# The "JaW PrinT" Study:

# Jaw reconstruction With Printed or flexed Titanium and free tissue transfer.

A collaboration between Abertawe Bro Morgannwg University Health Board, University of South Wales and Renishaw PLC.

# Table of Contents

## List of Abbreviations

| | |
|---|---|
| ABMUHB | Abertawe Bro Morgannwg Health Board |
| CAD-CAM | Computer aided design – Computer aided manufacture |
| CMF | Cranio-maxillo-facial (surgery) |
| CBCT | Cone-beam computer tomography (dental) |
| CT | Computer tomography (medical) |
| H&N | Head & Neck (surgery) |
| HRQOL | Health related quality of life |
| ORN | Osteoradionecrosis (of the mandible) |
| PI | Principal investigator |
| PSI | Patient-specific implant |
| SLM | Selective laser melting |
| 3D | Three-dimensional |

## 1.0 Study Team

| | |
|---|---|
| Mr Alexander Goodson | Postgraduate (PhD) student investigator |
| Professor Mark Williams | Chief Investigator & PhD Director of Studies |
| Mr Madhav Kittur | Principal Investigator for ABMU Health Board |
| Mr Peter Evans | Co-investigator, ABMU Health Board |

### 1.1 Details of Research Team


Name: Professor Mark Williams
Role: Chief Investigator
Address: Faculty of Life Sciences and Education
University of South Wales
Cemetery Road
Glyntaff
CF37 4BD

Telephone: 01443 654578
Email: mark.williams@southwales.ac.uk

Name: Mr Alexander Goodson
Role: PhD Student Investigator
Address: Faculty of Life Sciences and Education
University of South Wales
Glyntaf Campus
Pontypridd, CF37 1DL
Telephone: 01443 654578
Email: alex.goodson@southwales.ac.uk

Name: Mr Madhav Kittur
Role: Principal Investigator for ABMU Health Board
Address: Morriston Hospital
Heol Maes Eglwys
Morriston
Swansea
SA6 6NL
Telephone: 01792 703162
Email: madhav.kittur@wales.nhs.uk

Name: Mr Peter Evans
Role: Co-investigator
Address: Morriston Hospital
Heol Maes Eglwys
Morriston
Swansea
SA6 6NL
Telephone: 01792 703162
Email: peterllewelyn.evans@wales.nhs.uk

# 2.0 Literature Review and Study Rationale

## 2.1 Introduction / context

Head and neck (H&N) cancer includes cancers originating from various (and often overlapping) sub-sites in the head and neck region (including the oral cavity, pharynx, larynx, nose and paranasal sinuses). H&N cancer is the eighth most common cancer in the UK (2014). In the UK (mainland) it is four times commoner in men than women, and geographically European age-standardised (AS) incidence rates are higher in males in Wales than England (with rates highest in Scotland overall for both sexes). H&N cancer incidence has increased in both sexes since the 1990s with a greater percentage increase amongst females, closing the gender difference in incidence over time.(Cancer_Research_UK)

For head and neck cancer in general, late stage disease is a commoner presentation than early stage disease (62% are stage III/IV at presentation

versus 38% at stage I/II).(NICR, 2016) Consequently, major resective surgery, aiming for cure (with immediate reconstruction for optimal functional outcome) is commonplace. In the case of oral cancer specifically, advanced tumours frequently involve the mandible (lower jaw bone), requiring resection/removal of part of the mandible to a variable extent, depending on the nature of the tumour (with/without postoperative radiotherapy, depending upon patient and tumour-specific factors).

Radiotherapy is commonly used in head and neck cancer in isolation (as an alterative to surgery), most commonly for laryngeal and tongue base tumours as it helps to preserve natural speech and swallowing. However for advanced squamous cell carcinomas (SCCs), combined treatment modalities (surgery and radiotherapy / chemotherapy and radiotherapy) offer the highest chance of cure.(Nutting, 2016) For patients in whom radiotherapy is used, there is an additional lifelong risk of developing osteoradionecrosis (ORN) of the mandible as a side-effect. Osteoradionecrosis is in effect, "hypovascularity and necrosis of bone followed by trauma-induced or spontaneous mucosal breakdown, leading to a non-healing wound."(Butterworth et al., 2016) In the latter stages of the disease process, ORN can result in pathological fracture of the mandible and/or an orocutaneous fistula, requiring free tissue transfer to repair the defect.(Lyons and Brennan, 2014) Consequently, in the context of managing head and neck cancer, mandibular reconstruction with titanium plates and free tissue transfer is commonly performed; not only for immediate reconstruction after surgical resection of advanced tumours, but also for treatment of late-stage ORN. Furthermore, similar techniques can be used for extensive and progressive (but histologically benign) jaw tumours.

Choice of reconstructive technique for mandibular defects depends on the amount of bone to be resected.(Brown et al., 2016) However, in larger defects, it is felt by many surgeons that the gold standard for mandibular reconstruction is a fibula free flap (autologous vascularized bone and soft tissue, transplanted from the leg and anastomosed to an arteriovenous supply in the neck) supported within an osseosynthesis plate to facilitate primary bony union/healing.(Kokosis et al., 2016) Other choices of bony free-flaps can be used such as the deep circumflex iliac artery (DCIA) flap, favoured over the fibula free flap by some authors.(Chen et al., 2014) Most osseosynthesis plates used for this purpose are composed of titanium, because of its intrinsic biocompatibility and high strength-to-weight ratio.(Parthasarathy, 2014). Traditionally, titanium was flexed or moulded intraoperatively by eye (during surgery) to reconstruct mandibular defects, without the modern benefits of preoperative 3D computer-aided planning. The process of flexing a rigid osseosynthesis plate for mandibular reconstruction inherently contributes to the overall duration of the surgery, is dependent upon the experience and skill of the surgeon and carries the risk of human error in dimensional accuracy of the reconstruction, simply because it is done 'by hand and by eye'. Furthermore, manually deforming titanium implants in this manner creates intrinsic stresses within the implanted material, potentially weakening the overall reconstruction in the long term whilst subjected to cyclical loading forces from mastication/chewing for example.(Park et al., 2016)

