A preliminary study, evaluating and optimizing the clinical workflows to enable a pilot RCT of 3-D printed dentures.

Sponsored by
The University of Leeds

REC Number: 18/YH/0288
IRAS Project ID: 246234
ISRCTN0: TBC

Version 0.7
4th April 2019

Chief Investigator:

Dr Andrew Keeling BSc, BDS, PhD,
MFGDP RCS (Eng), FHEA
Clinical Associate Professor
University of Leeds
School of Dentistry
Clarendon Way
University of Leeds
LS2 9LU
E-mail: a.j.keeling@leeds.ac.uk
Telephone: 01133431762

Principal Investigator (Leeds site):

Dr Paul Hyde BChD, PhD, DGDP RCS (Eng)
MGDS RCS (Eng) FHEA
Clinical Associate Professor
University of Leeds
School of Dentistry
Clarendon Way
University of Leeds
LS2 9LU
E-mail: t.p.hyde@leeds.ac.uk
Telephone: 0113 343 8515

1. KEY CONTACTS

Chief Investigator

Dr Andrew Keeling. Clinical Associate Professor, University of Leeds, School of Dentistry, Clarendon Way, University of Leeds, LS2 9LU. E-mail: a.j.keeling@leeds.ac.uk. Telephone: +44 (0)1133431762

Principal Investigators

Dr T Paul Hyde, Principal Investigator Leeds site, Associate Professor in Restorative Dentistry. Leeds School of Dentistry, Worsley Building, Clarendon Road, University of Leeds, LEEDS, LS2 9LU. Email: t.p.hyde@leeds.ac.uk.Telephone: +44 (0)113 343 8515.

Prof Damien Walmsley, Principal Investigator Birmingham site, Professor, University of Birmingham, School of Dentistry, 5 Mill Pool Way, Edgbaston, Birmingham, B3 7EG. E-mail: a.d.walmsley@bham.ac.uk. Telephone +44 (0)1214665493

Prof Hugh Devlin, Principal Investigator Manchester site, Professor of Restorative Dentistry, University of Manchester, University Dental Hospital of Manchester, Higher Cambridge Street, Manchester, M15 6FH. E-mail Hugh.Devlin@Manchetser.ac.uk Telephone +44 (0)1612756849

Co-investigators

Prof David Wood, Professor of Biomaterials, School of Dentistry, University of Leeds, Clarendon Way, LS2 9LU. E-mail d.j.wood@leeds.ac.uk Telephone +44 (0)113 343 6192.

Dr Jianhua Wu, Lecturer in Medical Statistics/Biostatistics, School of Dentistry, Clarendon Way, Leeds, LS2 9LU. Email j.h.wu@leeds.ac.uk Telephone +44 (0)113 3433431.

Prosthodontic Research Laboratory

Mr Sean Dillon. Head of the Prosthodontic Research Laboratory, Leeds School of Dentistry, Worsley Building, Clarendon Road, University of Leeds, LEEDS, LS2 9LU Telephone: 011334 36236. Email: s.dillon@leeds.ac.uk

Digital Dentistry Research Laboratory

Ms Cecilie Osnes. Head of Digital Dentistry Research laboratory, Leeds School of Dentistry, Worsley Building, Clarendon Road, University of Leeds, LEEDS, LS2 9LU. E-mail: C.A.Osnes@leeds.ac.uk

Dental Translational Clinical Research Unit (DenTCRU)

Senior Trial Manager: TBC

Principal Statistician. Dr Jianhua Wu, Lecturer in Medical Statistics/Biostatistics, School of Dentistry, Clarendon Way, Leeds, LS2 9LU. Email j.h.wu@leeds.ac.uk Telephone +44 (0)113 3433431.

