A Pilot Randomised Controlled Trial of 3-D Printed Dentures

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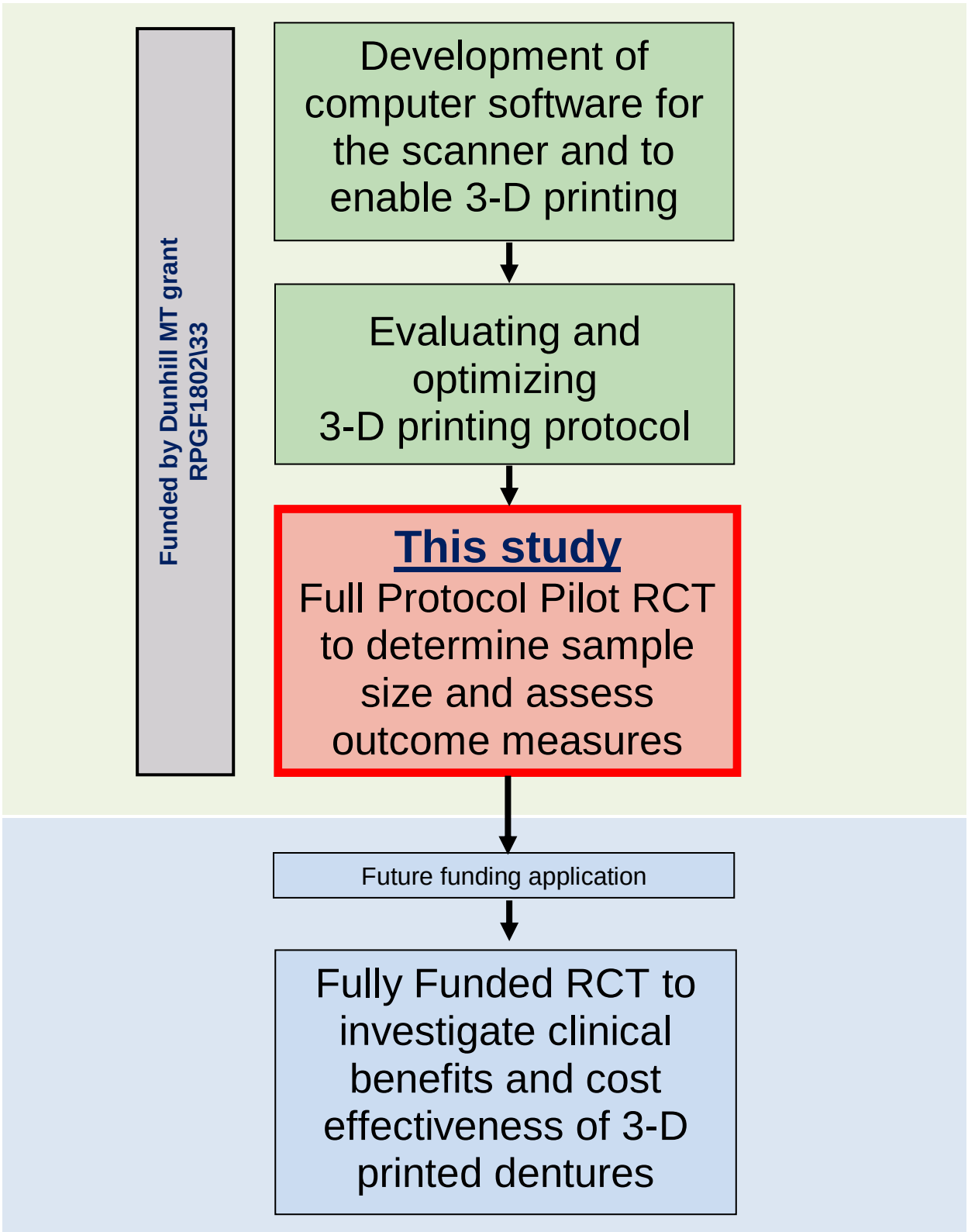

