1. Protocol details

1.1 PROTOCOL TITLE:

The incidence of hospital acquired pneumonia in patients who undergo temporary tracheostomy with oromaxillofacial resection and free flap reconstruction for head and neck cancer.

1.2 Names (titles), roles and contact details of:

Sponsor
Kings College London
Professor Reza Razavi
Vice President & Vice Principal (Research)
King's College London
Room 5.31, James Clerk Maxwell Building
57 Waterloo Road
London SE1 8WA
Tel: +44 (0)207 8483224
Email: reza.razavi@kcl.ac.uk

Chief Investigator/clinical supervisor
Dr Gareth Jones
Rehabilitation lead - Physiotherapy
Guy's Hospital
Great Maze Pond
London
SE1 9RT
Gareth.jones@gstt.nhs.uk
02071885111

Principle Investigator/Student
Rachel Wijayarathna
Highly specialist physiotherapist – head & neck oncology
Guy's Hospital
Great Maze Pond
London
SE1 9RT
Rachel.wijayarathna@gstt.nhs.uk
02071885110

Academic supervisor
Dr Andrea Xyrichis
Senior lecturer
Kings college London,
57 Waterloo Road,
London,
SE1 8WA
Andreas.xyrichis@kcl.ac.uk

0207 8483649

Clinical Supervisor
Mr Ricard Simo FRCS(ORL-HNS) PhD
Consultant Otorhinolaryngologist Head, Neck and Thyroid Surgeon
Clinical Lead in Head and Neck Surgery
Surgical Lead in Thyroid Cancer
Honorary Senior Lecturer KCL
Department of Otorhinolaryngology Head and Neck Surgery
3rd Floor Southwark Wing
Guy's and St Thomas' Hospital NHS Foundation Trust
St Thomas' Street
London SE1 9RT
Ricard.simo@gstt.nhs.uk
02071887188

Statistician – reviewed data plan, not affiliated in any other capacity
Mr Bola Coker
Senior Data Manager, NIHR GSTT/KCL Biomedical Research Centre
Visiting Senior Data Manager, School of Population Health & Environmental Sciences, KCL
Guy's & St Thomas' NHS Foundation Trust
5th Floor Addison House
London
SE1 1UL
020 7848 8687
bolaji.coker@kcl.ac.uk

1.3 Protocol details

Version number 1
Final
Date 24.09.2021

2 Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Gareth Jones

24/09/21

Signature Date

Sponsor Representative

R&D to Add
GSTFT

Signature Date

This Protocol template is intended for use with UK sites only.

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3 List of Abbreviations and Definitions

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

4 Summary/Synopsis

Title	The incidence of hospital acquired pneumonia in patients who undergo temporary tracheostomy with oromaxillofacial resection and reconstruction for head and neck cancer. *Version 1 – 24.09.2021*
Protocol Short Title/Acronym	HAP in temporary tracheostomy
Protocol Version number and Date	1 24.09.2021
Study Phase if not mentioned in title	Observational cohort
IRAS Number	295395
REC Reference	
Sponsor Reference	
Study Duration	7 months
Sponsor name	GSTT/KCL
Chief Investigator	Dr Gareth Jones
Funder	N/A
Medical condition or disease under investigation	Oromaxillofacial surgery in head and neck cancer
Purpose of research	*Retrospective data analysis identifying hospital acquired pneumonia in patients who undergo temporary tracheostomy with oromaxillofacial surgery and free flap reconstruction*
Primary objective	Undertake an adequately powered, robustly designed observational cohort study that describes the rates of hospital acquired pneumonia in patients who undergo a tracheostomy and those that undergo overnight intubation during oromaxillofacial surgery for HNC.
Secondary objective (s)	To investigate whether smoking history, respiratory history (COPD, asthma) or size of tumour are associated with an increased risk of developing hospital acquired pneumonia.
Number of Subjects/Patients	193
Study Type	Observational cohort
Endpoints	January 2023
Main Inclusion Criteria	Patients who underwent oromaxillofacial resection with free flap reconstruction and tracheostomy from 1st January 2018 to 31st December 2018. Patients who underwent oromaxillofacial resection with free flap reconstruction and with overnight intubation from 1st January 2014 to 31st December 2014
Statistical Methodology and Analysis	A power calculation has been used to determine the sample size required for statistical analysis of data. Statistical significance for rates of HAP will be tested between the two groups. It is anticipated that