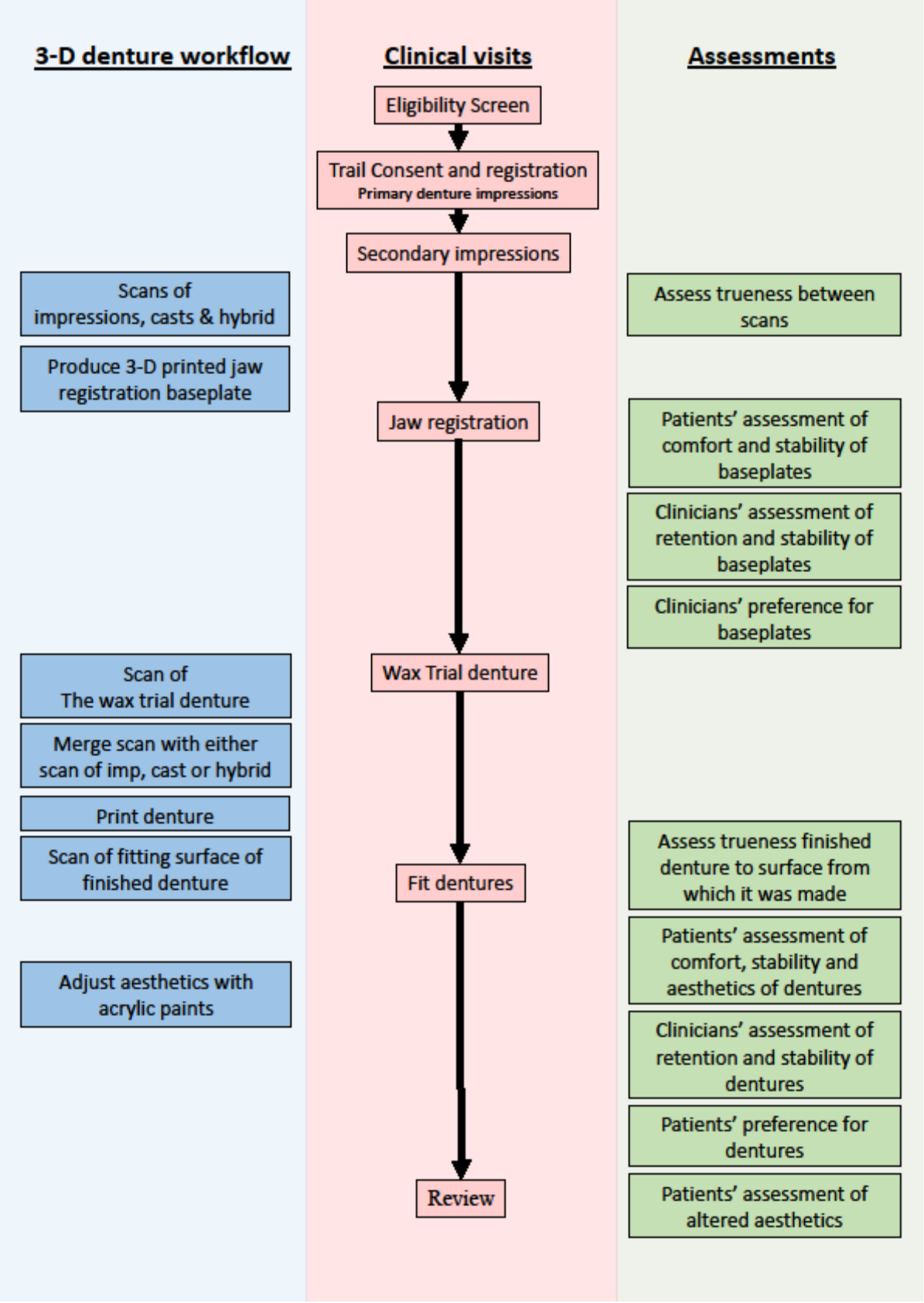
Head of Trial Management (Dentistry). TBC

2. TABLE OF CONTENTS

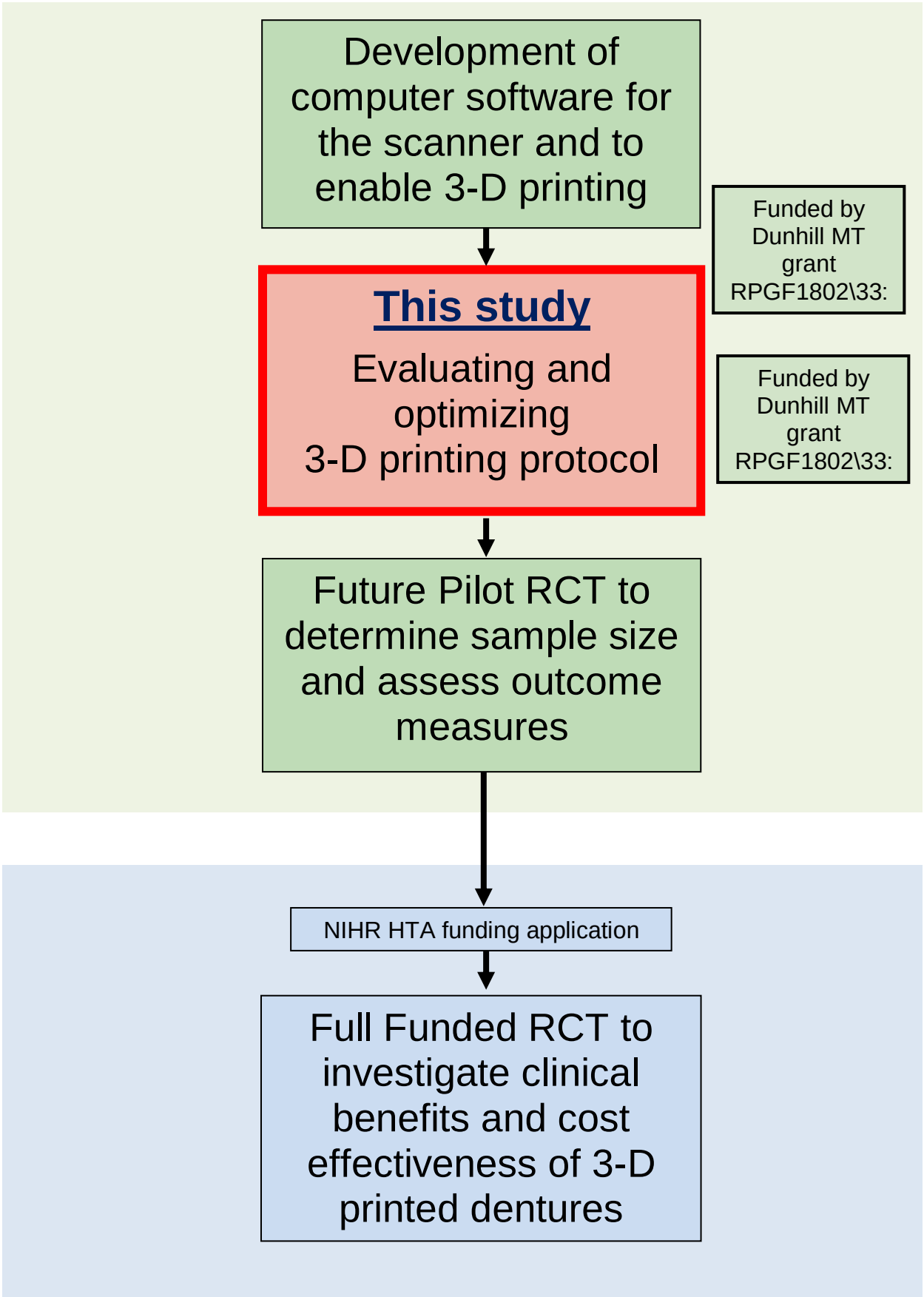
1. KEY CONTACTS 2
2. TABLE OF CONTENTS 3
3. STUDY FLOW DIAGRAM 5
4. LIST OF ABREVIATIONS 7
5. BACKGROUND AND INTRODUCTION 8
6. AIMS AND OBJECTIVES 9
   6.1 Primary Objectives 9
   6.2 Secondary Objectives 9
7. STUDY DESIGN 10
8. ELIGIBILITY 11
   8.1 INCLUSION CRITERIA 11
   8.2 EXCLUSION CRITERIA 11
9 RECRUITMENT 11
   9.1 RECRUITMENT TARGET 11
   9.2 INFORMED CONSENT AND ELIGIBILITY 11
   9.3 REGISTRATION 12
      9.3.1 NON-REGISTRATION 12
10. INTERVENTION DETAILS 13
   10.1 DENTURE CONSTRUCTION 13
   10.2 OVERVIEW OF CLINICAL RESEARCH 13
   10.3 WITHDRAWAL 14
11. ASSESSMENT AND DATA COLLECTION 15
   11.1 EXPECTED SCHEDULE OF EVENTS 15
   11.2 ASSESSMENTS 16
      11.2.1 Assessment of scans taken to manufacture fitting surface of denture 16
      11.2.2 Patient's assessment of comfort and stability of occlusal registration baseplates 16
      11.2.3 Clinician's assessment of the retention and stability of the baseplates 16
      11.2.4 Clinician's preference for the baseplates 16
      11.2.5 Assessment of the final fitting surface of the 3-D printed dentures 16
      11.2.6 Assessment of the final fitting surface of the conventional dentures 16
      11.2.7 Patient's assessment of the comfort, stability and aesthetics of dentures 16
      11.2.8 Clinician's assessment of the retention and stability of dentures 16
      11.2.9 Patient's preference for the dentures 16
      11.2.10 Patient's assessment of the altered aesthetics 16
   11.3 DEFINITION OF END OF STUDY 17
12. SERIOUS ADVERSE EVENTS PROCEDURES 18
   12.1 GENERAL DEFINITIONS 18
   12.2 OPERATIONAL DEFINITION AND PROCEDURES 19
      12.2.1 Expected AEs / SAEs – Not Reportable 19
      12.2.3 Related and Unexpected SAEs (RU SAEs) 19
      12.2.2 Deaths 20
   12.3 REPORTING 20
   12.4 RESPONSIBILITIES 20
      12.4.1 Clinical Co-Investigators / Authorised Personnel 20
      12.4.2 Chief Investigator (or nominated individual in CI's absence) 20
      12.4.3 DenTCRU 20