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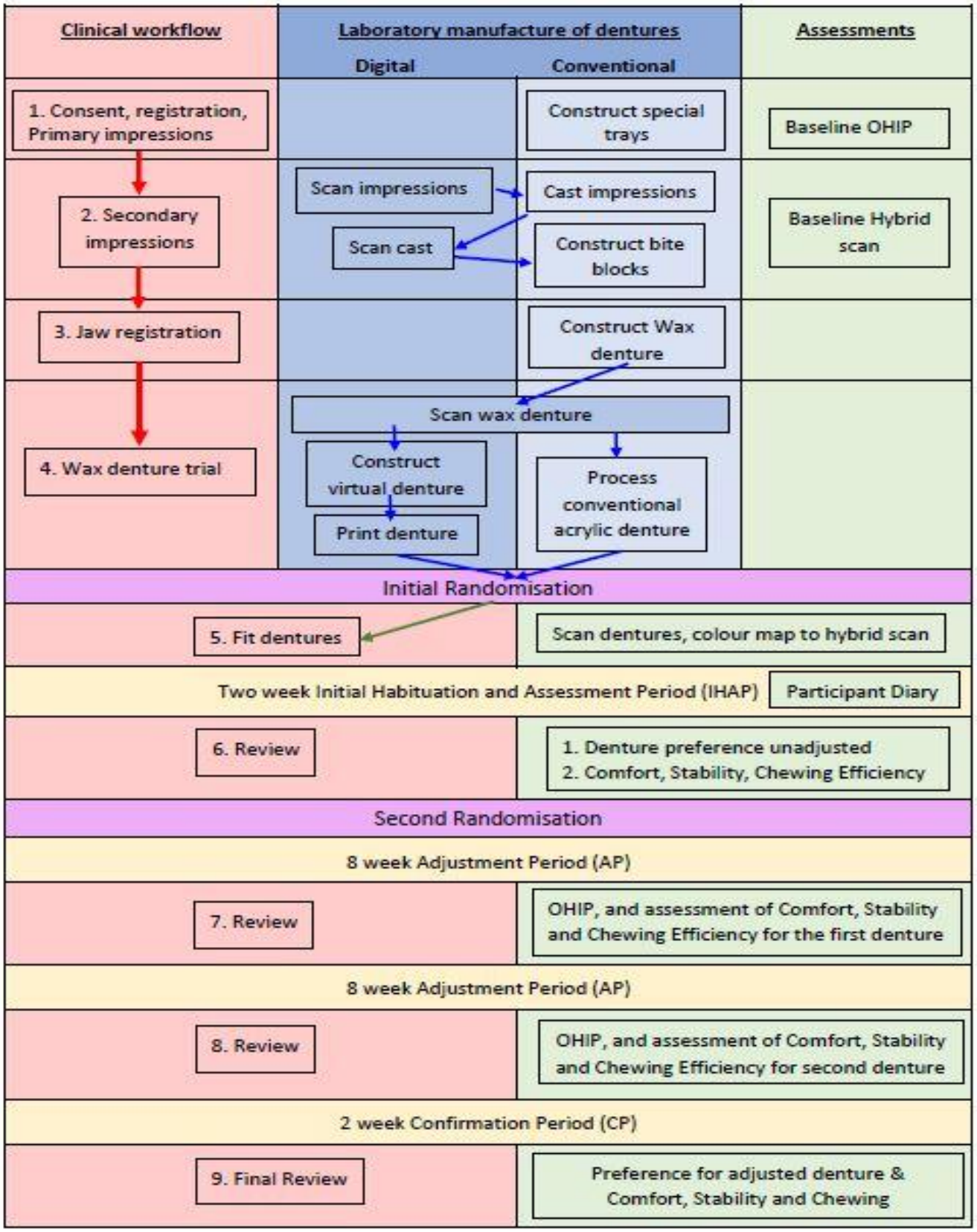

4. LIST OF ABBREVIATIONS

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
NHS	National Health Service
OHIP	Oral Health Impact Profile (Questionnaire)
OHIP-EDENT	Specialised OHIP for Edentulous people (people with no natural teeth)
PI	Principal Investigator
PIS/ICD	Participant Information Sheet/Informed Consent Document
QOL	Quality of Life
RCT	Randomised Clinical Trial and/or Randomised Controlled Trial
REC	Research Ethics Committee
RES	Research Ethics Service
RU SAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group

5. STUDY ORGANISATIONAL STRUCTURE

5.1 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 (DenTCRU) - The DenTCRU at the University of Leeds will be delegated responsibility for the conduct of the study in accordance with the UK Policy Framework for Health and Social Care Research.

5.2 OPERATIONAL STRUCTURE

Chief Investigator – The Chief Investigator leads on the design, conduct, co-ordination and management of the study.

Trial Management Group (TMG) - The TMG, comprising the Chief Investigator, Principal Investigators (PI), 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 and regulatory authorities (iv) 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 Research Programme Manager at DenTCRU will be responsible for the day-to-day running of the study including study administration, data management and safety reporting. The DenTCRU Lead Statistician will be responsible for all statistical analyses.

6. 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 ageing 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. Our aim is to run a participant centred Randomised Controlled Trial (RCT) to compare the fit of 3-D printed dentures with the current 'gold standard' of denture production. Before conducting this RCT, two crucial stages are required:

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

Then, using the newly determined clinical workflow:

2. A pilot RCT is required, in order to test the protocol and determine sample size for the established primary outcome.

The first of these stages has now been completed (IRAS application 18/YH/0288). The data we obtained from this stage has allowed us to develop the workflow in this protocol. This new workflow has set a new standard for the production of 3-D printed dentures.

