IRB #	HSC20130085H

COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Case selection and treatment protocol for immediate dental implants in the esthetic zone: a controlled clinical trial.

NCT number: NCT02154581

IRB Approval Date: 06-06-2014

Unique Protocol ID: HSC20130085H

FORM C

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RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

For Sections: **1**. "Purpose and Objectives"; **3**. "Study Design"; and **4**. "Study Population," and **5 – 12**, you may copy and paste the relevant passages from the sponsor's full protocol or grant application (citing the page number and section is **unacceptable**).
Section 2, "Background" is the only part of this form where you may cite the relevant passages (page number and section) from the sponsor's full protocol or grant application. This section may be used to also describe local standards of practice or add information pertinent to the local IRB review of a multicenter study.

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

Title of Project:
Case selection and treatment protocol for immediate dental implants in the esthetic zone: a controlled clinical trial.

1. Purpose and objectives. *List the purpose and objectives:*

1. To objectively evaluate the esthetic outcomes of Type 1 implant placement in patients with thick and thin periodontal biotypes.
2. To test the hypothesis that in patients with thin periodontal biotype, Type 1 implant placement in conjunction with guided bone regeneration and subepithelial connective tissue grafting can achieve similar soft tissue contours, soft tissue height, and esthetics as patients with thick periodontal biotypes.
3. To document additional radiographic and clinical outcomes of single tooth replacement using Straumann Bone Level SLActive Implants for one year post-loading.

2. Background.

Describe past experimental and/or clinical findings leading to the formulation of your study.

For research involving investigational drugs, describe the previously conducted animal and human studies.

For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.

Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (page number and section) or if none, ensure background includes references.

a. Background

Immediate placement of implants into extraction sockets was termed “Type 1” implant installation at the 3rd ITI consensus conference, Gstaad, Switzerland (Hämmerle et al. 2004). Immediate implant placement (Type 1) has been documented as a predictable, safe and effective approach to replace extracted teeth, with success rates comparable to the ones reported for conventional delayed implant placement in healed sites (Lang et al. 1994, Brägger et al.1996, Wilson et al.1998, Paolantonio et al. 2001, Covani et al. 2003 & 2004, Chen et al. 2009, Cornelini et al., 2004 & 2005, Schropp et al. 2005, Ferrara et al. 2006, Juodzbalys & Wang 2007). The 4th ITI consensus conference (Stuttgart, Germany, 2008) pointed out that although efforts have been made to document the esthetic outcomes of immediately placed implants, relatively few studies used objective parameters to evaluate esthetic results (Chen & Buser 2009).

One of the major esthetic concerns following immediate implant placement is the recession of the facial peri-implant mucosa, which has been reported with variable extent and incidence rate (Wöhrle 1998, Grunder 2000, Kan et al. 2003, Cangini & Cornelini 2005, Cornelini et al. 2005, Lindeboom et al. 2006, Wagenberg & Froum 2006, Chen et al. 2007, Judozbalys & Wang 2007, Kan et al. 2007, Evans & Chen 2008, Palatella et al. 2008). According to these studies, the incidence of peri-implant mucosal recession (up to 1mm) ranges between 8 and 40%. Moreover, studies reported that up to 2mm of peri-implant mucosal recession can follow immediate implant placement. There is little discussion that discrepancies between the positions of soft tissue margins around a tooth and its contralateral counterpart in the esthetic zone can lead to an asymmetric smile and results in suboptimal esthetic outcomes, which may not meet patients’ expectations. Several risk indicators for peri-implant mucosal recession following immediate implant placement have been identified, including a thin gingival biotype (Kan et al. 2003, Chen et al. 2007, Evans & Chen 2008), a facial malposition of the implant (Chen et al. 2007, Evans & Chen 2008, Chen et al. 2009), and a thin or non-intact facial bone wall (Kan et al. 2007, Chen et al. 2005, 2007). Based on the recognition of these risk indicators, it has been suggested that immediate implant placement should only be considered as a valid treatment option after careful risk analysis and case selection are performed (Kan et al. 2003, Chen et al. 2007, 2009).

Connective tissue grafts have been used to improve esthetic outcomes of implant therapy in esthetic sites (Grunder et al. 1996, Price & Price 1999, Khoury & Happe 2000, Kan et al. 2005). The most compelling evidence supporting the use of connective tissue grafts in conjunction with immediately placed implants derives from a prospective controlled clinical trial with a follow-up of up to 9 years (Bianchi & Sanfilipo 2004). In this clinical trial, sites treated with subepithelial connective tissue grafts and immediate implant placement presented better esthetic outcomes than sites that received immediately placed implants only. More specifically, over 95% of the sites treated with subepithelial connective tissue grafts in combination with immediate implant placement had marginal soft tissue discrepancies of 1mm or less with the free gingival margins of adjacent teeth, compared to only 80% of the sites receiving solely immediate implants.

Experimental and clinical studies have shown that the void formed between the immediately placed implant and the bony walls of the fresh extraction socket is filled with new bone when left to heal spontaneously without any regenerative procedure. However, this is obtained at the cost of horizontal and, to a lesser extent, vertical ridge resorption (Paolantonio et al. 2001, Covani et al. 2003, Botticelli et al. 2004a, 2004b, Araujo et al. 2006, Chen et al. 2007, Ferrus et al. 2010). Recent evidence from experimental and clinical studies showed that grafting marginal defects around immediately placed implants can limit these resorptive events (Cornelini et al. 2004, Chen et al. 2007, Araujo et al. 2011). This in turn, may prevent unfavorable soft tissue remodeling at implants placed in esthetic areas (Cornelini et al. 2004).

Taken together, immediate implant placement results in similar implant survival rates as conventional delayed placement in healed sites. However, the occurrence of mid-facial peri-implant mucosal recession is a common finding following immediate implant placement and results in significant esthetic shortcomings. Numerous risk factors leading to this undesirable outcome have been identified and clinical treatment protocols have been suggested to counteract their potential negative effect. Even though most authors acknowledge that risk analysis and careful case selection are key to achieving successful esthetic outcomes in immediately placed implants, no study has been identified in which parameters associated with development of peri-implant mucosal recession were controlled for and the esthetic outcomes assessed by means of objective measures. Consequently, objective guidelines for case selection and treatment protocols for immediate implant placement in the esthetic area remain to be established.

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b. Current practice

Type 1 implant placement is regularly done in maxillary anterior sites and can be considered as standard care procedure.

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

This controlled, randomized clinical trial (RCT) is designed to achieve optimal esthetic and clinical outcomes in implants placed immediately following tooth extraction (Type 1 implant placement) in combination with guided bone regeneration. Sites with a thin periodontal biotype will also receive a subepithelial connective tissue graft, while sites with thick tissue biotype will not receive any connective tissue graft. The results of the proposed clinical trial will provide clinicians with guidelines for case selection and treatment protocols for immediate implant placement in the esthetic zone.

This study will evaluate esthetics objectively using calibrated, blinded examiners to determine the apico-coronal position of the mid-facial and proximal soft tissue margins and by the pink and white esthetic scores (PES/WES) described by Belser et al. (2009). Secondary treatment outcomes will include: probing pocket depth (PPD), modified plaque index (mPI), modified sulcus bleeding index (mSBI), early and late failures, survival rate, success rate, and radiographic bone level changes.

