of Participants

If the SSI rate is deemed unacceptably high in either study arm, the study may be prematurely terminated. This will be communicated to all investigators. In the event of early termination, no further randomisation will occur, but patients who have already undergone treatment will still be followed up at 7 and 30 days. If patients are lost to follow-up or withdraw their consent to be contacted at 7 and 30 days this will be recorded in the data capture sheet but they will not be replaced.

# Outcomes and Future Plans

The results of the study will be published in a clinical study report, and submitted to peer-review in a relevant journal. The results of the project will be presented as group data, individual data will not be available.  If individual patient data is reported or made available at the request of the HREC, medical journals or other relevant party, it will be available only as non-identifiable patient level data.

# Statistics

All randomised participants will be included in statistical analysis. Chi squared analysis will be used to test the statistical significance of any difference in the rate of SSI between the two groups, with a level of significance of 5%. Assuming a rate of SSI of up to 20% in both groups [2], and using a significance level of 5%, group sizes of 50 participants would be powered at 80% to show a difference of 20% between groups.

# Other Study Documents

Appendix A: Patient information and consent form

Appendix B: Case report form

# References

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