PROTOCOL

To investigate the utility of 3D intra-oral gingival imaging to score gingival health compared to the visual clinical assessment

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1. Introduction

1.1 Background Information

Gingivitis is ubiquitous to all populations and is caused by inadequate control of dental plaque. This causal relationship was first demonstrated by Löe et al (1965) using what is now universally known as the 'experimental gingivitis model'. During a three-week phase of non-toothbrushing and starting from a zero plaque and gingivitis status, plaque accumulated around the gingival margins and gingivitis developed. Removal of plaque by resuming toothbrushing was followed by re-establishment of gingival health, proving there is a direct link between plaque and gingivitis. Gingivitis precedes periodontal disease in the majority of cases, which is when teeth lose bone and are eventually lost. 50% of our population is susceptible to periodontitis which is a debilitating oral condition. Gingivitis is generally assessed by clinical examination of the gingivae looking for visual signs of gingival inflammation such as redness, bleeding and swelling or a combination of these signs (Löe and Silness 1963; Löe 1967; Saxton and van der Ouderaa 1989; Lobene et al 1986). Various indices measuring gingivitis have been described that are based on these clinical signs, but inevitably they are subjective, only semi- quantitative and examiner drift in scoring may occur within the practical limits of a clinical trial assessment (Eaton et al 1997).

With the increased use of technology in the dental arena, there is more scope to be able to record accurate 3D images of the mouth which can be used by dentists as aids in assessment and monitoring of oral health and disease using non-invasive methodologies.

3D scanning with increased accuracy and resolution, means it is now possible to capture a great detail of the oral hard and soft tissue information. These scans are time efficient, easy to record and available for future reference. They currently employed to construct complex dental implant retained prostheses and also to monitor orthodontic treatment and position of teeth with a high degree of accuracy.

The aim of this study is to investigate the accuracy of 3D intra-oral scanner images (3Shape Trios Scanner) to monitor gingival health compared to traditional assessments made with standard clinical assessments and indices of the gingival tissues. In this study, 3D intra-oral images will be captured and graded according to the modified gingival index (MGI) and compared against standard clinically derived MGI assessments, within the same subject. This study also aims to evaluate the sensitivity of the 3D scanner to differentiate between healthy gingivae and gingivitis, as measured by indirect assessment of images (using MGI). Gingival health assessed by gingival colour and texture will be compared between clinical assessment and assessment of captured scans. If the scans correlate to the clinical scores this technique would allow oral healthcare professionals to scan the mouth, with algorithms determining

gingival health and disease, in accordance with the New 2017 Classification of Periodontal Diseases (Caton et al 2018), using a non-invasive methodology.

2. Study Objectives

2.1 Primary Objective(s)

To compare the accuracy of intra-oral 3D scanner derived assessment of gingival inflammation compared to standard clinically derived direct scoring of clinical inflammation, both using the modified gingival index (MGI).

2.2 Secondary Objective(s)

1. To evaluate the sensitivity of the intra-oral 3D scanner derived assessment of gingival inflammation to differentiate between healthy gingivae, mild gingivitis, moderate and severe gingivitis (MGI 0, 1, 2, 3, 4).

2. To examine inter-examiner variability of scoring clinical gingival health from intra-oral 3D scanner images using MGI.

3. To compare colour and textual changes in scanned images against clinically derived MGI scores of gingival healthy and diseased sites

3. Study Design

3.1 Study Outline

This study is a blind (blind to the clinicians assessing the 3D image scans) single visit study in healthy participants. Sufficient participants aged over 18 years will be recruited to the study to ensure approximately 210 sites within the mouth are scored in total across all participants assessed. The scorable sites will be recorded by the MGI score (0, 1, 2, 3 and 4), Appendix A. The sites for assessment will be the buccal and lingual margin of each scorable tooth with one score provided for the full buccal margin and one MGI score for the full lingual/palatal margin. It is anticipated that up to 100 participants may be recruited.