## 2.2 Computer aided 3D planning and customisation of mandibular reconstruction osseosynthesis plates

Three dimensional (3D) planning and virtual surgery has evolved in recent years and it is postulated that it improves efficiency, accuracy, creativity and reproducibility in CMF surgery in particular.(Steinbacher, 2015) Rapid prototyping is a process by which a stereolithigraphic resin model can be produced following collection of data from 3D imaging such as computer tomography (CT) scanning. The process of virtual surgery (following analysis of 3D imaging data) provides the means to rapid-prototype a stereolithigraphic resin model/mould upon which a titanium implant can be flexed, pressed or moulded preoperatively (and most importantly, checked against the stereolithigraphic model) for subsequent intraoperative use. This technique has become commonplace in UK maxillofacial centres. When compared to traditional intraoperative shaping techniques, it improves accuracy and efficiency in mandibular reconstruction (notably eliminating the time taken during surgery to bend the plate by eye that would otherwise be required using the traditional approach, yet allowing as much time as needed by the technician preoperatively to achieve the best 'handmade' result possible).(Gil et al., 2015) Nevertheless, this type of 'customisation' still remains open to considerable inaccuracies/human errors of the technician in flexing the plate by hand. Furthermore the risk of introducing mechanical weaknesses by flexing the plate remains.

Besides producing patient-specific implants (PSIs), 3D planning and virtual surgery facilitates the production of intraoperative surgical cutting and drilling guides/'stents', which improve accuracy of bone cuts (osteotomies) in mandibular reconstruction with fibula free flaps and aids precise placement of osseointegrated dental implants (Wang et al., 2016, Allum, 2008).

## 2.3 3D printing in mandibular reconstruction

It is clear that to date, 3D CAD-CAM has improved the accuracy of mandibular reconstructions in head & neck oncology surgery. With the advent of "3D printing" (more specifically selective laser melting; SLM), it has been proposed by one author group that laser sintered mandibular reconstruction plates reduce the duration of surgery and frequency of complications, as well as producing a more accurate reconstruction due to the elimination of human error in the final stages of fabrication (in contrast to the "pre-flexing to a rapid-prototyped stereolithigraphic model" approach). The authors suggest that further randomized studies would be useful to determine whether CAD-CAM mandibular reconstruction is economically sustainable in maxillofacial oncology surgery (Tarsitano et al., 2016). Currently a team in Hong Kong are prospectively evaluating clinical outcomes and complications of laser sintered mandibular reconstruction plates in a proposed series of 48 patients (Su, 2017). However, to date there are no randomized trials comparing clinical and

economic outcomes in 3D-printed mandibular reconstruction plates and cutting guides versus manually pre-flexed plate techniques.

### 2.4 Summary

In summary, 3D printing (SLM) of titanium provides an opportunity to negate the impact of human error in customisation of mandibular reconstruction osseosynthesis plates and alignment of osteotomies, potentially improving upon the predictability and precision of mandibular reconstruction in head & neck cancer patients. However, with a lack of high-level evidence to date, there is no clear consensus on whether the SLM approach provides a better treatment solution when compared to other more established, but potentially more crude techniques of plate customization (pre-flexing to a rapid prototyped model). Consequently a situation of clinical equipoise exists and in this context, warrants a well-designed observational study to evaluate any differences between the two treatment approaches.

## 3.0 Study aims and objectives

### 3.1 Primary outcome

Primarily, the study aims to evaluate:

1. Predictability and resultant dimensional accuracy of mandibular reconstructions performed using:

    - Fibular free-flap reconstruction of the mandible with a customized pre-flexed mandibular reconstruction plate and cutting guides (Treatment pathway A)

    OR

    - Fibular free-flap reconstruction of the mandible with a customized SLM mandibular reconstruction plate and cutting guides (Treatment pathway B)

### 3.2 Secondary outcomes

Secondarily, the study aims to compare treatment pathways A and B for:

2. The duration of surgery (in particular individual components of the surgery such as flap warm ischaemia time, duration of osteotomies and plate fixation procedures.

3. The operators' perceptions of the overall intraoperative usability, confidence with the technique and immediate satisfaction of the surgical result.
4. The need to make minor adjustments to either the plate, osteotomy or screw holes in order to fit the plate during surgery.
5. Incidence of postoperative complications (as recorded during inpatient stay as well as at 6 weeks, 6 months and 1 year outpatient follow up visits), for example:
    a. Localised infection
    b. Plate extrusion/exposure
    c. Length of hospital stay (including duration of intensive care / high-dependency / ward requirements)
    d. Mal / non / delayed-union of the bony components of the mandibular reconstruction (from objective analysis of clinically routine postoperative CT scan imaging)
    e. Plate fractures/failures
6. Medium-term (up to 1 year) functional outcomes, for example:
    a. Feasibility of dental implant rehabilitation (specifically in the technical context of clinical and/or radiological perspective of bone quality and anatomy as well as in the holistic context of the patient's suitability overall, in order to determine the importance of reconstructed bony anatomy in the decision processes and planning of dental rehabilitation)
    b. Objective evaluation of changes in dental occlusion (with the aid of dental model analysis).
    c. Objective assessment of changes in facial aesthetics (facial symmetry based upon baseline and postoperative 3D photography (stereophotogrammetry).
7. Patient-perceived quality of life:
    a. using a validated quality of life assessment tools:
        i. University of Washington Quality of Life Questionnaire v4
        ii. Short-form Derriford appearance scale (DAS24)
        iii. Liverpool oral rehabilitation questionnaire
    b. by time to return to work / social status at 1 year (where applicable)
8. Economic implications (with economic analysis taking the above clinical and social outcomes into account).

