A clinical trial to evaluate the effectiveness and safety of Dual Energy Cone Beam Computed Tomography (DE-CBCT) imaging for quantitative measurement of jaw bone density

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Protocol Number:	**IRB#20-001768**
Version Date:	16 November 2020
Investigational Product:	Dual-energy Cone Beam Computed Tomography Unit, *RCT720*
Sponsor:	Ray Co. Ltd
Funding Organization:	Seoul National University Seoul, S. Korea
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Coordinating Center:	If applicable

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the project's sponsors with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: IRB#20-001768

Protocol Title: A clinical trial to evaluate the effectiveness and safety of Dual Energy Cone Beam Computed Tomography (DE-CBCT) imaging for assessment of jaw bone density

Protocol Date:

_____ _____

Investigator Signature *Date*

Print Name and Title	
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PERSONNEL AND RESPONSIBIITIES

Sanjay M Mallya, BDS, MDS, PhD, Principal Investigator
Dr. Mallya will serve as the PI of this project. He will be the primary contact person for all administrative and research issues related to this project. He will coordinate with the UCLA School of Dentistry Research Office and/or the UCLA Office of Intellectual Property and Industry Sponsored Research for proposal submission and post award processing. He will co-ordinate preparation and submission of all documentation needed for Institutional Review Board review and approval of this project and ensure that all procedures are carried out as per institutional guidelines for human subjects research. He will coordinate with the UCLA School of Dentistry Finance Office on all post-award budgetary management of this contract. He will assume primary responsibility for the planning and execution of the proposed image analyses. He will coordinate with the Information Technology support staff to design and implement the appropriate data management and storage plans. He will coordinate with the staff research associate to implement procedures for timely submission of results to project sponsors as required.

Tara Aghaloo, DDS, PhD, Co-Investigator
Dr. Aghaloo will serve as a co-investigator on this project. She will participate in the design, execution and analyses of the data as described in this proposal. She will coordinate with the CRC for this study for patient recruitment, as appropriate. As needed, she may participate in administrative aspects of this proposal, as described above.

Sotirios Tetradis, DDS, PhD, Co-Investigator
Dr. Tetradis will serve as a co-investigator on this project. He will participate in the design, execution and analyses of the data as described in this proposal. As needed, he may participate in administrative aspects of this proposal, as described above.

Reuben Kim, DDS, PhD, Co-Investigator
Dr. Kim will serve as a co-investigator on this project. He will participate in the design, execution and analyses of the data as described in this proposal. As needed, he may participate in administrative aspects of this proposal, as described above.

Staff Research Associate, To Be Hired
The SRA will provide support to Principal- and Co-investigators on all administrative aspects of this study, including IRB preparation and submission, coordination with project sponsors and collaborators, documentation of informed consent, maintenance of research data, collation of results and coordination within the research group meetings and with collaborators to ensure appropriate project advancement.

STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812).

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the UCLA Institutional Review Board (IRB) for review and approval obtained before any participant is enrolled. Any amendment to the protocol will be submitted to the UCLA IRB for review and approval before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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List of Abbreviations

AE	adverse event
BD	bone density
CFR	Code of Federal Regulations
CRF	case report form
CBCT	cone beam computed tomography
CT	computed tomography
DE-CBCT	dual-energy cone beam computed tomography
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MDCT	multidetector computed tomography
QC	Quality Control
PI	Principal Investigator
UADE	Unanticipated Adverse Device Effect

1 PROTOCOL SUMMARY

1.1 Synopsis

TITLE	A clinical trial to evaluate the effectiveness and safety of Dual Energy Cone-Beam Computed Tomography (DE-CBCT) imaging for assessment of jaw bone density
SPONSOR	Ray Co., Ltd.
DEVICE MANUFACTURER	Ray Co., Ltd.
RATIONALE	Current radiologic imaging modalities used in dentistry provide information on the morphology of the hard tissues. Additional information on the density of bone has practical relevance, for example, in dental implant treatment planning, where local bone quality is a known strong predictor of successful implant osseointegration. The Dual-Energy Cone Beam Computed Tomography (DE-CBCT) device is designed to overcome limitations of traditional imaging and will provide assessment of jaw bone density in additional to morphological information. This clinical trial will examine the application of DE-CBCT to assess jaw bone density and compare Hounsfield units (HU) values with multidetector CT, an established standard for assessing BD.
STUDY DESIGN	This is a single center, open-label trial, designed to enroll 24 patients. Both, the researcher and the subject know the treatment the participant is receiving.
PRIMARY OBJECTIVE	To evaluate the effectiveness and safety of DE-CBCT to evaluate jaw bone density and compare HU values with those of multidetector CT, an established standard for assessing BD.
NUMBER OF SUBJECTS	24 patients

SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Patients who need x-ray imaging for dental treatment planning and/or diagnosis 2. Males or females aged older than 21 3. Can follow instructions to be positioned into the CT scanner 4. Can remain physically immobile during the CT scan acquisition 5. Voluntarily sign and date the informed consent Exclusion Criteria: 1. Pregnancy 2. Patients who are unable to comprehend the risks of the study to provide informed consent 3. Extensive dental restorations, maxillofacial prosthesis, or orthopedic hardware that likely may cause artifacts and degrade quality, as determined by the study radiologists
TEST DEVICE, *MODEL*, PURPOSE	Dual Energy-Cone Beam Computed Tomography (DE-CBCT), *RCT720*
CONTROL DEVICE, *MODEL*, PURPOSE	Multidetector Computed Tomography (MDCT),
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 30 days ***Total Study period:*** *12 months* ***Enrollment & Follow-up:*** *1 month* The total duration of the study is expected to 12 months. Once enrolled, the test subject will be on the study for one month including recruitment and final subject follow-up.
STUDY METHOD	The study is based on two visits (VISIT 1 and VISIT 2) • DAY 0 (enrollment): Subject is queried for inclusion/exclusion criteria and informed about the study. If he/she agrees to participate, inclusion/exclusion criteria and informed consent will be documented. An imaging stent, which bears radiopaque markers, will be also created for each patient. • VISIT 1: Inclusion/exclusion criteria will be reconfirmed and the DE-CBCT imaging will be completed. • VISIT 2 (no more than 30 days since the enrollment): Inclusion/exclusion criteria will be reconfirmed and MDCT imaging completed. *- Depending on availability of scheduling on MDCT unit, Visit 2 may occur on the same day as Visit 1.*
Clinical Assessments	The following assessments will be performed and recorded on Case Report Form: • Demographics • Any relevant medical history • Site-specific BD assessment (Region of Interest, ROI) • Adverse Events
PRIMARY ENDPOINT	Jaw BD (HU values) assessed by DE-CBCT and by MDCT
SECONDARY ENDPOINT	Agreement between the BD assessments by evaluators

SAFETY EVALUATIONS	**Incidence of adverse events (AE):** Adverse events on the days of the study visits will be documented. The PI/staff evaluates the severity of AE and the causal relationship using 'safety evaluation criteria.' The PI will report the case to the investigator/sponsor and IRB subsequently.
PLANNED INTERIM ANALYSES	None
STATISTICS **Primary Analysis Plan**	• The correlation between DE-CBCT and MDCT HU values of bone density will be performed using Pearson. • The agreement between DE-CBCT and MDCT HU values of bone density will be performed using Bland-Altman plots. • In order to evaluate the observer reliability, Kappa statistics will be performed.
Rationale for Number of Subjects	The correlation coefficient of human mandibular bone density (in HU) between CBCT and MDCT was observed to be 0.89, according to the study conducted by Parsa et al. (Reference paper: Bone quality evaluation at dental implant site using multidetector CT, micro-CT, and cone beam CT) Using the formula below, the number of patients is calculated to be 7. $\mathrm{n} = \left(\frac{z_{\alpha/2} + z_{\beta}}{\mathrm{C}(r_0)}\right)^2 + 3, \qquad \mathrm{C}(r_0) = \frac{1}{2}\ln\left(\frac{1+r_0}{1-r_0}\right)$ Since we have three age groups (7x3 = 21) and expect the dropout rate to be 10% (21x(1+0.1)=24), a total of 24patients will be enrolled for the current study.

1.2 Schema

Day 0	
PRE-STUDY SCREENING and RECRUITMENT	• Inform patients about the study • Identify and screen potential subjects for inclusion and exclusion criteria • Obtain informed consent • Fabricate stent for enrolled patients

Acceptable time frame: Day 1 to day 30	
VISIT 1	• Acquire dual energy CBCT scan of the jaws

Acceptable time frame: Day 1 to day 30	
VISIT 2*	• Acquire MDCT scan of the jaws

* Visit 2 shall not be more than 30 days before/after visit 1.
* Depending on availability of scheduling on MDCT unit, Visit 2 may occur on the same day as Visit 1.

1.3 Schedule of activities

Procedures	**Screening**	**Study Visit 1**	**Study visit 2 (≤30 d from visit 1)**
Allowable windows for visit	Day 0	Day 1	Day 30
Informed consent	X	X	
Demographics	X	X	
Medical history	X	X	
DE-CBCT		X	
MDCT			X

2 INTRODUCTION

2.1 Study Rationale

Current imaging modalities used in dentistry include 2-dimensional radiographs, and 3-dimensional CT imaging. All of these x-ray-based modalities provide information on the morphology and architecture of the dental hard tissues and alveolar bone. Although these images display relative degrees of solidity within these hard tissues, they are of limited value for reliable, qualitative assessment of the bone density. Information on the jaw bone density has practical relevance, for example, in dental implant treatment planning, where local bone quality is a known strong predictor of successful implant osseointegration.

The Dual-Energy Cone Beam Computed Tomography (DE-CBCT) device is designed to overcome limitations of traditional dental imaging and will provide assessment of jaw bone density in additional to morphological information. This clinical trial will examine the application of DE-CBCT to assess jaw bone density and compare this novel device with multidetector computed tomography (MDCT).

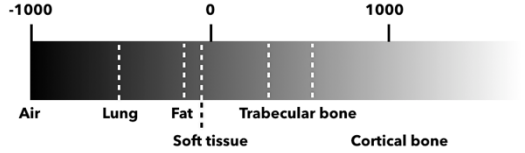
2.2 Background and Significance

Computed tomography (CT) is an x-ray-based imaging technique that produces cross-sectional images of the body. In all CT techniques, a collimated x-ray source and a detector revolve around the patient. The detector records photon attenuation by assessing the number of photons that exit the patient, registering this information at several hundred angles through the rotational arc. Complex mathematical algorithms translate this attenuation data into a three-dimensional (3D) map that spatially locates the attenuating structures.[1]

MDCT is the most widely used CT scanner design across the world. In MDCT, multiple rows of detectors are incorporated into the array in the *z*-axis (craniocaudal axis, patient's head to foot), allowing capture of multiple image slices during each gantry revolution. Current detector spatial resolution allows imaging of submillimeter dimensions. Volumetric acquisition with isotropic imaging allows reformatting in planes different from the axial acquisition, without compromising image quality. Contemporary MDCT scanners have 64 to 128 rows of detectors, with some vendors manufacturing scanners with 320 and 640 detector rows.