This protocol outlines the work of the second stage, namely the pilot RCT, to test the full RCT protocol and determine the sample size required for a future grant-funded RCT.

7. AIMS AND OBJECTIVES

The overarching aim of this research programme 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 this extensive research programme (outlined in Section 3a.).

The specific aim of this pilot RCT is to determine the sample size to be used in the definitive future RCT study.

7.1 PRIMARY OBJECTIVE

The primary objective for this pilot RCT is to compare 3-D printed and traditional dentures in order to enable a sample size calculation for a future RCT.

7.2 SECONDARY OBJECTIVES

To assess the:

- Trueness and precision of the conventional and the 3-D printed dentures produced.
- Participant preference for the finished dentures before adjustment.
- Participant preference for the finished dentures after adjustment.
- Impact of the dentures, after an eight-week period, on participants' perceived oral health quality.
- Participant assessment of comfort, mobility and chewing efficiency for dentures produced by traditional methods and by 3-D printing, before adjustment.
- Participant assessment of comfort, mobility and chewing efficiency for dentures produced by traditional methods and by 3-D printing, after adjustment.

7.3 PRIMARY RESEARCH QUESTION

What would be the required sample size for a full protocol RCT which investigated the participants' preference for 3-D printed dentures or conventional dentures?

8. STUDY DESIGN

This is a pilot, patient-centred, multi-centre, cross-over, double-blind, randomised, controlled clinical trial, which will provide data for future research. The specific design for this pilot RCT is based on a published protocol, which has been successful in robustly differentiating participant preferences for different types of dentures.

For each participant the aim is to produce two sets of dentures which are similar but produced by either the traditional processing or by 3-D printing. After fitting the dentures the participants will be asked to state which is their preferred set of dentures; Participants will assess the comfort, mobility and chewing efficiency of each set of dentures. The participants will complete the OHIP-EDENT (Oral Health Impact Profile for Edentulous people) questionnaire which enquires about their quality of life while wearing each of the dentures over an eight-week period. Within the constraints of the study timelines and the participating research sites' appointment system there will be no limits on the number of return visits the participant may

request. There are nine scheduled visits for this study; when necessary, there may be capacity to have additional unscheduled visits (see Section 12.1 for more details).

A period of two weeks (referred to in this protocol as the “Initial Habituation and Assessment Period”) has been included prior to the single denture assessment periods (referred to in this protocol as the “Adjustment periods”). In this Initial Habituation and Assessment Period, participants are given both sets of dentures. The purpose of this period is twofold; firstly to establish whether either set of unadjusted dentures is preferred and secondly, to allow the participant to habituate to the feel of the new dentures before individually assessing them.

Following the two Adjustment Periods, the two-week Confirmation Period will allow the participant to take away both sets of dentures and identify which denture they prefer. The participant will return for a final visit to complete their formal assessment of the dentures.

9. ELIGIBILITY

9.1 INCLUSION CRITERIA

Patients who:

1. Are edentulous.
2. Are available for follow up.
3. Require replacement complete dentures.
4. Are able and willing to complete the informed consent process.
5. Are aged over 60 years at the time of signing the Informed Consent Form.

9.2 EXCLUSION CRITERIA

Patients who:

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

10. RECRUITMENT AND REGISTRATION

10.1 RECRUITMENT

The recruitment target requires that 18 participants are recruited over a period of six months. Participants will be recruited from the routine clinics and/or waiting lists for replacement of complete dentures at Leeds Dental Institute (LDI), the University Dental Hospital of Manchester, and Birmingham Dental Hospital.

The proposed outcome measures (see Section 7.2) have not been used to investigate 3-D printing of dentures before. This causes a significant issue for calculating the sample size for the future grant funded RCT.

In estimating the number of cases we will need, we have looked at previous use of cross over RCTs in denture studies. The estimated number of cases needed is 18. **Please note:** although calculated using the best evidence, this is essentially an empirical estimate.

10.2 INFORMED CONSENT AND ELIGIBILITY

This research is being carried out in the three NHS Teaching Hospitals attached to the university dental schools in Birmingham, Leeds and Manchester. 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 in taking informed consent to GCP standards. Informed written consent for entry into the study must be obtained prior to registration.

All the patients who have been accepted for treatment for the provision of complete dentures at the three sites will be identified as potential participants. This assessment of the need for complete dentures is carried out directly by members of their clinical care team during their routine consultation visit. Patients who are identified as potential participants may be approached directly at their consultation visit by a member of their clinical care team. Alternatively, if they have previously been identified as requiring dentures and they have been placed on a waiting list, they will be approached by members of the clinical care team by using the ethically approved standardised letter.

