Clinical Study Protocol 1

Study Title:	A study to compare caries detection in pediatric population between the iTero Element 5D system and bitewing radiographs as a diagnostic aid for the detection of primary carious lesions above the gingiva
Funder:	Align Technology, Ltd. Derech Yitshak Rabin 1, Petach Tikva , Israel 03-6341441
Protocol Version/Date:	June 1st, 2022

TABLE OF CONTENTS

Clinical Study Protocol 1

STUDY SUMMARY

Title	A clinical study to compare caries detection in children between the iTero Element 5D system (NIRI) and bitewing radiographs (BWR) as a diagnostic aid for the detection of primary carious lesions above the gingiva.
Purpose	A comparison of caries detection in pediatric population between the iTero Element 5D system and bitewing radiographs as a diagnostic aid for the detection of primary carious lesions above the gingiva.
Design	This is a non-significant risk, single site, prospective clinical study. The study will be conducted in the department of pediatric dentistry of the faculty of dental medicine of the Hebrew university, Israel
Objectives	**Primary Objective:** The objective of this study is to compare caries detection in pediatric population between the iTero Element 5D system and bitewing radiographs as a diagnostic aid for the detection of primary interproximal carious lesions above the gingiva. **Secondary Objectives**: • To compare users' experience using a qualitative questionnaire • To compare carious lesions depth as appears in NIRI and BWR images to clinical depth observed during caries excavation
Primary Endpoint	**Primary effectiveness endpoint measures:** The iTero 5D will be non-inferior to BWR in detecting the existence of primary interproximal caries lesions above the gingiva in pediatric population. **Secondary effectiveness endpoint** • Qualitative users' feedback relating to: chair time, the ability to capture tooth surfaces (reachability), patient's experience (gag reflex, discomfort) will be collected through questionnaire • Lesion depth will be documented in cases where caries debridement was conducted. NIRI and BWR images will be compared to the clinical findings
Study Device	iTero Element 5D
Eligibility Criteria	Inclusion Criteria: A subject will be considered eligible if the following inclusion criteria are fulfilled: • Ages 4-9 years • Subjects scheduled for bilateral BWR as part of their standard of care

	• Subjects with a recent bilateral BWR which were obtained up to 14 days prior to study visit Exclusion Criteria: A subject will be considered ineligible if any one of following exclusion criteria are fulfilled: • Subjects who have been diagnosed with epilepsy • Subjects with a known allergy to latex or plastic • Subjects with allergies to any dental or oral health products • Subjects who have undergone a dental treatment since the acquisition of the recent bilateral BWR
Sites	This study will be conducted in the department of pediatric dentistry of the Hadassah Medical Center, Faculty of Dental Medicine, Hebrew University of Jerusalem, Israel
Sample Size	70 subjects
Length of Study	Approximately 6 months

Clinical Study Protocol 1

1. INTRODUCTION AND BACKGROUND

1.1 BACKGROUND

In 2007, Cadent Ltd. (now Align Technology, Ltd.) started marketing intraoral scanner systems to the dental industry. iTero scans have been used in more than 3.6 million restorative crowns, bridges, and custom implant abutment cases and more than 13.5 million iTero orthodontic scans, for a total of 17.1 million scans.

The iTero Element 5D system is an intraoral scanner with near-infrared imaging (NIRI) technology.

Near-infrared Imaging (NIRI) is a nonionizing imaging technology that leverages differences in scattering and absorption of near-infrared light depending on the degree of tooth mineralization. In vivo[1] and vitro[2] studies investigating the iTero Element 5D system for the detection of caries have yielded encouraging results.

This prospective study is designed to compare caries detection in pediatric population between the iTero Element 5D system and bitewing radiographs as a diagnostic aid for the detection of primary interproximal carious lesions above the gingiva without using harmful radiation.