13. ENDPOINTS 21
13.1 PRIMARY ENDPOINTS 21
13.2 SECONDARY ENDPOINTS 21
14. STATISTICAL CONSIDERATIONS 21
14.1 SAMPLE SIZE 21
14.2 PLANNED RECRUITMENT RATE 21
15. STATISTICAL ANALYSIS 22
15.1 GENERAL CONSIDERATIONS 22
15.2 PRIMARY ENDPOINT ANALYSIS 22
15.3 SECONDARY ENDPOINT ANALYSIS 22
16. DATA MONITORING 22
16.1 CLINICAL GOVERNANCE ISSUES 22
17. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS 23
17.1 QUALITY ASSURANCE 23
17.2 ETHICAL CONSIDERATIONS 23
18. CONFIDENTIALITY 23
18.1 ARCHIVING 24
19. STATEMENT OF INDEMNITY 24
20. STUDY ORGANISATIONAL STRUCTURE 24
20.1 RESPONSIBILITIES 24
20.2 OPERATIONAL STRUCTURE 24
20.3 FUNDING 25
21. PUBLICATION POLICY 25
21.1 AUTHORSHIP AND ACKNOWLEDGEMENT 25
21.2 DATA RELEASE 25
21.3 PROCESSES FOR THE DRAFTING, REVIEW AND SUBMISSION OF ABSTRACTS AND MANUSCRIPTS 25
21.4 DUNHILL REQUIREMENTS 26

3. STUDY FLOW DIAGRAM



3a. Where this Preliminary Study fits within the overall programme to develop 3-D printed dentures



4. LIST OF ABREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DenTCRU	Dental Translational Clinical Research Unit
GCP	Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
ITT	Intention To Treat
NHS	National Health Service
OHIP	Oral Health Impact Profile (Questionnaire)
OHIP-EDENT	Specialised OHIP for Edentulous people (people with no natural teeth)
OHRQoL	Oral Health Related Quality of Life
PI	Principal Investigator
PIS/ICD	Patient Information Sheet/Informed Consent Document
QOL	Quality of Life
RCT	Randomised Clinical Trial and/or Randomised Controlled Trial
REC	Research Ethics Committee
RU SAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group

5. BACKGROUND AND INTRODUCTION

The Adult Dental Health Survey gives details of the numbers of edentulous patients in the UK. The epidemiology demonstrates an uneven distribution of edentulous patients when they are defined by age, sex, socio-economic class, and geographical area of residence. The older the patients in the sample are the higher the number of edentulous patients, the lower the socio-economic status the higher the edentulous rate, there are more women than men who are edentulous, and the further north the patients in the sample live the higher the edentulous rate. For many of these patients, we can expect them to rely on the NHS to provide dental treatment.