Extraction sites for the study will include maxillary first premolars and anterior teeth with intact adjacent teeth. Implants placed for this study will be SLActive surface, bone level design, Straumann BL RC (Bone Level Regular Cross-fit) 4.1mm or BL NC (Bone Level Narrow Cross-fit) 3.3mm diameter implants at 8, 10, 12 or 14mm in length.

Immediate implant placement (Type 1) resulting in a horizontal defect dimension (HDD) (gap) will receive freeze-dried bone allograft (FDBA) (Straumann Allograft GC®). Moreover, the site will be slightly overcontoured with FDBA (FDBA will be applied on the external side of the socket) and will be covered by a resorbable membrane (BioGide®).

Additionally, in sites with a thin tissue biotype, a subepithelial connective tissue graft harvested from the palatal mucosa will be placed underneath the full mucoperiosteal flap. The harvested connective tissue grafts will be 10x15x1mm (length x width x thickness) in size. Flap adaptation and closure will allow for a partially submerged transmucosal healing.

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4. Study Population(s).

You will be drawing subjects from one or more populations. In medical research, for example, a population can be individuals with type 2 diabetes controlled with diet, or a population of healthy individuals. In social behavioral research, a population can be individuals attending an education program, etc.

4.a. How many different populations are you enrolling in this study?	One
4.b. For each different population, provide a short descriptive **label**: *(e.g., normal-healthy, diabetics, parents, children, etc.)* *Copy and paste additional labels as needed →*	1. Normal healthy

4.c. For each specific population identified in **4b**, provide the following information in the table provided below.
*(For studies with **more than one** population, copy all of table 4.c. and paste to insert additional tables.)*

Population # 1	**Population Descriptive Label:** Normal healthy

(1) Identify the criteria for **inclusion**:

1. The patient is 18 years or older.

2. Ability to understand and provide informed consent before starting the study.

3. Ability and willingness to comply with all study requirements.

4. The patient, if of child-bearing potential, has a negative urine pregnancy test.

5. Adequate oral hygiene to allow for implant therapy consistent with standards of care.

6.Adequate bone volume to accommodate the planned endosseous dental implant placement according to immediate placement protocols utilizing Straumann Bone Level implants RC 4.1mm or Bone Level Implant NC 3.3 mm at 8, 10,12 or 14mm in length.

7. One tooth in the anterior maxilla (first pre-molar to first pre-molar) requiring extraction resulting in a single- tooth gap planned to be restored with a dental implant as determined by the patient's dental provider.

8. The site to be treated is surrounded by two natural teeth.

9. Except the site to be treated, none of the maxillary incisors, canines and first pre-molars display marginal soft tissue recession.

10. Following extraction, intact extraction socket bony walls are present.

11. Primary stability of implant consistent with standards of care is achieved at the time of implant placement.

12. Patient must be able to pay for fees related to the surgical implant placement related to extraction, grafting of the implant site, and half of the cost of the crown at the time of implant placement.

(2) Identify the criteria for **exclusion**:

1. Patient reports tobacco use within the last five years. Tobacco use for this study is defined as a current smoking habit with moderate or heavy smoking (more than 10 cigarettes per day) or tobacco chewing use.
2. History of alcoholism or drug abuse within the past 5 years.
3. Severe wear with an etiology of bruxism or clenching habits.

4. Patient has significant untreated periodontal disease (grade III or IV), caries, or clinical or radiographic signs of infection within two adjacent tooth positions of implant area.
5. History of HIV infection, Hepatitis B or C.
6. Patients with a history of systemic disease that precludes standard dental implant therapy or alters daily activities to a level consistent with ASA III classification (including cardiovascular, hepatic, renal, gastrointestinal, metabolic, neurologic, pulmonary, endocrine, autoimmune, or psychiatric disorders).
7. Presence of local inflammation or mucosal diseases such as lichen planus.
8. Patient history consistent with high risk for subacute bacterial endocarditis.
9. Current hematological disorder or warfarin (or similar) therapy.
10. Patient has a disease that affects bone metabolism, such as, but not limited to, osteoporosis, hyperthyroidism, hyperparathyroidism, congenital connective tissue disorders (e.g., osteogenesis imperfecta), or Paget's disease.
11. Patient is taking medications or having treatments known to have an effect on bone turnover, including: thiazide diuretics, calcitonin, systemic steroids, bisphosphonates, vitamin D (>800 IU/day), estrogen or progesterone therapy.
12. Current steroid treatment: defined as any person who within the last two years has received for two weeks a dose equivalent to 20 mg hydrocortisone.
13. Patient currently undergoing chemotherapy.
14. Patient history of radiation treatment to the head or neck.
15. Physical or mental handicaps that would interfere with patient's ability to exercise good oral hygiene on a regular basis.
16. Use of any investigational drug or device within the 30 day period immediately prior to implant surgery.
17. Patient is pregnant.
18. Extraction sites having anatomic conditions that preclude immediate implant placement.

(3)	**Recruitment Process – identifying potential subjects** Describe plans about how the population will be **identified** for the purpose of recruiting. *(e.g., database search, personal contacts, referrals, patients under the care of the research team, etc.)*

Subjects will be drawn from both new and existing patients of the UTHSCSA Graduate Periodontics Clinic. No other means of identifying subjects will be used. No chart review or retrospective search for patients will be performed. Subjects will be those referred for periodontal treatment and dental implant therapy.

Who will access PHI to **identify** potential participants? *Select one*

☑	Only those with existing legitimate access to PHI will use it to identify potential subjects
☐	There is a need to allow those without existing legitimate access to PHI to use it to identify potential subjects *(submit Form J, HIPAA Waiver)*

FORM C

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(4)

Recruitment Process – first contact

Describe how **initial contact** will be made with potential subjects

(e.g., researchers will contact potential subjects or subjects will contact the researchers or make appoints to see researchers after learning of the study).

Describe how those making initial contact have a legitimate access to the subjects' identity and the subjects' information. *(Consider whether a HIPAA Waiver is needed to disclose PHI to member of the research team who do not have legitimate access.)*

Initial patient contact with potential subjects will take place at the initial consultation visit following referral for tooth extraction and future implant placement. Patients meeting the inclusion and exclusion criteria will be informed of all procedures and responsibilities of this study. All the treating dentists, the PI and Co-PI will have access to all patient records and PHI.

(5)

Recruitment process – setting

Describe the **setting** in which an individual will be initially approached.

(e.g., private room, inpatient unit, waiting area, group setting, over internet, over phone, in public). Also, describe all interaction between the research staff and the potential subject between the time they contact the research team or vice versa and the time they sign a consent form (including pre-screening activities-see instructions for detailed guidance)

The patient will be initially approached by one of the dentists from the graduate periodontics clinic on the research team during the initial consultation visit following referral for future implant placement in a semi-private operatory (three floor to ceiling walls and one area open to a central walkway). All advantages, disadvantages, and risks will be identified. Patients who agree to participate will be asked to read, discuss with the treating doctor, and sign an informed consent document. The informed consent will be obtained prior to performing any study-related procedures. If interested and if the inclusion and exclusion criteria are met at the time of tooth extraction the patient will be enrolled in the study.