CBCT is an advanced imaging modality with several applications in dentomaxillofacial diagnosis and treatment planning.[2-8] In this technique, a cone-shaped x-ray beam and a detector rotate around the patient acquiring multiple projections that reconstructed into a volumetric image. Depending on the manufacturer and protocol, detector pixel elements are in the range of 70µm to 400µm, providing high resolution 3D volumetric imaging.

In CT data, each voxel in the reconstructed CT volume is represented by a numerical gray value (CT number).1 This number reflects the degree of x-ray attenuation and represents the average linear attenuation coefficient of that voxel. Major factors that influence the CT number include the tissue features (atomic number and density) and homogeneity and energy of the x-ray beam. CT numbers are expressed as Hounsfield units (HU), which expresses x-ray attenuation of a voxel relative to the attenuation of water. In the HU scale, the CT number of water is defined as zero, and the CT number of air is defined as −1000. The HU values of ~ 200 and higher represent densities of trabecular and cortical bone.



CBCT and HU: Assessment of BD has relevance in dentistry. The degree of mineralization of bone at dental implant sites are strong determinants of implant osseointegration and stability. Likewise, closer representation of attenuation and CT numbers are important for third party applications of CT data that use automatic segmentation for computer-aided design and computer-aided manufacturing applications. Current dental CBCT units do not apply a standard scaling system for representing CT numbers, and attempts to convert CBCT numbers to HU are unsuccessful. In particular, the cone beam geometry of the x-ray beam produces scatter radiation and consequently decrease the signal-to-noise ratio, with a practical negative impact on contrast resolution of the CBCT image.[1]

Studies from our group and others have shown that although the relationship between CBCT numbers and object density is linear, this relationship is influenced by several factors including imaging protocol and anatomic location.[9-15] Collectively, these factors result in an inhomogeneity of CT numbers on CBCT scans. For example, the CT number of the same object differed depending on the anatomical location in which it was imaged.[15] Specifically, the CT numbers of phantom objects were higher when placed within the anterior region of the jaw and lower in the posterior regions.[9,15] Importantly, objects with low x-ray attenuation suffered greater variability than objects with high attenuation.[9,15] Moreover, these CT numbers are markedly influenced by scanner settings.[11] Due to these inconsistencies in CT numbers through the CBCT volume, it is not feasible to apply mathematical equations that will accurately derive HU through the CBCT volume. Nevertheless, there is promise to harness the power of CT imaging to decipher more than just morphological information. In a prior clinical study, CBCT gray values assessed at edentulous implant sites showed a trend of decreasing gray values with bone quality type.[14]

Current CBCT imaging uses a poly-energetic x-ray beam, with peak energies typically in the range of 90kVp to 110kVp. Attenuation of the x-ray photons is a function of the absorber's atomic number and the energy of the incident photons, and the resultant gray value in an image pixel represents the magnitude of this attenuation. As described above, factors include scatter radiation and reconstruction algorithms impact the accuracy of the true attenuation. In DE-CBCT, attenuation data is assessed using two x-ray sources with different energy spectra. Following acquisition at both energies, mathematical algorithms are applied to compare attenuation between the two energies, and to translate this information into better estimates of bone mineral density. Thus, DE-CBCT provides an approach to assess both morphology and the chemical composition of bone. The proposed study will examine a new CT device, a DE-CBCT unit to provide additional valuable information on bone density, a factor that impacts surgical technique and successful osseointegration.

Practical Applications of BD assessment in dental implant treatment planning: CBCT imaging is widely used to evaluate edentulous sites for potential dental implant placement. Assessment of bone quantity and quality at the potential implant site is an essential objective of imaging. Bone quantity refers to the height and width of the residual alveolar bone. Bone quality represents the thickness of cortical bone, the abundance of trabecular bone, and the overall degree of mineralization.[14] In particular, local quality of bone is a key factor that influences successful osseointegration. The Lekholm and Zarb classification[16] is widely used to categorize bone quantity and quality for implant placement. This classification scheme continues to be used in clinical practice and is recorded as the subjective perception during drilling prior to implant placement. In this classification bone quality is categorized into four types:
Type 1: Predominantly cortical bone
Type II: Central core of dense trabecular bone surrounded by a thick layer of cortical bone
Type III: A thin layer of cortical bone surrounding dense trabecular bone
Type IV: A thin layer of cortical bone that surrounds low density trabecular bone

Another widely used assessment, the Misch classification scheme, attempts to categorize subjective radiologic appearance based on a range of HU.[17] Similar to the Lekholm and Zarb classification, this scheme is a subjective assessment, and this limits the depth of practical application for reliable prediction of successful osseointegration.

Misch classification of bone density.

TABLE 15.2 Misch Classification of Bone Density

Classification Type	Radiographic Appearance	Typical Anatomic Location	MDCT Density Range (HU)
D1	Primarily composed of dense cortical bone Marrow spaces are hardly visible	Occasionally in anterior mandible Rarely in posterior mandible	>1250
D2	Thick outer layer of porous cortical bone Coarse trabecular bone pattern	Commonly in anterior and posterior mandible Occasionally in anterior maxilla	850–1250
D3	Thinner layer of porous cortical bone Fine trabecular bone pattern	Commonly in anterior maxilla, posterior maxilla, and posterior mandible Occasionally in anterior mandible	350–850
D4	Faint to imperceptible outline of thin cortical bone Alveolar process is primarily composed of fine trabecular bone	Commonly in posterior maxilla Rarely in anterior maxilla	150–350

HU, Hounsfield units; *MDCT,* multidetector computed tomography.
Modified from Misch CE. *Contemporary Implant Dentistry.* 3rd ed. St. Louis: Mosby; 2008.

