ClinicalTrials.Gov PRS Coversheet

Official Title: Comparison of Porcine Collagen Membrane (Mucograft Seal) and Bovine Collagen Wound Dressing (HeliPlug) in Atraumatic Extraction Sites with DFDBA Bone Particulate Graft: A Randomized Controlled Trial

NCT Number: 0145-23-FB

Document Title: Study Informed Consent Version 2

Document Date: 1/16/2025

Biomedical

SECTION I

Therapeutic/Non-Therapeutic

Does your research involve a drug, medical device, technique or other intervention or strategy (including means like diet, cognitive therapy, behavioral therapy, exercise) to diagnose, treat or prevent a particular condition or disease: "THERAPEUTIC RESEARCH"?

Yes

1. Title of Protocol:

Comparison of Porcine Collagen Membrane (Mucograft Seal) and Bovine Collagen Wound Dressing (HeliPlug) in Atraumatic Extraction Sites with DFDBA Bone Particulate Graft: A Randomized Controlled Trial

Is a OneChart/EPIC Subject Friendly Short Title needed?

No

2. Responsible Personnel:

A. Principal Investigator (PI):

Killeen, Amy C - COD-Surgical Specialties - 402-472-7848 - akilleen@unmc.edu - alt #: 402-472-7848 - degree: DDS - address: DENT 2329 UNL EAST (68583-0740) - phone: 402-472-7848

B. Secondary Investigator (SI):

Reinhardt, Rick (Rick) A - COD-Surgical Specialties - 402-472-1287 - rareinha@unmc.edu - alt #: 402-472-1287 - degree: DDS - address: DENT 2170A UNL EAST (68583-0740) - phone: 402-472-1287

C. Participating Personnel:

Czechner, Otto Alexander - COD-Surgical Specialties - 402-472-3249 - oczechner@unmc.edu - alt #: 402-472-3249 - degree: DDS

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D. Lead Coordinator:

Christiansen, Megan (Megan) M - COD-Surgical Specialties - 402-472-6770 - megan.christiansen@unmc.edu - alt #: 402-472-1441 - degree: BS, RDH - address: DENT 2319 UNL EAST (68583-0740) - phone: 402-472-6770

E. Coordinator(s):

Are you adding a clinical trial management group?

No

F. Data/Administrative Personnel:

G. Are you a student or house officer?

No

3. Funding Source:

Check all that apply and provide the source of the funding.

Cooperative Group:

Center for Clinical and Translational Research (CCTR)

Federal (e.g., NIH) Grant - Provide source:

Other Grant:

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♦ Departmental funding

Commercial - Provide company name:

Department of Defense

Other - Provide source (e.g. personal funding):

4. Deadline for IRB Approval:

Yes - Explain and provide date:

♦ No

5. Contract:

Is there a contract associated with this study?

No

6. Agreements

Is there a Material Transfer Agreement (MTA) associated with this study?

No

Is there a Data Use Agreement (DUA) associated with this study?

No

Is there a Data Transfer Agreement (DTA) associated with this study?

No

7. Study Sites:

A. Provide the names and locations of all study sites where this research will be

conducted under the oversight of the UNMC IRB or Joint Pediatric IRB.

UNMC College of Dentistry, Lincoln NE

B. Will the research be conducted at external sites under the oversight of an external IRB?

No

C. Does UNMC, TNMC, CHMC or UNO serve as the lead site with responsibility for data and/or safety monitoring?

No

D. Does this study involve any international sites where the PI will either; 1) conduct 2) supervise or 3) receive / ship HBM or data to / from UNMC?

No

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E. Does this study involve face to face contact with subjects?

Yes

8. Principal Investigator Assurance

The PI understands and accepts the following obligations to protect the rights and welfare of research subjects in this study:

All information in this application is complete and accurate.

I will conduct the research as described in the application and the protocol.

I will not initiate any change without IRB approval except when it is necessary to reduce or eliminate a risk to the subject.

I will ensure that all research personnel are qualified and properly trained.

I will fulfill my responsibilities as PI, described in https://guides.unmc.edu/books/hrpp-policies-and-procedures/page/126-piqualifications-and-responsibilities

I will follow all applicable HRPP and institutional polices, and all applicable laws, statutes and regulations.

Killeen, Amy C - 2024-02-19 15:31:07.160

9. Principal Investigator Financial Interest Disclosure

A. As the PI, I declare:

♦ I have no financial interest in this research.

I have a financial interest in this research.

B. As the PI, I understand

♦ I must disclose any change in my financial interest during the course of this research within five (5) business days from the time the change becomes known.

C. As the PI, I certify that:

♦ No Responsible Personnel have a financial interest in this research.

The Responsible Personnel listed below have informed me that they have a financial interest in this research.

D. I have informed all Responsible Personnel that if there is any change in their financial interests during the course of this study it must be disclosed within five (5) business days from the time the change becomes known.

Killeen, Amy C - 2024-02-19 15:31:07.160

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SECTION II

PROTOCOL ABSTRACT

1. Provide a brief (less than 2500 characters) abstract of the research protocol.

(2500 characters)

This summary should include: 1)) a brief description of the purpose of the study, 2) eligibility criteria, 3) interventions and evaluations and 4) follow-up.

The purpose of this study is to compare the effectiveness of a porcine collagen membrane to a bovine collagen wound dressing for atraumatic extractions. These are both commonly used as a barrier and containment material over atraumatic extraction sites that are grafted for future implant placement. The study will include nonsmoking adults aged 18-75 requiring premolar or anterior tooth extraction and graft procedures, who are in good general health and willing to provide informed consent. Exclusion criteria include a history of radiation therapy or bisphosphonate use, pregnancy or breastfeeding, systemic conditions that affect bone healing, contraindications to dental implants, and inability to attend follow-up visits. The study will be a double-blind randomized controlled trial involving 24 patients who will be assigned to two groups. Prior to tooth extraction, baseline data will be collected; including gingival crevicular fluid (GCF) sampling, and a limited field Cone Beam Computed Tomography (CBCT) radiograph. A reference digital scan will be taken to measure volumetric changes in soft tissue. Routine, atraumatic extraction of the tooth under local anesthetic will be performed. Following extraction, hydrated AllOss 50/50 DFDBA:FDBA bone particulate will be condensed following a routine protocol. One group will receive Mucograft Seal over the graft, and the other group will receive Integra HeliPlug. Patients will be seen at a standard 2-week follow up to remove sutures, have a GCF sampling at the adjacent teeth and take another digital scan. Patients will be seen for an additional 6-week follow up to take a small (2mm) incisional biopsy for histological analysis. Another digital scan and GCF sampling will be taken. Final evaluation will be 3 months post-extraction and will include a localized CBCT evaluation for implant planning and another measure of soft tissue changes with a digital scan. At the time of implant surgery, the core of bone removed during osteotomy will be histologically analyzed for percentage of vital bone. Adverse events will also be recorded at each visit. The primary outcome measure will be the histological

composition of tissue at 6 weeks and volumetric tissue changes. The secondary outcome measures will be adverse events, bone density on the post-operative CBCT and percentage of vital bone at implant placement.

PURPOSE OF THE STUDY AND BACKGROUND

2. Purpose of the Study

What are the specific scientific objectives of the research?

The primary objectives of this study are to compare the efficacy of a porcine collagen

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membrane to a bovine collagen wound dressing for atraumatic extractions, in terms of their ability to act as a barrier and containment material over atraumatic extraction sites that are grafted for future implant placement. This will be measured by volumetric and linear dimensional changes in the soft tissue and the histological composition of keratinized tissue

after healing.

The secondary objectives of the study are to evaluate the radiographic bone density and percentage vital bone at implant planning and placement.

3. Background and Rationale

Describe the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project is intended to fill.

Extraction and graft procedures are commonly performed in dental clinics where future implant placement is desired due to the large soft and hard tissue dimensional changes that

occur as a socket heals (Araujo 2005, Chappuis 2017). While there are several techniques for ridge preservation, it is generally accepted that minimizing trauma from the extraction and flap reflection greatly decreases loss of hard and soft tissue (Fickl 2008). This is why a

popular method is some form of Bio-Col technique where a bone graft is condensed into the

socket and then a collagen wound dressing, or plug, is used to prevent wash out of the graft. (Sclar 1999, Kotsakis 2014). While cost effective, and easy to place without flap reflection, a collagen plug can be dislodged quickly and has been shown to have a large soft

tissue loss during healing (Morelli 2020, Thoma 2018). Therefore, other soft tissue alternatives have been investigated as an alternative membrane (Ghanaati 2017)

Several studies have investigated the efficacy of Mucograft Seal as a barrier membrane to promote bone regeneration in socket preservation techniques. (Jung 2013) Mucograft Seal is a porcine collagen membrane that is shaped ideally for easy coverage of a socket. Because it is a pure matrix of Type I and Type III collagen, it is able to stay more dimensionally stable, making it an ideal material to combat soft tissue reduction as a site heals. It is currently used as a replacement for free gingival grafting coverage, such as with the soft tissue punch technique (Jung 2004), but has not been compared to a collagen wound dressing for critical early healing characteristics such as inflammatory cytokines. Additionally, there is limited information on the specific histological composition at 6 weeks

post-operative healing in patients who undergo socket preservation with Mucograft Seal or Colla-Plug.