(6)

Recruitment process - advertisements

Will any advertising be used? ☐ Yes (attach) ☑ No ☐ Pending (will submit an amendment after approval)

If yes, please see Section 4, Form L for instructions on attaching copies of the information to be used in flyers or advertisements. Advertisements must be reviewed and approved by the IRB prior to use.

(7)

Consent Process

Describe the consent/assent **procedures** that will be used by the research team.

- Include how: information is provided; the consent interview is conducted; the consent is signed.
- Identify the study staff who will conduct the consent interview by their roles (e.g., investigator, research nurse).

***** If the consent process of a single subject will involve more than one member of the research team, describe how this process will be coordinated from start to finish.

****** If you expect this population will have individuals likely to have diminished decision-making capacity (not including incompetent or impaired decision making capacity), describe the assessment process for determining whether the individual is capable of giving informed consent (i.e., evaluation criteria, time intervals)

Once it is determined that the inclusion and exclusion criteria are both met, the patient will be informed of all risks, advantages, and disadvantages of the study treatment with Dr. Huynh-Ba (PI) or Dr DeGroot (Resident in periodontics for whom this research is his Master's project) in the aforementioned clinical setting. The consent form will be signed by the potential subject, one of the dentists from the graduate periodontics clinic on the research team completing the consent process, and a witness.

(8)

Consent Process – time between initial contact and obtaining consent

Describe the **timing** of obtaining informed consent, whether there is any waiting period between informing the prospective subject and obtaining consent. *(e.g., take consent home, waiting period of X hours, after consulting with family members, etc.)*

Following an informational discussion with the prospective subject, consent will be obtained before surgery (visit 2).Time to think about the study and allow for the patients to read over the consent form outside of the clinical setting will be offered. If the patient would like to become a subject for entry into the study, he or she can do so immediately or following a waiting period of up to the surgery (visit 2), typically at least 2 weeks. This is up to the discretion of the patient.

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(9)	Describe measures taken to **minimize** the possibility of coercion or undue influence during consent.
The patient will be presented with the option of enrolling in the study only if inclusion and exclusion criteria are met. After the purpose of the research project has been explained to the patient by Dr. Huynh-Ba (PI) or Dr DeGroot (Resident in periodontics for whom this research is his Master's project), the consent process will be completed by the treating dentist. The patient will have at least 2 weeks if he/she desires to do so, to consider whether or not they wish to participate in the study (refer to point (8) on the previous page). Potential research subjects will be reminded that the participation in the research is only done at their own discretion.	
(**10**)	Will subjects from this population be assigned to different research groups? *(e.g., treatment and control group)*
	☑ Yes ☐ No
If yes, list the groups by inserting a short descriptive title for each group. *E.g., experimental group A, B, etc., control group, etc.* - these labels are needed for the Risk: Benefit Analysis section Test group: Thin periodontal biotype Control group: Thick periodontal biotype	

5. Informed Consent for Research Involving Non-English Speaking Subjects – *choose either A, B or C*		
A.	☐	**N/A**. The primary investigator for this study will request a waiver of consent for all subjects in this study. (go to #6)
	☐	**N/A** This study does not involve interaction with living individuals; *(limited to use of identifiable information)*. (go to #6)

OR

B.	☐	**Only individuals who speak English will be enrolled**. *(if checked select one of the two statements below)*
	☐	There is **no** expected direct benefit for those participating. (go to #6)
	☐	There is an expected direct benefit for those participating. Excluding non-English speaking individuals is acceptable because: *(insert the rationale for excluding this population below* -- then go to #6)
		[Insert rationale here]

OR

FORM C

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C. ☑ **Individuals who do not speak English will be enrolled**.
The translated consent will be submitted to the IRB:
Select one Form B, item 12 should be checked

☐ Immediately following approval of the English consent.
(go to c(1) and c(2) below)

☑ Only after a potential non-English speaking participant is identified. Since this plan will delay enrollment pending IRB approval of a translated consent, provide justification that prospective non-English speaking subjects will not be excluded from beneficial research.
Choose one of the choices below:

☐ There is **no** expected direct benefit for those participating. (go to c(1) and c(2) below)

☑ There is an expected direct benefit for those participating.
Provide justification why the delay is acceptable below, then (go to c(1) and c(2)below)

The treatments provided in this study are elective in nature and any delay in treatment required for a translation into Spanish would be acceptable because they would not have any adverse effect on patient health.

C (1) If you are recruiting non-English speaking subjects, Describe the process for obtaining informed consent from prospective subjects in their respective language (or the legally authorized representative's respective language).

It is expected that any non-English speaking subject would be a subject speaking Spanish as a primary language. Informed consent would be obtained using a Spanish translation of the informed consent document. In addition, 4 of the dental assistants in our clinic are fluent in Spanish and could assist with questions from the subject.

C (2) In order to ensure that individuals are appropriately informed about the study when English is their second-language, describe a plan for evaluating the level of English comprehension, and the threshold for providing a translation, or explain why an evaluation would not be necessary.

Each subject for whom English is a second language will be evaluated for comprehension of English by reading a simple half-page patient treatment authorization form that we use in our clinic for all patients (which has English on one side and Spanish on the other). If the subject has any difficulty in comprehending this form, he/she will interact with one of our Spanish speaking clinic staff members to determine how comfortable the subject feels with the English document. If the subject expresses any reservation about his/her comprehension, a Spanish informed consent document will be provided.

6. Research Plan / Description of the Research Methods:

6.a. Provide a **comprehensive narrative** describing the **research methods**.
Provide the **order in which tests/procedures will be performed**,
the **setting** for these events and a description of the **methods used to protect privacy** during the study.
Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Below is a schematic illustration of the study design.