Pre-surgical assessment of bone quality is of high practical relevance. Success rates of implants placed implants placed in D4 have lower success rates. Modifications to surgical techniques have been devised to improve osseointegration of implants placed in low density bone.[18] In this study, jaw bone density assessed by DE-CBCT will be compared with that measured on MDCT, which is the gold standard for measuring bone density. The ability of DE-CBCT to provide information on jaw bone density could have tremendous impact on case selection and positively impact outcomes.

2.3 Risk-Benefit Assessment

2.3.1 Known potential risks

The risks from this study are related to radiation exposure. Subjects in this study will receive two x-ray examinations:

(a) *MDCT, Maxillofacial, without contrast, Standard treatment, CPT 70486:* The MDCT exam is acquired as standard treatment protocol for dental treatment planning. The typical dose (Dose-area product, DAP) for CT examination of head is 35,000-48,000 mGy•cm^2. [20]

(b) *DE-CBCT, Investigational device:* The radiation dose (DAP) is approximately 883 mGy•cm^2. Overall, the doses from DE-CBCT are low to negligible. Compared with MDCT, the radiation dose from DE-CBCT is approximately one fiftieth (2%).

The radiation doses are orders of magnitude below threshold doses needed to cause deterministic effects. Thus, we do not expect any immediate risks from radiation exposure.
The only potential risks of this added radiation are long-term risk of radiation induced cancer. As described above, the radiation doses delivered by the DE-CBCT device are several-fold lower than diagnostic CT scans, indicating that these risks are much lower than risks of current diagnostic imaging procedures.

2.3.2 Known potential benefits

There are no direct established health benefits from the DE-CBCT. However, the subjects' participation in this study will provide essential data that could potentially improve health outcomes, that would eventually benefit the society at large.

2.3.3 Risk-benefit assessment

Although participants do not benefit directly from the DE-CBCT scan, the additional risks are minimal. The device design, intended to deliver low doses for maxillofacial imaging, is the key method to minimize current risks, as well as risks to patients for potential future use.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary objective

To evaluate the effectiveness and safety of DE-CBCT to assess jaw bone density and compare these values with MDCT, an established standard for assessment of BD.

3.2 Secondary objective

To analyze the agreement between the BD assessments by the evaluators

4 STUDY DESIGN

4.1 Overall design

This study will test the hypotheses that DE-CBCT will be equivalent to MDCT to assess BD in the jaw bones.

The study design is an open-label clinical trial to evaluate the effectiveness and accuracy of DE-CBCT to assess BD in jaw bones. This single center trial will enroll 24 subjects, with equal gender distribution. In order to investigate the HU values of bone density across the intended patient population age range, the patients will be recruited according to the three classified age groups. Each study subject will receive both the investigational DE-CBCT and the standard of care MDCT scan, which serves as the control.

Age Group	Number of Patients
Below age 45 ($\leq$ 45 years old)	Male : 4 Female: 4
Older than 45 and less than 65 (45 – 65 years old)	Male : 4 Female: 4
Over age 65 ($\geq$ 65 years old)	Male : 4 Female: 4

The study-specific procedures will be completed in two visits at the UCLA Dental Center and the UCLA Ronald Reagan Hospital. Subjects recruited into the study are those requiring CT imaging for dental diagnosis or treatment planning, including but not limited to implant treatment planning, jaw bone pathoses, impacted teeth etc. In order to mark the ROI area, the dental surgeon will fabricate a custom acrylic stent worn by the patient during imaging. The stent incorporates radiopaque markers that indicate the location(s) and angulation(s) of the proposed ROI area.

The study-specific procedures are as below:

Screening	Informed consent	Study-specific process, 20-30 min
Visit 1	DE-CBCT (experimental scan)	~20 min

Visit 2	MDCT (Standard of care scan)	~20 min

Following scan acquisition, the study's investigators will evaluate the CT scan and make BD assessments at specific locations, as directed by the radiopaque markers in the stent. BD will be assessed in at least three individual sites per subject.

4.2 Scientific rationale

The basic premise of this study is that the investigational device (DE-CBCT) will provide accurate estimates of BD in the dento-alveolar bone. The accuracy of DE-CBCT assessments will be determined against the clinical gold standard for BD assessment. The outcome of this study will demonstrate the efficacy and accuracy of DE-CBCT to assess BD at jaw sites.

4.3 Blinding

Evaluators are able to distinguish DE-CBCT and MDCT by appearance and thus cannot be blinded to the modality. However, investigators measuring the BMD will be blinded to the measurements on the standard/experimental CT, and to measurements made by other investigators, until the measurement phase is completed. The statistician will remain blinded, until the data is locked and delivered for statistical analysis.

4.4 Justification for dose

Not applicable

4.5 End of study definition

A participant will be considered to have completed the study if he/she has completed both scheduled visits including the DE-CBCT and MDCT imaging.

5 STUDY POPULATION

5.1 Rationale for Number of Subjects

Based on the reference paper called "Bone quality evaluation at dental implant site using multislice CT, micro-CT, and cone beam CT," the correlation coefficient of human mandibular bone density (HU) between CBCT and MDCT was observed to be 0.89. In assumption that there also exists a correlation between the HU values of DE-CBCT images and MDCT images, Pearson's correlation analysis was considered for calculating the appropriate number of patients for the current study.
With 0.05 Type 1 Error (significance level 5%) and 80% statistical power, the number of patients is calculated to be 7. Further considering the three age groups and 10% of dropout rate will result in a total of 24 patients to be enrolled in the study.