Following the provision of informed consent, participants will be enrolled on to the study according to the inclusion/exclusion criteria. After enrollment participants will have their upper and lower anterior dental sextants (canine to canine area teeth) assessed for gingival inflammation using the Modified Gingival Index (MGI) by calibrated dental examiner 1. The MGI (0, 1, 2, 3 or 4) will be recorded clinically for scorable teeth in the upper and lower anterior sextants at 2 sites, the gingival unit buccally and lingual/palatally), per tooth. The clinician will also identify 2 sites (gingival units) in the mouth and score colour and texture of the gingival unit, appendix D. Following the clinical assessments, the examiner will use a 3D Intra-oral scanner to scan the mouth of each participant ensuring that all scorable teeth and gingivae are captured, Appendix B. The scanned images are recorded automatically by the scanner and form a pictorial patient report, Appendix C. A copy of this report will be provided to the participants for their own interest. The first and a second calibrated examiner will

evaluate the 3D Intra-oral scan and record the MGI for all scorable teeth in the upper and lower anterior sextants, (buccally and lingual/palatally), about 2 weeks after the initial scan . Two sites identified per volunteer will also be assessed for colour and texture of the gingival unit by these two examiners and the findings will be compared to the clinical MGI scores for a further comparison of health and gingival disease identification, Appendix D.

The images recorded from the 3D scanner will be stored using the participant's unique ID number. The 3D scans will be anonymised and blindly assessed by the two calibrated (MGI) examiners.

3.2 Selection of Participants

i) 3.2.1 Planned number of participants

Sufficient participants in good general health, aged 18 or over, male and female will be accepted onto the study in order to obtain approximately 80 sites with MGI 0, 40 sites with MGI 1, 40 sites with MGI 2, 40 sites with MGI 3 and a minimum of 10 sites with MGI 4 (scorable sites either from the buccal or palatal aspect).

The selection of suitable participants will be made according to the inclusion and exclusion criteria described in the following sections.

ii) 3.2.2 Inclusion Criteria

- Be aged 18 years and over, of either gender and in good health.
- Be willing and physically able to undergo all study procedures.
- Be willing and competent (verbally and cognitively) to give written informed consent.
- Have at least 20 natural teeth.

iii) 3.2.3 Exclusion Criteria

- Current participation in any other cosmetic trials, any dental clinical trials or clinical trials.
- Obvious signs of untreated caries or significant periodontal disease, which in the opinion of the Study Dentist, will affect either the scientific validity of the study.
- A periodontal pocket depth >4mm in the anterior upper or lower sextants.
- Any participant who, in the judgement of the investigator, should not participate in the study.
- Current orthodontic treatment.
- An immediate employee of the sponsor or the research team conducting the study. Employees of the Sponsor or research site not associated with the research team are eligible to participate.

3.3 Withdrawal of Participants.

- Participants may discontinue from the study at any time **without having to give a reason**. In addition, the Principal Investigator (PI) or designee has the right to withdraw a participant for any reason that is in the best interests of the participant.

3.4 Endpoints

iv) 3.4.1 Assessment

The following endpoint will be employed:

- Modified Gingival Index (Lobene) (MGI) derived from clinical assessment of gingival or from 3D-representations, Appendices A and B.
- Red colour threshold and gingivae surface texture in a predefined region of interest of the gingivae (Appendix D).

Assessment of Safety

Adverse events will be monitored throughout the study (section 5).

Soft and hard tissue assessments will be conducted. Any deviation from the screening assessments will be recorded as an adverse event.

3.5 Concomitant medication

Any concomitant medication, including food supplements and prophylactic treatments will be recorded in the case report form (CRF).

3.6 Assessments at Study Visit

The assessments to be conducted at the study visit are presented in Table 1.

Assessment	**Visit 1**
Informed Consent	X
Medical History Collection	X
Oral Soft and Hard Tissue Assessment	X
MGI/Colour/Texture Assessment	X
Intra oral scan of mouth	X
AE Recording	X
Remuneration	x

At the start of the study visit participants will be provided with a Participant Information Sheet containing detailed information about this study to read. The potential participant will be given the opportunity to ask any questions they may have with regards to the study. If the participants are willing to take part in this study, they will be asked to sign the Informed Consent form. Once informed consent has been obtained each participant will be assigned a

unique identification number and their eligibility criteria will be reviewed by the study clinician**.**

Those participants who qualify for entry onto the study will have their gingival health assessed by MGI (see Appendix A) in the upper and lower anterior sextants by examiner 1, and 2 gingival site units scores for colour and texture.