Information Gaps: The information gaps that this project is intended to fill are twofold. First, it aims to compare the effectiveness of Mucograft Seal and Colla-Plug in premolar and forward extraction and graft procedures through a randomized controlled trial, which will provide more conclusive evidence on the comparative efficacy of these two biomaterials. Second, the project aims to evaluate the histological composition of an incisional tissue biopsy at 6 weeks post-operative healing in patients who undergo these procedures with

either Mucograft Seal or Colla-Plug, which will provide valuable information on the tissue response to these biomaterials at an early stage of the healing process. By addressing these information gaps, the project aims to contribute to the development of more effective socket preservation techniques and biomaterials, which will benefit patients undergoing these procedures.

CHARACTERISTICS OF THE SUBJECT POPULATION

4. Accrual

A. Is this study conducted solely at sites under the oversight of the UNMC IRB (e.g. UNMC, Nebraska Medicine, CHMC, UNO)?

Yes

1. How many subjects will need to be consented (per group, as applicable) in order to achieve the scientific objectives of the research?

24 subjects will be enrolled - 12 in each group to account for a 10% drop out rate.

2. What is the statistical or other justification for the total number of subjects described above?

A sample size of 11 in each group provides 80% power to be able to detect an absolute difference in 20 percentage-points of converted mucosa between the collagen (i.e. 50%) and mucograft (i.e. 70%) groups at four weeks, assuming a standard deviation of 15 for percentage converted mucosa and an alpha level of 0.05, using a Wilcoxon Rank Sum test.

3. How long do you estimate it will take to accrue the required number of subjects?

9 months

5. Gender of the Subjects

A. Are there any enrollment restrictions based on gender?

No

6. Age Range of Subjects

A. Will adults be enrolled ?

Yes

1. What is the age range of the adult subjects?

19-75

2. What is the rationale for selecting this age range?

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This treatment is rarely performed in children below the age of 19 and after the age of 75,

adult subjects will typically show decreased wound healing due to age which could conflate

findings.

B. Will children (18 years of age or younger) be included in this research?

No

1. What is the justification for excluding children from participating in this research?

♦ Research is irrelevant to children (e.g. disease or condition rarely encountered in

children).

Knowledge being sought in the research is already available for children or will be obtained

from another ongoing study.

A separate study in children is warranted and preferable.

Insufficient data are available in adults to judge the potential risk in children.

Other. Explain.

7. Race and Ethnicity

Are there any subject enrollment restrictions based upon race or ethnic origin?

No

8. Vulnerable Subjects

A. Will prisoners be included in the research?

No

B. Select from the list all of the vulnerable populations that will specifically be recruited to participate in this research.

Decisionally-impaired persons

Critically ill patients

Students of the investigator

Employees of the investigator

Educationally disadvantaged individuals

Socially or economically disadvantaged individuals

Individuals with a stigmatizing illness or condition

Individuals from a marginalized social or ethnic group

Other.

♦ No vulnerable subjects will be specifically recruited

9. Inclusion Criteria

What are the specific inclusion criteria?

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1) adult patient seeking care at the UNMC College of Dentistry for extraction of a premolar or anterior tooth due to periodontal or endodontic defect, non-restorable caries or fracture

2) adult patient is considering dental implant placement to replace the extracted tooth and requires a bone grafting procedure in preparation for a dental implant

3) Nonsmoker

4) 19-75 years old

10. Exclusion Criteria

What are the specific exclusion criteria?

Exclusion criteria include a history of radiation therapy or bisphosphonate use, pregnancy,

systemic conditions that affect bone and soft tissue healing, contraindications to dental implants, and inability to attend follow-up visits.

11. Pregnancy and Contraception Requirements

A. Are women of child bearing potential (WOCBP) included in this research?

Yes

a. Are there any specific contraception requirements for subjects?

No

1. Provide justification for absence of contraception requirements

♦ There are no interventions that are likely to be of risk to a fetus

Investigational drug(s) is (are) not systemically absorbed

Investigational drug(s) is (are) systemically absorbed, but there is no evidence from human studies, or from clinical experience, that there is risk to a fetus

Other

B. Are pregnant women included in this research?

No

1. Provide justification for excluding pregnant women

Investigational drug(s) is (are) absorbed systemically, and there is evidence from animal or human studies, or from clinical experience, that there is risk to a fetus OR investigational drug(s) is (are) absorbed systemically, and there is a well-understood mechanism of action that may result in risk to a fetus

Intervention includes a procedure expected to be of risk to a fetus (eg, exposure to ionizing radiation, maximal exercise test)

Research is not relevant to pregnant women (e.g. disease or condition rarely encountered in

pregnant women)

Knowledge being sought in the research is already available for pregnant women or will be obtained from another ongoing study

A separate study in pregnant women is warranted and preferable

♦ Physiology of pregnancy precludes generalization to other populations

Other - explain

2. Describe how pregnancy status will be assessed (eg, self-report, urine pregnancy test, blood pregnancy test) and the frequency of monitoring during participation in the research.

Pregnancy status will be determined via self-report

3. Describe the plan should a female subject, or the partner of a male subject, become pregnant while research interventions are on-going (or during the period that contraception is required following the completion of the intervention).

Should a female subject become pregnant while research interventions are on-going, she will be dismissed from study.

C. Are breast feeding women excluded in this research?

No

Provide justification for the inclusion or exclusion of breast feeding women.

There are no interventions that are likely to be of risk to a nursing newborn.

METHODS AND PROCEDURES

12. Methods and Procedures Applied to Human Subjects

A. Are there any evaluations or tests that will be performed for the purpose of determining subject eligibility which would not be routinely conducted as part of standard clinical care of the prospective subject?

No

B. Describe the research plan, including all procedures, interventions, evaluations and tests.

Patients at the UNMC College of Dentistry who are seeking care to extract a premolar or anterior tooth due to a periodontal defect, endodontic defect or non-restorable caries or fracture, and who are considering a dental implant to replace the extracted tooth, will be made aware of this clinical study by the dental faculty or residents planning the treatment. Subjects will be given the consent form to take home and consider, and any questions will be answered, signed and witnessed.

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Twenty-four patients will be enrolled in this study. On the day of extraction, baseline data will be recorded/collected. These include the following:

1. A limited field CBCT will be taken of the tooth to be extracted.

2. Gingival crevicular fluid (GCF) sampling at the interproximal sites of teeth adjacent to the tooth to be extracted. The tooth to be extracted will be isolated with cotton rolls and GCF collection paper strips will be placed into the facial and lingual interproximal gingival sulci for 30 seconds. The paper samples will be pooled and placed in a plastic-capped vial labeled with the subject number and visit (example: N1-0, N2-1) and immediately frozen at -80° C. The GCF sample vials will not be labeled with any personal identifying information (subject 's name, age, tooth #, etc).

3. A digital intraoral scan will be taken to establish baseline tissue dimensions.

Routine atraumatic dental extraction under local anesthesia will be completed by the assigned periodontal resident (SM, NB, PS, JL, OC, DD) or oral surgery fellow and faculty (AK, RR).A statistician will generate a randomization schedule, after which someone not involved in the treatment of these patients will put each randomized treatment assignment into separate envelopes. The envelope will be given to the clinical provider after the extraction is completed. The extraction socket will be filled with 50:50 AlloOss DFDBA/FDBA allograft bone and covered with either a HeliPlug

collagen wound dressing or a Mucograft Seal membrane.

Subjects will be scheduled for a routine postoperative visit two weeks following the extraction. At this visit, suture removal and evaluation of the healing site will occur. GCF collection on the remaining adjacent teeth will occur as will an intraoral digital scan of the extraction site.

An additional post operative visit will occur at 6 weeks to do a final soft tissue healing evaluation. At this time a small (2mm) incisional biopsy will be taken and stored in 10% formalin that is labeled similarly to GCF sample tubes. We do not anticipate this tissue removal to have an impact on final healing of the underlying bone for the patient. This tissue will be processed with a hematoxylin and eosin stain and the width of keratinized tissue will be measured by a separate individual who is blinded to the treatment groups. GCF collection on the remaining adjacent teeth will also occur at this visit, as will an intraoral digital scan of the extraction site.

The final postoperative visit will be 3 months following the extraction. A limited-field CBCT will be taken to begin the process of implant treatment planning and measure bone height, width and volume. A final GCF collection on the remaining adjacent teeth will also occur at this visit, as will a final intraoral digital scan of the extraction

site.

GCF Cytokine Determination

At the time of analysis, each pooled GCF samples will be eluted using 100 µl of 1× PBS by gently agitating the samples on a rocker plate for 1 h at 4°C. Cytokine concentrations will be measured using a customized human cytokine and magnetic bead panel (Milliplex MAP kit; Millipore, Billerica, MA), and a MAGPIX instrument and software (Luminex Corporation, Austin, TX) per the manufacturers recommendations.