Below is the hypothesis and calculation formula:

- Hypothesis:

  Null hypothesis : $H_0 : \rho = 0$, Alternative hypothesis : $H1 : \rho = r_0 \neq 0$

- Formula:

$$\mathrm{n} = \left(\frac{z_{\alpha/2} + z_{\beta}}{\mathrm{C}(r_0)}\right)^2 + 3, \qquad \mathrm{C}(r_0) = \frac{1}{2}\ln\left(\frac{1+r_0}{1-r_0}\right)$$

ln : Log to the base of e

r_0 : Correlation coefficient value to be tested

α : Type 1 error

β : Type II error

$z_{\alpha/2}$: Value corresponding to 100(α/2)% in the standard normal distribution curve

z_{β} : Value corresponding to 100(β)% in the standard normal distribution curve

- Calculation:

① α=0.05, 1-β=0.80

② r_0=0.89

$$\mathrm{n} = \left(\frac{z_{\alpha/2}+z_{\beta}}{\mathrm{C}(r_0)}\right)^2 + 3,\ \mathrm{C}(r_0) = \frac{1}{2}\ln\left(\frac{1+r_0}{1-r_0}\right)$$
$$= \left(\frac{1.960+0.842}{1.422}\right)^2 + 3 = 6.88$$

③ Three age groups: 7 X 3=21

④ Dropout rate: 10%, n=24

5.2 Inclusion criteria

- Patients who need x-ray imaging for dental diagnosis and/or treatment planning
- Males or females aged older than 21
- Can follow instructions to be positioned into the CT scanner
- Can remain physically immobile during the CT scan acquisition
- Voluntarily sign and date the informed consent

5.3 Exclusion criteria

- Pregnancy
- Patients who are unable to comprehend the risks of the study to provide informed consent
- Extensive dental restorations, maxillofacial prosthesis, or orthopedic hardware that likely may cause artifacts and degrade quality, as determined by the study radiologists.

5.4 Lifestyle considerations

Not applicable

5.5 Screen failures

Patients who sign the informed consent will have satisfied all inclusion and exclusion criteria, and thus, it is unlikely that we will have screen failures. Screen failures could occur if a patient decides to revoke informed consent or provides additional data that changes eligibility assessment. In such cases, we will document relevant information including the reason for screen failure, and the specific criteria that are unmet.

As per the American College of Radiology practice parameters for imaging pregnant patients[19], diagnostic examinations of the head and neck do NOT require verification of pregnancy status, because

they do not directly expose the pelvic/abdominal area, and the scattered dose to the embryo/fetus is negligible. Nevertheless, pregnant patients are excluded from this study, following a markedly conservative approach to radiation safety.
Verification of pregnancy status will be via clinical history and is often sufficient for this examination. For example, women may attest that they cannot reasonably be pregnant, are between regular menstrual periods, or are on long-term birth control. From a scientific viewpoint, uncertainty regarding pregnancy typically exists in the early stages. Given the low radiation doses, the likelihood of effects on the embryo-fetus are negligible.

5.6 Strategies for recruitment

- The study will recruit subjects who are seeking dental treatment at the UCLA Dental Center.
- The target population is patients, 21 years and older.
- In this study, we will aim for an approximately equal gender distribution in the three age groups.
- Potential participants will be identified via the UCLA Dental Center Clinics, and participation opportunity will be publicized at these clinics and to relevant providers of dental treatment at the UCLA Dental Clinic via electronic and paper communication.
- Vulnerable populations are NOT a target of this recruitment.
- The subject will receive the standard of care MDCT scan at no charge, typically a $400 value. The DE-CBCT scan will be done at no charge.
- Participants will be reimbursed for parking at the UCLA School of Dentistry (Visit 1) and the UCLA Ronal Reagan Hospital (Visit 2), approximately $22 in value.
- Because this study involves an additional visit, participants will receive financial compensation of $100.

6 STUDY INTERVENTIONS AND ADMINISTRATION

6.1 Study intervention administration

6.1.1 Study intervention description

The device a Dual Energy-Cone Beam Computed Tomography (DE-CBCT), RCT720, is used to make the images of subjects' dento-alveolar bone. The study's radiologist will evaluate these images to make assessments of jaw bone density at specific sites.

6.1.2 Administration

The image will be taken once, preferably on the day of the patient's enrollment into the study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

The investigational device is a CT scanner that will be installed by the manufacturer in the UCLA Oral Radiology Clinic and will be used according to the instructions.

- Investigational Device Description
  The RCT720 is intended for 3D computed tomography for scanning hard tissues like bone and teeth. By rotating the C-arm which is embedded with a dual high voltage generator, all-in-one x-ray tube and a detector on each end, cone beam computed tomography(CBCT) images of dental maxillofacial are attained by recombining data from the same level that are scanned

from different angles. The dual energy can be used to obtain the HU value for confirming alveolar bone density.

- Manufacturer: Ray Co., Ltd.
- Trade Name: RCT720
- Common Name: Dental panoramic/tomography and cephalometric x-ray system
- Regulation Name: Computed tomography x-ray system
- Regulation Number: 892.1750
- Device Class: II

The control device is a CT scanner that is already installed at the UCLA Ronal Reagan Hospital for the standard diagnosis. It will be used according to the instructions.

- Control Device Description
  The Multi Detector Computed Tomography (MDCT) uses multiple x-ray tubes and detectors to produce tomographic images by recombining coplanar data obtained from different angles.

