PROTOCOL

A pilot study to evaluate the diagnostic accuracy of intraoral scan-derived visual features in detecting gingival inflammation using bleeding on probing as a reference

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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 with bleeding on probing and toothbrushing. 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 periodontitis in the majority of cases, which is when the bone around teeth is gradually lost and eventually the teeth fall out (Kinane et al 2017). 50% of the 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 (Löe and Silness 1963; Löe 1967; Saxton and van der Ouderaa 1989; Lobene et al 1986, Ainamo & Bay 1975). 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).

Importantly, the existing literature on gingival health and the clinical presentation of gingivitis in pigmented oral mucosa remains limited. Further research and education in this area are warranted to equip oral health professionals with the knowledge and skills needed to provide equitable, inclusive, and effective care for all patients, thereby improving oral health outcomes and promoting equality, diversity, and inclusion within clinical practice.

With the increased use of technology in dentistry, there is more scope to be able to record accurate 3D images of the mouth which can be used by oral healthcare professionals 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 detailed oral hard and soft tissue information (Daly et al 2020). These scans are time efficient, easy to record and available for future reference. They are currently employed to construct complex dental implant retained prostheses and to monitor orthodontic treatment and position of teeth with a high degree of accuracy (Mangano et al 2017).

The aim of this study is to investigate the diagnostic accuracy of 3D intra-oral scanner images (IOS) (3Shape Trios 6 Scanner®) to assess gingival health and disease across the range of gingival pigmentation according to the oral pigmentation index (DOPI) compared to traditional assessments.

Clinical assessments for bleeding Index (BI) (Ainamo & Bay 1975), DOPI (Dummett et al 1964) and gingival phenotype (Jepson et al 2018) will be recorded, with DOPI scores and gingival phenotype compared against scores derived from the intraoral scan 3D models from the same participants. 3D models will be scored with visual gingival inflammation features derived from the Modified Gingival Index (MGI)- (Lobene et al. 1986) and compared to the bleeding index at the same sites. If the scans agree closely with 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 2018 Classification of Periodontal Diseases (Caton et al 2018), using a non-invasive methodology. In the future, this may facilitate an automated solution that detects gingival inflammation, as an alternative to a BOP, and aid the diagnosis of gingivitis using IOS across the full range of oral pigmentation in gingival health and disease.

2. Study Objectives

2.1 Primary Objective

To compare the diagnostic accuracy and agreement of the on-scan visual gingival inflammation scores with clinical bleeding on probing scores at the same sites, across the range of gingival mucosa pigmentation, Dummett Oral Pigmentation Index (DOPI).

2.2 Secondary Objectives

- To assess the diagnostic accuracy and agreement between gingival pigmentation assessments derived from clinical examination and intraoral scans using the Dummett Oral Pigmentation Index (DOPI)
- To compare the diagnostic accuracy and agreement of the on-scan assessment in detecting gingival inflammation, defined as BOP-positive sites clinically, stratified by gingival phenotype, i.e., thin and thick.

3. Study Design

3.1 Study Outline

This is a single visit cross-sectional observational pilot study in healthy participants focusing on diagnostic accuracy and feature relevance. Participants will undergo a single visit involving clinical examination and intraoral scanning.

Following informed consent, 20 participants satisfying study inclusion/exclusion criteria will be enrolled onto the study. All teeth 7-7 in both arches (including those with crowns or bridges) will be scored clinically for DOPI (Appendix A) followed by gingival phenotype (Appendix E) and bleeding index (BI) (Appendix B). DOPI and BI will be recorded at 6 sites per tooth unit (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual). Gingival phenotype will be scored at 2 sites per tooth, buccal and lingual.

A 3D intraoral scan (IOS) will be produced for each participant and stored using the participant's unique ID number. This will take place after the DOPI clinical assessment and before the phenotype and BI assessment.

Subsequently, at least 2 weeks after the initial scan, the examiner will evaluate the anonymised scans. DOPI and gingival phenotype will be scored in the same way as was used clinically at the same sites. Visual gingival inflammation features will be scored (Appendix C) at the same sites as were probed for BOP clinically. The IOS will be further assessed on the same indices by external examiners but only exploratory analyses conducted.