Ten analytes will be measured: interleukin-1β (IL-1β), IL-4, IL-6, IL-8, IL-10, IL-13, IL-17 granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor alpha (TNF-α), interferon-gamma (INF-γ). Albumin for each sample also will be measured to normalize cytokine levels and control for serum contamination. The amounts of cytokines will be reported in picograms per albumin level and per 30-s sample.

Statistical Analysis

The percentage of converted mucosa will be documented at six weeks after an extraction, and differences in the width of keratinized tissue between the collagen and mucograft groups will be assessed using a Wilcoxon Rank Sum test. As a secondary analysis, we may also look at other related demographic (e.g. sex, age, etc.) and clinical (e.g. bone width, soft tissue volume, cytokine levels, etc.) characteristics to see if they have associations with the percent keratinized gingiva, using Spearman correlations for continuous variables, or Wilcoxon Rank Sum/Kruskal Wallis tests for categorical variables.

C. Select any of the following that apply to the research:

Phase I study

♦ Randomization

Placebo (or non-treatment arm)

Washout

Sensitive surveys or questionnaires

None of the above

Option chosen: Randomization

Describe randomization process and schedule

A statistician will generate a randomization schedule, after which someone not involved in the treatment of these patients will put each randomized treatment assignment into separate

envelopes, which will be given to the clinical provider close to the time the material will be placed, after the patient has been enrolled/consented into the study.

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D. Identify:

1. All procedures, interventions, evaluations and tests performed solely for research purposes (eg, administration of an investigational drug or a new psychological assessment instrument; randomization)

Procedures performed solely for research purposes include: the collection of gingival crevicular fluid (GCF); soft tissue biopsy at 6-weeks post-procedure.

2. All procedures, interventions, evaluations and tests performed for clinical indication but more frequently than they would be if the subject was not participating in the research (eg, extra blood tests; additional radiology exams)

It is not typical to have an intraoral scan done at post-operative visits. However, this takes less than 2 minutes to perform and has no contraindications or risks. It is simply a data collection process for dentists to measure changes in our patients over time.

E. Describe briefly the statistical methods used to analyze the data (or reference the appropriate section of the detailed protocol or grant).

The percentage of converted mucosa will be documented at six weeks after an extraction, and differences in the width of keratinized tissue between the collagen and mucograft groups will be assessed using a Wilcoxon Rank Sum test. As a secondary analysis, we may also look at other related demographic (e.g. sex, age, etc.) and clinical (e.g. bone width, soft

tissue volume, cytokine levels, etc.) characteristics to see if they have associations with the

percent keratinized gingiva, using Spearman correlations for continuous variables, or Wilcoxon Rank Sum/Kruskal Wallis tests for categorical variables.

F. Does this study involve the collection of blood, urine, saliva or other human biological material (HBM)?

Yes

1. Does this research involve genetic testing including Genome Wide Association Studies (GWAS), Whole Genome Sequencing (WGS) or Whole Exome Sequencing (WES)?

No

G. Does this study involve the creation of a tissue bank for future unspecified research? This includes un-used (excess) blood, urine, or tissue, obtained for clinical indication or for research, or additional human biological material collected specifically for future research.

No

DRUGS, BIOLOGIC DRUGS AND DEVICES

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13. Drugs and Biologic Drugs

1. Does this research involve the use of drugs or biologics?

Yes

A. Are any of the drugs or biologics used in this research not FDA-approved?

No

B. Are any of the drugs used in this study FDA Approved?

Yes

1. Will data obtained from this research study be used to support a new indication, new labeling or a change in advertising of an FDA-approved drug or biologic?

No

2. Will the use of an FDA-approved drug in this research study involve a route of

administration, dosage level or patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product?

No

C. Do any of the sponsors of this research require compliance with ICH-GCP?

No

14. Devices

1. Does this research involve a medical device(s) (including an in vitro device [IVD] (assay), and medical software)?

No

CONFIDENTIALITY AND PRIVACY

15. Confidentiality and Privacy

A. Describe where research data will be stored. Check all that apply.

Box@unmc.edu (secure UNMC or UNO designated cloud-based storage site)

Microsoft Office 365 application (including SharePoint, OneDrive for Business, Teams or Streams) (UNMC, UNO or NU system instance) (secure UNMC or UNO designated cloudbased storage site)

Other secure UNMC or UNO designated cloud-based storage site - describe:

OnCor Clinical Trial Management System (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO)

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CCORDA database (biostatistics) (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO)

RITO-hosted databases (for example, REDCap, CV-QOR, Onchem Trials, XNAT) (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO)

Nebraska Medicine PACS (for image files) (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO)

Other secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO - describe:

On an NSRI or designated high security .gov storage site

On a VA-approved storage vehicle for a VA-approved study

On a remote secure server and/or database maintained by the sponsor accessible through the internet

On a secure server and/or database hosted and maintained by another institution accessible through the internet

On a device or mobile application provided by the sponsor to upload data to a coordinating center or central database

On a device or mobile application being developed by a sponsor or by a UNMC, CHMC or UNO investigator

On a device or mobile application that connects to the internet through UNMC or NM network (wired or wireless)

On an encrypted, password protected portable computer, or flash drive

Other - describe:

♦ In hard copy (other than signed Consent Forms)

Option chosen: In hard copy (other than signed Consent Forms)

a. Please provide justification for use of hard copies

Data collection is easiest and most secure in our department when done with hard copies. The room is secured by key card access and data will be stored in locked cabinets. Only authorized personnel will be able to access them.

Option chosen: In hard copy (other than signed Consent Forms)

b. Will hard copies will be transported from one site to another, on or off campus?

No

B. Will any of the following subject identifiers be recorded (at any time) in association

with the research data?

Yes

1) Indicate the subject identifiers that will be recorded. Check all that apply.

Name

♦

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DATES (e.g. date of study visit, date of sample collection, birth, admission, discharge)

Postal address information: street address, city, county, precinct, ZIP code

Telephone numbers

Fax numbers

Electronic mail addresses

Social Security numbers

♦ Medical Record numbers

Health plan beneficiary numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers and serial numbers

Web Universal Resource Locators (URLs) Internet Protocol (IP) address numbers

Biometric identifiers, including finger and voice print

Full face photographic images [and any comparable images]

No Identifier

2) Will a unique subject identifying number (e.g., S1, S2, S3), characteristic or code be used to link data to any of the identifiers listed above?

Yes

a. Where will the key (that links the unique subject identification code to the subject's name or other identifier) be stored?

The key will be stored in a locked filing cabinet within a locked room in the Cruzan Center for Dental Research. The unique identifier that will be sued to code the data is as follows: each subject will be given a number (i.e. N1, N2…N25). The specific appointment visit (baseline, 2 weeks, 3 months) data will be coded as follows: N1-0 (baseline), N1-2 (two weeks), N1-3 (3 months).

b. Does the code number include the subject's initials or other subject identifier as part of the code?

No

3) What is the justification for recording the specific subject identifiers listed above? Check all that apply.

♦ Schedule appointments

Collect continuous clinical information from the medical records

♦ Follow-up with subjects

Link stored tissue with subject identification for it to be withdrawn in the future if requested

Compensation

Other. Explain.

4) How long will the subject identifiers be maintained in association with the research data?

Subject identifiers will be maintained until data have been statistically analyzed and reports

published and no less than 7 years following completion of research per Nebraska state law

and NRPP policy.

5) How will all of the identifiable research data be destroyed (e.g., all identifiers stripped from the data and destroyed, hard copies shredded etc) when the identifiable data is no longer required?

Subject identifiers will be stripped from the data and destroyed once it is no longer required.

C. Will research data that contain subject identifiers be disclosed to:

Other investigators at UNMC, NM, UNO or CHMC who are not listed in Section I of this application?

No

2. Investigators outside of UNMC, NM, UNO or CHMC?

No

3. Will research data that contain subject identifiers be disclosed to any commercial sponsor or contract research organization (CRO), or to any other external organization or entity (e.g., NCI cooperative groups)?

No

D. What provisions will be in place to protect the subject's privacy? Check all that apply.

♦ Ensuring that only personnel listed on the IRB application Section I.3(A-E) are present during the consent process.

♦ Ensuring that the fewest number of individuals possible are aware of the subject's participation in the research.

♦ Ensuring that the research activities are performed in as private of a place as possible.

Other. Explain.

E. Does this research involve data banking at UNMC, NM, UNO or CHMC, or by an outside organization (e.g. NCI Cooperative Group, pharmaceutical company) for future research that is not related to this study?

No

RISK/BENEFIT ASSESSMENT

16. Potential Risks

What are the potential risks associated with each research procedure, intervention, evaluation and/or test? If data are available, estimate the probability that a given harm may occur and its potential reversibility.

Potential risks associated with soft tissue sampling at 4-weeks includes minimal pain and adjacent tooth sensitivity.

The soft tissue and GCF specimens will be collected in plastic-capped vials and frozen until analysis. These vials will be labeled with the subject's number and visit (N1-0, N2-2) and will not be labeled with any personal identifying information, thus breach of confidentiality is not at risk.

Potential risks associated with limited view CBCT include increase exposure to radiation. This risk is inherent to any dental radiography and the limited-view CBCT pre-extraction and post-extraction is standard therapy for dental implant treatment planning.