	data will not normally distributed and non-parametric testing will be used (Mann Whitney U/Chi-square depending on data type. Odds ratios using logistic regression will be used to explore the risk factors for HAP in this scenario which have previously been indicated to have been smoking, respiratory history and tumour size.
Human Tissue Samples (if applicable)	n/a
Data collected/storage (if applicable)	n/a

4. Introduction

This study aims to explore the rates of hospital acquired pneumonia (HAP) in those that undergo temporary tracheostomy with oromaxillofacial surgery (OMFS) and free flap reconstruction for head and neck malignancy. The study also aims to identify risk factors that may be associated with developing a HAP in this patient cohort. This introduction provides a background to the study, outlining surgical management of these cancers, the risks and benefits associated with siting a tracheostomy. It outlines the importance of knowing the risks associated with tracheostomy placement which in turn could allow the exploration into interventions that may any risks identified.

4.1 Head and neck cancer incidence

Head and neck cancer (HNC) involves epithelial malignancies of the upper airway and digestive tract (e.g. oral and nasal cavities, paranasal sinuses, pharynx and Larynx). They are heterogeneous group of tumours and are the eighth leading cause of cancer in the United Kingdom (UK) (Ferlay et al. (2010)with an annual incidence rate of 12,422 new cases (Cancer Research UK 2016-2018). OMF cancer comprises of malignant tumours located within the jaw, face, mouth and neck. Owing to pattern of HNC spread, lymph node excisions within the neck, termed neck dissection, are often performed alongside excision of the primary tumour Bullock et al. (2019). OMF malignancy rates have risen by more than 30% since the 1990's (OCIU head and neck profiles) as a result an increasing number of patients are undergoing extensive surgical resections and gruelling oncological treatment regimes. OMF malignancy is commonly diagnosed around 70 years of age and 69% of cases are diagnosed in men (Cancer research UK 2016-2018). Lifestyle & environmental factors can significantly increase the risk of developing OMF cancer, smoking can increase the chance of developing OMF cancer by up to 91% and excessive alcohol consumption by up to 81%. Socioeconomic deprivation is also attribute to high OMF cancer rates, increasing the risk of developing OMF cancer by up to 64% in females and 101% in males (Huber & Dort, 2018). A number of co-morbidities affecting major organ systems are directly correlated with smoking, high alcohol consumption and social deprivation. This combined with the risks of major OMF surgery (OMFS) can result in high treatment complication rates, further adding to the complexity in managing this disease (Goepfert et al., 2017).

4.2 Head and Neck cancer treatment

HNC treatment can consist of one, or a combination of treatments that includes radiotherapy, chemotherapy, immunotherapy and/or surgery. The covariance between the health and fitness of the patient, and the site, type, and stage of cancer, determine the nature, duration, and intensity of treatment. Between 45-75% of patients undergo oral and maxillofacial surgery as their primary treatment (Cancer research UK 2015-17). Surgery includes removal of the tumour & surrounding nodes with free flap reconstruction using autogenous bone grafting from a secondary donor site to improve aesthetics, speech, and swallow function. Resection of tumours within the oral cavity and maxillofacial area significantly impact on the structures involved with breathing, mastication, speech, swallowing and cosmetic appearance (Wang, Fu, Liu, Liu, and Cao (2018). The location of these tumours means airway security during and after surgery is paramount. Reconstruction of these areas with free tissue transfer (bone and soft tissue) and microvascular surgery repairs the defect and with rehabilitation, restores function (Patel, Kim, and Ghali (2019). The magnitude of insult to these two surgical sites is considerable as is the risk of post-operative complications, further compounded by the patients' chronic medical and lifestyle co-existing conditions (McMahon et al., 2013).