## 4.0 Study design

JaW PrinT is a 'real-world' prospective observational pilot study, evaluating the clinical effectiveness, usability and economics of two approaches to mandibular reconstruction surgery (figure 1). Patient participants will be recruited prospectively over a minimum period of 18 months (with observation of at least 10 participants in each treatment pathway). The figures are based upon the historical clinical practice of the research site, with both techniques in equal use;

choice depending on resources, surgical training requirements and surgeon's clinical preference.

As a purely observational study, treatment choice will be made in the normal clinical manner and will in no way be influenced by the study itself.

Participants will be followed up at their routine outpatient clinics (6 weeks, 6 months and 1 year postoperatively) with prospective outcomes data collection (figure 1).

**PI to prospectively identify potential study participants from weekly maxillofacial and H&N surgery clinics**

- Participants to be recruited over a minimum period of 18 months; minimum of 10 patients in each treatment pathway.
- On clinic, potential participants will be asked by the PI if they are interested in taking part in the study.
- The PI, after meeting the potential participant, will confirm their eligibility.
- Eligible participants meeting inclusion and exclusion criteria will be sent an invitation letter with a participant information sheet and a consent form (emphasizing the option to either decline or accept the offer of study participation).

→ Do not enter study

**Consent**

- At the next routine clinical appointment, the potential patient participant's decision will be noted.
- Should the patient wish to participate, the PI will obtain their written informed consent accordingly.

**Preoperative baseline data collection** (CRF01 form).

- Medical history and screening of comorbidities (including comorbidity score & performance status), smoking and alcohol status.
- Evaluate for history of any previous radiotherapy treatment (date started and completed, regime details).
- Physical assessment (BMI, oral hygeine status).
- Detailed social history
- University of Washington QoL Questionnaire v4.
- Short-form Derriford appearance scale (DAS24).
- Liverpool oral rehabilitation questionnaire.
- 3D Photograph (Stereophotogrammetry) of the head and neck
- Baseline clinical blood tests (FBC, U&E, Clotting screen)

**Treatment allocated in normal clinical manner by surgeon to either pathway A (surgery with pre-flexed plate) or pathway B (surgery with SLM plate).**

Participant blinded to treatment allocation at this stage

**Pathway A** (Customized pre-flexed plate) n ≥10

**Pathway B** (Customized SLM plate) n ≥10

**Perioperative / inpatient data collection** (CRF02 form).

- Prior to commencing surgery, bite registration to be obtained (using viscoelastic silicone impression putty)
- At surgery, record of:
  - Times at which mandibular osteotomies are first started (cutting guides first placed onto mandible) and completed
  - Time of knife-to-skin for flap harvest
  - Time of flap detachment
  - Time of completing fixation of the plate (with flap) in its final resting position (i.e. when completion of fixation to the residual mandible)
  - Time of completing arterial anastomosis
- Record of need for any intraoperative adjustment to the plate, osteotomies and/or planned drill hole positions.
- Surgeon rating of usability, confidence of use, satisfaction with reconstructive procedure.
- Scrub nurse rating of usability, confidence of use, satisfaction with reconstructive procedure.
- Record of days-stayed on ITU / HDU and/or Ward, date of discharge.
- Record of all complications as inpatient (peri & post operative).