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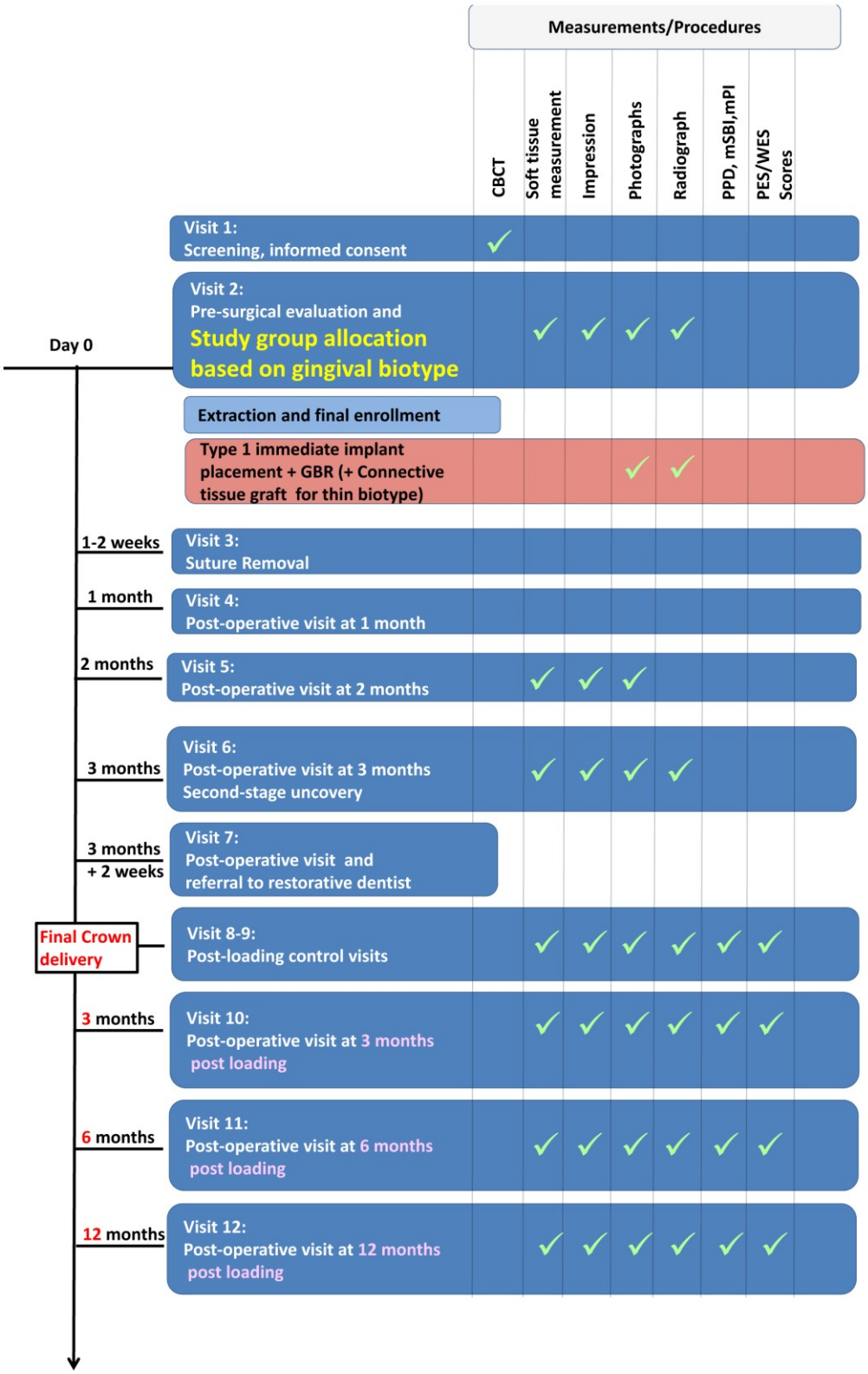

- **Visit 1: Screening Examination**

Part of standard care, a complete medical and dental history of each patient will be obtained and reviewed with the patient. The overall health of the periodontium will be assessed. All patients will be informed of any disease findings from the examination and will undergo a hygiene phase of therapy that will include oral hygiene instructions, scaling, root planing, and an occlusal adjustment (if needed), provided patients have not had this treatment in the last three months. The initial treatment of scaling and root planing, oral hygiene instructions, and maintenance of good plaque control pre-surgically are identical whether the patients are involved in this study or not. All the aforementioned steps will be carried out by the Periodontics resident. This part of the treatment is called the hygienic phase or phase one therapy.

If the patient presents with a situation that might fit the indication of the study, i.e. the patient needs one tooth to be extracted (including maxillary first premolars, canines or incisors) and replaced with a dental implant, the treating dentist will get Dr Guy Huynh-Ba, or Dr Bradley DeGroot to perform the following steps:

- Explanation to the patient of the purposes of the study and the planned procedures related to the study.
- Explanation to the patient of the risks and possible complications of participation in the study.
- The patient shall be notified that inclusion in the study is conditional upon satisfying the inclusion and exclusion criteria.
- Patient will be given the opportunity during the appointment to ask any question that he/she may have. The consent form will be given to the patient for review and time, until visit 2 (but not shorter than 2 weeks), will be given to the patient to sign the Implant Study Consent form if he/she decided to participate in the study. The patient may sign the consent immediately if he/she would like to do so.

As part of standard care for dental implant placement, the patient will have cone beam computed tomography (CT) taken in the UTHSCSA radiology department. All the diagnostic work pertaining to the dental implant placement, as per standard care, will be performed and/or coordinated by the Periodontics residents in charge of the patient.

Impressions will be made prior to the surgical visit and poured in stone to obtain initial study casts

Once the patient has successfully gone through phase one therapy, the patient will be given an appointment for the extraction of the tooth, i.e. visit 2.

- **Visit 2: Extraction, Final enrollment and Implant placement**
- If the patient has agreed to sign the consent form it will be obtained from him/her. If not, standard care will be provided and the patient will not be included in the study.
- At the day of the planned extraction, the medical history will be updated.
- Female patients of child-bearing potential will complete a urine pregnancy test provided free-of-charge (a negative result is required to enter the study).
- Patient's periodontal biotype will be determined by measuring the gingival thickness. This will be done by first sounding the gingiva apical to the free gingival margin using an endodontic file and then measuring the depth of penetration. Additionally, a periodontal probe will be placed in the gingival sulcus and judged as either visible (thin tissue) or not visible (thick tissue) in order to confirm the finding. Patients will then be assigned to either the treatment group (thin tissue biotype) or the control group (thick tissue biotype)
- Photographs will all be taken perpendicular to the facial surface of the site of interest surrounded by 1 tooth and a half on each side. Photographs at all subsequent visits will be taken in a similar fashion. Assessment of soft tissue dimensions including mid-buccal mucosa, proximal papillae will be taken prior to tooth extraction, at baseline, i.e. at the time of implant placement; at 2 and 3 months post implant placement; and immediately, 3, 6, and 12 months after implant loading. Measurements will be made on the photographs taken from the casts. Photographs will be taken intraorally with a periodontal probe as a calibration reference. Measurements will be performed on the digital photographs of the casts and intra-orally using software (Gingival Status Software). Mid-buccal and proximal measurements of mucosal tissues will be based on linear references from adjacent incisal edges.
- A patient customized bite-block film holder will be made. Duralay resin (Reliance Dental Mfg Co.) will be fitted around a stock plastic film holder and allowed to set in the patient's mouth while he/she will be biting

down. The impression of the patient's occlusion in the Duralay resin will allow reproducing accurately the positioning of the film in the patient's mouth, thus allowing the recording of reproducible periapical radiographs of the site of interest, i.e. the site of extraction and the prospective implant placement site. This patient individualized film-holder will be used for every periapical radiograph taken during the course of the study (including visit 2, 6, 9, 10, 11, and 12). A pre-operative periapical radiographic image will be taken before the extraction as per standard care using this individualized film holder.