Following MGI assessment, examiner 1 will use the 3Shape scanner to acquire a scan of the oral hard and soft tissues in the upper and lower anterior sextants. The examiner will ensure the scan captures all scorable teeth and gingivae. The scan will be saved using the participants unique identification number. This completes the participant study visit.

Approximately 2 weeks after the last clinical assessment, examiner 1, and a second examiner (examiner 2) will assess the anonymized 3D oral scans for each scorable tooth for each participant using the MGI scoring system and grade the 2 identified sites for colour and texture.

Scoring intra-oral 3D scanner image assessments of gingival health using the modified gingival index (MGI) will be compared to the clinically derived assessments.

4. Safety Monitoring

4.1 Adverse Event and Medical Device Incidents

An adverse event (AE) is any untoward medical occurrence in a participant, whether or not related to the study procedures. Adverse events include any occurrence that is new in onset, an exacerbation of a pre-existing condition and clinically significant laboratory values.

An incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have lead to the death of a patient or user or of other persons or to a serious deterioration in their state of health.

4.1.1 Exceptions

The following medical occurrences will not be reported as AEs;

- Pre-treatment Adverse Events; Any medical occurrence that occurs after informed consent, but before any study assessment is considered as medical history and only recorded as an AE if it worsens during the study.
- Pre-existing medical condition; Events that occur with comparable frequency and severity to the participant's baseline condition are reported as medical history, not AEs.

4.1.2 Study Specific Expected Adverse Event

There are no AEs known to be associated with the use of the 3D intra-oral camera and/or procedures in this study.

4.2 Reporting of Adverse Events and Incidents

The handling and reporting of AEs has been formally delegated by the University of Bristol, as Sponsor, to UH Bristol.

All SAEs must be reported to the UH Bristol contact (0117 3420233) by investigational staff within 24 hours of their knowledge of the event. The initial SAE report may be incomplete but must provide the minimal information which is the study number, participant number, start date and SAE term.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study within 24 hours. The Sponsor has a legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies. Prompt notification of incidents by the investigator is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects. The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents to the ethics committee.

5. Statistical Considerations

5.1 Sample Size Calculation

The study will recruit sufficient consenting adult healthy participants (up to 100 if required) who satisfy the eligibility criteria listed in section 3.2. The primary objective to compare scoring clinical gingival health versus scoring intra-oral 3D scanner images of gingival health using the modified gingival index (MGI), to differentiate between healthy gingivae, mild gingivitis (MGI 1 and 2) and moderate to severe gingivitis (MGI 3 and 4). One of the secondary objectives is to examine inter-examiner variability of scoring clinical gingival health from intra-oral 3D scanner images using the modified gingival index.

5.2 Definition of Analysis Population

Participant data will be used except where a participant has been significantly non-compliant with the protocol.

5.3 Statistical Methods

MGI scores recorded by examiner 1 for clinical scoring; and MGI scores recorded by examiner 1 from the scans for the same 210 gingival sites are compared by constructing a crosstabulation, highlighting disagreements between scores indicating healthy gingivae, partial mild gingivitis, mild inflammation of the entire gingival unit, moderate gingivitis and

severe gingivitis (MGI 0, 1, 2, 3 and 4). Disagreement probabilities will then be calculated for disagreements between consecutive scores, with confidence intervals. This process will be repeated with MGI coarsened to a 3-point scale, 0, 1-2 or 3-4. These two models will be compared to determine the degree to which the scanned images enable subtler discrimination between MGI 1 and 2 and between MGI 3 and 4. Both row and column disagreement proportions will be calculated, which are analogous to complements of sensitivity and specificity and positive and negative predictive values.

MGI scores recorded by examiner 1 for clinical scoring; and MGI scores recorded by examiner 2 from the scans are compared in exactly the same way.