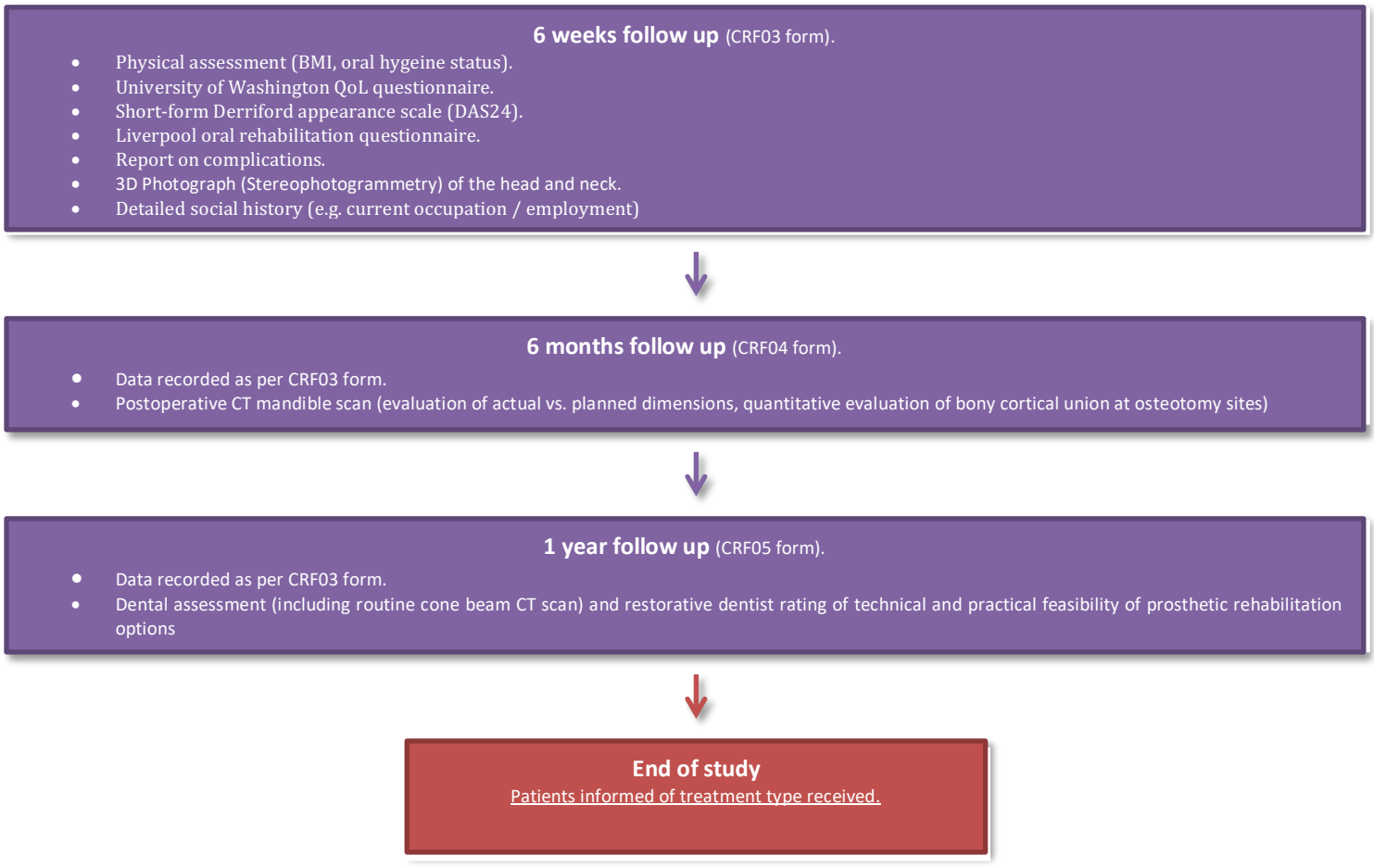


Figure 1. The JaW PrinT study design

## 4.1 Inclusion criteria

- Age over 18 years
- Able to provide informed consent
- A planned fibular free-flap reconstruction of the mandible
- Planned post operative surveillance CT scan 6 months following surgery

## 4.2 Exclusion criteria

- Clinically unfit or inappropriate (based upon prognosis/life expectancy) for reconstruction using free tissue transfer techniques
- Patients with planned surgical defects involving reconstruction of the condyle: i.e. Brown class Ic, IIc or IVc. *(Clinical use of printed plates for condylar reconstructions would in effect be 'off-licence' and non-standard treatment which is beyond the remit of an observational research study).*
- Flap failure within the study follow-up period, as this would require early removal of the flap and therefore preclude collection of follow-up outcome data. However, any flap failures (and associated clinical complications/events) will be recorded and reported.

## 4.3 Recruitment

Participants will be recruited prospectively as they present as new patient cases to the ABMU Maxillofacial and Head & Neck cancer multidisciplinary team (MDT) clinics. Once a potential patient participant has been given his/her diagnosis and it is confirmed by the principal investigator (PI) that he/she meets the inclusion criteria, clinic staff will provide the potential participant with an invitation letter introducing the study as well as a patient information sheet and consent form (explaining the available options of participating or refraining from the study). Patients will be allowed up to 24 hours to decide whether or not to participate as to avoid any impact/delay on the scheduling of their clinical treatment. The PI will obtain written informed consent from willing participants.

## 4.4 Treatment pathway allocation

Upon recruitment, provision of informed consent and collection of baseline data, as per standard clinical practice, the patient participant's CT scan data is used to produce a virtual surgical plan for the mandibular resection and fibular free-flap reconstruction. Once the clinically optimal reconstructive surgical plan is established by the surgeon and technician, the choice of surgical approach will be made in the routine clinical manner by the surgeon: Pathway A (pre-flexed customized mandibular reconstruction plate and cutting guides) or to pathway B (SLM customized mandibular reconstruction plate and cutting guides). Both

treatment pathways are already part of routine/standard clinical practice at ABMUHB.

The expected/planned patient numbers for this study are based upon the historical workload of the Oral and Maxillofacial Surgery department at Abertawe Bro Morgannwg University Health Board (ABMUHB) of 10-20 cases annually. A recruitment period of 18 months with follow-up for 1 year fits within the time constraints of the postgraduate student investigator's PhD timeline.

## 4.5 Study procedures

### 4.5.1 Baseline Assessment

This will be performed using a "baseline case report form" (CRF01), which will include past medical history (with attention to any history of previous radiotherapy to the head and neck region); a 'systems review' to screen for undisclosed comorbidities as well as smoking and alcohol status. The patient participant's comorbidity and performance status scores will also be recorded. The qualitative/subjective assessment of oral hygiene status (good/fair/poor) by a consultant oral and maxillofacial surgeon will also be recorded. Collected from routine clinical preoperative tests, BMI and serum albumin concentration will be recorded as an indicator of nutritional status, along with a full blood count, urea and electrolytes and clotting screen. Baseline quality of life assessment will be performed using the University of Washington QoL Questionnaire v4 (Rogers et al., 2002)(Appendix A). A baseline assessment of the participant's perceived appearance and oral function will be evaluated using the short-form Derriford appearance scale (DAS24) (Carr et al., 2005) which is suited as a research of appearance in H&N cancers (Djan and Penington, 2013), and the Liverpool oral rehabilitation questionnaire(Pace-Balzan et al., 2006) (Appendix B) respectively. Presurgical facial aesthetics will also be evaluated by means of assessing facial symmetry with stereophotogrammetry (clinical 3D photography in the medical illustration department) of the head and neck region.

### 4.5.2 Perioperative/inpatient data collection

During the inpatient phase of the participant's medical treatment, all data will be recorded on the "inpatient case report form" (CRF02).

To evaluate the presurgical dental occlusion (if occluding teeth present), a bite registration will be taken whilst the patient participant is anaesthetised. These will be obtained using a viscoelastic silicone impression material.