2. DESCRIPTION AND INDICATIONS FOR USE

2.1 DEVICE DESCRIPTION

The iTero Element 5D (figure 1) is an intra-oral optical scanner for acquiring digital impressions. The system digitally captures the 3D geometry and color of the patient's intraoral dental structures using a proprietary optical, non-contact, focus detection technique using a Class 1 laser technology.

Figure 1. The iTero Element 5D

The iTero Element 5D incorporates near-infrared illumination capabilities used to provide a near-infrared image of the teeth enabling the detection of both occlusal and proximal caries, at the various stages, ranging from initial enamel caries to established caries reaching the DEJ.

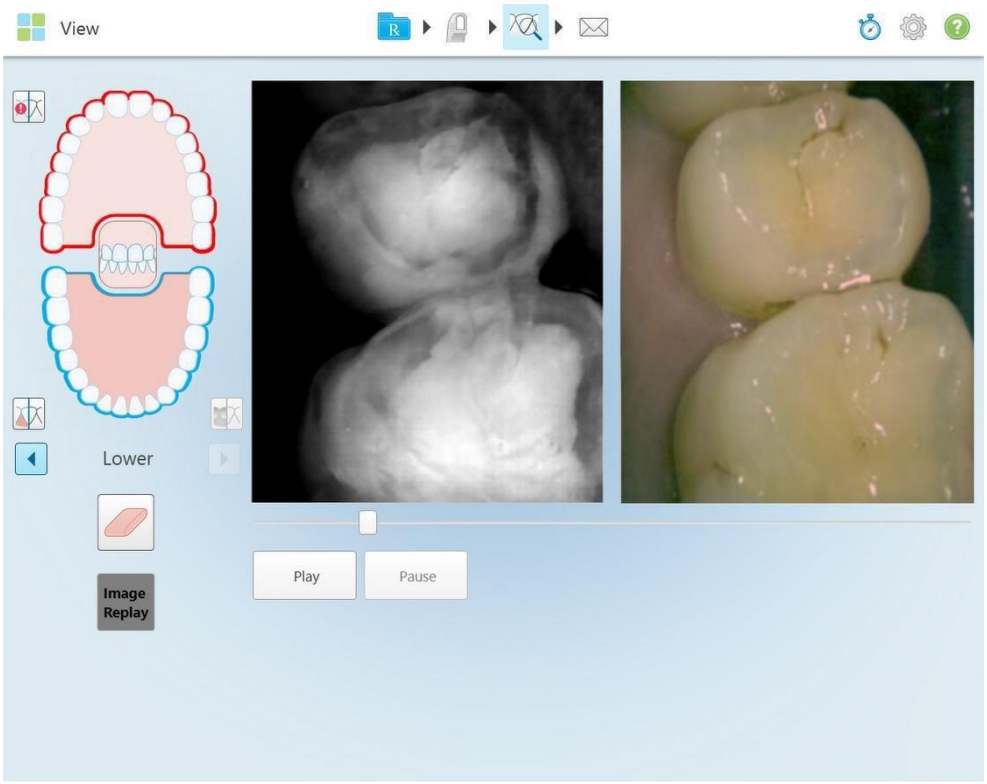

Figure 2. The NIR Cam mode. NIR images are displayed on the main screen while a color image is displayed in the View Finder window

NIR functionality is implemented by using 850nm wavelength LEDs. Incorporating both the NIR images and the color images captured by the system can aid in the detection of caries (Figures 3 and 4).