If they are approached directly at the consultation visit they will be asked if they are interested in taking part in the research. If they express an interest, the research project will be outlined to them and they will be given a Participant Information Sheet (PIS) to take away with them. They will also receive an appointment to return and discuss participation.

Those potential participants who are already on a waiting list for treatment, will be approached using the standard letter accompanied by the PIS. The standard letter invites potential participants who are interested in finding out more about the study to contact the research team by telephone. When they ring the team they will be asked to leave details and will subsequently be called back by an appropriately trained member of the research team. When they are contacted they will receive detailed information about the rationale, design and personal implications of the study. Following information provision, patients will have the opportunity to ask questions and if they wish to pursue participation they will be offered an appointment to further assess their eligibility.

When the potential participant attends the appointment to discuss the research they will be approached by a GCP-trained member of the research team and given an opportunity to ask further questions and discuss the research. If they wish to take part in the research, they will be asked to sign the written consent form.

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 site's Authorised Delegation Log, although the Principal Investigator should be informed of any patients approached to participate by any other member of the site research team.

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 site's Authorised Delegation Log is permitted to take informed consent. The right of the potential participant to refuse consent without giving reasons will be respected. Further, the participant 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 form and consent process detailing the date of consent and all those present will be kept in the patient's hospital notes. The original consent forms will be filed in the local Investigator Site File (ISF), a copy of the consent form will be given to the participant and a copy will be returned to the Dental Translational Clinical Research Unit (DenTCRU) at the University of Leeds.

If a participant withdraws consent from further study procedures or if, for any reason, they are no longer able to consent during the study, the data collected from the participant will be retained and analysed to inform the results of this study.

10.3 REGISTRATION

Following confirmation of eligibility and written informed consent patients will be registered into the study by an authorised member of staff at the research site, as detailed on the Authorised Delegation Log.

The member of staff registering the patient must complete the Recruitment Log to allocate an individual participant study ID number. They must then complete the Eligibility and Registration Case Report Form (CRF). A copy of the Eligibility and Registration CRF must be kept at the site and the original must be sent to DenTCRU by post.

After registration the research site will:

- Add the individual participant study ID number to all study documentation.
- Send a scanned copy of the completed consent form to DenTCRU via secure NHS email to leedsth-tr.3ddentures-dentcru@nhs.net
- Ensure the participants are notified of their appointment dates.

10.4 NON-REGISTRATION

The site research team 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
- date screened
- the reason not eligible for participation in the study OR
- eligible but declined and the reason for this OR
- other reason for non-registration

This information will be collected by the local research site study team. The original log will be retained by each research site until the end of the study recruitment period. A scanned copy of the log will be sent to DenTCRU on a monthly basis via NHS email to

leedsth-tr.3ddentures-dentcru@nhs.net

11. RANDOMISATIONS

Participants will undergo two randomisations:

1. Initial randomisation
2. Second randomisation

Both randomisations will be via sealed envelopes created by the DenTCRU lead statistician and the Research Programme Manager. Randomisation will be blocked using random block sizes to ensure balance between groups. The sealed envelopes will be stored in a secure locker within the School of Dentistry Prosthodontic Research Laboratory at the University of Leeds. Access will be restricted to the Head of the Prosthodontic Research Laboratory or any other member of the Prosthodontic/Digital Dentistry Research Laboratory team who has been approved by the Chief Investigator as detailed on the Authorised Delegation Log. Participant study ID numbers will be pre-allocated in advance of the trial starting to evenly distribute the randomisation allocations across the three participating research sites. The participants and the clinical members of the study team providing the intervention at each site will be blind to the allocations.

11.1 INITIAL RANDOMISATION

The purpose of the initial randomisation is to establish the order of testing during the Initial Habituation and Assessment Period. This initial randomisation will take place once the finished 3-D printed dentures have been delivered to a research site, to determine the colour marking (yellow/blue) of the dentures and the order in which they are tested during this Initial Habituation and Assessment Period (conventional yellow/3-D printed blue or 3-D printed yellow/conventional blue).

The participants are randomised so that half the participants wear the conventional dentures first and half wear the 3-D printed dentures first; half the 3-D printed dentures will be coded one colour (yellow), as will half the conventional dentures. Similarly, half the 3-D printed dentures will be coded the other colour (blue), as will half the conventional dentures. This is achieved by laboratory staff at each site placing coloured dots on the dentures and the dentist asking the participants to wear the yellow colour-coded dentures first.

Once the colour markings have been applied, the Initial Randomisation CRF must be completed, a copy must be retained by the laboratory staff at the sites and the original must be returned by post to DenTCRU.