  - Manufacturer: To Be Established by UCLA Radiology
  - Trade Name: Multidetector Computed Tomography
  - Common Name: Whole body computerized tomography X-ray imaging device
  - Regulation Name: To Be Established by UCLA Radiology
  - Regulation Number: To Be Established by UCLA Radiology
  - Device Class: II

6.2.2 Formulation, appearance, packaging, and labeling

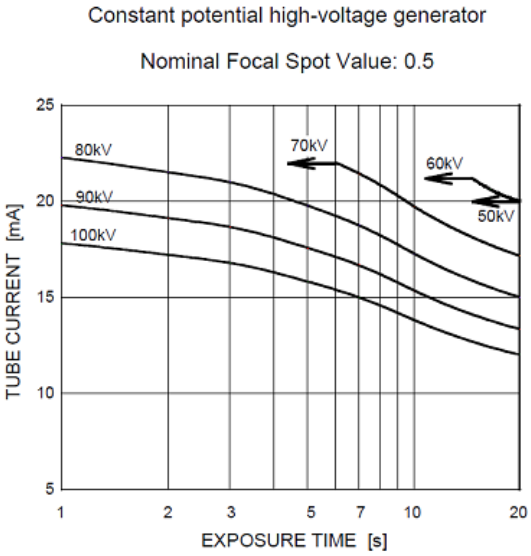
- Investigational Device (RCT720)
  - Appearance and Formulation:

No.	Label	Function
(1)	Vertical carriage	Device which supports the rotating arm
(2)	CT Detector	Part embedded with a detector used for acquiring the CT imaging where the X-ray penetrating the subject is received then converted into an electrical signal and sent to the controller.
(3)	X-ray generator	Part which generates the X-ray for imaging
(4)	Touch Monitor	Includes functions (height adjustment, alignment beam on/off, product initialization) that can control the basic settings for product operation
(5)	Handle	Part grabbed by the patient to get in position for imaging
(6)	Column	Part which adjusts the product height according to the patient's height
(7)	Base	Part which supports the entire equipment system

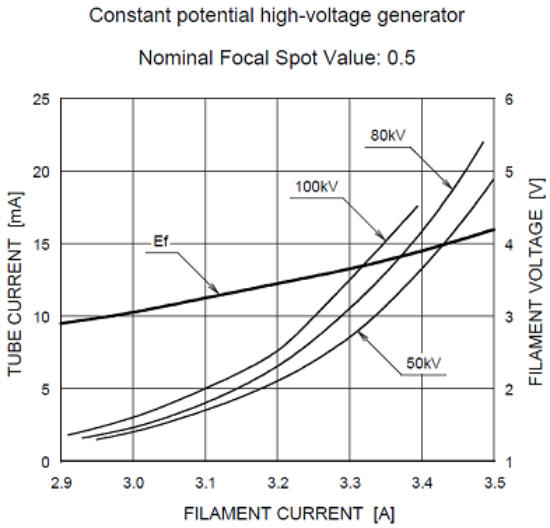
- Technical Specifications
  1) X-ray tube:

- Focal sport dimension: 0.5mm
- Maximum tube voltage (imaging): 50~100kVp
- Target angle: 5°
- Inherent filtration: 0.8mm Al at 50kV
- X-ray tube characteristic curve:

a. Maximum rating chart:

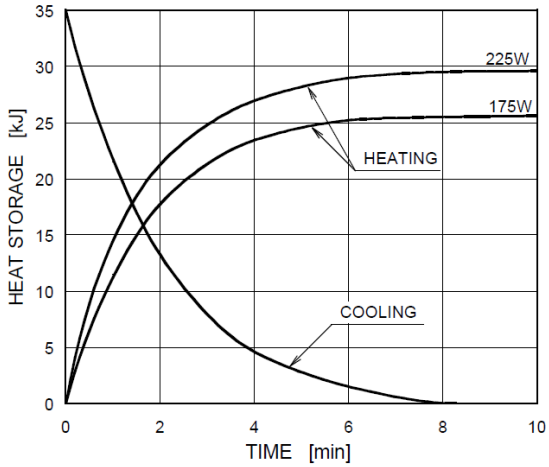


b. Emission & Filament characteristics:



c. Anode thermal characteristics:

Anode Thermal Characteristics



2) High Voltage Generator:

- Power: Single phase 100-240VAC, 50/60Hz
- Power consumption: 2.5kVA Max
- Maximum power: 1.53kW
- Tube voltage and tube current control range:

Modality	Tube Voltage (kV)	Tube Current (mA)	kW (kV x mA)
CT	60~90	4 ~ 17 (Maximum permissible tube current =1.12kW / set tube voltage)	Max 1.12

3) X-ray Controller (Collimator):

Modality	Magnification ratio	Exposure time
CT (Patient)	1.44	~14sec

4) Detector:

Modality	Sensor type
CT (FXDD-0606CA)	Flat panel X-ray sensor Detector pixel size: 119㎛ Pixel Matrix: 1256(W) x 1256(H) Sensing Area : 149.5 (W)x 149.5 (H)mm FOV : 160mm x 100mm(Max.)

5) Console PC main frame:

- OS : Windows 10, 64Bit or higher
- CPU : Intel Dual core or better
- RAM : 8GB or higher
- HDD : 1TB or higher

- Network: Ethernet network
- Display: 32 bit color display or higher
- Resolution : 1366×768 or higher

6) Column:
- Movement range: Column stroke (max and min height difference) 670mm
- Vertical Movement: Powered movement

7) Alignment Beam (for patient positioning):
- Laser Class(by IEC60825-1) : Class I
- Wavelength: 650nm±20nm
- Output : <1mW

8) Software
- Name: RayScan
- Version: Ver 1.0 higher

- Packaging and Labeling:
- Each component of the device will be sealed in a 'bubble wrap' to prevent the damage and packaged in a cardboard box. On the surface of the box and on the main body of the device, the statement "CAUTION-Investigation Device. Limited by Federal Law to Investigational Use" will be posted. Further information on the purpose of the investigation, name and place of business of the manufacturer, distributor, the quantity of contents, and a description of all relevant contraindications, hazards, adverse effects, warnings, and precautions will be included in the labeling.

- Control Device (MDCT)
    - MDCT device already installed and in operation at UCLA Ronald Reagan Hospital. Routine maintenance performed as per institutional and state radiation regulatory agencies.