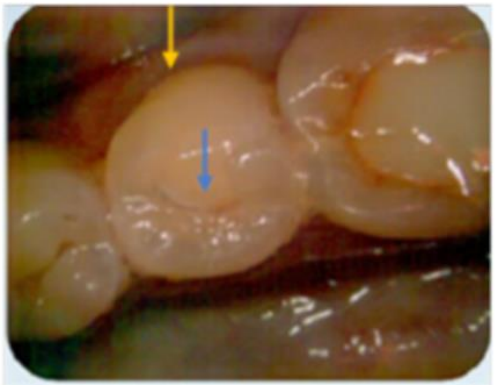

Figure 3.
Color Image as captured by the iTero Element

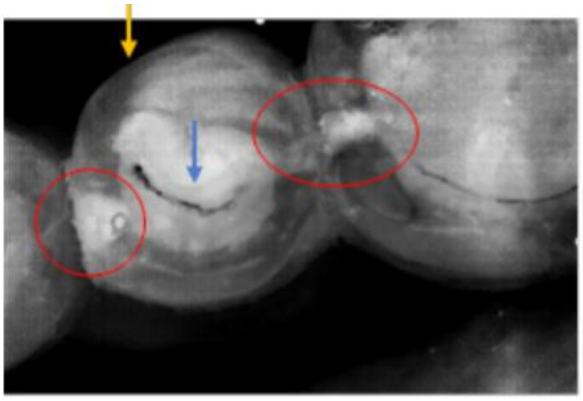

Figure 4.
NIRI image demonstrating two proximal carious lesions (Red circles)

2.2 iTero Element 5D Intended Use

The iTero Element 5D system is indicated for intra oral scanning. NIRI technology of the iTero Element 5D aids in detection and monitoring of interproximal caries lesions above the gingiva without using harmful radiation.

3. STUDY PURPOSE AND OBJECTIVES

3.1 STUDY OBJECTIVES

The objective of this study is to scan subjects intraorally with iTero Element 5D system and compare caries detection in pediatric population to common practice (bitewing radiographs) as a diagnostic aid for the detection of primary interproximal carious lesions above the gingiva.

3.2 SECONDARY OBJECTIVES:

- To compare users' experience using a qualitative questionnaire
- To compare carious lesions depth as appears in NIRI and BWR images to clinical depth observed during caries excavation when indicated.

3.3 DEFINITIONS

Term or Abbreviation	Definition
AE	Adverse Event
BWR	Bite Wing Radiographs
CRF	Case Report Form
DEJ	Dentin-enamel junction
Device	iTero Element 5D system
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions for Use
Investigator	The person responsible for the conduction of this study at each individual site. This person will be

	the treating dentist. The term "Investigator" is used synonymously in this Protocol with "Principal Investigator", "Dentist" and "Doctor".
IR	Infrared
NIR	Near Infra-red
NIRI	foutcome
PID	Patient Identification Number
SAE	Serious adverse event
Funder	Align Technology, Ltd.
Study Monitor or Clinical Research Associate (CRA)	Person who monitors the study data for completeness, accuracy through on-site visits, remote monitoring, etc.

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is a non-significant risk, single site, prospective study to be conducted in the department of pediatric dentistry of the Hadassah Medical Center, Faculty of Dental Medicine, Hebrew University of Jerusalem, Israel. Subject participation will require one visit during which consent, screening, enrollment, and imaging will be performed. An additional follow-up call to the Investigator will take place a month later to review patient records and capture any clinical information recorded since last trial visit if a treatment was planned.

Each subject will be assigned a unique ID number that will link to their data. De-identified data sets will be used for analysis.

Clinical and diagnostic methods to be used during this study are those that are routinely used in the diagnosis of caries in this site, which include bitewing radiographs (BWR). This standard of care is provided for all site's patients, including the patients who don't participate in this clinical study.

A standard set of BWR for subjects ages 4-9 years will be taken to include the complete dentition of the subjects. Any recent bilateral BWR which were obtained up to 14 days prior to study visit may be used. **No additional x-ray should be taken for the sole purpose of this trial.**

In addition to the routine clinical diagnostics, the subjects will be scanned using the 5D system. The investigator will capture a full arch scan of the maxillary arch and mandibular arch of each subject with the iTero Element 5D system. For each subject, the Investigator will grade carious lesions in the BWR and Element intra-oral scan according to ADA staging guidelines[3]. The results will be documented using

Caries Evaluation Forms. The Investigator will assess and document the findings of each diagnostic test separately before reviewing the next test.