17. Risk Classification

What is the overall risk classification of the research?

Minimal risk

♦ Greater than minimal risk

18. Minimization of Risk

A. Describe how the subjects of the research will be monitored by the investigators and other research personnel to ensure their safety.

Subjects of the research will be monitored with follow-up phone calls. If any postoperative

concerns develop, they will be seen in the graduate periodontal clinic for follow-up.

B. Describe how the data collected will be monitored to ensure the safety of subjects. Identify who will perform the ongoing data and safety analysis, and describe the frequency of data analysis. If there is an independent Data and Safety Monitoring Board (DSMB) provide the charter, or describe (1) the composition of the DSMB membership, (2) the frequency of DSMB meetings and reports.

Data collection will be monitored by study personnel and if a decline in the subject's periodontal condition is noted, they will be referred to the graduate periodontal residency at

UNMC College of Dentistry for a full evaluation. The contact information for the study investigators and personnel are on the consent form that will be sent home with each

subject.

C. Describe the auditing plan for research conducted. Identify who will conduct the audits and specify the audit frequency.

Ten percent of the case report forms will be reviewed by the Associate Dean of Clinics, Dr. Amir Fahr, at the COD semi-annually and audited against the primary dental record. Any violations or unexpected outcomes will be reported to the IRB.

D. Describe the specific subject withdrawal criteria.

Subjects will be withdrawn if they are non-compliant to their postoperative appointments.

E. Describe the stopping rules for the research (e.g., the specific criteria for halting or early termination of the study).

If 10% of subjects suffer an adverse event, such as bleeding or pain associated with the soft

tissue sampling greater than that expected associated with a similar extraction without sampling, the study will be stopped.

F. Describe plans and resources available to promptly address any subject injury.

The investigators are board-certified periodontists or periodontal residents, so any adverse effects will be addressed with a thorough evaluation and appropriate treatment.

19. Potential Benefits to the Subject

Is there the prospect for direct benefit (eg, research on diagnosis or treatment of disease)?

No

20. Potential Benefits to Society

Describe the potential benefits to society that may reasonably be expected to result from this research.

A potential benefit to society would be clarification and understanding of the soft tissue healing capabilities of common materials used for this procedure.

FINANCIAL OBLIGATIONS AND COMPENSATION

22. Financial Obligations of the Subject

A. Who will pay for research procedures, interventions, evaluations and tests? Check all that apply.

Sponsor

Grant

CRC, CCTR

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Costs or fees waived by Nebraska Medicine, UNMC- P, CHMC or CSP

♦ Department/Section funds

Other. Explain

B. Will any of the research procedures, interventions, evaluations and tests described above be charged to the Subject, the Subject's health insurance, or

Medicare/Medicaid?

Yes

1. Provide additional detail and justification for charging as noted.

The subject will be not be charged for any research procedures or interventions. The subject

will be charged for non-research related procedures (extraction, bone graft, limited view

CBCT).

C. Are there any other financial obligations that the subject will incur as a result of

participating in the study?

No

23. Compensation to the Subject for Participation

A. Will the subject receive any compensation for participation?

No

PRIOR REVIEW

24. Prior IRB Review

A. Has this study (or one substantially similar) been previously submitted to the UNMC

IRB (or the Joint Pediatric IRB) and then withdrawn by the investigator for any reason?

No

B. To the best of your knowledge, has this study (or one substantially similar) been

considered by another IRB and disapproved?

No

SUBJECT IDENTIFICATION & RECRUITMENT

25. Method of Subject Identification and Recruitment

A. Will prospective subjects learn about the research and then contact the investigator

about participation (for example, in response to a print, electronic, radio or television

advertisement; referral by a clinician or other specifically for this research)?

No

B. Will the investigator make the initial contact with the potential subject to tell him/her about the research (for example, by contacting existing or past previous patients or research participants; or by contacting prospective subjects thru school records, or thru support groups or other Interest Groups; or thru use of the Hospital Opt-In Database)?

Yes

1. How will prospective subjects be identified?

Patients that meet the study criteria will be identified in the UNMC COD clinic during normal

clinical treatment.

2. Will potential subjects be screened for eligibility prior to informed consent?

No

3. How will potential subjects be approached and invited to participate?

Eligible patients will be asked if they want to participate in the study.

a. Describe the process of initial contact

Patients that would otherwise be presenting to the clinic for extraction and grafting will be invited to participate in the study.

b. Who will make the initial contact?

One of the investigators or collaborators.

c. Does that person have ethical access to information about potential subjects?

Yes

i. Describe

All investigators and collaborators are responsible for supervising dental students in patient

care in the clinic where potential subjects are treated, therefore direct contact with potential

subjects and their records is part of that supervision.

C. Will this study be listed in the clinical trial registry at www.clinicaltrials.gov?

Yes

1. Provide the NCT#.

NCT application has been submitted, awaiting NCT#. Will inform the IRB when it comes

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through.

2. Identify who holds the NCT#

♦ PI

Sponsor

OBTAINMENT OF INFORMED CONSENT

26. Waiver or Alteration of Informed Consent

A. Is a complete waiver or alteration of consent requested?

No

27. Waiver of Signed Consent

Is a waiver to obtain signed consent requested?

No

29. Process of Informed Consent

A. When will the prospective subject/parent(s)/guardian(s)/LAR be approached relative

to their/the subject's actual participation in the study?

Prospective subjects will be approached after it has been determined that they have a nonrestorable anterior or premolar tooth that needs extraction and they have expressed interest

in replacing the tooth with a dental implant. Subjects will be referred to the graduate

periodontal clinic where they will be approached by study personnel (periodontal resident) about their interest in participating in the study.

B. Where will informed consent be obtained, and how will the environment be conducive to discussion and thoughtful consideration?

Informed consent will be obtained in a private room in the Cruzan Center for Dental Research.

C. Who will be involved in the process of consent and what are their responsibilities?

The investigators will explain the research, ask questions to be certain that the subject understands the procedure, and answer any subject questions. Additionally, investigators will also ask questions to ensure that subjects understand their rights as research subject

D. Is there any limitation on the amount of time allotted to the process of consent?

No

E. How will the process of consent be structured for subjects who are likely to be more

vulnerable to coercion or undue influence?

All subjects approached about this study will already have made the decision to extract the tooth and have expressed interest in implant replacement of that tooth. Additionally, they will

already have been counseled on the process of extraction, grafting and implant placement; including the costs and time required for successful treatment.

Investigators acknowledge concerns regarding the potential subject misinterpreting the study as standard of care, or having his/her decision regarding participation influenced by concerns about disappointing or offending his/her care provider by having the introductory and informed consent conversations completed by study personnel who are not familiar to the subject. The subject will not have had previous contact with study personnel, thus

minimizing the concern about disappointing or offending his or her provider. Additionally, extreme care will be taken during discussion/description of the study with the subject to highlight that the removal of soft tissue is not standard of care for routine extraction and implant preparation.

F. Will non-English speaking subjects be enrolled in this research?

Yes

Describe the plan to conduct the process of informed consent in the language of the subject/parent(s)/guardian(s)/LAR

The process of informed consent in the language of the subject includes utilization of interpretation services via video (Language Link) or in-person interpreter.

G. How will it be determined that the subject/parent(s)/guardian(s)/LAR understood the information presented?

The investigator will question the subject concerning his/her understanding of all elements of the informed consent. This will include having the subject describe what will be done to them along with the risks

31. Information Purposely Withheld

Will any information be purposely withheld from the subject during the research or after completion of the research?

No

RESOURCES

33. Describe the resources available to safely conduct this study at each study sites specified in Section I.7.

1. Funding for all research-related expenses have been secured through departmental

funds.

2. Research procedures will be conducted in the Cruzan Center for Dental Research at the UNMC College of Dentistry.

3. Laboratory space for the GCF tests will be available in the laboratory of one of our investigators (RR).

4. Emergency equipment and personnel services are routinely available in the periodontal clinic during operation, during which all patient-based procedures will be performed.

LITERATURE REVIEW

34. References

Provide a full listing of the key references cited in the background (Section II.3). The references should clearly support the stated purpose of the study.

Araujo, M.G. and J. Lindhe, Dimensional ridge alterations following tooth extraction. An experimental study in the dog. J Clin Periodontol, 2005. 32(2): p. 212-8.

Chappuis, V., M.G. Araujo, and D. Buser, Clinical relevance of dimensional bone and soft tissue alterations post-extraction in esthetic sites. Periodontol 2000, 2017. 73(1): p. 73-83.

Fickl, S., et al., Tissue alterations after tooth extraction with and without surgical trauma: a volumetric study in the beagle dog. J Clin Periodontol, 2008. 35(4): p. 356-63.

Ghanaati, S., et al., Evaluation of the tissue reaction to a new bilayered collagen matrix in vivo and its translation to the clinic. Biomed Mater, 2011. 6(1): p. 015010.

Jung, R.E., et al., Radiographic evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial. J Clin Periodontol, 2013. 40(1): p. 90-8.

Jung, R.E., D.W. Siegenthaler, and C.H. Hammerle, Postextraction tissue management: a soft tissue punch technique. Int J Periodontics

Restorative Dent, 2004. 24(6): p. 545-53.