3.2 Selection of Participants

Recruitment routes for this study are as follows: Staff and students at the University of Bristol, individuals who have expressed an interest in being contacted about dental clinical trials and are signed up to the Clinical Trials Unit database, individuals who respond to study posters, information in staff bulletins. Initial study information providing a brief outline of the study with contact details for study staff and a link to the participant information sheet will be distributed via posters and via personal contact details (individuals on the database who have given permission to be contacted in this way only). Potential participants will be asked to contact the clinical trials team for more information about the study.

3.2.1 Planned number of participants

20 participants in good general health aged 18 or over, will be accepted onto the study in order to obtain sufficient examples of gingival health/disease across the range of gingival mucosa pigmentation for each of the 4 groups listed below, 5 participants will be recruited on the basis of their predominant DOPI obtained from simple visual examination, for whom both inflamed and non-inflamed gingivae are visible.

GROUP 0
DOPI Score 0 - No clinical pigmentation (pink-coloured gingiva)
5 participants with predominant DOPI 0

GROUP 1
DOPI Score 1 - mild clinical pigmentation (mild light brown pigmentation)
5 participants with predominant DOPI 1

GROUP 2
DOPI Score 2 - moderate clinical pigmentation (medium brown or mixed pink and brown pigmentation)
5 participants with predominant DOPI 2

GROUP 3
DOPI Score 3 - heavy clinical pigmentation (deep brown or blue-black pigmentation)

5 participants with predominant DOPI 3

Intra-oral photographic examples of the different DOPI scores, BOP and gingival inflammation features will be taken.

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

3.2.2 Inclusion Criteria

- Be aged 18 years and over of either gender and in good general 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 10 natural teeth, not including crowns/bridges
- No oral lesions or conditions
- No systemic disease/ medication affecting the gingival tissues
- Non smokers
- Both inflamed (MGI 2-4) and non-inflamed gingivae/ minimally inflamed gingivae (MGI 0,1) that are visible on simple visual examination

3.2.3 Exclusion Criteria

- Current participation in any other cosmetic trials or any clinical trials.
- Obvious signs of untreated caries, which in the opinion of the Study Dentist, will affect the scientific validity of the study.
- Current orthodontic treatment
- Participant who has undergone depigmenting 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

3.4.1 Assessments

The following endpoint assessments will be employed:

- Bleeding on probing (BOP) (Appendix B)
- Visual gingival inflammation features (Appendix C)
- Dummett Oral Pigmentation Index (DOPI) (Dummett et al 1964) (Appendix A)

3.4.2 Calibration of examiners

The clinical examiner will undergo a calibration exercise. Following a theoretical component a range of phenotype, DOPI and MGI will be assessed and discussed with a gold standard examiner, and this will be repeated until agreement is reached. Following agreement 10 training volunteers will be scored blind by the examiner for pigmentation and phenotype and differences between gold standard and examiner summarized. These volunteers will not participate in the study.

3.4.3 IOS interpretation

The examiner will assess the IOS scans at least 2 weeks after the clinical examination. The scan of the gingivae identified in the clinical assessment will be scored as inflamed (MGI 2-4) or non-inflamed gingivae/minimally inflamed gingivae (MGI 0,1) and descriptors from the MGI categories given for more granular detail (Appendix C). Gingival phenotype (Appendix E), and DOPI (Appendix A) will be scored from the scanned images at identified sites. The IOS scans may be by looked at and scored by external examiners but any data recorded by anyone other than the study examiner will not be included in this main study's analysis.

3.4.4 Timelines

3-6 months clinical phase and interpretation of IOS phases.

3.4.5 Remuneration

Participants will be remunerated £50 for screening only and completion of the study visit.

3.4.6 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	**Screening**	**Visit 1**
Informed Consent	X	
Medical History Collection	X	X*
Oral Soft and Hard Tissue Assessment	X	X*

Assessment	Screening	Visit 1
DOPI (0-3) recording		X
Intra oral scan of mouth		X
Gingival phenotype recording		X
BOP recording		X
AE Recording		X

*if screening and visit 1 are not following on from each other on the same day

Screening visit

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 at the screening visit. Once informed consent has been obtained each participant will be assigned a unique identification number and their eligibility will be reviewed by the study clinician against the inclusion/exclusion criteria and oral soft and hard tissue assessment. The screening and visit 1 will follow on from each other on the same day or be separate visits if participant requests.