In cases where caries debridement indicated, carious lesion depth will be documented during and compared to NIRI and BWR images. **All treatment decisions will be made according to the standard of care in the clinic and no treatment will be conducted for the sole purpose of the study.**

The study will include an interim analysis to assess the iTero Element 5D system useability among the first 20 pediatric subjects. Based on the findings' evaluation, modifications in the study protocol for the remaining 50 subjects will be considered.

Once images from the iTero Element 5D system and the bilateral BWR are obtained, the subject will have completed the study visit.

Data regarding caries treatments that were executed in accordance with the clinic standard of care during a follow-up period of 1 month post study visit will be captured in the CRF.

Duration of the study is estimated to be six months.

All participating doctors and designated office coordinators will be trained on the clinical study protocol and Good Clinical Practices (GCP).

4.1.1 MATERIALS

See section 2.

4.1.2 METHODS

4.1.2.1 INCLUSION CRITERIA

A subject will be considered eligible if the following inclusion criteria are fulfilled:

- Ages 4-9 years
- Subjects scheduled for bilateral BWR as part of their standard of care
- Subjects with a recent bilateral BWR which were obtained up to 14 days prior to study visit

4.1.2.2 EXCLUSION CRITERIA

A subject will be considered ineligible if any one of following exclusion criteria are fulfilled:

- Subjects who have been diagnosed with epilepsy
- Subjects with a known allergy to latex or plastic
- Subjects with allergies to any dental or oral health products
- Subjects who have undergone any dental treatment since the acquisition of the recent bilateral BWR

4.1.2.3 SCHEDULE OF STUDY VISITS

Subject participation will require one patient visit during which consent, screening, enrollment, imaging and study exit will be completed.

- **Initial Visit**

1. Review inclusion and exclusion criteria (Eligibility criteria)
2. Inform subject and obtain written assent form
3. Enrollment Form
4. Intraoral Scan: Subjects will be scanned intraorally using the iTero Element 5D system.
5. Acquisition of recent BWR data.
6. Caries Evaluation Form

4.1.3 END STUDY

The End of Study occurs when a subject has completed all study-related procedures and follow-up. When all subjects have completed the study, a report will be written concluding the findings from the study. Subsequent clinical evaluation and treatment, if indicated will be performed after study completion by each patient's dentist.

4.2 NUMBER OF SUBJECTS/ ASSIGNMENT TO TREATMENT GROUPS

70 subjects will be enrolled in one site.

The study will include an interim analysis to assess the iTero Element 5D system useability among the first 20 pediatric patients. Based on the findings' evaluation, modifications in the study protocol for the remaining 50 subjects will be considered.

4.3 SITE

This study will be conducted by Prof' Moti Moskovitz in the department of pediatric dentistry of the Hadassah Medical Center, Faculty of Dental Medicine, Hebrew University of Jerusalem, Israel. The Investigator will be proficient with the use of the iTero Element 5D system.

4.4 SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time for any reason. The Investigator may withdraw the subject at any time for any reason. If any subject withdraws or is withdrawn from the study, any non-study records that were taken while the subject was enrolled in the study will not be shared with the study Funder and there will be no requirement to continue treatment according to this protocol. Withdrawal from the study will not result in any penalties and will not preclude or interfere with the Investigator's treatment of the subject outside of the study. Additional subjects may be enrolled to substitute for any withdrawn subjects until the study target enrolment is reached.

The schedule of all study activities and procedures is provided in Table 1. No additional invasive or other burdensome interventions in comparison to the standard care will be performed.

Data will be entered into a database, located on a secure server. Each subject will be assigned a unique ID number which will link to their data. Data will be examined for completeness and checked for accuracy. De-identified data sets will be used for analysis.