- Prior to surgery, the patient will be instructed to rinse with an 0.12% chlorhexidine solution for one minute as per standard care.
- At the time of surgery, local anesthesia and, at the patient's request, conscious sedation will be administered according to patient need and investigator preference. Patients may be attached, at the investigator's discretion, to an automated vital signs monitor for continuous monitoring of blood pressure, pulse rate, electrocardiogram, blood oxygen saturation, and respirations.
- Extraction will be performed with a minimal flap elevation, if needed, to allow evaluation of the socket walls.
- Following tooth extraction, a final determination of enrollment into the study will be conducted based on inclusion/exclusion criteria.
- The thickness of the buccal wall plate of the socket will be measured using a caliper 1 mm from the crest
- If meeting study criteria, the full mucoperiosteal flap will be extended with releasing incisions as needed and the subject will have the implant placed according to the following guidelines:
  In the sagittal plane (Mesio-Distal): The implant will be placed at least 1mm away from the adjacent root surfaces.
  In the vertical plane (Corono-Apical): The mid-facial implant shoulder will be placed approximately 3 to 4mm apically to the mucosal margin of the future implant supported crown.
  In the horizontal plane (Buccal-Lingual): The mid-facial implant shoulder will be placed approximately 2mm lingually to the internal border of the buccal socket wall as suggested by Chen et al. 2007.
- Following immediate implant placement, the void between the implant and bone walls socket, i.e. the horizontal defect dimension (HDD), will be filled using FDBA (Straumann Allograft GC®). The implant site will be overcontoured with FDBA on the external aspect of the extraction site and will be covered by a resorbable collagen membrane (BioGide®).
- A 2mm high healing abutment will be placed on the implant before being submerged.
- Intraoral photographs will be taken after implant installation and before GBR.
- For sites with a **thin periodontal biotype**, a connective tissue graft taken from the palate will be secured to the buccal flap.
- Flap adaptation and suturing will be performed, leaving the implant to heal in a partially submerged fashion.
- A standardized radiograph (using a bite-block) will be taken from the implant site.
- Post-operative measures will include antibiotics coverage, possibly methylprednisolone (Medrol Dosepack) and prescription of a 0.12% Chlorhexidine mouthrinse to be used twice daily for one minute over the course of two weeks. All these medications are used as part of standard care procedures.

- **Visit 3: Suture removal**
- Patients will return 7-14 days after surgery for suture removal and observation of wound healing

- **Visits 4: Post-operative visit at 1 month after implant placement**
- The patients will return one month (± 14 days) after placement for observation of wound healing

- **Visit 5: Post-operative visit at 2 months after implant placement**
- The patients will return at two months (± 14 days) after implant placement for assessment of soft tissue contours

- **Visit 6: Post-operative visit at 3 months after implant placement**
- The patients will return at 3 months (± 14 days) after implant placement for assessment of soft tissue dimensions as described under Visit 2.
- Intraoral photographs will be taken.
- Impression will be taken

- Second stage uncovery of the implant will be performed

- **Visit 7: Post-operative visit at 2 weeks after second stage surgery**
- The patients will return at 2 weeks (± 7 days) after second stage surgery for the observation of wound healing
- The patient will be referred back to his/her dental practitioner for the completion of the prosthetic procedure.

- **Visit 8 and 9: Post loading control visits**
- As soon as the patient has received his/her temporary crown (visit 8) and/or his definitive crown (visit 9), these visits will allow the examiners to assess the contour, contact points and occlusion of the prostheses and appropriate feedback will be provided to the restorative dentist.
- Evaluation will be performed after delivery of the definitive crown for assessment of soft tissue dimensions (mid-buccal and proximal papillae) (visit 9 only).
- Intraoral photographs will be taken (Visits 8 and 9)
- Impressions will be taken for assessment of soft tissue dimensions (mid-buccal and proximal papilla) (visit 9 only)
- A standardized radiograph (using a bite block) will be taken of the implant site (visit 9 only)
- Clinical parameters including PPD, mPI, and mSBI will be recorded (visit 9 only)

Clinical parameters including probing pocket depth (PPD), modified plaque index (mPI), modified sulcus bleeding index (mSBI) will be recorded using a periodontal probe at 6 sites around the implant.

Probing pocket depth will be measured using a periodontal probe inserted in the peri-implant sulcus with a light force (approximately 15N) to the nearest millimeter. The mPI and the mSBI will be recorded following the guidelines by Mombelli et al. (1984). Hence, using a periodontal probe, the different values recorded are described thereafter:

Modified plaque index: 0: No detection of plaque
1: Plaque only recognized by running the probe along the peri-implant mucosal margin
2: Plaque can be seen by the naked eye
3: Abundance of soft matter

Modified sulcus bleeding index:
0 No bleeding when a periodontal probe is passed along the peri-implant mucosal margin
1 Isolated bleeding spot visible
2 Blood forms confluent red line along the margin
3 Heavy or profuse bleeding

- PES/WES scores will be determined (visit 9 only)

- **Visit 10: Post-operative visit at 3 months after implant loading**
- Evaluation will be performed at 3 months (± 14 days) after implant loading for assessment of soft tissue dimensions (mid-buccal and proximal papillae).
- Intraoral photographs will be taken.
- Impression will be taken for assessment of soft tissue dimensions (mid-buccal and proximal papillae).
- Clinical parameters including PPD, mPI and mSBI will be recorded.
- A standardized radiograph (using a bite-block) will be taken from the implant site.
- PES/WES scores will be determined.

- **Visit 11: Post-operative visit at 6 months after implant loading**
- Evaluation will be performed at 6 months (± 21 days) after implant loading for assessment of soft tissue dimensions (mid-buccal and proximal papillae).
- Intraoral photographs will be taken.
- Impression will be taken for assessment of soft tissue dimensions (mid-buccal and proximal papillae).
- Clinical parameters including PPD, mPI and mSBI will be recorded.
- A standardized radiograph (using a bite-block) will be taken from the implant site.
- PES/WES scores will be determined.

- **Visit 12: Post-operative visit at 12 months after implant loading**
- Final evaluation will be performed at 12 months (± 30 days) after implant loading for assessment of soft tissue dimensions (mid-buccal and proximal papillae)
- Intraoral photographs will be taken
- Impression will be taken for assessment of soft tissue dimensions (mid-buccal and proximal papillae)
- Clinical parameters including PPD, mPI and mSBI will be recorded
- A standardized radiograph (using bite-block) will be taken from the implant site
- PES/WES scored will be determined

The following section described how the PES/WES scores are recorded. This section and is reproduced from the original article by Belser et al. 2009 (Belser UC, Grütter L, Vailati F, Bornstein MM, Weber HP, Buser D. Outcome evaluation of early placed maxillary anterior single-tooth implants using objective esthetic criteria: a cross-sectional, retrospective study in 45 patients with a 2- to 4-year follow-up using pink and white esthetic scores. J Periodontol. 2009 Jan;80(1):140-51.):

"PES: *In contrast to the original proposal, the PES comprises the following five variables: mesial papilla, distal papilla, curvature of the facial mucosa, level of the facial mucosa, and root convexity/soft tissue color and texture at the facial aspect of the implant site.*

A score of 2, 1, or 0 is assigned to all five PES parameters. The two papillary scores (mesial and distal) are assessed for the complete presence (score 2), incomplete presence, (score 1), or absence (score 0) of papillary tissue. The curvature of the facial soft tissue line, also defined as the line of emergence of the implant restoration from the soft tissues, is evaluated as being identical (score 2), slightly different (score 1), or markedly different (score 0) compared to the natural control tooth and, thus, provides a natural symmetrical or disharmonious appearance. The level of the facial peri-implant mucosa is scored by comparison to the contralateral tooth in terms of an identical vertical level (score 2), a slight (≤1 mm) discrepancy (score 1), or a major (≥1 mm) discrepancy (score 0).Finally, the proposed index combines three additional specific soft tissue parameters as one variable: the presence, partial presence, or absence of a convex profile (in analogy to a root eminence) on the facial aspect, as well as the related mucosal color and surface texture. The latter two elements basically reflect the presence or absence of an inflammatory process, which, in turn, may adversely affect the appearance of an anterior single-tooth implant restoration. To attain a score of 2 for this combination variable, all three parameters are more or less identical compared to the control tooth. A value of 1 is assigned if two criteria are fulfilled, whereas a score of 0 is assigned if none or only one parameter matches the control site.