MGI scores recorded by examiners 1 and 2 from the scans are compared by constructing a crosstabulation as above. As well as the disagreement probabilities, analyses will also be performed based on MGI as a 0 to 4 scale. Thus a root mean square difference in scores will be calculated, and systematic variation between the two observers assessed by examining the mean difference.

It is possible that for one or more gingival sites the two observers agree on their scores from the scan but disagree with the clinical score. In this event, the relevant scan will be reviewed carefully to try to determine whether the scanning process has introduced some specific artefact leading to this pattern of disagreements. The original 3 scores for that site will be used in the statistical analyses nonetheless.

Additional investigation of the images will be undertaken to explore the sensitivity of the device, including the ability of gingival colour and texture assessment from visual and captured images to distinguish between healthy and diseased sites. Further analyses may be undertaken on these anonymised images to compare healthy and diseased sites.

6. Monitoring

The University of Bristol has a policy for monitoring 10% of studies. Monitoring of studies is conducted in accordance with UH Bristol monitoring policy in relation to the service level agreement with the University of Bristol. The monitor must maintain the confidentiality of the study documents.

7. Data Handling and Record Keeping

There will be at least one CRF for each participant entered into the study. It is the responsibility of the PI to ensure the completeness and accuracy of the CRF and to authorise only trained members of staff to complete the CRF.

The CRF must be completed legibly, using a black ballpoint pen. Erroneous values and/or text must not be obliterated. Instead, the error must be crossed out with a single line, the correct value/text added, and the correction signed or initialled and dated.

There will be study specific records to record the identification of any data to be recorded directly on the CRFs or other written or electronic record of data, and to be considered to be source data.

All site staff must ensure that the participant's anonymity will be maintained. On all documents participants must be identified only by an identification code and not by their names. The PI or designee must keep a separate confidential enrolment log that matches identifying codes with the participant's names and addresses. The PI or designee must maintain these documents at the site.

It is the responsibility of the PI or designee to maintain adequate clinical study records. Copies of all study material must be archived for a period of at least 15 years after the end of the study (or more as legally required). All documents must be archived in a secure place and treated as confidential material.

8. Quality Standards

It is the responsibility of the PI to ensure that the study is conducted in accordance with the principles of Good Clinical Practice, the 2008 version of the Declaration of Helsinki and according to applicable local laws and regulations concerning studies conducted on human participants which are outside of the definition of a medicinal product or medical device.

Quality assurance audits may be performed by the sponsor or any ethics committee or regulatory authority during the course of the study or at study completion.

9. Ethics and Informed Consent

The PI or designee must submit a copy of the protocol, participant information sheet and consent form to an Independent Ethics Committee (IEC) who must provide written approval before study specific procedures commence. The IEC must also approve any other information that is given to participants such as advertisements and may require other documents such as study product documentation.

The PI or designee must obtain informed consent from each participant participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study. The consent must be obtained before any study-specific procedures are performed. It must be made completely and unambiguously clear to each participant that they are free to refuse to participate in the study, or that they can withdraw their consent at any time and for any reason, without incurring any penalty or withholding of treatment. The participant must be

given their own copy of the information sheet and signed consent form. The original signed informed consent must be kept on file by the PI or designee.

Any modification to the agreed protocol must be agreed by both the sponsor and the PI and approved in writing by the IEC/IRB. Written approval must be obtained from the IEC/IRB before any amendment is implemented, unless immediate change is required to eliminate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). Major/substantial amendments to the protocol that affect the scope of the study at the participant level should be reflected in the consent form and active participants re-consented.

10. Sponsorship, Finance and Insurance

The sponsor of the study is the University of Bristol. The study will be funded by GlaxoSmithKline Consumer Healthcare.

The participants will receive a voucher for £20 in acknowledgement of their participation in the study.

This study will be sponsored by the University of Bristol. The University has Clinical Research/ Public Liability Insurance to cover the liability of the University to research participants. In the event that something goes wrong and a participant is harmed during the research study there are no special compensation arrangements. If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Bristol University or the NHS Trust or one of the other parties to the research, but they may have to pay their own legal costs.