4.3 Airway security during surgery

Airway security in OMFS is a subject of wide controversy and discussion (Goetz, Burian, Weitz, Wolff, and Bissinger (2019)), unlike other major head and neck surgery where tracheostomy insertion is necessary due to more extensive resections on more than one critical structure responsible for breathing, speaking, eating and drinking. Some units' preference is to insert a tracheostomy to maintain a secure airway during surgery (Marsh, Elliott, Anand, and Brennan (2009)). In contrast, others mitigate the risk associated with tracheostomy insertion by opting for overnight intubation either via endotracheal (ETT) or nasopharyngeal (NP) intubation (Singh, Sankla, & Smith, 2016Singh, Sankla, and Smith (2016)). In the acute post-operative phase intraoral swelling can occlude the upper airway necessitating a means of airway security (Coyle, Shrimpton, Perkins, Fasanmade, and Godden (2012); (Goetz et al., 2019). The risk of catastrophic bleed and loss of perfusion resulting in flap loss is thought to be around 5% (Bianchi, Copelli, Ferrari, Ferri, and Sesenna (2009)); (Zubair et al. (2020)), however timely resolution is paramount, risk of morbidity or mortality increases in the instance of catastrophic bleed. In the event of flap loss, the surgical insult a patient receives for a second flap from another site increases the risk of post-operative complications, length of stay and functional recovery. Intraoral swelling can make emergency endotracheal intubation challenging, and insertion of emergency tracheostomy may be required (Coyle et al. (2012)). As such, OMFS management of intra and post-operative airway security in the UK is variable (Rogers, Russell, and Lowe (2017)).

4.4 Temporary tracheostomy insertion

Tracheostomy formation is more prevalent than either methods of intubation - a UK national survey observed that 69% (39/57) of maxillofacial units would "usually" or "almost always" insert a tracheostomy for uncomplicated free flap surgery, whilst 24% preferred ETT intubation to mitigate morbidity associated with tracheostomy insertion (Marsh et al. (2009)). This suggests that for HNC surgeons the dominant risk is airway security, which is best managed by tracheostomy formation despite the secondary risks created. The risks associated with tracheostomy insertion are widely acknowledged with reported complication rates between 8-45% (Margaret J Coyle et al. (2013)). They include tracheal stenosis, respiratory arrest due to tube blockage or displacement, haemorrhage, fistula, failure to decannulate, pneumothorax, injury to surrounding structures and hospital acquired pneumonia (HAP) (Coyle et al., 2013; Crosher, Baldie, and Mitchell (1997)). Tracheostomy complications can be life threatening and distressing for patients, and are associated with an increased length of stay and mortality. Pulmonary complications such as HAP in patients who undergo tracheostomy for all types of head and neck surgery are reported to be around 45% (Morton 1990). Patients who develop a HAP have a longer critical care and hospital stay. For example, Castling, Telfer, and Avery (1994) reported a 4 day admission to ICU and hospital LOS of 25 days compared to 2 and 14 days in those who did not develop a HAP. Increased care needs involving a number of specialist clinicians, equipment such as tracheostomy tubes, suction, methods of humidification and antimicrobial medications individually and collectively have financial implications for the cost of patient care. Rates of HAP specifically in OMFS is unknown, if such data was available and was found to be clinically or statisitically significant in either the tracheostomy group or overnight inubation group work investigating methods to reduce the rate of HAP, such as early mobility or humidification would be justified.