At surgery, overall time from knife to skin, to transferring the patient participant off the operating table will be recorded. Furthermore the timings of specific landmarks of reconstructive components of surgery will be recorded:

- Times at which mandibular osteotomies are first started (when mandibular cutting guides first touches mandible) and completed (when mandibular cutting guides removed)

- Time of knife-to-skin for flap harvest
- Time of flap detachment
- Time of completing fixation of the plate in its final resting position (i.e. when completion of fixation to the residual mandible)
- Time of completing arterial anastomosis

To evaluate the impact of cutting guides on the fit of the bony flap, the surgeon will be asked to record the number of subsequent adjustments needed to the mandibular/fibular osteotomies, drill holes and/or the plate itself.

To further evaluate the efficiency of either surgical technique (and any potential 'learning curve' effect), the surgeon and scrub nurse will be asked to provide a 5-point Likert scale rating for the following criteria at the end of the operation:

- Ease of use
- Confidence in performing the technique
- Immediate satisfaction with reconstructive component of surgery

In the immediate postoperative (inpatient) phase of recovery, dates of stay in the intensive care unit (ITU), high dependency unit (HDU) and/or the inpatient ward will be recorded, along with a final discharge date. During this period, any postoperative complications are to be recorded if/as they occur.

### 4.5.3 6 weeks follow up

This will include reporting of any complications since discharge from hospital, as well as repetition of some data collected in the baseline assessment, using the "6 weeks case report form" (CRF03). Specific data to be collected includes:

- Physical assessment (BMI, oral hygeine status, report on wound healing).
- University of Washington QoL questionnaire.
- Short-form Derriford appearance scale (DAS24).
- Liverpool oral rehabilitation questionnaire.
- Report on complications.
- Stereophotogrammetry (3D photography) of the head and neck.

### 4.5.3 6 months follow up

The "6 months case report form" (CRF04) will be used to collect identical data to that collected at 6 weeks follow-up. This follow up point is selected as in the case of cancer surgery, it is a standard follow-up point for assessment of signs of early disease recurrence. For this reason, routine medical CT scanning to evaluate for disease recurrence is performed. A 3D render of DICOM data from this clinical scan can be used to dimensionally and volumetrically compare the actual bony reconstruction with the preoperative plan, evaluating overall accuracy and precision of the reconstructive technique used. Furthermore, CT assessment of bony union will be performed using a quantitative numerical rating score, adapted from Akashi et al.(Akashi et al., 2015)

### 4.5.4 1 year follow up

The “1 year care report form” (CRF05) will be used to collect identical data to that collected at 6 weeks follow-up. Furthermore, in some cases routine clinical and radiographic (cone beam CT) dental assessment is performed 1 year postoperatively with a view to further dental rehabilitation (with dental implants in some patients). From this dental assessment, we would aim to evaluate the clinician’s opinion (using a 5 point Likert scale) of the patient participant’s overall suitability for dental rehabilitation (if not already in place) with a variety of possible prosthetic solutions:

- Simple dentures
- Bridge
- (Multiple) single tooth implants
- Implant retained bridge
- Implant retained dentures

Dental radiology (cone beam CT) if used as part of this routine dental assessment will also be analysed to further evaluate any bony (dimensional/volumetric/healing) changes that occur over time.
Post-surgical dental occlusion would clinically routinely be evaluated with a bite registration. This can be compared to the pre-surgical bite registration to evaluate the impact of the reconstructive surgery on dental occlusion.

## 5.0 Risk management

All clinical testing (physical, serological and radiological) performed within this study is within the remit of standard clinical care and therefore the study itself will not put the participant at additional risk of medical complications or side-effects.

For qualitative data collection, validated scoring tools will be used wherever possible.

Both treatment pathways (A & B) observed in this study constitute routine surgical practice, with both techniques routinely used at ABMUHB. Both are gold-standard treatment with subtle differences in technique; neither is experimental in any way. Consequently any clinical complications can be dealt with in the normal clinical manner, regardless of the study.

It will be made clear to participants from the start of their involvement that they are free to withdraw from the study at any time, without any reason and without any impact upon their standard of care. Participants will be given the contact details for the study team, with their primary link being their centre’s PI who will supervise both their clinical care and data collection throughout the study period.

Should clinical need require deviation from the study protocol and subsequent exclusion as to avoid confounding effects on study results, this will be disclosed and reported in the results. Where it is felt that any data collected was unaffected by this process, it will be used wherever feasible.

## 6.0 Statistical analysis

Data will be collated and analyzed using a statistical software package. Descriptive statistics will be used for baseline measures, categorical statistics for questionnaire outcome data, and relationships will be evaluated using tests of correlation and comparison, along with regressional analysis.

## 7.0 Data management and quality control

Data will be collated and stored in compliance with the Data Protection Act 1998 and the ABMUHB data protection policy. All data used beyond the participant's immediate clinical environment will be anonymized accordingly.

The study team will meet throughout the study with quarterly meetings to discuss and audit participant recruitment, data collection and any issues with the study protocol that may arise.

All clinical records will remain within ABMUHB and stored within the patient's clinical records in the normal manner. Case Report Forms (CRFs) will be kept in the PI's office in a locked cabinet. To maintain anonymity from the earliest stage, recruited participants will be assigned a numeric identity code (instead of identifiable information such as age or date of birth) from the beginning. Once anonymised, patient data will be stored electronically on a password-protected laptop computer and backed-up on an external hard drive on a daily basis.

As anonymised raw data, CRFs will be physically stored for 15 years beyond the termination of the study by the PI (as the data custodian). This strategy is based upon the recommendations of the ABMUHB research and development department (where local policy advises a data storage period of 5 to 15 years following termination of the study) and the UK Policy Framework for health and social care research(Health_Research_Authority, 2017). Identifiable data that requires storage for clinical reasons alone, will only be stored in the usual NHS clinical manner according to NHS Wales policy (The_National_Assembly_For_Wales, 2000).