11.2 SECOND RANDOMISATION

The aim of the second randomisation is to establish the order of testing during the two 8-week Adjustment Periods. This second randomisation will occur at the conclusion of the Initial

Habituation and Assessment Period to determine the colour re-marking (red or green) of the dentures; half the 3-D printed dentures will be coded one colour (green), as will half the conventional dentures. Similarly, half the 3-D printed dentures will be coded the other colour (red), as will half the conventional dentures. This colouring process will again be performed by laboratory staff at each participating site and the dentist asking the participants to wear the red colour-coded dentures first. This second randomisation will be balanced for order of testing in the Initial Habituation and Assessment Period.

The Second Randomisation CRF must be completed, a copy must be retained by the laboratory staff at the sites and the original must be returned by post to DenTCRU to provide evidence that randomisation has taken place.

Careful records are needed to keep track of the colour coding and randomisation allocation. In this way the participants and the clinical members of the study team at each research site are kept blind to the colour coding; they do not know which denture is being assessed. Unblinding will only be performed once all clinical assessments for all participants have been completed.

11.3 WITHDRAWAL

In line with usual dental care and in the best interest of the participant, cessation or alteration of protocol intervention at any time will be at the discretion of the clinical team. Withdrawal from, or non-attendance for protocol intervention, will be documented in the corresponding CRF. A participant may withdraw without giving a reason. However, where participants do 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 CRF for subsequent analysis.

12. INTERVENTIONS

Please refer to the Study Flow Diagram in Section 3b as you review this section.

12.1 DENTURE CONSTRUCTION

The 3-D printed dentures will be produced by the NHS Dental Laboratory (Leeds Dental Institute) in collaboration with the Prosthodontic Research Team at the University of Leeds. The conventional dentures will be produced at each NHS participating site as part of the participant's standard NHS treatment. In outline, the clinical visits and associated laboratory procedures for denture production are:

Study Stage	Study Activity
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 jaw registration blocks
5.	Clinical visit 3: jaw registration;
6.	Dental Laboratory: articulation, production of wax trial dentures
7.	Clinical visit 4: wax trial denture insertion;
8.	Dental Laboratory: Processing of dentures into acrylic
9.	Clinical visit 5: denture fit;
10	Two-week Initial Assessment/Habituation Period (IAHP)
11.	Clinical visit 6: review;
12.	First eight-week Adjustment Period
13.	Clinical visit 7: review;
14.	Second eight-week Adjustment Period
15.	Clinical visit 8: review;
16.	Two-week Confirmation Period
17.	Clinical visit 9: final review

The details of the additional procedures required for this pilot RCT are:

- Pre-treatment baseline assessment of denture related quality of life is undertaken using the Oral Health Impact Profile questionnaire (OHIP-EDENT).
- An impression scan, and a cast scan allow the creation of a hybrid scan. These baseline scans are undertaken in the digital laboratory after Stage 3. They do not involve any extra participant contact.
- The trial denture is scanned and that scan merged with the hybrid scan of the fitting surface to produce a printable digital file; again, this is undertaken in the digital laboratory after the wax trial denture insertion (Stage 7). There is no additional participant contact for this procedure.
- The 3-D printed dentures are printed and polished; a process undertaken in the dental laboratory during Stage 8. No additional participant contact.
- An assessment of the two sets of dentures is undertaken by the participant during the two-week Initial Habituation and Assessment Period where the participant rotates the wearing of the dentures and records their comments in a structured diary; Stage 10.
- Primary outcome of the participant's preferred denture is recorded at Stage 11.
- The participant is given one set of dentures to wear for the first eight-week Adjustment Period (Stage 12).
- Participant returns and completes OHIP-EDENT assessment of quality of life (Stage 13 above).
- The participant is given the other set of dentures to wear for an eight-week Adjustment Period. (Stage 14)
- Participant completes OHIP-EDENT assessment of quality of life (Stage 15)
- Participant is given both sets of dentures for the two-week Confirmation Period (Stage 16).
- Participant assessment of comfort, stability and chewing capacity of both sets of dentures is recorded during Stage 17.
- Final choice of the adjusted dentures takes place in the final clinical visit (Stage 17).

See the Study Flow Diagram in Section 3b and Schedule of Events in Section 13.1.

12.2 OVERVIEW OF COMMITMENT FOR PARTICIPANTS

This pilot RCT consists of a minimum of nine scheduled clinical visits for each participant. Participants may request extra visits during the denture construction and adjustment stages ("unscheduled visits").
Normally, denture construction takes a minimum of five visits. In recognition of the extra commitment (i.e. the 4 additional research visits participants will be asked to attend) we propose a payment of £12.50 per visit up to a maximum of £50, to compensate for their travel costs.

An authorised member of staff at the research sites may call the participants before each visit to clinic, to remind them of the date and time of their appointment.