4.5 Endotracheal and Nasopharyngeal intubation

Despite temporary tracheostomy insertion continuing to be the preferred choice for airway security, there is some evidence that the current approach might need to adapt; patient experience data has shown that given the choice, patients would avoid tracheostomy formation if possible (Nakarada-

Kordic, Patterson, Wrapson, and Reay (2018)). Furthermore there are studies demonstrating that patients who undergo these procedures can be safely managed with overnight intubation. M. J. Coyle et al. (2013), and Singh et al. (2016) both demonstrated that overnight ETT intubation was associated with a lower rate of HAP (10% vs 38% and 6% Vs 12% respectively), and shorter hospital length of stay (12.9 Vs 18.0 days and 20.4 Vs 27.2 days P=0.03 respectively). Despite these data demonstrating more favourable outcomes when compared with tracheostomy, standardised criteria to assess complication outcomes were not used increasing the risk of detection bias. Statistical integrity is also questionable due to absent power calculations or small sample sizes. As a result the evidence justifying intubation remains equivocal. However, anecdotally, the evidence supports the notion that not only will patients avoid the risks and morbidity associated with tracheostomy insertion, they will be able to speak cough and clear secretions independently sooner (Coyle 2012) which will positively impact their overall post-operative recovery and experience.

4.6 Patient experience

There are few papers that have reported on patient experience with a tracheostomy, however it is an emerging theme of interest. Sherlock, Wilson, and Exley (2009) explored the hospital experience of patients who had a temporary tracheostomy sited for medical or surgical reasons, conducting 8 semi-structured interviews over a 12-week period. Patients reported finding the physical and psychological effects more disturbing than expected; experiencing discomfort, fear, and frustration when attempting to talk, eat and drink, and during routine care-activities (e.g. suction to remove tracheostomy secretions). A study conducted by Rogers et al. (2017) using a multi-staged approach to record the experience of a patients who underwent tracheostomy during surgery for HNC reported similar findings. They conducted 15 semi-structured interviews, and used themes identified during these interviews to construct a postal questionnaire. The response rate was a respectable 69% (86/125) and found 60% of patients would "very much" avoid a tracheostomy if at all possible. Patients also reported they had "very much or "quite a bit" of a problem with tracheostomy communication, routine care, choking, discomfort, and sleeping. The Rogers et al (2017) study included selected comments from patients who underwent tracheostomy and included:

> *"Horrendous. I used to be a nurse with children and you don't realise what it is like. I would sooner be dead than go through it again. It is a horrible, fearful, horrendous feeling especially when coughing and sucking down the tracheostomy. It was difficult to get a comfortable position getting the oxygen, alright when removed, over quite quickly. You don't know what it is like unless you have had it done. The feeling of sucking out was awful".*

These findings support the notion that temporary tracheostomy should not be considered a minor or routine procedure and that the risk of life-threatening airway compromise should be balanced against the risks associated with tracheostomy as well as poor patient experience. However further work fully exploring the experience of patients who undergo temporary tracheostomy is needed and any outcomes that may improve experience such as specialist tracheostomy nurses and pre-operative patient counselling could be investigated.

4.7 Summary and the research problem

The association between lifestyle and environmental factors and increased risk of developing HNC cancer are widely acknowledged. Smoking, alcohol consumption, socioeconomic status and low mental wellbeing are important determinants and highly prevalent factors affecting the onset,

prognosis and recovery from HNC (McCarter et al. (2018)). Rates of morbidity and mortality are higher in those who present with co-morbidities associated with the above-mentioned risk factors.

There is some evidence in support of safely managing OMFS patients with overnight intubation, however work needs to be done to establish what patients are suited to either method of airway protection. Tracheostomy remains the method of choice for airway security during OMFS, despite demonstrated and assumed risks associated with insertion, the associated financial burden and emerging evidence reporting on poor patient experience. HAP remains a prevalent perceived risk in those that undergo tracheostomy and is associated with increased length of critical care, and hospital length of stay, morbidity, and mortality. There is a need to accurately identify and quantify HAP rates with both methods of airway protection in OMFS. If such data were available clinicians and patients could make informed decisions on the best method of airway protection for the surgical procedure they are undergoing. If rates were found to be high in either scenario, and any patient risk factors were associated with the development of a HAP, further work could explore what pre or pre or post-operative interventions could be deployed to help reduce the risk of developing a HAP.