## 8.0 Ethical considerations

All treatments provided to study participants are normal, routine clinical practice at ABMUHB.

Apart from HRQOL questionnaires and gaining informed written consent for the research study, all investigations/tests in this study are routine clinical practice at ABMUHB for patients undergoing jaw reconstruction surgery. With regards to some specific tests:

- Clinical 3D photography (stereophotogrammetry) is routinely available and commonly used for ABMUHB patients undergoing facial reconstructive surgery, although not routinely in all cases. In this study, stereophotogrammetry (3D photos) will be obtained at baseline (preoperatively), as well as 6 weeks, 6 months and 1 year post operatively. This has been discussed with the Medical Illustration department at Morriston Hospital.

- Dental bite registrations are routinely performed after jaw reconstruction surgery in order to plan the patient for rehabilitation with dental prostheses. In some, dental impressions and bite registrations are obtained prior to the surgery as well but not in all cases. In this study, we plan to obtain dental impressions (immediately before surgery whilst under general anaesthesia) as well as several months later (as per routine practice). The study team felt that collecting the preoperative dental impressions at the beginning of the participant's surgery provides an opportunistic, efficient, safe and controlled setting in which to do this.

The above items are explained fully (in lay terms) in the patient information sheet.

## 9.0 Funding

This study is funded externally through KESS, in partnership with Renishaw plc and the University of South Wales and includes the cost of consumables/equipment and other incidental costs relating to the study itself.

*Knowledge Economy Skills Scholarships (KESS) is a pan-Wales higher level skills initiative led by Bangor University on behalf of the HE sector in Wales. It is part funded by the Welsh Government's European Social Fund (ESF) convergence programme for West Wales and the Valleys.*

## 10.0 Study timeline

The study timeline is illustrated in the following Gantt chart (figure 2).

## 11.0 References


AKASHI, M., HASHIKAWA, K., KAKEI, Y., SAKAKIBARA, A., HASEGAWA, T., MINAMIKAWA, T. & KOMORI, T. 2015. Sequential evaluation for bone union of transferred fibula flaps in reconstructed mandibles: panoramic X-ray versus computed tomography. *Int J Oral Maxillofac Surg,* 44**,** 942-947.

ALLUM, S. 2008. Immediately loaded full-arch provisional implant restorations using CAD/CAM and guided placement: maxillary and mandibular case reports. . *Br Dent J.,* 204**,** 377-381.

BROWN, J., BARRY, C., HO, M. & SHAW, R. 2016. A new classification for mandibular defects after oncological resection. *Lancet Oncol,* 17**,** e23-30.

BUTTERWORTH, C., MCCAUL, L. & BARCLAY, C. 2016. Restorative dentistry and oral rehabilitation: United Kingdom National Multidisciplinary Guidelines. *JLO,* 130**,** 41-44.

CANCER_RESEARCH_UK Oral cancer incidence statistics.

CARR, T., MOSS, T. & HARRIS, D. 2005. The DAS24: A short form of the Derriford Appearance Scale (DAS59) to measure individual responses to living with problems of appearance. *British Journal of Health Psychology,* 10**,** 285-298.

CHEN, S., CHEN, H., HORNG, S., TAI, H., HSIEH, J., YEONG, E., CHENG, N., HSIEH, T., CHIEN, H. & TANG, Y. 2014. Reconstruction for osteoradionecrosis of the mandible: superiority of free iliac bone flap to fibula flap in postoperative infection and healing. *Ann Plast Surg,* 73**,** 18-26.

DJAN, R. & PENINGTON, A. 2013. A systematic review of questionnaires to measure the impact of appearance on quality of life for head and neck cancer patients. *J Plast Reconstr Aesthet Surg,* 66**,** 647-659.

GIL, R., ROIG, A., ARRANZ OBISPO, C., MORLA, A., MARTI PAGES, C. & LLOPIS PEREZ, J. 2015. Surgical planning and microvascular reconstruction of the mandible with a fibular flap using computer-aided design and rapid prototype modelling, and precontoured titanium reconstruction plates: a prostpective study. . *Br J Oral Maxillofac Surg,* 53**,** 49-53.


Figure 2. Gantt chart illustrating the study timeline

| **Quarter** | **1st** | **2nd** | **3rd** | **4th (1 yr)** | **5th** | **6th** | **7th** | **8th (2 yrs)** | **9th** | **10th** | **End of Study** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Participants recruited*** | | | | | | | | | | | - Unblinding of study participants<br>- Dissemination of data<br>- Peer-reviewed publication<br>- Presentation |
| ***Participants complete study*** | | | | | | | | | | | |
| ***Landmark events*** | Study team meet | Study team meet | Study team meet | Study team meet | Study team meet<br><br>First participant completes study | Study team meet | Study team meet | Study team meet | Study team meet | Study team meet<br><br>Last participant completes study | |