12.3 IMPLICATIONS FOR TRIAL DELIVERY DURING COVID-19 PANDEMIC

During the COVID-19 pandemic we will adhere to local NHS Trust protocols for the treatment of outpatients across the participating Dental Hospitals. Wherever possible face-to-face trial appointments will be minimised and we will adhere to local best practice recommendations; this may include telephone / video-conferencing consultations and mail outs (this could include denture provision). Adjustments to dentures can be made at the participant's request if necessary. Trial-specific working instructions will be regularly updated to comply with local NHS Trust guidelines in order to maintain participant safety at all times during COVID-19.

13. ASSESSMENT AND DATA COLLECTION

The study consists of a minimum of nine dental hospital visits for each patient known as "scheduled events". Participants are expected to request extra visits during the denture construction and adjustment stages ("unscheduled events"). Participants will be encouraged to request extra visits if needed at any time throughout the course of the study; therefore the total number of visits will be varied.

Study data will be recorded by research staff on Case Report Forms (CRFs). After each clinic the local research team will post the original paper CRFs to DenTCRU at the University of Leeds. When all local approvals to run this study are obtained, details on the schedule of CRFs, data to be collected and guidance on the completion of CRFs will be given to the site research staff at the site initiation visit and to new staff trained by the person appointed by the local site PI.

The digital scan images will be produced locally at each research site and pseudonymised with the participant's individual study ID number. The study team based in the digital dental laboratory at the University of Leeds will remotely dial into the scanning equipment at the remote sites via a secure encrypted connection. The Leeds digital lab team will then download the scanned images into a Zip folder held on a password protected computer in a locked lab. These images will then be processed using bespoke in-house software in order to assemble a master scan file.

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. Within the local

Investigator Site File, the Recruitment Log will record the individual participant study ID number allocated to each participant against the participant's name, and personal details. **Once allocated a study number, all subsequent CRFs will only identify the participant by their individual participant study ID number, their initials and date of birth.**

13.1 SCHEDULE OF EVENTS

Research activities	Stage	Screening	Impressions		Denture Construction			Initial Habituation & Assessment Period (IHAP)	Adjustment Periods		Confirmation Period
	Visit		1	2	3	4	5	6	7	8	9
	Week	-1 to 1	1	3	5	7	9	11	19	27	29
	Appointments		1st Imps	2nd Imps	Jaw reg	Wax try-in	Fit	Review	After 8 weeks	After 8 weeks	After 2 weeks
Screening eligibility criteria		✓									
Informed consent & Registration			✓								
Randomisations							✓	✓			
OHIP Edent			✓						✓	✓	
5-Point Likert Assessment of dentures								✓	✓	✓	✓
Participant Preference Assessment of dentures								✓			✓
Participant Diary							✓	✓			
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓	✓

13.2 ASSESSMENTS

The primary purpose of this pilot study is to calculate the sample size needed for a full RCT using the primary outcome (which is the participant's preference for the dentures before they are adjusted). In addition to the assessment of the primary outcome, the secondary outcome measures (of the future RCT) will also be investigated here in the pilot RCT. Thus, this is a full protocol pilot study and it is anticipated that the data collected here may be combined with that collected in the planned future trial.

The NIHR provide a useful definition for both "Pilot" and "Feasibility" studies. (See: https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/research-programmes/RfPB/Guidance%20Documents/Guidance_on_feasibility_studies.pdf). Under these definitions, this is a full protocol pilot study, "a version of the main study that is run in miniature".
Please read this section in conjunction with the Study Flow Diagram in Section 3b.

The assessments, listed in the order in which they are used, are:

13.2.1 BASELINE ORAL HEALTH IMPACT PROFILE (OHIP-EDENT)

Timing: at Clinical Visit 1

OHIP-EDENT is a validated questionnaire specifically designed to assess edentulous participants' quality of life. The OHIP-EDENT questionnaire is widely used in the prosthodontic literature (1273 publications to date). This baseline will allow the assessment of any improvement/deterioration in the participants' quality of life through the provision of dentures. Statistical plan for the analysis of OHIP-EDENT scores is detailed in Section 14.4.

13.2.2 PARTICIPANT DIARY

Timing: after Clinical Visit 5

During the two-week Initial Habituation and Assessment Period each participant is given a diary. The diary has two purposes. Firstly, it is to instruct them as to when to wear each of the dentures. The order in which the dentures are worn is randomised. Although a carryover effect is not anticipated, this initial randomisation limits any possible period effect (and allows any carryover period effect to be assessed). The second reason for the diary is to allow the participant to make notes of difficulties and/or benefits of wearing each denture. Previous experience of this protocol has shown that the participants benefit from referring to their diary when answering the questionnaire in the assessments below.