The dentures with which they are provided, impact on their quality of life and nutritional status. In an aging population the nutritional status and the quality of life of edentate individuals can be improved by the provision of better quality dentures.

Experts in prosthodontics concur that the accuracy of the fit of a denture is an important issue for improving comfort, stability and chewing efficiency of the denture. Traditionally dentures are formed by curing acrylic resins with heat, while under pressure and encased in a plaster mould. Despite the high pressure, the contraction which occurs on curing the resin produces a well-documented distortion of the dentures. This distortion has the capacity to impact on the comfort and stability of the finished dentures. It is not uncommon for dentures to require adjustment when they are fitted.

3-D printing offers the possibility of eliminating the distortion which occurs during the curing of acrylic resins. We'd like to run a patient centred Randomised Controlled Trial (RCT) to compare the fit of 3-D printed dentures with the current 'gold standard' of denture production. However before that RCT is possible 2 crucial steps are required:

1 the clinical workflow of 3-D printed dentures needs to be investigated and standardised to establish a new 'gold standard' for 3-D printed dentures.

2 a pilot RCT is required in order to test the protocol (in particular the new dependant outcome variables) and determine sample size for the established primary outcome.

This protocol outlines the investigation of the first of these issues and aims to optimize the clinical workflow for 3-D printed dentures.

6. AIMS AND OBJECTIVES

The overarching aim of this research program is to significantly impact on the quality of denture production within NHS dentistry. To achieve this objective, we aim to provide evidence of effectiveness and cost effectiveness of 3-D printing dentures. This current study sits within the preliminary stages of this extensive research program.
The specific aim of this preliminary study is to determine which clinical workflow is the optimum one to use for a pilot RCT of 3-D printed dentures.

6.1 Primary Objective

- To establish which clinical workflow is the optimum one to use for a pilot RCT of 3-D printed dentures.

6.2 Secondary Objectives

- To establish the patient participants' assessment of comfort, stability and aesthetics for the finished dentures.
- To establish the patient participants' assessment of the comfort and stability of the 3-D printed bases for occlusion registration.
- To establish the clinicians' assessment of the retention and stability of the 3-D printed bases for occlusal registration.
- To establish the clinicians preference for the different base plates of the 'occlusion registration' blocks.
- To establish the clinicians assessment of retention and stability the finished dentures
- To establish by an open ended question (to be analyzed qualitatively) the perceptions of the patient participants to post-production alteration of the appearance of their dentures.
- To establish the patient participants' preferences for the finished dentures
- To establish by an open ended question (to be analyzed qualitatively) the reason given by the patient participants for their preferences for dentures.

7. STUDY DESIGN

A prospective cohort study of 20 patient participants is proposed. For each patient, the aim is to produce 2 sets of dentures; both dentures will be constructed using the same impression and both dentures will use the same wax trial denture to produce the final the dentures. However one denture will be processed digitally (3-D printed) and the other denture will be processed by traditional analogue methods. The purpose of the traditional denture is to provide a reference denture against which the 3-D denture can be assessed. The clinical workflow of the 20 patients will vary to allow the patients and the clinicians to assess the benefits of the different workflows on the production of the 3-D printed dentures. Three aspects of the workflow are to be investigated in this preliminary study.

1. **The use of a 3-D printed baseplate for the 'occlusion registration'** stage of denture construction will be assessed. Each patient will have a traditional baseplate and a 3-D printed baseplate constructed. The clinician carrying out the research will assess the 2 baseplates for retention and for stability and then state their preferences. The patient will assess the two baseplates for comfort and for stability.
2. **The use of a scan of either: the impression, or the cast of the impression or a hybrid of the 2** for the construction of the 3-D printed dentures, will be assessed. The patients will assess each of the dentures for comfort, stability and appearance. The dentist carrying out the research will assess the dentures for retention and stability. The patients will use the traditionally produced dentures as a reference for their decisions.
3. **The use of the post production aesthetic improvements to 3-D printed dentures**. The patient will be asked if they would like to have the appearance of their 3-D printed dentures altered by post-production application of acrylic paints (CE marked denture finishing acrylics produced by GC). If they do, a dental technician will discuss the changes they wish to make. After the alterations the patient will be asked in open ended questions to assess the new appearance. Their replies will be recorded verbatim for qualitative analysis and later discussion.

In addition to the workflow analysis, the patients will be asked if they have a preference for either the conventional denture or the 3-D printed denture. This is assessed with a view to using patient preference as the primary outcome measure for the future pilot RCT. If they have a preference the participants will be asked in an open ended question to explain why they have a preference.

Alongside the clinical study, a laboratory study will investigate the trueness of fit of the new dentures. Digital scans of the 3 surfaces (mentioned in 2 above) will be overlaid to produce colour contoured maps highlighting differences between the scans. Similarly, after the dentures are constructed, scans of the fitting surface of the dentures will be compared with the scans from which they were printed to highlight differences between the scans.

The results from these investigations will be collated and analysed. With the results of all the investigations available and circulated the research team will gather for an open discussion of the results and the best way forward for a clinical workflow for a future pilot RCT of 3-D printed dentures.