HEALTH_RESEARCH_AUTHORITY 2017. UK Policy Framework for health and social care research v3.3.
KOKOSIS, G., SCHMITZ, R., POWERS, D. & ERDMANN, D. 2016. Mandibular Reconstruction Using the Free Vascularized Fibula Graft: An Overview of Different Modifications. *Arch Plast Surg,* 43**,** 3-9.
LYONS, A. & BRENNAN, P. 2014. Osteoradionecrosis a new classification. *Br J Oral Maxillofac Surg,* 52**,** e64-e65.
NICR 2016. Northern Ireland Cancer Registry, Queens University Belfast, Incidence by stage 2010-2014.
NUTTING, C. 2016. Radiotherapy in head and neck cancer management: United Kingdom National Multidisciplinary Guidelines. *JLO,* 130**,** 66-67.
PACE-BALZAN, A., CAWOOD, J., HOWELL, R., BUTTERWORTH, C., LOWE, D. & ROGERS, S. 2006. The further development and validation of the Liverpool Oral Rehabilitation Questionnaire: A cross-sectional survey of patients attending for oral rehabilitation and general dental practice. *Int J Oral Maxillofac Surg,* 35**,** 72-78.
PARK, S., LEE, D., LEE, J., KIM, Y., KIM, L. & NOH, G. 2016. Stability of the permanently bent plates used in mandibular reconstructive surgery. *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC).* Orlando, FL.
PARTHASARATHY, J. 2014. 3D modeling, cusom implants and its future perspectives in craniofacial surgery. *Annals of Maxillofacial Surgery,* 4**,** 9-18.
ROGERS, S., GWANNE, S., LOWE, D., HUMPRHIS, G., YUEH, B. & WEYMULLER, E. 2002. The addition of mood and anxiety domains to the University of Washington Quality of Life Scale. *Head & Neck,* 24**,** 521-529.
STEINBACHER, D. 2015. Three-Dimensional Analysis and Surgical Planning in Craniomaxillofacial Surgery. *J Oral Maxillofac Surg,* 73**,** S40-S56.
SU, Y. 2017. *Three-Dimensional Printing of Patient-Specific Titanium Plates in Jaw Surgery: A Pilot Study* [Online]. https://clinicaltrials.gov/ct2/show/NCT03057223: U.S. National Institutes of Health. [Accessed 2/4/17 2017].
TARSITANO, A., BATTAGLIA, S., CRIMI, S., CIOCCA, L., SCOTTI, R. & MARCHETTI, C. 2016. Is a computer-assisted design and computer-assisted manufacturing method for mandibular reconstruction economically viable? *J Craniomaxillofac Surg,* 44**,** 795-799.
THE_NATIONAL_ASSEMBLY_FOR_WALES 2000. For the record - Managing Records in NHS Trusts and Health Authorities. *Welsh Health Circular*.
WANG, Y., ZHANG, S., FAN, S., ZHANG, D., HUANG, Z., CHEN, W., YE, J. & LI, J. 2016. Mandibular reconstruction with the vascularised fibula flap: comparison of virtual planning surgery and conventional surgery. . *int J Oral Maxillofac Surg,* 45**,** 1400-1405.

# 12.0 Appendices

## Appendix A

**University of Washington Quality of Life Questionnaire**
**(UW-QOL v4)**

*This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by ticking one box for each question.*

1. **Pain**. (Tick one box: ☑ )

| | |
|---|---|
| I have no pain. | (100) |
| There is mild pain not needing medication. | (75) |
| I have moderate pain - requires regular medication (e.g. paracetamol). | (50) |
| I have severe pain controlled only by prescription medicine (e.g. morphine). | (25) |
| I have severe pain, not controlled by medication. | (0) |

2. **Appearance**. (Tick one box: ☑ )

| | |
|---|---|
| There is no change in my appearance. | (100) |
| The change in my appearance is minor. | (75) |
| My appearance bothers me but I remain active. | (50) |
| I feel significantly disfigured and limit my activities due to my appearance. | (25) |
| I cannot be with people due to my appearance. | (0) |

3. **Activity**. (Tick one box: ☑ )

| | |
|---|---|
| I am as active as I have ever been. | (100) |
| There are times when I can't keep up my old pace, but not often. | (75) |
| I am often tired and have slowed down my activities although I still get out. | (50) |
| I don't go out because I don't have the strength. | (25) |
| I am usually in bed or chair and don't leave home. | (0) |

4. **Recreation**. (Tick one box: ☑ )

| | |
|---|---|
| There are no limitations to recreation at home or away from home. | (100) |
| There are a few things I can't do but I still get out and enjoy life. | (75) |
| There are many times when I wish I could get out more, but I'm not up to it. | (50) |
| There are severe limitations to what I can do, mostly I stay at home and watch TV | (25) |
| I can't do anything enjoyable. | (0) |

5. **Swallowing**. (Tick one box: ☑ )

| | |
|---|---|
| I can swallow as well as ever. | (100) |
| I cannot swallow certain solid foods. | (70) |
| I can only swallow liquid food. | (30) |
| I cannot swallow because it "goes down the wrong way" and chokes me. | (0) |

6. **Chewing**. (Tick one box: ☑ )

| | |
|---|---|
| I can chew as well as ever. | (100) |
| I can eat soft solids but cannot chew some foods. | (50) |
| I cannot even chew soft solids. | (0) |

12

7. **Speech**. (Tick one box: ☑ )

| | |
|---|---|
| My speech is the same as always. | (100) |
| I have difficulty saying some words but I can be understood over the phone. | (70) |
| Only my family and friends can understand me. | (30) |
| I cannot be understood. | (0) |

8. **Shoulder**. (Tick one box: ☑ )

| | |
|---|---|
| I have no problem with my shoulder. | (100) |
| My shoulder is stiff but it has not affected my activity or strength. | (70) |
| Pain or weakness in my shoulder has caused me to change my work / hobbies. | (30) |
| I cannot work or do my hobbies due to problems with my shoulder. | (0) |

9. **Taste**. (Tick one box: ☑ )

| | |
|---|---|
| I can taste food normally. | (100) |
| I can taste most foods normally. | (70) |
| I can taste some foods. | (30) |
| I cannot taste any foods. | (0) |

10. **Saliva**. (Tick one box: ☑ )

| | |
|---|---|
| My saliva is of normal consistency. | (100) |
| I have less saliva than normal, but it is enough. | (70) |
| I have too little saliva. | (30) |
| I have no saliva. | (0) |