13.2.3 PARTICIPANT PREFERENCE FOR THE DENTURES BEFORE ADJUSTMENT

Timing: at Clinical Visit 6

Participant preference before adjustment has been chosen to be the primary endpoint because it is the driving motivation to ascertain which method of denture manufacture is

most acceptable to the participant prior to subsequent denture adjustment. (See Section 14 Statistical Analysis)

13.2.4 PARTICIPANT ASSESSMENT OF THE COMFORT STABILITY AND CHEWING EFFICIENCY OF EACH DENTURE

Timing: at Clinical Visit 6

After the two-week Initial Habituation and Assessment Period each participant is asked to score the two dentures using 5 point Likert scale assessing the three domains of Comfort, Stability and Chewing Efficiency.

See Section 14.3 for the statistical analysis plan for these Likert scales.

There is a second randomisation at this point to decide which denture is worn during the first eight-week Adjustment Period.

13.2.5 OHIP-EDENT AFTER THE FIRST EIGHT-WEEK ADJUSTMENT PERIOD

Timing: at Clinical Visit 7

The participants are asked to wear one denture for eight weeks. During those eight weeks they are encouraged to return for any adjustments that they require.

After the participant has worn the dentures for eight weeks, they will be asked to re-assess their quality of life though the OHIP-EDENT questionnaire. See Section 14.4 for the statistical analysis plan for the OHIP-EDENT questionnaires.

13.2.6 OHIP-EDENT AFTER THE SECOND EIGHT-WEEK ADJUSTMENT PERIOD

Timing: at Clinical Visit 8

After Clinical Visit 7 the participant is asked to wear the second denture for an eight-week adjustment period (randomised for denture order). During those eight weeks they are encouraged to return for any adjustments that they require.

After the participant has worn the dentures for eight weeks, they will be asked re-assess their quality of life though the OHIP-EDENT questionnaire. See Section 14.4 for the statistical analysis plan for the OHIP-EDENT questionnaires.

13.2.7 PARTICIPANTS' ASSESSMENT OF THE COMFORT, STABILITY AND CHEWING EFFICIENCY OF DENTURES OF BOTH DENTURES

Timing: at Clinical Visit 9

After the two Adjustment Periods the participants take both set of dentures away for the two-week Confirmation Period. On their return at Clinical Visit 9 they will be asked to assess both dentures for comfort stability and chewing efficiency.

See Section 14 for statistical analysis of this assessment.

13.2.8 PREFERENCE FOR ADJUSTED DENTURES

Timing: at Clinical Visit 9

After the two Adjustment Periods the participants take both set of dentures away for the two-week Confirmation Period. During these two weeks they use the dentures as they wish. When they come back at Clinical Visit 9 they assess which set of dentures they prefer. See Section 14 for statistical analysis of this assessment.

13.3 DEFINITION OF THE END OF THE STUDY

The end of the study is defined as the date of the last participant's final assessment visit at the end of the Confirmation Period.

14. STATISTICAL ANALYSIS

14.1 CALCULATION OF SAMPLE SIZE FOR A DEFINITIVE RCT

The results from this study will be used for sample size calculation for a definitive RCT if a preference difference is found between conventional denture and 3-D printed denture. The unadjusted proportion discordance will be retained for this study and a discordant difference of 0.1 will be used to calculate the sample size using McNemar's test.

14.2 UNADJUSTED AND ADJUSTED DENTURE PREFERENCE (13.1.3 and 13.1.8 above)

The outcome of preference for unadjusted dentures and the secondary outcome of preference for adjusted denture will be presented as a 2×2 table for paired data and analysed using McNemar's test for paired data**.**

		3-D printed denture	
		Prefer/satisfactory	Not prefer/unsatisfactory
Conventional denture	Prefer/satisfactory	Number with no preference (like both)	Number who prefer denture produced conventionally
	Not prefer/unsatisfactory	Number who prefer denture produced by 3-D printing	Number with no preference (dislike both)

14.3 STATISTICAL ANALYSIS OF REPEATED LIKERT SCALES (13.1.4, and 13.1.7 above)

Differences between Likert scores (measuring comfort, stability and chewing efficiency) for each denture will be calculated and compared using the Wilcoxon test for matched pairs. Likert scores will be presented by a p-value based on a Wilcoxon Test score. Scores will be compared between conventional and 3-D printed dentures at the end of Habituation/Assessment Period and the Confirmation Period.

Summary statistics and frequency distributions will also be presented for each denture for two time points. In addition summary statistics and frequency distributions will be presented for the difference between the two dentures.