Kotsakis, G., et al., Flapless alveolar ridge preservation utilizing the

"socket-plug" technique: clinical technique and review of the literature. J Oral Implantol, 2014. 40(6): p. 690-8.

Morelli, T., et al., Three-Dimensional Volumetric Changes After Socket Augmentation with Deproteinized Bovine Bone and Collagen Matrix. Int J Oral Maxillofac Implants, 2020. 35(3): p. 566-575.

Sclar, A.G., Preserving alveolar ridge anatomy following tooth removal in conjunction with immediate implant placement. The Bio-Col technique. Atlas Oral Maxillofac Surg Clin North Am, 1999. 7(2): p. 39-59.

Thoma, D.S., et al., Clinical and histologic evaluation of different approaches to gain keratinized tissue prior to implant placement in fully edentulous patients. Clin Oral Investig, 2018. 22(5): p. 2111-2119.

SECTION III

SUBMISSION DEADLINE

A. Full Board Review:

The IRB meets twice monthly, on the first and third Thursday of the month, with the exception of January and July when the IRB meets only on the third Thursday of the month. No more than 15 applications (e.g., initial review of a new study, re-review of a tabled study) will be reviewed at each meeting. All reviews are performed on a firstcome first-served basis. The IRB meeting schedule and deadline dates can be found on

the IRB website at www.unmc.edu/irb.

B. Expedited Review

Applications that qualify for expedited review have no submission deadline and can be reviewed independent of the IRB meeting schedule. Call the Office of Regulatory Affairs for assistance in determining if your study meets the requirements for expedited review.

ADDITIONAL REVIEW REQUIREMENTS

Final IRB approval and release of studies is contingent upon approval by the following UNMC committees or departments. Check the appropriate boxes:

UNMC and NM - Pharmacy & Therapeutics (P&T) Committee (Required for studies involving drugs)

Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) (Required for studies involving cancer)

Institutional Biosafety Committee (IBC) (Required for studies involving the use of gene transfer and vaccines)

Investigational Device Review Committee (IDRC) Review by the IDRC is required for all protocols involving the use of investigational or marketed devices

Billing Grid (Required for all studies involving billing for hospital/clinic services)

Coverage Analysis (Departments requiring this analysis have been specified by the Organization)

Conflict of Interest (COI) Management Plan (Required for all studies with declared COI by study personnel)

Sponsored Programs Administration (SPA)/UNeHealth grants and contracts

Pathology approval for collection of tissue samples required for this study

Radiation Committee Approval

Other Review

♦ None of the above organizational requirements apply to this study

Institutional Review Board (IRB)

SECTION IV

COVID-19

Human Subjects Research Safety Plan

For studies involving face-to-face encounters, the research team under the responsibility of the principal investigator will agree to comply with the following safety measures:

1. Masking of the researcher(s) during a face-to-face encounter

2. Cleansing of any surface and/or equipment utilized before and after a subject encounter

3. The Biosafety Officer (jenna.mckenzie@unmc.edu) will be notified if obtaining saliva, nasal, sputum or stools samples to ensure safe collection, handling, and processing plan is in place

4. Suggest addressing the current health of the subject before commencing faceto-face research via questions below:

Have you or anyone in your household tested positive or had a fever, chills, cough, shortness of breath, diarrhea, nausea, vomiting, recent loss of taste or smell, tiredness or fatigue, or muscle aches? If yes, the monitor will not be allowed on campus.

Have you recently traveled to an area with a widespread outbreak or had close contact with a person known to have COVID-19, MERs-CoV or Ebola?

Have you traveled outside of the country within the past month? If so, where did you travel and when did you return?

Have you had a recent SARS-COV-2 antibody test or nasal swab and if so

when and what were the results?

♦ I acknowledge this requirement.

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Version 2 - PROTOCOL # 0145-23-FB Page 27 of 2IRB PROTOCOL # 0145-23-FB Page 1 of 27 Biomedical SECTION I Therapeutic/Non-Therapeutic Does your research involve a drug, medical device, technique or other intervention or strategy (including means like diet, cognitive therapy, behavioral therapy, exercise) to diagnose, treat or prevent a particular condition or disease: "THERAPEUTIC RESEARCH"? Yes 1. Title of Protocol: Comparison of Porcine Collagen Membrane (Mucograft Seal) and Bovine Collagen Wound Dressing (HeliPlug) in Atraumatic Extraction Sites with DFDBA Bone Particulate Graft: A Randomized Controlled Trial Is a OneChart/EPIC Subject Friendly Short Title needed? No 2. Responsible Personnel: A. Principal Investigator (PI): Killeen, Amy C - COD-Surgical Specialties - 402-472-7848 - akilleen@unmc.edu - alt #: 402-472-7848 - degree: DDS - address: DENT 2329 UNL EAST (68583-0740) - phone: 402-472-7848 B. Secondary Investigator (SI): Reinhardt, Rick (Rick) A - COD-Surgical Specialties - 402-472-1287 - rareinha@unmc.edu - alt #: 402-472-1287 - degree: DDS - address: DENT 2170A UNL EAST (68583-0740) - phone: 402-472-1287 C. Participating Personnel: Czechner, Otto Alexander - COD-Surgical Specialties - 402-472-3249 - oczechner@unmc.edu - alt #: 402-472-3249 - degree: DDS Davis, Richard Duke - COD-Surgical Specialties - 402-472-3249 - ridavis@unmc.edu - alt #: 402-472-3249 - degree: DDS Version 2 - PROTOCOL # 0145-23-FB Page 1 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 2 of 27 Ingalsbe, Greg Greg Ryan - COD-Surgical Specialties - 402-472-1311 - gingalsbe@unmc.edu - alt #: 402-472-3249 - degree: DMD - address: DENT 2311 UNL East (68583-0740) - phone: 402-472-1311 Lee, Joyce Ab-Ye - COD-Surgical Specialties - 402-472-3249 - joylee@unmc.edu - alt #: 402-472-3249 - degree: DDS Scanlan, Christine I - COD-Surgical Specialties - 402-472-1311 - christine.scanlan@unmc.edu - alt #: 402-472-3249 - degree: DDS - address: DENT 2311 UNL EAST (68583-0740) - phone: 402-472-1311 Schlemmer, Paula Christina Co - COD-Surgical Specialties - 402-472-3249 - pschlemmer@unmc.edu - alt #: 402-472-3249 - degree: DDS - address: DENT 2311 (Zip 68583) - phone: 402-472-3249 D. Lead Coordinator: Christiansen, Megan (Megan) M - COD-Surgical Specialties - 402-472-6770 - megan.christiansen@unmc.edu - alt #: 402-472-1441 - degree: BS, RDH - address: DENT 2319 UNL EAST (68583-0740) - phone: 402-472-6770 E. Coordinator(s): Are you adding a clinical trial management group? No F. Data/Administrative Personnel: G. Are you a student or house officer? No 3. Funding Source: Check all that apply and provide the source of the funding. Cooperative Group: Center for Clinical and Translational Research (CCTR) Federal (e.g., NIH) Grant - Provide source: Other Grant: Version 2 - PROTOCOL # 0145-23-FB Page 2 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 3 of 27 ♦ Departmental funding Commercial - Provide company name: Department of Defense

Other - Provide source (e.g. personal funding): 4. Deadline for IRB Approval: Yes - Explain and provide date: ♦ No 5. Contract: Is there a contract associated with this study? No 6. Agreements Is there a Material Transfer Agreement (MTA) associated with this study? No Is there a Data Use Agreement (DUA) associated with this study? No Is there a Data Transfer Agreement (DTA) associated with this study? No 7. Study Sites: A. Provide the names and locations of all study sites where this research will be conducted under the oversight of the UNMC IRB or Joint Pediatric IRB. UNMC College of Dentistry, Lincoln NE B. Will the research be conducted at external sites under the oversight of an external IRB? No C. Does UNMC, TNMC, CHMC or UNO serve as the lead site with responsibility for data and/or safety monitoring? No D. Does this study involve any international sites where the PI will either; 1) conduct 2) supervise or 3) receive / ship HBM or data to / from UNMC? No Version 2 - PROTOCOL # 0145-23-FB Page 3 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 4 of 27 E. Does this study involve face to face contact with subjects? Yes 8. Principal Investigator Assurance The PI understands and accepts the following obligations to protect the rights and welfare of research subjects in this study: All information in this application is complete and accurate. I will conduct the research as described in the application and the protocol. I will not initiate any change without IRB approval except when it is necessary to reduce or eliminate a risk to the subject. I will ensure that all research personnel are qualified and properly trained. I will fulfill my responsibilities as PI, described in https://guides.unmc.edu/books/hrpp-policies-and-procedures/page/126-piqualifications-and-responsibilities I will follow all applicable HRPP and institutional polices, and all applicable laws, statutes and regulations. Killeen, Amy C - 2024-02-19 15:31:07.160 9. Principal Investigator Financial Interest Disclosure A. As the PI, I declare: ♦ I have no financial interest in this research. I have a financial interest in this research. B. As the PI, I understand ♦ I must disclose any change in my financial interest during the course of this research within five (5) business days from the time the change becomes known. C. As the PI, I certify that: ♦ No Responsible Personnel have a financial interest in this research. The Responsible Personnel listed below have informed me that they have a financial interest in this research. D. I have informed all Responsible Personnel that if there is any change in their financial interests during the course of this study it must be disclosed within five (5) business days from the time the change becomes known. Killeen, Amy C - 2024-02-19 15:31:07.160 Version 2 - PROTOCOL # 0145-23-FB Page 4 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 5 of 27 SECTION II PROTOCOL ABSTRACT 1. Provide a brief (less than 2500 characters) abstract of the research protocol. (2500 characters) This summary should include: 1)) a brief description of the purpose of the study, 2) eligibility criteria, 3) interventions and evaluations and 4) follow-up. The purpose of this study is to compare the effectiveness of a porcine collagen membrane to a bovine collagen wound dressing for atraumatic extractions. These are both commonly used as a barrier and containment material over atraumatic extraction sites that