11. Registration, Reporting and Publication Policy

Statistical analysis will be performed for the study and a final study report will be prepared. Except for compelling legal reasons, neither the sponsor nor the site staff will communicate to third parties any result of the clinical study before the report has been released by the sponsor by mutual agreement.

As registration of the clinical study is strongly recommended by the ethics committee, the registration of the clinical study will be conducted by the Sponsor.

12. References

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Eaton K, Rimini FM. The achievement and maintenance of inter- examiner consistency in the assessment of plaque and gingivitis during a multicentre study based in general dental practices. J Clin Periodontol 1997; 24: 183–8. doi: https://doi.org/10.1111/j.1600-051X.1997.tb00489.x

Appendix A – MGI Assessment

The scoring of gingival health will be carried out by two trained dental examiners who have been standardised in the indices. Teeth are examined and scored by one examiner and both will perform the 3D intra-oral scans assessments.

Gingival condition is assessed using the Modified Gingival Index (Lobene, 1986) which is a non-invasive visual evaluation of gingival health. For the clinical assessment each scorable tooth in the upper and lower anterior sextants will be classified as healthy or exhibiting gingivitis on a 5-point scale. For each scorable tooth, 2 gingival unit sites will be assessed and recorded at the gingival margin of the buccal and lingual/palatal surfaces). The 5-point scale is as follows:

0 = normal (absence of inflammation)

1 = mild inflammation (slight change in colour, little change in texture) of any portion of the gingival unit

2 = mild inflammation of the entire gingival unit

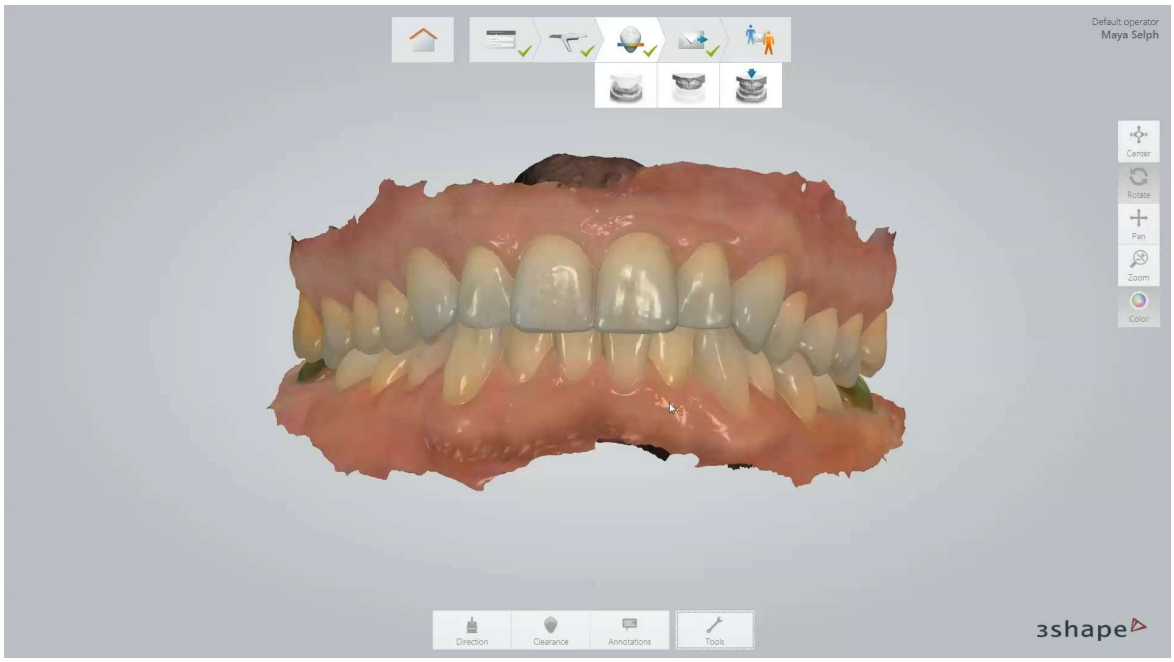
3 = moderate inflammation (moderate glazing, redness, oedema, and/or hypertrophy) of the gingival unit

4 = severe inflammation (marked redness and oedema/hypertrophy, spontaneous bleeding, or ulceration) of the gingival unit.