4.5 CLINICAL DATA MANAGEMENT

CASE REPORT FORMS

The Case Report Forms (CRF) for this Study are as follows:

- Subject Enrollment Form
- Caries Evaluation Forms
- User experience questionnaire
- Data regarding caries extend observed during caries excavation
- Withdrawal Form (if applicable)
- Adverse Event Form (if applicable)
- Protocol Deviation Form (if applicable)

5. STATISTICAL AND ANALYTICAL PLANS

5.1 HYPOTHESIS

The test results can be summarized in the following 2x2 table:

	X-ray is the ground truth	
NIRI	**Negative (no caries)**	**Positive (caries)**
Negative (no caries)	P_{00}	P_{01}
Positive (caries)	P_{10}	P_{11}

Where P_{ij} = the percentage of tooth surfaces under certain condition out of all included surfaces.

As we are taking X-ray as the ground truth, P_{01} is the percentage of surfaces that can be detected as caries by X-ray but not NIRI (NIRI missed detection rate), P_{10} is the percentage of surfaces that can be detected by NIRI, but not X-ray (NIRI over detection rate). By showing that NIRI over detection rate (P_{10}) is not less than NIRI missed detection rate (P_{01}) by non-inferiority margin of M, we can conclude that NIRI is non-inferior than X-ray in detecting caries. Thus, P_{10}-P_{01} provides a measure for assessment of a non-inferiority between two procedures.

Null Hypothesis: P_{10}-$P_{01} \leq$ -M

Alternate Hypothesis: P_{10}-$P_{01} >$ -M

5.2 ASSUMPTIONS

5.2.1 Test results

By assuming [3]:

1. 50% of the participants will have active caries
2. On average there are 1 carious surface per patient with active caries
3. there is minimum of 2 naïve IP surfaces per pediatric patient which may be captured in BWR

Approximately, out of all patients included in the trial, 1.8% of all tooth surfaces are carious and 98.2% of all tooth surfaces are non-carious.

Based on previous iTero 5D study[1], we can assume that for NIRI, the sensitivity for early enamel lesions is 0.51 and specificity is 0.90.

The assumed test results can be summarized as:

	X-ray is the ground truth	
NIRI	**Negative (no caries)**	**Positive (caries)**
Negative (no caries)	88.38%	0.88%
Positive (caries)	9.82%	0.92%

5.2.2 Non- inferiority margin

Based on relevant literature [5] and the results from previous trials, we can assume that the non-inferiority margin to be 5%.

5.3 SAMPLE SIZE

Sample size can be calculated from the sample size equation for comparing paired nominal data by using McNemar's test [4]:

$$n = \frac{[z_\alpha\sqrt{p_{01}+p_{10}} + z_\beta\sqrt{p_{01}+p_{10}-(p_{01}-p_{10})^2}]^2}{(p_{10}-p_{01})^2}$$

Similar formulae can be obtained for the one-sided non-inferiority test by substituting $z_{\alpha/2}$, p_{10} with z_α and $p_{10}+M$:

$$n = \frac{[z_\alpha\sqrt{p_{01}+p_{10}+M} + z_\beta\sqrt{p_{01}+p_{10}+M-(p_{01}-p_{10}-M)^2}]^2}{(p_{10}+M-p_{01})^2}$$

where significance level $\alpha = 0.05$, power $1-\beta = 0.8$, non-inferiority margin M = 5%, assumed detection rate $p_{01} = 0.22\%$, $p_{10} = 2.46\%$

The minimum sample size required is 89 surfaces. Assuming the drop off rate to be 30%, an additional 39 surfaces will be recruited, so the total number of surfaces needed for the clinical trial is 128. assuming a minimum of 2 naïve IP surfaces per paediatric patient.

The minimum required patient count and site count 70 patients in one trial site.

5.4 STUDY MEASURES

5.4.1 Primary effectiveness endpoint measures

The iTero 5D will be non-inferior to BWR in detecting the existence of primary interproximal caries lesions above the gingiva.