11. **Mood**. (Tick one box: ☑ )

| | |
|---|---|
| My mood is excellent and unaffected by my cancer. | (100) |
| My mood is generally good and only occasionally affected by my cancer. | (75) |
| I am neither in a good mood nor depressed about my cancer. | (50) |
| I am somewhat depressed about my cancer. | (25) |
| I am extremely depressed about my cancer. | (0) |

12. **Anxiety**. (Tick one box: ☑ )

| | |
|---|---|
| I am not anxious about my cancer. | (100) |
| I am a little anxious about my cancer. | (70) |
| I am anxious about my cancer. | (30) |
| I am very anxious about my cancer. | (0) |

---

Which issues have been the most important to you during the past 7 days?
Tick ☑ **up to 3 boxes.**

| | | |
|---|---|---|
| Pain | Swallowing | Taste |
| Appearance | Chewing | Saliva |
| Activity | Speech | Mood |
| Recreation | Shoulder | Anxiety |

**GENERAL QUESTIONS**

**Compared to the month before you developed cancer**, how would you rate your health-related quality of life? (Tick one box: ☑ )

| | |
|---|---|
| Much better | (100) |
| Somewhat better | (75) |
| About the same | (50) |
| Somewhat worse | (25) |
| Much worse | (0) |

In general, would you say your **health-related quality of life** during the past 7 days has been: (Tick one box: ☑ )

| | |
|---|---|
| Outstanding | (100) |
| Very good | (80) |
| Good | (60) |
| Fair | (40) |
| Poor | (20) |
| Very poor | (0) |

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (Tick one box: ☑ )

| | |
|---|---|
| Outstanding | (100) |
| Very good | (80) |
| Good | (60) |
| Fair | (40) |
| Poor | (20) |
| Very poor | (0) |

---

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

## Appendix B

Liverpool Oral Rehabilitation Questionnaire v3

NAME:…… DATE:……

Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| 1. Did you experience difficulty with chewing? | 1 | 2 | 3 | 4 |
| 2. Did you have pain when you chew? | 1 | 2 | 3 | 4 |
| 3. Did you experience difficulty with swallowing solids? | 1 | 2 | 3 | 4 |
| 4. Did you experience difficulty with swallowing liquids? | 1 | 2 | 3 | 4 |
| 5. Did food particles collect under your tongue? | 1 | 2 | 3 | 4 |
| 6. Did food particles stick to your palate? | 1 | 2 | 3 | 4 |
| 7. Did food particles stick inside your cheeks? | 1 | 2 | 3 | 4 |
| 8. Did you have mouth dryness? | 1 | 2 | 3 | 4 |
| 9. Did you have problems with drooling? | 1 | 2 | 3 | 4 |
| 10. Did you experience problems with speech? | 1 | 2 | 3 | 4 |
| 11. Were you upset by your facial appearance? | 1 | 2 | 3 | 4 |
| 12. Were you upset by the appearance of your mouth? | 1 | 2 | 3 | 4 |
| 13. Were you upset by the appearance of your lips? | 1 | 2 | 3 | 4 |
| 14. Were you upset by the appearance of your teeth? | 1 | 2 | 3 | 4 |
| 15. Did your chewing ability affect your social life? | 1 | 2 | 3 | 4 |
| 16. Did your chewing ability influence your choice of foods? | 1 | 2 | 3 | 4 |
| 17. Did you experience difficulty with opening your mouth? | 1 | 2 | 3 | 4 |

1

18. Do you have any natural teeth in the jaw?

19. Do you have any natural teeth in the jaw?

| | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| 20. Were you embarrassed about conversing because of your dentures/implant retained teeth? | 1 | 2 | 3 | 4 |
| 21. Did you refuse dinner invitations because of embarrassment about your dentures/implant retained teeth? | 1 | 2 | 3 | 4 |
| 22. Did you feel loss of self-confidence because of embarrassment about your dentures/implant retained teeth? | 1 | 2 | 3 | 4 |
| 23. Did you find it difficult to open your mouth because of your dentures/implant retained teeth? | 1 | 2 | 3 | 4 |

24. Do you have an denture?

25. Do you have implant retained teeth?

If 'yes' to either of these questions then please answer Questions 26 to 31.
If both answers were 'no' then please go to question 32, in the next section.

| | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| 26. Were you dissatisfied with your upper denture/implant retained teeth? | 1 | 2 | 3 | 4 |
| 27. Did your upper denture/implant retained teeth cause soreness or ulceration of the gum? | 1 | 2 | 3 | 4 |
| 28. Did you find food particles collecting under your upper denture/implant retained teeth? | 1 | 2 | 3 | 4 |
| 29. Did you take out your upper denture/ implant retained teeth for eating? | 1 | 2 | 3 | 4 |

| | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| 30. Did you feel insecure with your upper denture/implant retained teeth? | 1 | 2 | 3 | 4 |
| 31. Were you worried that your upper denture/implant retained teeth might fall out? | 1 | 2 | 3 | 4 |

32. Do you have a denture?

33. Do you have implant retained teeth?

If 'yes' to either of these questions then please answer Questions 34 to 39.
If both answers were 'no' then please ignore these questions.

| During the past week: | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| 34. Were you dissatisfied with your lower denture/implant retained teeth? | 1 | 2 | 3 | 4 |
| 35. Did your lower denture/implant retained teeth cause soreness or ulceration of the gum? | 1 | 2 | 3 | 4 |
| 36. Did you find food particles collecting under your lower denture/implant retained teeth? | 1 | 2 | 3 | 4 |
| 37. Did you take out your lower denture/ implant retained teeth for eating? | 1 | 2 | 3 | 4 |
| 38. Did you feel insecure with your lower denture/implant retained teeth? | 1 | 2 | 3 | 4 |
| 39. Were you worried that your lower denture/implant retained teeth might fall out? | 1 | 2 | 3 | 4 |

40. Please describe any other issues that are important to your oral rehabilitation and have not been adequately addressed by our questions.