5 Trial objectives and purpose

Student MRes project

- To select patients according to a pre-defined set of inclusion and exclusion criteria
- Collect pre-determined quantitative data relevant to the study question using hospital medical records
- Describe patient demographic data and explore any relationship between these and the development of a HAP
- Assess rates of HAP using historical medical data and pre-defined criteria that identifies hospital acquired pneumonia
- Describe rates of HAP in patients who did not have a tracheostomy inserted for maxillofacial surgery with free flap reconstruction
- Describe rates of HAP in patients who did have a tracheostomy inserted for maxillofacial surgery with free flap reconstruction

6 Study design & Flowchart

6.1 Study Design

In 2017, a new maxillofacial surgeon was appointed to Guy's & St Thomas' NHS Foundation Trust who's preference was to insert a temporary tracheostomy for all patients undergoing oromaxillofacial surgery with free flap reconstruction. Prior to this there was a wide variation in case selection with the majority of patients undergoing overnight intubation. Since subsequent practice has now changed and all patients now undergo tracheostomy insertion within OMFS, a prospective design is not possible, therefore, a single site retrospective observational design will be adopted, allowing data from two cohorts of patients identified to be collected within a feasbile timeframe dictated by the module deadlines. Electronic and paper notes of patients from cohorts before and after the change in maxillofacial surgical practice (2014 and 2018) will be screened.

6.2 Primary outcome tool

HAP is an acute lower respiratory tract infection that is acquired after at least 48 hours of admission to hospital and is not incubating at the time of admission (BMJ best practice; Hospital acquired pneumonia (non covid-19) 2022). It is more common in patients that have undergone major surgery, those admitted to critical care, and those with a prolonged hospital admission (BMJ no 6 best practice). Developing a HAP is associated with an increase in morbidity and mortality as patients with these risk factors are also likely to have one or a combination of multiple co-morbidities, critical illness and frailty. Using a standardised outcome measure to assess the primary outcome reduces the risk of bias and increases reliability and reproducibility. The primary outcome in this study was hospital-acquired pneumonia as defined by the British Medical Journal (BMJ), best practice guidelines on hospital-acquired pneumonia (non-covid-19). The criteria are the following;

A new and/or persistent shadowing (consolidation) on chest x-ray, which is otherwise unexplained, plus at least two of the following confirms the diagnosis:

- Fever >38ºC (>100ºF)
- Leukocytosis (WBC >10 x 10^9/L) or leucopenia (WBC <4X10^9/L)
- Purulent sputum
- Decline in oxygenation

The primary investigator will identify eligible patients from a database collected as part of routine clinical care, trust service evaluation and audit. Electronic and paper records from eligible patients will be screened and data relevant to the study extracted and recorded. This data will then be analysed.

7 Subject selection

Participants will be identified by screening consecutive sets of case notes and electronic records for the years of 2014 (those before tracheostomy insertion was routine, therefore those who did not have a tracheostomy inserted) and 2017 (tracheostomy insertion was routine). Eligibility criteria includes all patients who underwent oromaxillofacial surgery with tracheostomy and free flap reconstruction. Only those with missing or unavailable data will be excluded. The PI is an employee of Guy's and St Thomas' NHS foundation trust (GSTT) and will be undertaking all aspects of data collection and recording. As employees of GSTT the CI and PI have undertaken all relevant information governance mandatory training permitting access to required data. The study will take place at a single site – Guy's & St Thomas' NHS Foundation Trust.