8. ELIGIBILITY

Subjects ≥18 years of age will be screened for enrolment and must meet the eligibility criteria below.

8.1 INCLUSION CRITERIA

1. Patients who are edentulous.
2. Subject is available for follow up.
3. Subject requires replacement complete dentures.
4. Subject is able and willing to complete the informed consent process.
5. Age over 18 years at the time of signing the Informed Consent Form.

8.2 EXCLUSION CRITERIA

Patients who:
1. Have (or have had) an oral tumour,
2. have denture stomatitis
3. require an obturator,
4. have extreme xerostomia (e.g. Sjögren's syndrome),
5. have known hypersensitivity to dental materials used in the research.
6. Are incapable of written informed consent

9 RECRUITMENT

9.1 RECRUITMENT TARGET

The recruitment target requires that 20 patients are recruited over a 3 month period. At least eight patients will be recruited from the routine clinic at Leeds Dental Institute's (LDI) with the remainder split between University Dental Hospital of Manchester, and the University of Birmingham, School of Dentistry.

9.2 INFORMED CONSENT AND ELIGIBILITY

The assessment of eligibility and the informed consent process will be undertaken by authorised members of staff at the three research sites who are qualified by training and / or experience in taking informed consent to GCP standards. Informed, written consent for entry into the study must be obtained prior to registration.

Patients will be approached during standard clinic visits. If they express an interest in the study they will be provided with verbal and written details about the study (Patient Information Sheet and Informed Consent Document). This will include detailed information about the rationale, design and personal implications of the study.

Provision of information regarding the study is permitted by any member of the site research team approved to do so by the Principal Investigator as detailed on the sites Authorized Personnel Log.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The Principal Investigator or any other clinically qualified member of the study team who has received GCP training and has been approved by the Principal Investigator as detailed on the sites Authorized Personnel Log is permitted to take informed consent. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will be free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment/care.

A record of the consent process detailing the date of consent and all those present will be kept in the patient's notes. The original consent forms will be filed in the Investigator Site File, a copy of the consent forms will be given to the patient and a copy will be retained in the local research file.

If Participants lose capacity to consent during the study, the participant and all identifiable data collected would be withdrawn from the study. Data which is not identifiable to the research team may be retained.

9.3 REGISTRATION

Following confirmation of eligibility and written informed consent patients will be registered into the study by an authorised member of staff.

The following information will be recorded at registration:

- Name of person registering patient
- Patient's initials
- Patient's date of birth
- Patient's gender
- Confirmation of eligibility
- Date of written informed consent
- Individual patient study number

The Individual patient study number will be used on all study documentation.

9.3.1 NON-REGISTRATION

The site research will be required to complete a log of all patients screened for eligibility who are not registered either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- age
- gender
- ethnicity
- date screened
- the reason not eligible for participation in the study OR
- eligible but declined and reason for this OR
- other reason for non-registration

10. INTERVENTION DETAILS

10.1 DENTURE CONSTRUCTION

In outline, the routine stages of denture production are:

1. Clinical visit 1: primary impressions.
2. Dental Laboratory: construction of customised impression tray
3. Clinical visit 2: secondary impressions;
4. Dental Laboratory: casting of impressions and construction of occlusal registration blocks
5. Clinical visit 3: occlusal registration;
6. Dental Laboratory: articulation, production of wax trial dentures
7. Clinical visit 4: trial insertion;
8. Dental Laboratory: Processing of dentures into acrylic
9. Clinical visit 5: delivery of denture;
10. Clinical visit 6: review;

The additional laboratory and clinical interventions undertaken for this study are:

- The impression scan, and the model scan and the created hybrid scan; these are undertaken in the digital laboratory after stage 3 above.
- The printing of an additional occlusal registration base plate, undertaken during stage 4, in the digital laboratory.
- The 3-D printed occlusal registration baseplate is placed in the patient participant's mouth for assessment by both the patient and by the clinician; undertaken during clinical occlusal registration stage (5 above).
- The trial insertion is scanned and that scan merged with a scan of the fitting surface to produce a printable digital file; undertaken in the digital laboratory after the clinical trial insertion (stage 7 above).
- The 3-D printed dentures are printed and polished; undertaken in the digital laboratory during stage 8 above.
- The 3-D printed dentures are inserted for assessment by the patient and clinician; undertaken at the clinical delivery stage (stage 9 above).
- The appearance of the dentures is altered by the use of acrylic paints and then assessed by the patient; undertaken at the fit and review stages (stage 9 and 10 above).

See the Study Flow Diagram in section 3 above.

10.2 OVERVIEW OF CLINICAL RESEARCH

There are no extra clinical visits for the patients in this preliminary investigation; however on the occasions where assessments will take place the appointment will be lengthened by up to 30 minutes. In order to undertake the assessments the patients will have additional clinical procedures during clinical visits 3, 5 & 6 (stages 5, 9 and 10 above). These are: the insertion of an additional occlusal registration block during clinical visit 3 (stage 5 above). The insertion of the extra denture in clinical visits 5 & 6 (stages 9 & 10 above).

10.3 WITHDRAWAL

In line with usual dental care, cessation or alteration of protocol intervention at any time will be at the discretion of the research team, Chief Investigator or the patients themselves. Withdrawal from, or non-attendance for protocol intervention, will be documented in the corresponding study paperwork (CRF's). Where patients wish to withdraw from the study, they will be asked if they wish to clarify why and if they do, the reason for withdrawal will be recorded on the study paperwork (CRF's) for subsequent analysis.