Visit 1

Eligible participants will have their oral pigmentation index (DOPI) assessed first (Appendix A), followed by gingival phenotype (Appendix E) and BOP (Appendix B) for all scorable teeth 7-7 in the upper and lower arches. The examiner will perform the IOS after scoring the DOPI and before performing the gingival phenotype and BOP assessments, ensuring that the scan captures all scorable teeth and gingivae. The scan will be saved using the participant's unique identification number. This completes the participant study visit, no interventions or treatments will be offered.

Intraoral scan assessment

At least 2 weeks after the clinical assessment, the examiner will assess the anonymized intraoral scans for each scorable site on the tooth for each participant using the gingival inflammation feature scoring (Appendix C), DOPI (Appendix A), and gingival phenotype (Appendix E). The scan can be manipulated in different orientations enabling the examiner to assess all relevant gingival areas.

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 led 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

Participants will be told that they should contact the study team using the details on the Participant Information Sheet in the event of an adverse event up to 7 days after the study is completed. The phone number is a mobile that is manned out of hours. The study team will also ask participants about adverse events at the study visit. Adverse events will be documented, necessary procedures undertaken and followed up according to GCP. All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. 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 participants. 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 Consideration

5.1 Sample Size Calculation

With 5 participants recruited to each of 4 groups defined by predominant DOPI, there are potentially up to 24 x 6 x 20 = 2880 sites available for study. We assume conservatively that at least 800 bleeding and 800 non-bleeding sites will be scored across the 4 DOPI groups.

For the primary objective, we set a 75% target for sensitivity and specificity for on-scan dichotomised MGI to identify clinical binary BI, corresponding to that used in the recession and plaque studies, and calculate the resulting projected confidence interval width. An ordinary (Wald) 95% confidence interval for an observed proportion of 75% based on a sample of size 800 is from 72.0% to 78.0%. However, this needs to be widened to take account of non-independence within subjects. In these precedent studies, the resulting bootstrap intervals were widened by a factor around 2.5. So the anticipated confidence interval width for either parameter is from 67.5% to 82.5%.

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

For the binary variables studied – on-scan dichotomised MGI to identify clinical binary BI, and gingival phenotype on-scan vs clinical, sensitivity and specificity will be reported, with bootstrap confidence intervals to take account of non-independence within subjects.

These analyses will be run based on all 4 pigmentation groups together. Separate sensitivity and specificity estimates will also be calculated for low and high pigmentation groups and contrasted.

On scan and clinical pigmentation scores will be compared by crosstabulation and calculating misclassification probabilities.

Corresponding analyses at participant level will be developed using either an average score across sites, or for pigmentation, a maximum score.

6. Monitoring

Monitoring of studies is conducted in by the sponsor according to Good Clinical Practice (GCP) (ICH. Topic e6 (r2) guideline for good clinical practice. Nov 2016). 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. 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 (GCP), 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. Written approval must be obtained from the IEC 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 3Shape.

Participants will receive £50 in acknowledgement of their participation in the study. Participants who fail to meet the inclusion and exclusion criteria at the screening stage and cannot continue on the study or if they withdraw part way through the study, will be reimbursed £10 for their time.

The University have 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, 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.

Registration of the clinical study will be conducted by the Sponsor.

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Appendix A – Oral pigmentation index (DOPI) (Dummett et al 1964)

This index of oral pigmentation is commonly used due to its simplicity and ease of use. The scores are as follows:

- Score 0 - No clinical pigmentation (pink-coloured gingiva)
- Score 1 - Mild clinical pigmentation (mild light brown colour)
- Score 2 -Moderate clinical pigmentation (medium brown or mixed pink and brown colour)
- Score 3 - Heavy clinical pigmentation (deep brown or bluish black colour)

The gingivae will be scored at 6 points around the tooth, (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) using the oral pigmentation index.