7.1 Subject inclusion criteria

- Patients who underwent maxillofacial resection with free flap reconstruction and tracheostomy from 1st January 2018 to 31st December 2018.
- Patients who underwent maxillofacial resection with free flap reconstruction and with endotracheal intubation from 1st January 2014 to 31st December 2014
- Patients over the age of 18

7.2 Subject exclusion criteria

- Patients who did not undergo maxillofacial resection with free flap reconstruction and tracheostomy from 1st January 2018 to 31st December 2018 – not relevant and will not answer the study question
- Patients who did not undergo maxillofacial resection with free flap reconstruction and with endotracheal intubation from 1st January 2014 to 31st December 2014 - not relevant and will not answer the study question
- Patients under the age of 18

8 Study procedures

8.1 Subject recruitment

Subjects will not be recruited or consented. The study is a retrospective observational cohort study, reviewing retrospective data collected as part of routine clinical care.

8.2 Screening Procedures

The primary investigator will identify eligible patients from a database collected as part of routine clinical care, trust service evaluation and audit.

8.3 End of Study Definition

Full data collection and analyses.

9 Assessment of Safety

The study is an observational cohort study, involving analysis of retrospective patient data collected as part of routine clinical care. There are no interventions or contact with patients. The primary investigator is an employee of GSTT, and is directly involved in the delivery of clinical care to this patient group in their normal clinical role.

9.1 Ethics Reporting

The study is an observational cohort study, involving analysis of retrospective patient data collected as part of routine clinical care. There are no interventions or contact with patients.

10 Data

10.1 Data to be collected

The PI will identify eligible patients from a database collected as part of routine clinical care for trust service evaluation and audit. Electronic and paper records of eligible patients will be screened and data appropriate to the study extracted. Descriptive demographic data including age, gender, cancer site, stage, surgery type, neck dissection, flap site, and factors known to increase risk of HAP; smoking history, respiratory history, tumour size, hospital length of stay, and mortality will be recorded. The primary outcome tool will be retrospectively applied to case notes and electronic records of included patients, by a single therapist (the PI) between day 1 and 7 post operatively. It is anticipated data collection will take around 2 months.

10.2 Primary outcome tool

HAP is an acute lower respiratory tract infection that is acquired after at least 48 hours of admission to hospital and is not incubating at the time of admission (BMJ best practice). It is more common in patients that have undergone major surgery, those admitted to critical care, and those with a prolonged hospital admission (BMJ no 6 best practice). Developing a HAP is associated with an increase in morbidity and mortality as patients with these risk factors are also likely to have one or a combination of multiple co-morbidities, critical illness and frailty. Using a standardised outcome measure to assess the primary outcome reduces the risk of bias and increases reliability and reproducibility. The primary outcome in this study was hospital-acquired pneumonia as defined by the British Medical Journal (BMJ), best practice guidelines on hospital-acquired pneumonia (non-covid-19), the criteria is the following;

A new and/or persistent shadowing (consolidation) on chest x-ray, which is otherwise unexplained, plus at least two of the following confirms the diagnosis:

- Fever >38ºC (>100ºF)
- Leukocytosis (WBC >10 x 10^9/L) or leucopenia (WBC <4X10^9/L)
- Purulent sputum
- Decline in oxygenation

Data collected will be continuous, nominal, ordinal and discrete.

10.3 Data handling and record keeping

The PI can confirm that patient demographic data electronic data (e.g. Age, DOB, sex, past medical history, head and neck surgical and oncological history) will be transferred from their electronic patient record to the secure networked digital data store. Data will be backed up on a secure trust IT provided memory stick that will be stored in a locked filing cabinet stored within a room that can only be accessed with trust ID. All patient identifiable data and link back spreadsheets will be held at GSTT sites and not transferred to KCL during or after the study.

Any identifiable and personal data will only be accessed by the PI who is an employee of Guy's and St Thomas' NHS Foundation Trust and directly involved in the delivery of clinical care to this patient group, and is held to account on the NHS Trust's information governance policy. All data will be protected and confidentiality maintained following the NHS Code of Confidentiality (2003). Data will only be accessed by the PI and will be stored on a password protected, trust laptop that will be stored in a locked cupboard within an office that can only be accessed with trust ID (rehabilitation room on Blundell ward at Guy's Hospital). The data will be backed up on a trust provided encrypted memory stick.