11. ASSESSMENT AND DATA COLLECTION

Study data will be recorded by research staff on Case Report Forms (CRFs), stored locally in the site research files. Each research site will be expected to maintain a file of essential study documentation (Investigator Site File) and keep copies of all completed CRFs for the study at that site. At each research site the paper copies of the CRF's will be scanned and stored, with password protected access, on a password protected computer in the research office adjacent to the research site file.
Within the local research site file, the recruitment log will record the unique study number allocated to each participant against the participant's name, and personal details. Once allocated a study number, all subsequent CRF's will only identify the participant by reference to their unique study number and their initials. Apart from the consent form and the recruitment log stored at each local research site, no other CRF documentation will record the name or the full personal data of the participants.
Each week the data collected on the electronic scans of the CRF's will be sent by encrypted NHS e-mails of the local research nurse to the authorized NHS research nurse within the DenTCRU research unit at Leeds. These CRF files do not contain the name or directly identifiable personal data of the research participants. The paper consent forms will be securely stored in the local research site file (they are NOT sent to the Sponsors).

Any participant data/documentation sent electronically for analysis to Leeds DenTCRU will be anonymized, only identifying the participants by their unique study number, and initials.

Full training and guidance on the completion of CRFs together with details on the schedule of CRFs will be given to the site research staff when all local approvals to run this study are obtained.

11.1 EXPECTED SCHEDULE OF EVENTS

Phase B Clinical Assessment Study	Start	Finish
Trueness and precision of impression v model data	01/12/2018	27/06/2019
IRAS approval of phase B	12/04/2018	30/06/2018
Training of clinical and support staff phase B	01/09/2018	31/10/2018
Recruitment phase B	**14/11/2018**	02/02/2019
Denture construction phase B	**01/12/2018**	30/05/2019
Patient and expert assessment Phase B	06/03/2019	14/07/2019
Analysis phase B	01/08/2019	31/08/2019
Writing and publication of academic papers B	01/09/2019	16/10/2019

11.2 ASSESSMENTS

11.2.1 Assessment of scans taken to manufacture fitting surface of denture

- Overlaying digital colour contour mapping of each scan on the other scans.
- Assessment of trueness between scans.

11.2.2 Patients' assessment of comfort and stability of occlusal registration base plates

- 5 part Likert scale questionnaires.

11.2.3 Clinician's assessment of the retention and stability of the baseplates

- 5 part Likert scale questionnaire.

11.2.4 Clinician's preference for the baseplates

- Overall preference for either baseplate
- Options for 'no preference both satisfactory' and 'no preference both unsatisfactory'
- to be analysed by McNemar's test

11.2.5 Assessment of the final fitting surface of the 3-D printed dentures

- Digital scans of the finished denture fitting surface
- Overlaid digital colour contour mapping of each denture with the scan from which it was made.

11.2.6 Assessment of the final fitting surface of the conventional dentures

- Digital scans of the finished denture fitting surface
- Overlaid digital colour contour mapping of the denture with the scan of the dental model from which it was made.

11.2.7 Patients' assessment of the comfort, stability and aesthetics of dentures

- 5 part Likert scale questionnaires.

11.2.8 Clinician's assessment of the retention and stability of dentures

- 5 part Likert scale questionnaires.

11.2.9 Patient's preference for the dentures

- Overall preference for either denture
- Options for 'no preference both satisfactory' and 'no preference both unsatisfactory'
- to be analysed by McNemar's test

11.2.10 Patient's assessment of the altered aesthetics

- Open ended questions
- Responses recorded verbatim
- Analysed qualitatively

11.3 DEFINITION OF END OF STUDY

The end of the study is defined as the date of the last patient's final assessment visit.

12. SERIOUS ADVERSE EVENTS PROCEDURES

12.1 GENERAL DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial's subject which does not necessarily have a causal relationship with this device/procedure and can include:

- any unintentional, unfavorable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

A Serious Adverse Event (SAE) is defined in general as an untoward (unfavourable) event which is:

- fatal or life-threatening*
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- constitutes a congenital anomaly or a birth defect or
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

* The term life-threatening in the definition of a SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

A SAE occurring to a patient which, in the opinion of the Chief Investigator, is Related and Unexpected will be reported to the main Research Ethics Committee (main REC).

The National Research Ethics Service (NRES) defines related and unexpected SAEs as follows:

- 'related' – that is, it resulted from administration of any research procedures; and

- 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence.

12.2 OPERATIONAL DEFINITION AND PROCEDURES

12.2.1 Expected AEs / SAEs – Not Reportable

It is expected that there will be minimal risks associated with the procedures of this study. For the purposes of this study, adverse events related to the study intervention will be collected and recorded in the CRFs and followed as appropriate. These adverse events may include (but does not represent an exhaustive list):

- Trauma from the impression procedure, examples would include:
    - cuts from sharp impression trays,
    - abrasions from impression trays
    - lips over stretched and cracked
- Vomiting from the impression procedure
- Allergic reaction from impression materials
- Allergic reaction to the acrylic impression tray

In recognition of this, only events fulfilling the definition of a related adverse event or serious adverse events will be reported in this study. All adverse event or serious adverse events **not** classified as 'related' will not be reported.