6.2.3 Product storage and stability

- Investigational Device (RCT720)

- Storage condition
  1) Temperature range : -10 ~ 50 ℃
  2) Relative humidity : 10 ~ 90 %
  3) Atmospheric pressure range : 700 ~ 1060 hPa

6.2.4 Preparation

- Investigational Device (RCT720)

The following is the instruction for how to use the investigational device. User manual must be referred for the details.

1) Preparation
   a. Only the trained user can operate the device.
   b. Before using the product, the user must read the user manual.
   c. After confirming that all cables are properly connected, connect the device to the power cable.
   d. Check if the switch and the device are operating properly.
2) Operation
   a. Turn the power switch to “ON.”
   b. Turn on the PC and execute ‘RayScans.’
   c. Click [MWL] on the upper left of the screen and [New] button on the lower right to register a new patient.
   d. Select the scanning mode and set the desired values for the tube voltage and the tube current.
   e. After adjusting the height of the device to a patient’s height using the remote control or the touch screen, press the [ready] button on the PC or touch screen.
   f. When the irradiation switch lightens up in green, press the irradiation switch until scanning is completed. Release the irradiation switch, if emergency occurs.
   g. In case of an emergency, press the [Emergency] switch located in front of the power switch. To restart, turn the [emergency] switch to clockwise direction, until the pressed power switch pops out.
   h. When scanning is completed, save the image and exit ‘RayScans.’
   i. Press the power switch to “OFF” to turn off the power.
   j. In order to reboot the device, wait 5 to 10 seconds after the device is turned off. Then, press the power switch to the “ON” position.
3) Cautions
   a. Store in a place where there is no possibility of occurrence of adverse effects due to air pressure, temperature, humidity, ventilation, sunlight, dust, salt, and etc.
   b. During the use, the device and the patient must be monitored.
   c. Clean regularly with a neutral detergent and make sure the solution does not enter the device.

d. Using an antiseptic solution such as ethyl alcohol, disinfect the area directly contacted by the patient.
e. The device and components must be regularly inspected.

6.3 Measures to minimize bias

This study does not include randomization into control and treatment groups. Each subjects' CBCT scan is used as the control to the investigational DE-CBCT scan.

6.4 Study intervention compliance

Not applicable. The intervention is a CT scan, and does not require adherence beyond the imaging visit.

6.5 Concomitant therapy

No restriction for participation in the study

6.5.1 Rescue medication

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study intervention

The intervention (patient imaging) occurs in one visit. The only reason to not do the patient imaging would be new information that changes the inclusion/exclusion. The study team will document relevant information including demographics, reason for discontinuance, and the specific criteria that are unmet. Since the study is a single imaging intervention, discontinuance from the study has no impact on the patient's safety or well-being and requires no further action from the study team.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- Development of new conditions that would change inclusion/exclusion criteria
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive CT for 30 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

7.3 Lost to follow up

A participant will be considered lost to follow-up if he or she fails to return for one or more of the two study visits and is unable to be contacted by the study staff.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit to the earliest available date, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls, within a 1-week span). These contact attempts should be documented in the participant's study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Study scheme

Screening for eligibility

Prior to the appointment, patients will be identified by their UCLA dental provider as potentially needing a CT scan of the jaws for treatment planning. The patients will be prescreened by a member of the research team for age eligibility. The study staff will coordinate with UCLA Dental Clinic staff to identify patients and meet with them during their visit.
Patient recruiters such as dental surgeons will also be briefed on the nature of the study and the inclusion and exclusion criteria to assist in identifying potential patients for screening. During the

screening visit, the research team will confirm eligibility via the inclusion and exclusion criteria and explain the risks of the study to the patients.

Enrollment (Day 0)

1. Patients that are cleared through the screening eligibility and who voluntarily sign the informed consent will be enrolled into the study. The patient will be cleared through the screening eligibility based on the inclusion and exclusion criteria. If not suitable for the enrollment, the reason will be recorded on the Case Report Form.

2. An imaging stent will be created for the scanning. This stent, fabricated by the treatment team, bears radiopaque markers to provide location information on the CT scan, and typically requires lag time for laboratory fabrication. Patients will be scheduled for the CT scan by the research team, in coordination with the surgical team.

Study Procedure: DE-CBCT scan (Visit 1)

1. Patients scheduled for their imaging procedures will be confirmed by the research team via the name and date of birth and assigned an alphanumeric code.

2. For women in childbearing age, pregnancy status will be confirmed and recorded.

3. The region of interest (example: tooth number, potential implant site) that requires radiographic imaging will be recorded.

4. DE-CBCT: Prior to imaging, the DE-CBCT unit will be calibrated using a hydroxyapatite (HA) standard phantom. Calibration is performed by taking the images for three times with the tube energy settings of 60 kV / 90 kV. The device will be calibrated three times throughout the study period- prior to the initiation of the study, half the number of patients are recruited, before the end of the study.

    - The details of the HA phantom are as follows:
      - Manufacturer: QRM GmbH, Germany
      - Material: CaHP (Calcium Hydroxy Apatite)
      - HA Concentration (mg/cm^3): 0, 100, 200, 400, 600, 800, 1000, 1200
      - Calibration protocol: ISO 9001 QM-System

5. Following the calibration, the research staff will acquire a DE-CBCT imaging. Either mandible or maxilla, depending on the tooth number (imaging site), will be imaged. The appropriate imaging mode will be selected depending on patient size and field of view, and the tube energy set at 60 kV / 90 kV. The DE-CBCT will be acquired with the imaging stent in place.

6. Subject will be scheduled for MDCT scan (Visit 2). The next visit must be within 30days after the visit 1. Depending on the availability of scheduling on MDCT unit, Visit 2 may occur on the same day as Visit 1.