Any identifiable and personal data will only be accessed by the investigator who is also an employee of Guy's and St Thomas' NHS Foundation Trust and in their clinical role deliver clinical care to this patient group,and is held to account on the NHS Trust's information governance policy. All data will be protected and confidentiality maintained following the NHS Code of Confidentiality (2003).

All data files containing data will be anonymised using a code that does not allow direct identification of the participant. The key to the code will be stored in a separate file together with the personal details of each participants. The key, personal details and log will be stored only on the secure storage facility. This data will be stored using a password-protected excel spreadsheet.

Patient's hospital numbers will not be held in the same database as clinical data. It will be stored in a separate database and linked through a unique study number. On initial identification it will be stored in a separate password protected database that will be saved on a secure trust laptop, stored in a locked cabinet in a room that can only be accessed with trust swipe ID access.

The data (stored on password protected computers that are stored in a secure office of the PI at Guy's Hospital Site) generated by the study will be analysed in commercially available software (SPSS) by the PI.

The data will not include any participant identifiable data. Anonymized participant characteristic and study data for this study will be stored securely in Microsoft Excel files – it is a small non-interventional observational study and while we do not envisage the characteristic data changing, if it does then separate files will be created to create an audit trail.

The data will be analysed on the Guy's Hospital site, on a GSTT laptop, by the PI only. All participant-identifiable data will have already been removed from the laptop and transferred to an encrypted external storage device (an encrypted USB device provided by the GSTT IT department kept in a locked filing cabinet in locked, secured offices in an area that can only be entered with a security swipe-card at Guy's Hospital. The encrypted external storage device will be backed-up on a secure networked digital datastore that is accessible only to the PI on PCs that are password protected at login kept in locked, secured offices in an area that can only be entered with a security swipe-card at Guys hospital. Any GSTT laptop will not therefore have participant-identifiable data kept on its hard drive.

Excel spreadsheets will be used, data stored within excel spreadsheets will be periodically saved as a PDF (to lock the data) and saved in a password protected folder with the Excel database. The PDF will be printed off and validated by the PI. A hard copy will be retained securely should the Excel file become corrupt as a back-up.

Data Protection:

Data will be processed according to trust information governance processes and the PI is compliant with all information governance mandatory training and good clinical practice principles

No data will be obtained that is not required for the current study and its stated end points

Every effort will be made to ensure data will be recorded accurately and thoroughly checked prior to analysis

Data for the current study will be kept on a secured GSTT trust laptop in a secure, locked office accessed only by trust ID for a maximum of 5 years

All patients identified as eligible for the study will be assigned a code the code will be kept on a secure GSTT trust laptop within a secured locked office at GSTT

No data will be disclosed outside of the EU. The outcomes of the study may presented at national and international conference that may include the EU, and/or published in peer review journals that include the EU - all data will be deidentified.

11 Statistical considerations

Statistician advising on power calculation and analysis procedure.

Mr Bola Coker
Senior Data Manager, NIHR GSTT/KCL Biomedical Research Centre
Visiting Senior Data Manager, School of Population Health & Environmental Sciences, KCL
Guy's & St Thomas' NHS Foundation Trust
5th Floor Addison House
London
SE1 1UL
020 7848 8687
bolaji.coker@kcl.ac.uk

11.1 Sample size calculation (some pilot/feasibility studies may not require a formal sample size calculation)

The sample size required is 193. Using G*Power 3.1.9.2 Universität Düsseldorf: G*Power (hhu.de) the study has been powered at 80%, with a type 1 error of 5%, two-tailed, to detect an effect size difference, expressed as an odds ratio, of 2.33 using binary logistic regression. It is assumed that 30% of patients that did not have a tracheostomy inserted for maxillofacial surgery with free flap reconstruction (2014 cohort) develop HAP. It is further assumed that the 2018 cohort (those with endotracheal intubation) will make up 41% of the combined cohort. The primary independent variable will be binary to represent the two cohorts being studied.