The five described parameters (5 x 2) add up, under optimum conditions, to a score of 10.

WES: *The WES specifically focuses on the visible part of the implant restoration itself (i.e., the part of the implant crown that emerges from the peri-implant mucosa) and is based on the five following parameters: general tooth form; outline and volume of the clinical crown; color, which includes the assessment of the dimension's hue and value; surface texture; and translucency and characterization.*

A score of 2, 1, or 0 is assigned to all five parameters. Thus, in case of an optimum implant restoration, a maximum total WES of 10 is reached. All five parameters are assessed by direct comparison with the natural, contralateral reference tooth, estimating the degree of match or eventual mismatch. In the case of an optimum duplication of the esthetically relevant features inherent to the control tooth, a maximum WES score of 10 is possible.

Hence, the highest possible combined PES/WES score is 20, which represents a close match of the peri-implant soft tissue conditions and the clinical single- tooth implant crown compared to the respective features present at the contralateral natural tooth site. To facilitate the objective appreciation of some of the parameters, the fabrication of study casts, in addition to standardized clinical photographs, is indispensable. The clinical photographs are primarily used to assess general tooth/crown form, tooth/crown color, incisal translucency and characterization, as well as soft tissue color, curvature, and level. The study cast evaluation completes the PES/WES assessment, facilitating the objective appreciation of crown outline, volume, and surface texture, in addition to root convexity and soft tissue texture."

L) Patient Withdrawal Criteria:

Patients will be discontinued from the study prematurely if:

- The patient is non-compliant with the study protocol.
- An adverse event occurs, whether or not Study Device related, which precludes continued treatment.
- The patient requests to be withdrawn from the study.
- The Principal Investigator decides that it is in the patient's best interest.

If a patient withdraws from the study at any time either at his request or at the Principal Investigator's discretion, the reason(s) for withdrawal will be recorded by the Principal Investigator on the relevant pages of the patient chart. The patient will be entitled to be treated according to the standard care irrespective of his/her study participation status.

- **Data Analysis:**

After definitive crown delivery and at 3, 6, and 12 months after implant loading, the PES/WES score will be recorded for all implant supported crowns.

Additional outcome measures will include position of the peri-implant mucosal margins, clinical parameters (PPD, mPI, mSBI), evaluation of radiographic bone level changes, frequency of implant failure, clinical complications such as infections, or study-related adverse events. Implant failure will include clinical lateral mobility of the implant, peri- implant radiolucency with clinical signs of infection associated with the implant to include suppuration, pain, and swelling. These parameters will be measured over the 16-18-month observation period.

The main goal of the present study is to establish guidelines for case selection and treatment protocols for Type 1 implant placement in the esthetic zone, therefore, only descriptive methods will be used to report the clinical and esthetic outcomes.

As secondary analysis, longitudinal changes of clinical parameters will be assessed using student t-test with $p<0.05$. Difference of mid facial gingival height and interproximal papilla height will be assessed using student t test with a $p<0.05$.

- **Sample size:**

The objective of this study is to characterize the mucosal healing patterns following tooth extraction, and immediate implant placement procedures. Ultimately, it is the resultant soft tissue position that will determine esthetic success. As such, a clinically significant treatment difference > 1.0mm in buccal soft tissue margin position in an apical coronal direction would be important to identify. Based on previous studies of soft tissue changes associated with implant therapy in which standard deviations ranged from 0.9-1.2 mm, we are using a standard deviation of 1.0 mm for each treatment group for sample size estimation. To detect differences between the thin and thick periodontal biotype groups, 13 patients per treatment group will be required using a two-sample comparison of means with 80% power and $p=0.05$ considered statistically significant. Given the potential for several patients to withdraw from the study protocol, we anticipate enrolling 34 patients for each treatment group in order to obtain 13 patients completing the study protocol.

- **Risks:**

The treatment modalities evaluated in the present study are well-documented and accepted treatment modalities. Accordingly, the risks associated are not specific to the study but are related to any kind of implant/periodontal surgical procedure.

Risks to a patient participating in this study include those associated with any periodontal surgery. The most frequently stated risks are excessive bleeding, nerve damage, damage to the surrounding soft tissue, and infection, plus dehiscence or migration of the graft materials. Additional risks are associated with the use of general or local anesthesia and, at the patient's request, conscious sedation. The potential risk for any of the above adverse side effects is less than 1% (Curtis, et al. 1985). Post-surgical pain ranging from mild to severe occurs virtually 100% of the time.

As with any dental implant placement and as per standard care it will be explained to the patient that there are certain inherent and potential risks in any procedure that include, but are not limited to: swelling; pain; bruising;

recession of the gums, increased tooth sensitivity; temporary or permanent increased tooth mobility, unaesthetic exposure of crown margins; stretching of the corners of the mouth which may result in cracking and bruising; restricted opening or discomfort in the jaw muscles or joint(s); possible nerve injury with change in sensation and/or numbness to the lip, chin, gingiva (gums, including palate), teeth and/or tongue which may be temporary or permanent; infection; damage to adjacent teeth, nasal cavity, and sinuses; premature exposure of barrier membrane; loss or migration of bone graft out of defect; sloughing of tissue graft; gum recession (shrinkage); failure of implants to heal/integrate with surrounding bone; medical emergencies requiring life saving procedures and/or admission to a hospital.
Bone and soft tissue grafting materials are attained in many ways, often from cows, pigs, or human cadavers. The donors have no positive history of known systemic disease, and blood tests are negative for any infections. The tissues are tested for bacterial contaminants, and processed under strict laboratory conditions known to kill all bacteria and viruses, under experimental conditions. Material is placed in a vacuum-sealed sterile container until it is ready to be opened during surgery. While infection via an implanted biological material can never ruled out completely, this material is considered to be extremely safe due to the processing involved and from the fact that no case of disease transmission has ever been found with the materials.
All these risks are part of any surgical implant placement and are not specific to the study.

6.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 6.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Local Standard Practice Indicate whether the intervention is considered acceptable practice locally
1	Type 1 implant placement: immediate implant placement following tooth extraction with CT graft (thin biotype)	☑
2	Type 1 Implant placement: Immediate implant placement following tooth extraction without CT graft (thick biotype)	☑
3	Insert study intervention 3 here	☐

6.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

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6.c.
Study Intervention #1
Type 1 implant placement: immediate implant placement following tooth extraction with CT graft (thin biotype)

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Experimental	Benefits: Increased soft tissue volume at time of surgery which could lead to better esthetic outcomes

For this intervention, **list the reasonably foreseeable risks**
List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. The need to know what to report promptly later = a requirement to estimate frequency (Instructions).