Appendix B – Bleeding on probing index (BI) (Ainamo & Bay,1975).

Method of examination:

A UNC15 periodontal probe is passed into the gingival crevice at six separated points (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) and if bleeding occurs within 10 to 15 seconds, a positive score of 1, is given. It has been shown that the scores obtained with this index correlate substantially with GI (Löe and Silness, 1963) and MGI (Lobene et al 1986) this has been used in profile studies and short-term studies.

Scoring criteria:

- 0 Absence of bleeding
- 1 Presence of bleeding

Appendix C – Visual gingival inflammation features

The Modified Gingival Index (MGI) (Lobene et al, 1986) was developed as a non-invasive (no probing technique) to the assessment of gingival inflammation, not requiring probing, thus suitable for use on-scan.

The following criteria are adopted:

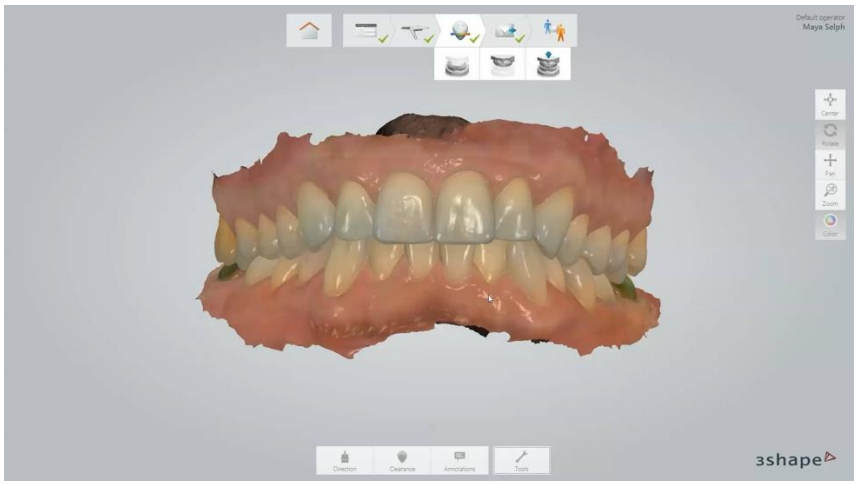
Score	Criteria
0	Absence of inflammation
1	Mild inflammation or with slight changes in color and texture but not in all portions of gingival marginal or papillary
2	Mild inflammation, such as the preceding criteria, in all portions of gingival marginal or papillary
3	Moderate, bright surface inflammation, erythema, edema and/or hypertrophy of gingival marginal or papillary
4	Severe inflammation: erythema, edema and/or marginal gingival hypertrophy of the unit or spontaneous bleeding, papillary, congestion or ulceration

Gingival margins on the intra-oral images will be scored at 6 sites, (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) as 0 (health/minimal gingivitis score 0-1 on the MGI index) or 1 (gingivitis score 2-4 on the MGI index). The examiner will also record descriptors such as change in morphology or colour.

Appendix D – 3D Intra-oral Assessment

A 3D intra-oral scan of the participant's mouth will be obtained using a 3Shape Trios intra-oral scanner and stored using the participant's unique identification number.

At least 2 weeks after the clinical examination, the study examiner will perform the gingival assessments visually from the IOS 3D models for 7-7 teeth, scoring visual gingival inflammation features - as described in Appendix C, Dummett-Gupta Oral Pigmentation Index (DOPI) score (Appendix A), and thick or thin gingival phenotype assessment (Appendix E), blinded to the preceding clinical assessments.



Appendix E – Gingival phenotype clinical assessment (Jepson et al 2018).

Gingival phenotype will be assessed by using a UNC15 periodontal probe to measure the gingival thickness (GT) observing the periodontal probe shining through gingival tissue after being inserted into the sulcus:

0) Probe visible: thin (≤1 mm).

1) Probe not visible: thick (> 1 mm).

One buccal and one lingual score will be recorded for each tooth.

Note: Probe visibility was tested in samples of subjects with specified gingival pigmentation. It is unknown whether the same outcomes are to be expected in populations with different gingival pigmentations.