12.2.3 Related and Unexpected SAEs (RU SAEs)

All Related and Unexpected SAEs occurring from the date of consent up to the last follow up appointment must be recorded on the Related Unexpected Serious Adverse Event Form and faxed to both the sponsor and DenTCRU **within one working day** of the research staff becoming aware of the event. The original form should also be posted to the DenTCRU in real time and a copy retained at site.

For each Related and Unexpected SAE the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- date of SAE
- its duration (start and end dates; times, if applicable)
- action taken
- outcome

Any follow-up information should be faxed to DenTCRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

All Related / Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the main REC and Sponsor by the DenTCRU on behalf of the Chief Investigator within 15 days.

12.2.2 Deaths

Deaths in the study population are not expected during the course of the study. Additionally there may be deaths due to other causes within the study population.

All deaths occurring from the date of consent up to the last assessment visit at the end of the confirmation period must be recorded and faxed to the DenTCRU **within 7 days** of the research staff becoming aware of the event. The original form should also be posted to the DenTCRU in real time and a copy retained at site.

12.3 REPORTING

Safety issues will be reported to the Main REC in the annual progress report. An annual summary of all events will also be reported to the CI and Sponsor. Expedited reporting of events to the main REC and the Sponsor will be subject to current NRES guidance, DenTCRU SOPs and Sponsor requirements.

12.4 RESPONSIBILITIES

12.4.1 Clinical Co-Investigators / Authorised Personnel

1. Checking for SAEs when patients attend for study intervention.
2. Judgment in assessing:
   - Seriousness
   - Causality
   - Expectedness
3. To ensure all Related and Unexpected SAEs are recorded and reported to the DenTCRU within 24 hours of becoming aware and to provide further follow up information as soon as available.
4. To report Related and Unexpected SAEs to local committees in line with local arrangements.

12.4.2 Chief Investigator (or nominated individual in CI's absence)

1. Assign relatedness and expected nature of SAEs where it has not been possible to obtain assessment by authorised personnel.
2. Undertake SAE review.
3. Review all events assessed as Related & Unexpected in the opinion of authorised personnel. In the event of disagreement between authorised personnel's assessment and the Chief Investigator, authorised personnel's assessment may be upgraded or downgraded by the Chief Investigator prior to reporting to the Sponsor and through them to the main REC.

12.4.3 DenTCRU

1. Expedited reporting of RU SAEs to the main REC and Sponsor within required timelines.
2. Preparing annual safety reports at least annually to the main REC and Sponsor. Safety may be reported more frequently if appropriate.
3. Expedited reporting of other safety issues, including an increase in the rate of occurrence in severity of RU SAEs, to the main Sponsor and through them to the REC within required timelines.

13. ENDPOINTS

13.1 PRIMARY ENDPOINT

Patients' assessment of comfort, stability, and aesthetics of each form of the finished dentures.

13.2 SECONDARY ENDPOINTS

1. Digital colour contour mapping of fitting surface scans on the other scans.
2. Patient perception of comfort and stability of occlusal registration baseplates
3. Clinicians assessment of retention and stability of occlusal registration baseplates
4. Clinicians preference for occlusal registration baseplate
5. Digital colour contour mapping of denture fitting surface scans with the surfaces from which they were constructed.
6. Clinicians assessment of retention and stability of the finished dentures
7. Patient preference for finished dentures.
8. Patients assessment of the altered aesthetics

14. STATISTICAL CONSIDERATIONS

14.1 SAMPLE SIZE

This is a preliminary study. It is designed to eliminate confounding variables for a pilot RCT which, in turn, will enable a definitive RCT of 3-D printed dentures. Specifically the pilot RCT will enable an accurate sample size calculation for the definitive RCT.

This is the first project to investigate the clinical workflow for 3-D printed dentures. The proposed outcome measures have not been used in this form before. This causes a significant issue for calculating the sample size for this study. The overall sample size is 20 participants. Please note: although calculated using the best evidence, this is essentially an empirical estimate. Therefore, it is not certain the sample size will be sufficient for significant statistical findings. The primary outcome measure has therefore been supplemented in two ways. Firstly we will be conducting laboratory investigations into the trueness of the 'fit' of the dentures produced by each of the clinical workflows. Secondly we will use expert clinical assessment of the dentures (via Likert scales assessing specific criteria), to enhance the patient centred primary assessments. By supplementing the patient centred primary outcome in this way we can be confident the sample size will be sufficient to select a clinical workflow which can eliminate significant confounding variables from the future pilot RCT.

14.2 PLANNED RECRUITMENT RATE

The planned rate of recruitment is up to two patients per fortnight in each of the 3 research centres for the 8 week recruitment period of the study.

15. STATISTICAL ANALYSIS

15.1 GENERAL CONSIDERATIONS

Statistical analysis is the responsibility of the DenTCRU Statistician. A full statistical analysis plan will be written before any analyses are undertaken.

15.2 PRIMARY ENDPOINT ANALYSIS

Patients' assessment of comfort, stability, and aesthetics on 5 point Likert scales for each of the finished dentures will be assessed by Wilcoxon test.

15.3 SECONDARY ENDPOINT ANALYSIS

a) Likert Scores

There are 4 assessments within the study which use 5 point Likert scales (measuring comfort, stability, aesthetics, retention). Differences between Likert scores throughout the study will be calculated and compared using the Wilcoxon test.

b) Patient preferences for the finished dentures:

Preference results will be presented as a 2×2 table for paired data and analysed using McNemar's test for paired data to estimate the difference in proportions of patients preferring dentures 3-D printed to those made conventionally. The difference in proportions will be presented with a 95% confidence interval.

c) Clinicians' Preference for occlusal registration baseplates

Preference results expressed at the end of the occlusal registration appointment will be presented as a 2×2 table for paired data and analysed using McNemar's test for paired data to estimate the difference in proportions of clinicians preferring 3-D printed baseplates to those preferring conventional baseplates. The difference in proportions will be presented with a 95% confidence interval.

d) Colour contour maps of the separation in digital scans superimposed on other scans

Visual assessment by the expert clinical team. It is not planned to quantify the differences for this preliminary study.