	Not serious	**Serious**
Likely These risks are expected to occur in more than 20 out of 100 subjects.	• Risk related to surgical procedures: Swelling, pain, bleeding.	• None
	Not serious	**Serious**
Less likely These risks are expected to occur in 5-20 subjects or less out of 100 subjects.	• Risk related to surgical procedures: Bruising, stretching of the corners of the mouth	• None
		Serious
Rare These risks are expected to occur in less than 5 subjects out of 100		• Risk related to surgical procedures: Nerve damage, infection, damage to the surrounding soft tissue, recession (shrinkage) of gums, migration of the graft material, increased tooth sensitivity, increased tooth mobility, unaesthetic exposure of the crowns, damage to adjacent teeth, nasal cavity, sinuses, medical emergencies. • Risk related to pain medications and antibiotics: Allergic reactions such as hives, rash and even-life threatening reactions called anaphylaxis
▪ **Rare** ▪ Less than 1 subject in 1000000		• Transmission of infectious disease to subject, such as hepatitis or nerve diseases, which may not show up for many years after infection (this risk is greatly reduced by using processing treatments shown to be capable of reducing this risk). So far, no report of any incidence related to the use of Straumann Allograft GC® bone graft and Bio-Gide® membrane is known.

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6.c.
Study Intervention #2
Type 1 Implant placement: Immediate implant placement following tooth extraction without CT graft (thick biotype)

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Control	Benefits: none

For this intervention, **list the reasonably foreseeable risks**
List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. The need to know what to report promptly later = a requirement to estimate frequency (Instructions).

	Not serious	**Serious**
Likely These risks are expected to occur in more than 20 out of 100 subjects.	• Risk related to surgical procedures: Swelling, pain, bleeding..	• None
	Not serious	**Serious**
Less likely These risks are expected to occur in 5-20 subjects or less out of 100 subjects.	• Risk related to surgical procedures: Bruising, stretching of the corners of the mouth	• None
		Serious
Rare These risks are expected to occur in less than 5 subjects out of 100		• Risk related to surgical procedures: Nerve damage, infection, damage to the surrounding soft tissue, recession (shrinkage) of gums, migration of the graft material, increased tooth sensitivity, increased tooth mobility, unaesthetic exposure of the crowns, damage to adjacent teeth, nasal cavity, sinuses, medical emergencies. • Risk related to pain medications and antibiotics: Allergic reactions such as hives, rash and even-life threatening reactions called anaphylaxis
▪**Rare** ▪Less than 1 subject in 1000000		• Transmission of infectious disease to subject, such as hepatitis or nerve diseases, which may not show up for many years after infection (this risk is greatly reduced by using processing treatments shown to be capable of reducing this risk). So far, no report of any incidence related to the use of Straumann Allograft GC® bone graft and Bio-Gide® membrane is known

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6.d. List of ALL other research procedures or components not listed in table 6.b.
All of the research procedures for this study should be listed in either table 6.b. or 6.d.

Consider grouping similar procedures under a single component. E.g., blood work, CT = safety assessments)
(Click here for example)

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be done as part of standard practice.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(any performed outside frequency or timing for acceptable local practice)*	**Column C** **Risks** List the reasonably expected risks under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
	Summary for the whole study			
Visit1 to 12	Medical/Dental history	1		No risk
	Phase one therapy	1		No risk
	Information about implant placement procedure	1		No risk
	Information about study		1	No risk
	Cone Beam Computed Tomography (CBCT)	1		No risk
	Diagnostic work pertaining dental implant placement	1		No risk
	Informed Consent		1	No risk
	Medical history update	1		No risk
	Urine pregnancy test		1	No risk
	Impression		6 for both groups	No risk
	Periodontal biotype determination		1	No risk
	Photographs	2	6 for both groups	No risk
	Soft tissue assessment (on photographs and casts)		6 for both groups	No risk
	Fabrication of individualized bite-block		1 for both groups	No risk
	Radiograph	6		No risk
	Local Anesthesia	2 for both groups		No risk
	I.V Sedation	2 for both groups		No risk
	Chlorhexidine rinse	2 for both groups		Not serious and less likely: transient change in taste, staining (reversible) of teeth and soft tissues
	Extraction	1		Not serious and likely: Swelling, pain, bleeding.
	Final determination of enrollment in the study		1	No risk
	Implant placement	1		Not serious and likely: Swelling, pain, bleeding Not serious and less likely: Bruising, stretching of the corners of the mouth

				Serious and rare: Nerve damage, infection, damage to the surrounding soft tissue, recession (shrinkage) of gums, migration of the graft material, increased tooth sensitivity, increased tooth mobility, unaesthetic exposure of the crowns, damage to adjacent teeth, nasal cavity, sinuses, medical emergencies.
	Osseous measurements		1	No risk
	Bone Grafting	1		Not serious and likely: Swelling, pain, bleeding Not serious and less likely: Bruising, stretching of the corners of the mouth Serious and rare: Nerve damage, infection, damage to the surrounding soft tissue, recession (shrinkage) of gums, migration of the graft material, increased tooth sensitivity, increased tooth mobility, unaesthetic exposure of the crowns, damage to adjacent teeth, nasal cavity, sinuses, medical emergencies.
	Connective tissue Grafting	1 (test group) 0 (control)		Not serious and likely: Swelling, pain, bleeding Not Serious and less likely: Bruising, stretching of corners of the mouth Serious and rare: Nerve damage, infection, damage to surrounding palatal tissue, increased sensitivity, unaesthetic exposure of the crowns, severe bleeding, medical emergencies.
	Prescription of methylprednisolone	1		Serious and rare: hypersensitivity reaction
	Prescription of Antibiotic	1		Serious and rare: hypersensitivity reaction
	Suture removal	2		No risk
	Wound healing evaluation	4		No risk
	Second stage uncovery	1		No risk
	Referral to restorative dentist	1		No risk
	Feedback to referral dentist	2		No risk
	Recording of clinical parameters (PPD, MPI, mSBI)	4		No risk
	PES/WES score determination	4		No risk
	Detailed procedures for each study visit			
1	**Visit 1: Screening Examination**			
	Medical/Dental history	1		No risk
	Phase one therapy	1		No risk
	Information about implant placement procedure	1		No risk
	Information about study		1	No risk
	Cone Beam Computed Tomography (CBCT)	1		No risk