are grafted for future implant placement. The study will include nonsmoking adults aged 18-75 requiring premolar or anterior tooth extraction and graft procedures, who are in good general health and willing to provide informed consent. Exclusion criteria include a history of radiation therapy or bisphosphonate use, pregnancy or breastfeeding, systemic conditions that affect bone healing, contraindications to dental implants, and inability to attend follow-up visits. The study will be a double-blind randomized controlled trial involving 24 patients who will be assigned to two groups. Prior to tooth extraction, baseline data will be collected; including gingival crevicular fluid (GCF) sampling, and a limited field Cone Beam Computed Tomography (CBCT) radiograph. A reference digital scan will be taken to measure volumetric changes in soft tissue. Routine, atraumatic extraction of the tooth under local anesthetic will be performed. Following extraction, hydrated AllOss 50/50 DFDBA:FDBA bone particulate will be condensed following a routine protocol. One group will receive Mucograft Seal over the graft, and the other group will receive Integra HeliPlug. Patients will be seen at a standard 2-week follow up to remove sutures, have a GCF sampling at the adjacent teeth and take another digital scan. Patients will be seen for an additional 6-week follow up to take a small (2mm) incisional biopsy for histological analysis. Another digital scan and GCF sampling will be taken. Final evaluation will be 3 months post-extraction and will include a localized CBCT evaluation for implant planning and another measure of soft tissue changes with a digital scan. At the time of implant surgery, the core of bone removed during osteotomy will be histologically analyzed for percentage of vital bone. Adverse events will also be recorded at each visit. The primary outcome measure will be the histological composition of tissue at 6 weeks and volumetric tissue changes. The secondary outcome measures will be adverse events, bone density on the post-operative CBCT and percentage of vital bone at implant placement. PURPOSE OF THE STUDY AND BACKGROUND 2. Purpose of the Study What are the specific scientific objectives of the research? The primary objectives of this study are to compare the efficacy of a porcine collagen Version 2 - PROTOCOL # 0145-23-FB Page 5 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 6 of 27 membrane to a bovine collagen wound dressing for atraumatic extractions, in terms of their ability to act as a barrier and containment material over atraumatic extraction sites that are grafted for future implant placement. This will be measured by volumetric and linear dimensional changes in the soft tissue and the histological composition of keratinized tissue after healing. The secondary objectives of the study are to evaluate the radiographic bone density and percentage vital bone at implant planning and placement. 3. Background and Rationale Describe the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project is intended to fill. Extraction and graft procedures are commonly performed in dental clinics where future implant placement is desired due to the large soft and hard tissue dimensional changes that occur as a socket heals (Araujo 2005, Chappuis 2017). While there are several techniques for ridge preservation, it is generally accepted that minimizing trauma from the extraction and

flap reflection greatly decreases loss of hard and soft tissue (Fickl 2008). This is why a popular method is some form of Bio-Col technique where a bone graft is condensed into the socket and then a collagen wound dressing, or plug, is used to prevent wash out of the graft. (Sclar 1999, Kotsakis 2014). While cost effective, and easy to place without flap reflection, a collagen plug can be dislodged quickly and has been shown to have a large soft tissue loss during healing (Morelli 2020, Thoma 2018). Therefore, other soft tissue alternatives have been investigated as an alternative membrane (Ghanaati 2017) Several studies have investigated the efficacy of Mucograft Seal as a barrier membrane to promote bone regeneration in socket preservation techniques. (Jung 2013) Mucograft Seal is a porcine collagen membrane that is shaped ideally for easy coverage of a socket. Because it is a pure matrix of Type I and Type III collagen, it is able to stay more dimensionally stable, making it an ideal material to combat soft tissue reduction as a site heals. It is currently used as a replacement for free gingival grafting coverage, such as with the soft tissue punch technique (Jung 2004), but has not been compared to a collagen wound dressing for critical early healing characteristics such as inflammatory cytokines. Additionally, there is limited information on the specific histological composition at 6 weeks post-operative healing in patients who undergo socket preservation with Mucograft Seal or Colla-Plug. Information Gaps: The information gaps that this project is intended to fill are twofold. First, it aims to compare the effectiveness of Mucograft Seal and Colla-Plug in premolar and forward extraction and graft procedures through a randomized controlled trial, which will provide more conclusive evidence on the comparative efficacy of these two biomaterials. Second, the project aims to evaluate the histological composition of an incisional tissue biopsy at 6 weeks post-operative healing in patients who undergo these procedures with Version 2 - PROTOCOL # 0145-23-FB Page 6 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 7 of 27 either Mucograft Seal or Colla-Plug, which will provide valuable information on the tissue response to these biomaterials at an early stage of the healing process. By addressing these information gaps, the project aims to contribute to the development of more effective socket preservation techniques and biomaterials, which will benefit patients undergoing these procedures. CHARACTERISTICS OF THE SUBJECT POPULATION 4. Accrual A. Is this study conducted solely at sites under the oversight of the UNMC IRB (e.g. UNMC, Nebraska Medicine, CHMC, UNO)? Yes 1. How many subjects will need to be consented (per group, as applicable) in order to achieve the scientific objectives of the research? 24 subjects will be enrolled - 12 in each group to account for a 10% drop out rate. 2. What is the statistical or other justification for the total number of subjects described above? A sample size of 11 in each group provides 80% power to be able to detect an absolute difference in 20 percentage-points of converted mucosa between the collagen (i.e. 50%) and mucograft (i.e. 70%) groups at four weeks, assuming a standard deviation of 15 for percentage converted mucosa and an alpha level of 0.05, using a Wilcoxon Rank Sum test. 3. How long do you estimate it will take to accrue the required number of subjects? 9 months 5. Gender of the Subjects A. Are there any

enrollment restrictions based on gender? No 6. Age Range of Subjects A. Will adults be enrolled ? Yes 1. What is the age range of the adult subjects? 19-75 2. What is the rationale for selecting this age range? Version 2 - PROTOCOL # 0145-23-FB Page 7 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 8 of 27 This treatment is rarely performed in children below the age of 19 and after the age of 75, adult subjects will typically show decreased wound healing due to age which could conflate findings. B. Will children (18 years of age or younger) be included in this research? No 1. What is the justification for excluding children from participating in this research? ♦ Research is irrelevant to children (e.g. disease or condition rarely encountered in children). Knowledge being sought in the research is already available for children or will be obtained from another ongoing study. A separate study in children is warranted and preferable. Insufficient data are available in adults to judge the potential risk in children. Other. Explain. 7. Race and Ethnicity Are there any subject enrollment restrictions based upon race or ethnic origin? No 8. Vulnerable Subjects A. Will prisoners be included in the research? No B. Select from the list all of the vulnerable populations that will specifically be recruited to participate in this research. Decisionally-impaired persons Critically ill patients Students of the investigator Employees of the investigator Educationally disadvantaged individuals Socially or economically disadvantaged individuals Individuals with a stigmatizing illness or condition Individuals from a marginalized social or ethnic group Other. ♦ No vulnerable subjects will be specifically recruited 9. Inclusion Criteria What are the specific inclusion criteria? Version 2 - PROTOCOL # 0145-23-FB Page 8 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 9 of 27 1) adult patient seeking care at the UNMC College of Dentistry for extraction of a premolar or anterior tooth due to periodontal or endodontic defect, non-restorable caries or fracture 2) adult patient is considering dental implant placement to replace the extracted tooth and requires a bone grafting procedure in preparation for a dental implant 3) Nonsmoker 4) 19-75 years old 10. Exclusion Criteria What are the specific exclusion criteria? Exclusion criteria include a history of radiation therapy or bisphosphonate use, pregnancy, systemic conditions that affect bone and soft tissue healing, contraindications to dental implants, and inability to attend follow-up visits. 11. Pregnancy and Contraception Requirements A. Are women of child bearing potential (WOCBP) included in this research? Yes a. Are there any specific contraception requirements for subjects? No 1. Provide justification for absence of contraception requirements ♦ There are no interventions that are likely to be of risk to a fetus Investigational drug(s) is (are) not systemically absorbed Investigational drug(s) is (are) systemically absorbed, but there is no evidence from human studies, or from clinical experience, that there is risk to a fetus Other B. Are pregnant women included in this research? No 1. Provide justification for excluding pregnant women Investigational drug(s) is (are) absorbed systemically, and there is evidence from animal or human studies, or from clinical experience, that there is risk to a fetus OR investigational drug(s) is (are) absorbed