7. Before the patient returns home, the study staff will educate the subject to contact him/her if adverse events such as nausea, vomiting, hair loss, and oral inflammation occur.

Study Procedure: MDCT scan (Visit 2)

1. Patients scheduled for their MDCT imaging procedures will be confirmed by the imaging facility via the name and date of birth and assigned screening number.
2. For women in childbearing age, pregnancy status will be re-confirmed and recorded.
3. The region of interest (example: tooth number, potential implant site) that requires radiographic imaging will be recorded. The imaging site for MDCT scan will be identical to the one for DE-CBCT scan.
4. The patient will be imaged using the standard clinical protocol for MDCT, and simultaneous scanning of the calibration phantom (QRM-BDC/6).

8.2 Efficacy assessments

BD Assessment

In each patient's MDCT and DE-CBCT scans, discrete regions of interest (ROIs) will be made in the area where radiographic imaging is necessary for the dental diagnosis and treatment plan. The ROI will be angulated, sized, and positioned to mark the treatment area. Using the software tools, the BD will be assessed and recorded. The assessments at each location will be recorded and the HU values of DE-CBCT will be correlated with those of MDCT.

Assessments will be made independently by two oral and maxillofacial radiologists. Each radiologist will make these assessments twice, with at least one month between the two assessments.

8.3 Safety assessments

As described, the primary risk from the DE-CBCT examination is from ionizing radiation. With the low dose used in this procedure, we do not anticipate any deterministic radiation-related effects. The lack of such events will be documented after each examination.

8.4 Adverse events and serious adverse events

8.4.1 Definition of adverse event

An Adverse Event (AE) in this clinical trial includes any unfavorable and unintended signs, or symptoms associated with the use of DE-CBCT and CBCT, whether or not considered intervention related.

AE may be expected (ex: symptoms related to deterministic radiation effects) or unexpected.

Unexpected AE is a sign or symptom not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity than expected based on the information in the Investigator's Brochure.

8.4.2 Serious adverse event

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.3 Classification of an adverse event

Severity of event

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to study intervention
All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Expectedness
The Principal investigator in collaboration with the co-Investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up
All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI or his designee will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4.5 Adverse event reporting

The PI/designee will record non-serious adverse events and report them to project sponsor within 30 working days after investigator first learns of the effect.

8.4.6 Serious adverse event reporting

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.4.7 Reporting events to participants

Not applicable. The investigational device exposes subjects to low levels radiation and we do not anticipate any adverse events that require us to contact participants to ensure their health and safety.

8.4.8 Events of special interest

Not applicable.

8.4.9 Reporting of pregnancy

Not applicable.

9 STATISTICAL CONSIDERATIONS

In this study, we seek to recruit 24 patients to evaluate the effectiveness and safety of DE-CBCT for assessing jaw bone density compared to the current clinical gold standard for BD measurement, MDCT. This primary objective will be analyzed by correlating DE-CBCT HU values to MDCT HU values and Pearson will be performed for the correlation. The higher the correlation coefficient, the more DE-CBCT correlated to MDCT, meaning DE-CBCT is equivalent to the clinical use of MDCT.

To evaluate the accuracy of DE-CBCT and its equivalence to MDCT, we will analyze the agreement between the two methods using Bland-Altman plots.

To evaluate the intra- and inter-observer reliability, observer we will use Kappa statistics to:

1. Quantify the level of agreement between duplicate assessments by the same radiologist
2. Quantify the level of agreement between independent assessments by the two radiologists

<u>Evaluation analysis group</u>

In this clinical trial, the data from PP analysis group (Per-Protocol Analysis Set) will be analyzed.

① Per Protocol Analysis Set:
The PP analysis group includes subjects who complete the study according to the study plan without a significant violation of the protocol- from voluntarily agreeing to participate in the study to finishing the scanning of both DE-CBCT and MDCT. If the quality of image is affected by the metal prosthesis, the subject corresponding to the image is excluded from the PP analysis group.

② A major violation of the study plan to be excluded from the PP analysis group:
The quality of the image, especially the area where ROI is located, is degraded by the metal prosthesis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and study oversight considerations

10.1.1 Informed consent process

10.1.1.1 Consent/Assent and other informational documents provided to participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Informed consent document.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study discontinuation and closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide

the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

10.1.4 Future use of stored specimens and data

Data collected for this study will be analyzed and stored at the UCLA School of Dentistry. During the conduct of the study, an individual participant can choose to withdraw consent to have their CT scans stored for future research. However, withdrawal of consent with regard to scan data storage may not be possible after the study is completed.

10.1.5 Key roles and study governance

Principal Investigator	**Medical Monitor**
Sanjay M. Mallya, BDS, MDS, PhD	*Kyungyoon Kang, CEO, MSA, RAC*
UCLA School of Dentistry	*K-Biotech Incorporated*
10833 LeConte Ave *Los Angeles, CA 90095-1668*	*201 South 4th Street, Suite 727* *San Jose, CA95112*
310 825 1689	*812 345 7485*
smallya@dentistry.ucla.edu	Kyungyoon.kang@kbiotechsolutions.com

10.1.6 Clinical monitoring

Clinical monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.7 Data handling and record keeping

10.1.7.1 Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system.

10.1.7.2 Study records retention

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents may be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. The sponsor will inform the PI when these documents no longer need to be retained.

10.1.8 Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.
The study team will use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to sponsor. Protocol deviations will be sent to the UCLA Institutional Review Board (IRB).

10.1.9 Publication and data sharing policy

The study will follow institutional and sponsor guidelines for data sharing and publication.

10.1.10 Conflict of interest policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design,

conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. UCLA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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