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	Diagnostic work pertaining dental implant placement	1		No risk
	Impressions		1	No risk
2	**Visit 2: Extraction/implant Placement**			
	Informed consent		1	No risk
	Medical history update	1		No risk
	Urine pregnancy test		1	No risk
	Photographs		1	No risk
	Soft tissue assessment (On photographs and casts)		1	No risk
	Periodontal Biotype Determination		1	No risk
	Fabrication of the individualized Bite-block		1	No risk
	Radiograph	1		No risk
	Local anesthesia	1		No risk
	I.V. sedation	1		No risk
	Chlorhexidine rinse	1		No risk
	Extraction	1		Not serious and likely: Swelling, pain, bleeding.
	Final determination of enrollment in the study		1	No risk
	Implant placement	1		Not serious and likely: Swelling, pain, bleeding Not serious and less likely: Bruising, stretching of the corners of the mouth Serious and rare: Nerve damage, infection, damage to the surrounding soft tissue, recession (shrinkage) of gums, migration of the graft material, increased tooth sensitivity, increased tooth mobility, unaesthetic exposure of the crowns, damage to adjacent teeth, nasal cavity, sinuses, medical emergencies.
	Osseous measurements		1	No risk
	Bone Grafting	1		Not serious and likely: Swelling, pain, bleeding Not serious and less likely: Bruising, stretching of the corners of the mouth Serious and rare: Nerve damage, infection, damage to the surrounding soft tissue, recession (shrinkage) of gums, migration of the graft material, increased tooth sensitivity, increased tooth mobility, unaesthetic exposure of the crowns, damage to adjacent teeth, nasal cavity, sinuses, medical emergencies.
	Connective Tissue Grafting	1 (test group) 0 (control group)		Not serious and likely: Swelling, pain, bleeding Not Serious and less likely: Bruising, stretching of corners of the mouth, Serious and rare: Nerve damage, infection, severe bleeding, medical emergencies.
	Radiograph (standardized)	1		No risk
	Prescription of Antibiotic	1		Serious and rare: hypersensitivity reaction
	Prescription of methylpredisolone	1		Serious and rare: hypersensitivity reaction

	Prescription of Chlorhexidine rinse	1		Not serious and less likely: transient change in taste, staining (reversible) of teeth and soft tissues
3	**Visit 3: Suture removal**			
	Suture Removal	1		No risk
	Wound healing evaluation	1		No risk
4	**Visit 4: Post-op 1 month after implant placement**			
	Wound healing evaluation	1		No risk
5	**Visit 5: Post-op 2 months after implant placement**			
	Wound healing evaluation	1		No risk
6	**Visit 6: Post-op 3 months after implant placement and uncovery**			
	Impression		1	No risk
	Photographs		1	No risk
	Radiograph	1		No risk
	Soft tissue assessment (On photographs and casts)		1	No risk
	Local anesthesia	1		No risk
	I.V. sedation	1		No risk
	Second stage uncovery	1		Not serious and likely: Swelling, pain, bleeding
	Chlorhexidine rinse	1		No risk
7	**Visit 7: Post-op 2 weeks after uncovery**			
	Suture removal	1		No risk
	Wound healing evaluation	1		No risk
	Referral to restorative dentist	1		No risk
8-9	**Visit 8 and 9: Post-loading visits**			
	Photographs	1		No risk
	Radiograph (standardized)	1		No risk
	Feedback to referral dentist	2		No risk
10	**Visit 11: 3 months post-loading evaluation**			
	Impression		1	No risk
	Photographs		1	No risk
	Soft tissue assessment (On photographs and casts)		1	No risk
	Recording of clinical parameters (PPD, MPI, mSBI)	1		No risk
	Radiograph (standardized)	1		No risk
	PES/WES score determination		1	No risk
11	**Visit 11: 6 months post-loading evaluation**			
	Impression		1	No risk
	Photographs		1	No risk
	Soft tissue assessment (On photographs and casts)		1	No risk
	Recording of clinical parameters (PPD, MPI, mSBI)	1		No risk
	Radiograph (standardized)	1		No risk
	PES/WES score determination		1	No risk
12	**Visit 12: 12 months post-loading evaluation**			
	Impression		1	No risk
	Photographs		1	No risk
	Soft tissue assessment (On		1	No risk

	photographs and casts)			
	Recording of clinical parameters (PPD, MPI, mSBI)	1		No risk
	Radiograph (standardized)	1		No risk
	PES/WES score determination		1	No risk

7. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

The present study involves two procedures that have been extensively documented in the literature and are considered as well-accepted treatment modalities. The purpose of this study is to compare the outcomes of these two well-accepted treatment modalities. The risks involved with these procedures are the ones related to any implant surgery and are not specific to the present research project. Accordingly, as per standard care the patient will be treated in such way to minimize infection including the careful preparation and draping of the patient, use of gentle and clean surgical technique, use of pre-sterilized package components, prescription of antibiotic, methyl-prednisolone and a chlorhexidine 0.12% antiseptic rinse following the surgery.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Any adverse events will be managed directly by the patient's operators and the attending periodontal faculty. All the operators are dentists trained to manage medical and dental emergencies that may occur during treatment.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

If yes, describe here

8. Confidentiality of the Research Information

a. Specify **where** the data and/or specimens will be stored and **how** the researcher will **protect the confidentiality** of subject information.

Data will be stored in a cabinet in the PI's office which will be locked at all times unless the PI is his office. Protected health information will only be accessed by the research team involved with the treatment of the patient.

Describe specimen storage - where and how protected?

b. Will all electronic data be stored in accordance with the institution's information security policy and encryption standards?

☑ Yes ☐ No, if no explain below

The data will be kept on the PI computer which is password protected and is in the office of the PI which is locked at all time when the PI is not present.

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9. Payment. (payment of subjects should be included in the consent form)

a. Describe the incentives (e.g., inducements) being offered to subjects for their time during participation in the research study.

Subjects will receive parts of study related treatment at no cost. The materials free of charge for the patient will include the implant and the bone graft material. Also the patient will not be charged for the implant placement (both groups) nor for the connective tissue graft (test group). However, the patient will be charged the bone grafting procedure and the resorbable collagen membrane. Moreover, patients will be financially responsible for subsequent implant provisional and/or definitive restorations.

b. If monetary compensation is offered, indicate how much the subjects will be paid and describe the terms and schedule of payment.

IRB policy requires a provision for providing partial payment to subjects who withdraw before the completion of the research. For *VA research, payment to human subjects participating in research is prohibited when the research is integrated with the patient's medical care and when the research makes no special demands on the patient beyond those of standard medical care. Payment may be permitted, with IRB approval, under certain circumstances. Consult with the VA R&D Office to discuss payment of subjects.*

Subjects will not be compensated for their participation in the study.

10. Costs to Subjects. (costs to the subject should be included in the consent form)

a. Describe any costs for care associated with research (including a breakdown of standard of care procedures versus research procedures), costs of test drugs or devices, and research procedure costs that are the subject's responsibility as a consequence of participating in the research.

Costs associated with transportation resulting as a consequence of participating in the research will be the subject's responsibility. With the exception of the incentives described under 9.a. all the other costs will be the patient's responsibility.

b. Describe any offer for reimbursement of costs by the sponsor for research related injury care. (Attach a copy of the section of the clinical trial agreement or contract describing research related injury care – the information in this section must match the injury section of the consent form).

If a subject is injured as a result of the research procedures, the injury will be treated. No compensation will be given to the subject as a result of the injury and he/she will be responsible for any charges related or unrelated to the injury.

11. PI-Sponsored FDA-Regulated Research

If the PI is the IND/IDE holder, or has agreed to perform any of the IND/IDE holder's sponsor obligations, the PI is considered a sponsor (sponsor investigator) and must meet additional requirements. (Form O, O-1 and P provide details)

[see Office of Clinical Research policies]

☑ N/A. The PI is not the IND or IDE holder, or has not agreed to perform sponsor obligations

a. Has the PI completed the CITI module: Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices?

☑ Yes ☐ No. If no, complete the training prior to submitting this protocol

b. Describe the PI's experience/knowledge/training related to serving as a sponsor-investigator.

FORM C

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