14.4 STATISTICAL ANALYSIS PLAN FOR THE OHIP-EDENT QUESTIONNAIRE (13.1.5 and 13.1.6 above)

Overall OHIP-EDENT scores at the end of each Adjustment Period (i.e. by period) will be analysed using an ANOVA model appropriate for an AB/BA cross-over design. Domain scores and overall OHIP-EDENT scores will be presented as summary statistics and frequency distributions by period and overall. The model will incorporate denture as a fixed effect and participant as a random effect. Participant effects will be treated as random

effects in the model since participants will be randomly selected (ref). (The mean difference in OHIP-EDENT between the dentures will be estimated with 95% confidence intervals.)

Normality checks will be made on the OHIP-EDENT distribution. Additionally, a normality check on the residuals from the model described above will be made. Both normality checks will be done using a normal QQ-plot.

There is a possibility of a period effect, and as such a period effect t-test will be performed. Although a carryover effect is not anticipated, a carryover t-test will also be performed to test for carryover. If such effects are shown to be statistically significant, then the model will incorporate these effects (both as fixed effects).

Baseline will not be included in the model since when subtracting each participant's baseline from both outcome measurements, the effect of the baseline totally disappears and the cross-over differences would be just the same if baseline had never been used (ref).

OHIP-EDENT scores will be presented by mean difference between dentures with 95% confidence intervals.

15. SERIOUS ADVERSE EVENTS PROCEDURES

15.1 GENERAL DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a participant or clinical trial 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 participant 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 participant 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 participant which, in the opinion of the Chief Investigator, is Related and Unexpected will be reported to the main Research Ethics Committee (main REC).

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

- **related** to the study (i.e. they resulted from administration of any research procedures) and

- **unexpected** (i.e. not listed in the protocol as an expected occurrence)

15.2 OPERATIONAL DEFINITION AND PROCEDURES

15.2.1 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 event will be collected in this study and reported to the main REC. All adverse events or serious adverse events **not** classified as 'related' will not be collected as part of this study.

15.2.2 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, collated by the study team at DenTCRU and sent to the Sponsor 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.

Email address for Reporting RU SAEs:
leedsth-tr.3ddentures-dentcru@nhs.net
Include **'URGENT - 3-D RU SAE'** in the email subject

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

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

Any follow-up information should be emailed to DenTCRU at the address above 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 and Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the Sponsor **within one working day** and to the main REC by the DenTCRU on behalf of the Chief Investigator **within 15 days**.

15.2.3 DEATHS

Deaths in the study population are not expected during the course of the study.

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 emailed to the DenTCRU **within 7 days** of the research staff becoming aware of the event and reported to the Sponsor. The original form should also be posted to DenTCRU in real time and a copy retained at site.

Email address for Reporting DEATHS:
leedsth-tr.3ddentures-dentcru@nhs.net

15.3 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 Sponsor. Expedited reporting of events (as detailed in Section 15.2.2) to the main REC and the Sponsor will be subject to current RES guidance, DenTCRU Standard Operating Procedures (SOPs) and Sponsor requirements.

15.4 RESPONSIBILITIES

15.4.1 CLINICAL CO-INVESTIGATORS / AUTHORISED PERSONNEL

1. Checking for SAEs when participants attend for study intervention.
2. Judgement 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.

15.4.2 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 and Unexpected in the opinion of authorised personnel. In the event of disagreement between the authorised personnel's assessment and the Chief Investigator, the 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.

15.4.3 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 on behalf of the 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.

16. DATA MONITORING

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

16.1 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants 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 participants prior to registration into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant 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 participants into the study. The DenTCRU (University of Leeds) will provide the Main REC with a copy of the final protocol, participant 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 by the 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 participants to record personal details including name and date of birth.
- Participant name will be collected when a participant 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 an individual participant study ID number and will include two patient identifiers, usually the participant's initials and date of birth.
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
- Consent from participants 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 participants for the data collected for the study to be used to evaluate safety and develop new research.
- Where central monitoring of source documents by DenTCRU (or copies of source documents) is required (such as denture scans), the participant'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 participant withdraws consent from further intervention and / or further collection of data, all collected data will always be included in the final study analysis.

19. 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. Data and documents held by the participating research sites will be archived on site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

20. STATEMENT OF INDEMNITY

This study is sponsored by The University of Leeds, which is responsible for the design and management of the research and will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to participants 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 participants under this duty of care.

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

20.1 FUNDING

This study is funded by The Dunhill Medical Trust grant *RPGF1802\33: 3-D Printed Dentures; Development and assessment of cost-effective workflows to enhance clinical delivery*.

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 on the following ICMJE criteria:

- substantial contribution to the conception and design, or acquisition, analysis, or interpretation of data
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work

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 should be acknowledged in all publications, as should Dunhill Medical Trust (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 MEDICAL TRUST REQUIREMENTS

All publications must acknowledge The Dunhill Medical Trust as the study's funding source.