systemically, and there is a well-understood mechanism of action that may result in risk to a fetus Intervention includes a procedure expected to be of risk to a fetus (eg, exposure to ionizing radiation, maximal exercise test) Research is not relevant to pregnant women (e.g. disease or condition rarely encountered in pregnant women) Version 2 - PROTOCOL # 0145-23-FB Page 9 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 10 of 27 Knowledge being sought in the research is already available for pregnant women or will be obtained from another ongoing study A separate study in pregnant women is warranted and preferable ♦ Physiology of pregnancy precludes generalization to other populations Other - explain 2. Describe how pregnancy status will be assessed (eg, self-report, urine pregnancy test, blood pregnancy test) and the frequency of monitoring during participation in the research. Pregnancy status will be determined via self-report 3. Describe the plan should a female subject, or the partner of a male subject, become pregnant while research interventions are on-going (or during the period that contraception is required following the completion of the intervention). Should a female subject become pregnant while research interventions are on-going, she will be dismissed from study. C. Are breast feeding women excluded in this research? No Provide justification for the inclusion or exclusion of breast feeding women. There are no interventions that are likely to be of risk to a nursing newborn. METHODS AND PROCEDURES 12. Methods and Procedures Applied to Human Subjects A. Are there any evaluations or tests that will be performed for the purpose of determining subject eligibility which would not be routinely conducted as part of standard clinical care of the prospective subject? No B. Describe the research plan, including all procedures, interventions, evaluations and tests. Patients at the UNMC College of Dentistry who are seeking care to extract a premolar or anterior tooth due to a periodontal defect, endodontic defect or non-restorable caries or fracture, and who are considering a dental implant to replace the extracted tooth, will be made aware of this clinical study by the dental faculty or residents planning the treatment. Subjects will be given the consent form to take home and consider, and any questions will be answered, signed and witnessed. Version 2 - PROTOCOL # 0145-23-FB Page 10 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 11 of 27 Twenty-four patients will be enrolled in this study. On the day of extraction, baseline data will be recorded/collected. These include the following: 1. A limited field CBCT will be taken of the tooth to be extracted. 2. Gingival crevicular fluid (GCF) sampling at the interproximal sites of teeth adjacent to the tooth to be extracted. The tooth to be extracted will be isolated with cotton rolls and GCF collection paper strips will be placed into the facial and lingual interproximal gingival sulci for 30 seconds. The paper samples will be pooled and placed in a plastic-capped vial labeled with the subject number and visit (example: N1-0, N2-1) and immediately frozen at -80° C. The GCF sample vials will not be labeled with any personal identifying information (subject 's name, age, tooth #, etc). 3. A digital intraoral scan will be taken to establish baseline tissue dimensions. Routine atraumatic dental extraction under

local anesthesia will be completed by the assigned periodontal resident (SM, NB, PS, JL, OC, DD) or oral surgery fellow and faculty (AK, RR).A statistician will generate a randomization schedule, after which someone not involved in the treatment of these patients will put each randomized treatment assignment into separate envelopes. The envelope will be given to the clinical provider after the extraction is completed. The extraction socket will be filled with 50:50 AlloOss DFDBA/FDBA allograft bone and covered with either a HeliPlug collagen wound dressing or a Mucograft Seal membrane. Subjects will be scheduled for a routine postoperative visit two weeks following the extraction. At this visit, suture removal and evaluation of the healing site will occur. GCF collection on the remaining adjacent teeth will occur as will an intraoral digital scan of the extraction site. An additional post operative visit will occur at 6 weeks to do a final soft tissue healing evaluation. At this time a small (2mm) incisional biopsy will be taken and stored in 10% formalin that is labeled similarly to GCF sample tubes. We do not anticipate this tissue removal to have an impact on final healing of the underlying bone for the patient. This tissue will be processed with a hematoxylin and eosin stain and the width of keratinized tissue will be measured by a separate individual who is blinded to the treatment groups. GCF collection on the remaining adjacent teeth will also occur at this visit, as will an intraoral digital scan of the extraction site. The final postoperative visit will be 3 months following the extraction. A limited-field CBCT will be taken to begin the process of implant treatment planning and measure bone height, width and volume. A final GCF collection on the remaining adjacent teeth will also occur at this visit, as will a final intraoral digital scan of the extraction Version 2 - PROTOCOL # 0145-23-FB Page 11 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 12 of 27 site. GCF Cytokine Determination At the time of analysis, each pooled GCF samples will be eluted using 100 µl of 1× PBS by gently agitating the samples on a rocker plate for 1 h at 4°C. Cytokine concentrations will be measured using a customized human cytokine and magnetic bead panel (Milliplex MAP kit; Millipore, Billerica, MA), and a MAGPIX instrument and software (Luminex Corporation, Austin, TX) per the manufacturers recommendations. Ten analytes will be measured: interleukin-1β (IL-1β), IL-4, IL-6, IL-8, IL-10, IL-13, IL-17 granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor alpha (TNF-α), interferon-gamma (INF-γ). Albumin for each sample also will be measured to normalize cytokine levels and control for serum contamination. The amounts of cytokines will be reported in picograms per albumin level and per 30-s sample. Statistical Analysis The percentage of converted mucosa will be documented at six weeks after an extraction, and differences in the width of keratinized tissue between the collagen and mucograft groups will be assessed using a Wilcoxon Rank Sum test. As a secondary analysis, we may also look at other related demographic (e.g. sex, age, etc.) and clinical (e.g. bone width, soft tissue volume, cytokine levels, etc.) characteristics to see if they have associations with the percent keratinized gingiva, using Spearman correlations for continuous variables, or Wilcoxon Rank Sum/Kruskal Wallis tests for categorical variables. C. Select any of the following that apply

to the research: Phase I study ♦ Randomization Placebo (or non-treatment arm) Washout Sensitive surveys or questionnaires None of the above Option chosen: Randomization Describe randomization process and schedule A statistician will generate a randomization schedule, after which someone not involved in the treatment of these patients will put each randomized treatment assignment into separate envelopes, which will be given to the clinical provider close to the time the material will be placed, after the patient has been enrolled/consented into the study. Version 2 - PROTOCOL # 0145-23-FB Page 12 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 13 of 27 D. Identify: 1. All procedures, interventions, evaluations and tests performed solely for research purposes (eg, administration of an investigational drug or a new psychological assessment instrument; randomization) Procedures performed solely for research purposes include: the collection of gingival crevicular fluid (GCF); soft tissue biopsy at 6-weeks post-procedure. 2. All procedures, interventions, evaluations and tests performed for clinical indication but more frequently than they would be if the subject was not participating in the research (eg, extra blood tests; additional radiology exams) It is not typical to have an intraoral scan done at post-operative visits. However, this takes less than 2 minutes to perform and has no contraindications or risks. It is simply a data collection process for dentists to measure changes in our patients over time. E. Describe briefly the statistical methods used to analyze the data (or reference the appropriate section of the detailed protocol or grant). The percentage of converted mucosa will be documented at six weeks after an extraction, and differences in the width of keratinized tissue between the collagen and mucograft groups will be assessed using a Wilcoxon Rank Sum test. As a secondary analysis, we may also look at other related demographic (e.g. sex, age, etc.) and clinical (e.g. bone width, soft tissue volume, cytokine levels, etc.) characteristics to see if they have associations with the percent keratinized gingiva, using Spearman correlations for continuous variables, or Wilcoxon Rank Sum/Kruskal Wallis tests for categorical variables. F. Does this study involve the collection of blood, urine, saliva or other human biological material (HBM)? Yes 1. Does this research involve genetic testing including Genome Wide Association Studies (GWAS), Whole Genome Sequencing (WGS) or Whole Exome Sequencing (WES)? No G. Does this study involve the creation of a tissue bank for future unspecified research? This includes un-used (excess) blood, urine, or tissue, obtained for clinical indication or for research, or additional human biological material collected specifically for future research. No DRUGS, BIOLOGIC DRUGS AND DEVICES Version 2 - PROTOCOL # 0145-23-FB Page 13 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 14 of 27 13. Drugs and Biologic Drugs 1. Does this research involve the use of drugs or biologics? Yes A. Are any of the drugs or biologics used in this research not FDA-approved? No B. Are any of the drugs used in this study FDA Approved? Yes 1. Will data obtained from this research study be used to support a new indication, new labeling or a change in advertising of an FDA-approved drug or biologic? No 2. Will the use of an