Appendix B – 3D Intra-oral Assessment

A 3D intra-oral scan of the participant's mouth will be obtained using a 3Shape Trios Scanner intra oral scanner. The scan will be recorded using the participants unique identification number. The areas of the mouth that have been scanned automatically form a patient report. For this study, a copy of the pictorial report will be provided to the participant for their own interest, and will not be used as a diagnostic or advice tool for this study – see Appendix D.

The gingival assessment using MGI as described in Appendix A will be made by two examiners blinded to the clinical assessments at least 2 weeks after the clinical examination. The scan can be manipulated in different orientations to allow the dental examiner to observe and assess all the gingival areas of the mouth to be assessed.

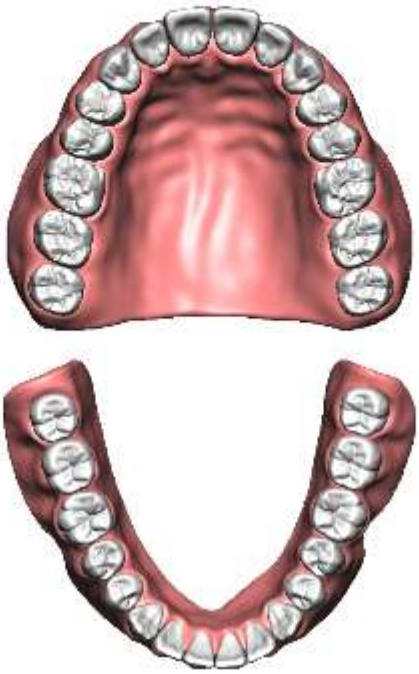


Appendix C – Patient Report

Below is an example of the format of the patient report that is automatically created following recording of the 3D oral scans for each participant. The date of the scan and the participants unique identification number will be the only identifiers recorded on the scan. A copy of the report will be provided to each participant for their own interest. The report will not be used as a diagnostic or advice tool as part of this study.

Creation date: 19/01/2019 14.37.26 (GMT+01:00)

Dentist name:	Helen	**Case number:**	101855209_20190119_1437_26
Patient name:	CHINA PEN WIRELESS JAN 2019	**Lab name:**	Helen
Has additional scan:	False		



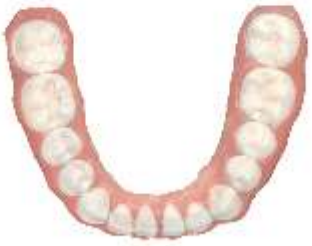
Restorations

Technical information:

Order form settings file(s) IDs:	Implant Studio_Implant Studio Indications
Order form settings file(s):	Implant Studio Indications.dmc
Clinic ID:	1818251499
Scan files	

Scan type	File name	Date
LowerJawScan	LowerJawScan.DCM	19/01/2019 14.41.05

Patient images:



Appendix D – Colour and Texture Assessment

Appropriate colour thresholds will be applied to the region of interest (ROI) of the two selected images using image analysis software (Ifran View or equivalent) using a bespoke algorithm to determine max. redness (intensity and area) in the ROI.

- Pink (80% of ROI presents a "redness" value below the predetermined red threshold) = "health", or
- Red (>20% of ROI presents a "redness" value above a predetermined red threshold) = "disease"

Post unblinding, further analysis of images against ROI "redness" against the clinical score will be conducted to explore whether "% redness" can be related to MGI score.

Appropriate image analysis will be applied to the ROI images using image analysis software (Ifran View or equivalent) using a bespoke algorithm, to estimate the surface texture based on the colour composition of the image.

- Images presenting stippled pattern will be classified as "health", or
- Images with no obvious stippling will be classed as "disease"

Prescribed thresholds and image analysis procedures will be documented in the ROI Image Analysis Procedure.