5.4.2 Secondary effectiveness endpoint measures

The iTero 5D will be non-inferior to BWR when comparing clinical findings during caries debridement

5.5 STATISTICAL ANALYSIS PLAN

Statistical tests will be performed to show comparison between iTero NIRI technology of the iTero Element 5D and bite-wing x-ray in detecting the existence of primary interproximal caries lesions above the gingiva

- Two-sided McNemar's Chi-square test to show if there is a statistically significant difference between the detection ability of the iTero NIRI technology of the iTero Element 5D and bite-wing x-ray

- Asymptotic Non-Inferiority test to show if the false positive (FP) rate (P_{10}) is non-inferior than false negative (FN) rate (P_{01}) with non-inferiority margin as 0.05, which means iTero NIRI technology of the iTero Element 5D is non-inferior than bite-wing x-ray in detecting primary interproximal caries

- One-sided binomial test to show if the false positive (FP) count (C_{10}) is significantly higher than false negative (FN) count (C_{01}), which indicates if iTero NIRI technology of the iTero Element 5D can detect more primary interproximal caries than bite-wing x-ray

- Kappa coefficient will be calculated to assess the agreement between two methods. (Moderate agreement (Kappa 0.41–0.60) is expected)

6. POTENTIAL SUBJECT RISKS

Generally, there are no additional risks to patients involved in this study. Patients undergoing dental diagnosis will not have any additional risk due to the 3D intraoral scan. Procedures and treatments described in this protocol are in accordance with current dentistry practices. All patient contacting material are commercially available, and have met all applicable regulatory standards.

Very rare, soft electrical shock. One case of soft electric shock originating from the backside of the base unit and without physical harm reported during 2018. For persons who have been diagnosed with Epilepsy, there is a risk of epileptic shock from the flashing light from the system. These persons are excluded from this clinical study. Potential minimal risk could be if a subject has an allergic reaction to the materials used during treatment.

7. SCHEDULE OF ASSESSMENT (TREATMENT PERIOD)

Table 1: Schedule of Assessments

Procedures/Forms	Visit 1	Week 5 1 month follow-up on patient records
Evaluation of eligibility criteria	X	
Informed Consent	X	
Intraoral Scan	X	
Obtain recent BWR Radiographs data	X	
CRF - Enrollment Form	X	
CRF - Caries Evaluation Form (BWR, 5D Intraoral scan)	X	
Review Patient records and capture any clinical information recorded since last trial visit, if treatment was performed.		X

8. REFERENCES:

1. Metzger Z, Colson DG, Bown P, Weihard T, Baresel I, Nolting T. Reflected near-infrared light versus bite-wing radiography for the detection of proximal caries: A multicenter prospective clinical study conducted in private practices. J Dent. 2021 Oct 24

2. Litzenburger F, Heck K, Kaisarly D, Kunzelmann KH. Diagnostic validity of early proximal caries detection using near-infrared imaging technology on 3D range data of posterior teeth. Clin Oral Investig. 2021 Oct 12.

3. Young, Douglas A., et al. "The American Dental Association caries classification system for clinical practice: a report of the American Dental Association Council on Scientific Affairs." The Journal of the American Dental Association 146.2 (2015): 79-86.
4.
5. National Institute of Dental and Craniofacial Research https://www.nidcr.nih.gov/research/data-statistics/dental-caries/adults
6. Kühnisch J. In vivo validation of near-infrared light transillumination for interproximal dentin caries detection. Clin Oral Investig. 2016 May;20(4):821-9.
7. Ahn, S., Park, S.H. and Lee, K.H., 2013. How to demonstrate similarity by using noninferiority and equivalence statistical testing in radiology research. Radiology, 267(2), pp.328-338.
8. Chow, S.C., Shao, J., Wang, H. and Lokhnygina, Y., 2017. Sample size calculations in clinical research. Chapman and Hall/CRC. page 155.