11.2 Statistical analysis

A power calculation will be used to determine the sample size required for statistical analysis of data. Statistical significance for rates of HAP will be tested between the two groups. It is anticipated that data will not normally distributed and non-parametric testing will be used (Mann Whitney U/Chi-square depending on data type). Odds ratios using logistic regression will be used to explore the risk factors for HAP in this scenario which have previously been indicated to have been smoking, respiratory history and tumour size.

12 Ethical considerations

The proposed work will be conducted according to the principles set out in the Helsinki Declaration (World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research involving Human Subjects, as amended by the 56th WMA General Assembly, Fortaleza, Brazil, October 2013.

Review within the host organisation incorporates directorate-level peer review led by its respective clinical research and audit lead, accountable to the Foundation Trust clinical governance directorate lead.

Masters projects are subject to a thorough review through KCL and review bodies. This provides assurance that there is valid research question and that the research has been confirmed as suitably designed.

Peer review has been undertaken anonymously and has been sent to GSTT R&D separately to maintain anonymity.

HRA approval is required.

Patient & Public involvement

Details of involvement: PPI remote meeting via video conferencing September 2021

Expert patients who had undergone oromaxillofacial resection with free flap reconstruction and temporary tracheostomy were contacted. They were invited to voluntarily take part in a small workshop that aimed to gain an insight into how important patient's feel this project will be, if they have any thoughts on the design of the project, handling and storage of patient data and the best timing and format to disseminate the results.

Who was involved?

Patients who had undergone oromaxillofacial resection with free flap reconstruction and temporary tracheostomy.

How were they involved?

5 patients agreed to participate, 2 requested to attend via video call and 3 had no preference. The decision was made to conduct the 1 hour meeting via video call using commercial and accessible video conferencing service supported by GSTT IT - MS teams. Prior to that meeting, the CI will communicate with members by email and/or telephone. The PI chaired the meeting and another physiotherapist working within head and neck surgical oncology recorded the minutes - the PI also reviewed the minutes after to ensure all discussion was accurately recorded.

How and when will you feedback? (Them to you, you to them).

Patients were asked if they would like to receive updates with regard to study progress, results and any publications, and if so in what format and how. All patients requested to receive updates from email, and would like to receive a lay version of results and study write up. Therefore the PI will feedback to the group members by email providing an update on study progress (outcome ethics, data collection, results and write up). Once complete a copy of a lay abstract of results will be sent via email.

13 Financing and Insurance

The lead sponsor, King's College London, will take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting. King's College London also provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions). The co-sponsor, Guy's & St Thomas' Foundation NHS Trust, take ultimate responsibility for arranging the initiation and management of this research, and will take responsibility for ensuring that appropriate standards, conduct and reporting are adhered to regarding its facilities and staff involved with the project.

14 Reporting and dissemination

Study results are planned to be published in a relevant head and neck peer reviewed journal, and presented at a relevant head and neck national/international conference. Raw data will not be published. Publications will be discussed with the sponsor.

Useful reading/websites

Integrated Research Application System (IRAS)
https://www.myresearchproject.org.uk/

Health Research Authority (HRA)
www.hra.nhs.uk

HRA Guidance for Patient Information Sheet and Informed Consent
http://www.hra.nhs.uk/research-community/before-you-apply/participant-information-sheets-and-informed-consent/

CONSORT statement

ICH Harmonised Tripartite Guidelines for Good Clinical Practice (1996)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Martin Bland et al, Statistical guide for research grant applications
http://www-users.york.ac.uk/~mb55/guide/guide.htm
Includes detailed information and definitions of many aspects required for a research protocol.

Declaration of Helsinki
(http://www.wma.net/en/30publications/10policies/b3/index.html)

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

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