16. DATA MONITORING

Data will be monitored for quality and completeness by the DenTCRU trial manager (University of Leeds). Missing data will be chased until it is received, confirmed as not available or the study is at analysis. The DenTCRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the DenTCRU/Sponsor.

16.1 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TMG and, where applicable, to the participating NHS Trust.

17. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

17.1 QUALITY ASSURANCE

The study will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research and through adherence to DenTCRU (University of Leeds) Standard Operating Procedures (SOPs).

17.2 ETHICAL CONSIDERATIONS

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996. Informed written consent will be obtained from the patients prior to registration into the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main Research Ethics Committee (Main REC) prior to entering patients into the study. The DenTCRU (University of Leeds) will provide the Main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

18. CONFIDENTIALITY

All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper, electronically and digitally research sites. The research sites will comply with all aspects of the Data Protection Act as modified in 2018 and operationally this will include:

- Consent from patients to record personal details including full name.
- Appropriate storage, restricted access and disposal arrangements for patient personal and clinical details.
- Consent from patients for access to their healthcare records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation.
- Consent from patients for the data collected for the study to be used to evaluate safety and develop new research.
- Patient name will be collected when a patient is registered into the study but all other data collection forms that are transferred to or from the DenTCRU (university of Leeds) will be coded with a study number and will include the patient's initials.
- Where central monitoring of source documents by DenTCRU (or copies of source documents) is required (such as denture scans), the patient's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to DenTCRU.

If a patient withdraws consent from further intervention and / or further collection of data, the Sponsor will be informed and all identifiable data will be destroyed.

18.1 ARCHIVING

At the end of the study, data will be securely archived in line with the Sponsor's procedures for a minimum of 5 years. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

19. STATEMENT OF INDEMNITY

This study is sponsored by The University of Leeds and The University of Leeds will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

As this is a clinician-led study there are no arrangements for no-fault compensation.

20. STUDY ORGANISATIONAL STRUCTURE

20.1 RESPONSIBILITIES

Chief Investigator - The Chief Investigator, as defined by the UK Policy Framework for Health and Social Care Research, is responsible for the design, management and reporting of the study.

Dental Translational Clinical Research Unit (University of Leeds) The DenTCRU will be delegated responsibility for the conduct of the study in accordance with the UK Policy Framework for Health and Social Care Research.

20.2 OPERATIONAL STRUCTURE

Chief Investigator – The Chief Investigator is involved in the design, conduct, co-ordination and management of the study.

Trial Management Group (TMG) - The TMG, comprising the Chief Investigator, Principal Investigators, and Co-investigators will be assigned responsibility for the clinical set-up, on-going management, promotion of the study, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC (iv) completing cost estimates and project initiation, (v) reporting of related unexpected serious adverse events, (vi) monitoring of screening, recruitment, treatment and follow-up procedures, (vii) auditing consent procedures, data collection, and database development.

Dental Translational Clinical Research Unit (DenTCRU) - The trial manager at DenTCRU will be responsible for the day-to-day running of the study including study administration, data management, safety reporting and all statistical analyses.

20.3 FUNDING

This study is funded by the Dunhill Medical Trust grant.

21. PUBLICATION POLICY

21.1 AUTHORSHIP AND ACKNOWLEDGEMENT

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and by contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, Co-Applicants and senior DenTCRU staff may be named as authors in any publication, and an appropriate first author agreed through discussion amongst the Trial Management Group (TMG) members. In addition, all collaborators will be listed as contributors for the main study publication, giving details of their roles in planning, conducting and reporting the study. The research team and Dunhill Medical Trust should be acknowledged in all publications, (as detailed below). Other key individuals will be included as authors or contributors as appropriate and at the discretion of the TMG.

21.2 DATA RELEASE

To maintain the scientific integrity of the study, data will not be released prior to the first publication of the results of the primary endpoint analysis, either for study publication or oral presentation purposes, without the permission of the TMG.

Individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the study until the main results of the study have been published, without the permission of the TMG.

21.3 PROCESSES FOR THE DRAFTING, REVIEW AND SUBMISSION OF ABSTRACTS AND MANUSCRIPTS

The agreed first author of abstracts is responsible for circulating these to the other members of the Trial Management Group (TMG) for review at least 15 days prior to the deadline for submission.

The agreed first author of manuscripts is responsible for ensuring:

- timely circulation of all drafts to all co-authors during manuscript development and prior to submission

- timely (and appropriate) circulation of reviewers' comments to all co-authors
- incorporation of comments into subsequent drafts
- communication with the TMG

The first author is responsible for submission of the publication and must keep the TMG and all authors informed of the abstract's or manuscript's status. On publication, the first author should send copies of the abstract or manuscript to the TMG, the Sponsor and to all co-authors, and ensure communication with the Dunhill Medical Trust.

21.4 DUNHILL REQUIREMENTS

All publications must acknowledge Dunhill Medical Trust as the study's funding source and include an appropriate disclaimer regarding expressed views and opinions.