FDA-approved drug in this research study involve a route of administration, dosage level or patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product? No C. Do any of the sponsors of this research require compliance with ICH-GCP? No 14. Devices 1. Does this research involve a medical device(s) (including an in vitro device [IVD] (assay), and medical software)? No CONFIDENTIALITY AND PRIVACY 15. Confidentiality and Privacy A. Describe where research data will be stored. Check all that apply. Box@unmc.edu (secure UNMC or UNO designated cloud-based storage site) Microsoft Office 365 application (including SharePoint, OneDrive for Business, Teams or Streams) (UNMC, UNO or NU system instance) (secure UNMC or UNO designated cloudbased storage site) Other secure UNMC or UNO designated cloud-based storage site - describe: OnCor Clinical Trial Management System (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO) Version 2 - PROTOCOL # 0145-23-FB Page 14 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 15 of 27 CCORDA database (biostatistics) (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO) RITO-hosted databases (for example, REDCap, CV-QOR, Onchem Trials, XNAT) (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO) Nebraska Medicine PACS (for image files) (secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO) Other secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO - describe: On an NSRI or designated high security .gov storage site On a VA-approved storage vehicle for a VA-approved study On a remote secure server and/or database maintained by the sponsor accessible through the internet On a secure server and/or database hosted and maintained by another institution accessible through the internet On a device or mobile application provided by the sponsor to upload data to a coordinating center or central database On a device or mobile application being developed by a sponsor or by a UNMC, CHMC or UNO investigator On a device or mobile application that connects to the internet through UNMC or NM network (wired or wireless) On an encrypted, password protected portable computer, or flash drive Other - describe: ♦ In hard copy (other than signed Consent Forms) Option chosen: In hard copy (other than signed Consent Forms) a. Please provide justification for use of hard copies Data collection is easiest and most secure in our department when done with hard copies. The room is secured by key card access and data will be stored in locked cabinets. Only authorized personnel will be able to access them. Option chosen: In hard copy (other than signed Consent Forms) b. Will hard copies will be transported from one site to another, on or off campus? No B. Will any of the following subject identifiers be recorded (at any time) in association with the research data? Yes 1) Indicate the subject identifiers that will be recorded. Check all that apply. Name ♦ Version 2 - PROTOCOL # 0145-23-FB Page 15 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 16 of 27 DATES (e.g. date of study visit, date of sample collection, birth, admission, discharge) Postal address information: street address, city, county, precinct, ZIP code Telephone numbers Fax

numbers Electronic mail addresses Social Security numbers ♦ Medical Record numbers Health plan beneficiary numbers Account numbers Certificate/license numbers Vehicle identifiers and serial numbers, including license plate numbers Device identifiers and serial numbers Web Universal Resource Locators (URLs) Internet Protocol (IP) address numbers Biometric identifiers, including finger and voice print Full face photographic images [and any comparable images] No Identifier 2) Will a unique subject identifying number (e.g., S1, S2, S3), characteristic or code be used to link data to any of the identifiers listed above? Yes a. Where will the key (that links the unique subject identification code to the subject's name or other identifier) be stored? The key will be stored in a locked filing cabinet within a locked room in the Cruzan Center for Dental Research. The unique identifier that will be sued to code the data is as follows: each subject will be given a number (i.e. N1, N2…N25). The specific appointment visit (baseline, 2 weeks, 3 months) data will be coded as follows: N1-0 (baseline), N1-2 (two weeks), N1-3 (3 months). b. Does the code number include the subject's initials or other subject identifier as part of the code? No 3) What is the justification for recording the specific subject identifiers listed above? Check all that apply. ♦ Schedule appointments Collect continuous clinical information from the medical records ♦ Follow-up with subjects Link stored tissue with subject identification for it to be withdrawn in the future if requested Version 2 - PROTOCOL # 0145-23-FB Page 16 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 17 of 27 Compensation Other. Explain. 4) How long will the subject identifiers be maintained in association with the research data? Subject identifiers will be maintained until data have been statistically analyzed and reports published and no less than 7 years following completion of research per Nebraska state law and NRPP policy. 5) How will all of the identifiable research data be destroyed (e.g., all identifiers stripped from the data and destroyed, hard copies shredded etc) when the identifiable data is no longer required? Subject identifiers will be stripped from the data and destroyed once it is no longer required. C. Will research data that contain subject identifiers be disclosed to: Other investigators at UNMC, NM, UNO or CHMC who are not listed in Section I of this application? No 2. Investigators outside of UNMC, NM, UNO or CHMC? No 3. Will research data that contain subject identifiers be disclosed to any commercial sponsor or contract research organization (CRO), or to any other external organization or entity (e.g., NCI cooperative groups)? No D. What provisions will be in place to protect the subject's privacy? Check all that apply. ♦ Ensuring that only personnel listed on the IRB application Section I.3(A-E) are present during the consent process. ♦ Ensuring that the fewest number of individuals possible are aware of the subject's participation in the research. ♦ Ensuring that the research activities are performed in as private of a place as possible. Other. Explain. E. Does this research involve data banking at UNMC, NM, UNO or CHMC, or by an outside organization (e.g. NCI Cooperative Group, pharmaceutical company) for future research that is not related to this study? Version 2 - PROTOCOL # 0145-23-FB Page 17 of

27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 18 of 27 No RISK/BENEFIT ASSESSMENT 16. Potential Risks What are the potential risks associated with each research procedure, intervention, evaluation and/or test? If data are available, estimate the probability that a given harm may occur and its potential reversibility. Potential risks associated with soft tissue sampling at 4-weeks includes minimal pain and adjacent tooth sensitivity. The soft tissue and GCF specimens will be collected in plastic-capped vials and frozen until analysis. These vials will be labeled with the subject's number and visit (N1-0, N2-2) and will not be labeled with any personal identifying information, thus breach of confidentiality is not at risk. Potential risks associated with limited view CBCT include increase exposure to radiation. This risk is inherent to any dental radiography and the limited-view CBCT pre-extraction and post-extraction is standard therapy for dental implant treatment planning. 17. Risk Classification What is the overall risk classification of the research? Minimal risk ♦ Greater than minimal risk 18. Minimization of Risk A. Describe how the subjects of the research will be monitored by the investigators and other research personnel to ensure their safety. Subjects of the research will be monitored with follow-up phone calls. If any postoperative concerns develop, they will be seen in the graduate periodontal clinic for follow-up. B. Describe how the data collected will be monitored to ensure the safety of subjects. Identify who will perform the ongoing data and safety analysis, and describe the frequency of data analysis. If there is an independent Data and Safety Monitoring Board (DSMB) provide the charter, or describe (1) the composition of the DSMB membership, (2) the frequency of DSMB meetings and reports. Data collection will be monitored by study personnel and if a decline in the subject's periodontal condition is noted, they will be referred to the graduate periodontal residency at UNMC College of Dentistry for a full evaluation. The contact information for the study investigators and personnel are on the consent form that will be sent home with each Version 2 - PROTOCOL # 0145-23-FB Page 18 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 19 of 27 subject. C. Describe the auditing plan for research conducted. Identify who will conduct the audits and specify the audit frequency. Ten percent of the case report forms will be reviewed by the Associate Dean of Clinics, Dr. Amir Fahr, at the COD semi-annually and audited against the primary dental record. Any violations or unexpected outcomes will be reported to the IRB. D. Describe the specific subject withdrawal criteria. Subjects will be withdrawn if they are non-compliant to their postoperative appointments. E. Describe the stopping rules for the research (e.g., the specific criteria for halting or early termination of the study). If 10% of subjects suffer an adverse event, such as bleeding or pain associated with the soft tissue sampling greater than that expected associated with a similar extraction without sampling, the study will be stopped. F. Describe plans and resources available to promptly address any subject injury. The investigators are board-certified periodontists or periodontal residents, so any adverse effects will be addressed with a thorough evaluation and appropriate treatment. 19. Potential Benefits to the Subject

Is there the prospect for direct benefit (eg, research on diagnosis or treatment of disease)? No 20. Potential Benefits to Society Describe the potential benefits to society that may reasonably be expected to result from this research. A potential benefit to society would be clarification and understanding of the soft tissue healing capabilities of common materials used for this procedure. FINANCIAL OBLIGATIONS AND COMPENSATION 22. Financial Obligations of the Subject A. Who will pay for research procedures, interventions, evaluations and tests? Check all that apply. Sponsor Grant CRC, CCTR Version 2 - PROTOCOL # 0145-23-FB Page 19 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 20 of 27 Costs or fees waived by Nebraska Medicine, UNMC- P, CHMC or CSP ♦ Department/Section funds Other. Explain B. Will any of the research procedures, interventions, evaluations and tests described above be charged to the Subject, the Subject's health insurance, or Medicare/Medicaid? Yes 1. Provide additional detail and justification for charging as noted. The subject will be not be charged for any research procedures or interventions. The subject will be charged for non-research related procedures (extraction, bone graft, limited view CBCT). C. Are there any other financial obligations that the subject will incur as a result of participating in the study? No 23. Compensation to the Subject for Participation A. Will the subject receive any compensation for participation? No PRIOR REVIEW 24. Prior IRB Review A. Has this study (or one substantially similar) been previously submitted to the UNMC IRB (or the Joint Pediatric IRB) and then withdrawn by the investigator for any reason? No B. To the best of your knowledge, has this study (or one substantially similar) been considered by another IRB and disapproved? No SUBJECT IDENTIFICATION & RECRUITMENT 25. Method of Subject Identification and Recruitment A. Will prospective subjects learn about the research and then contact the investigator about participation (for example, in response to a print, electronic, radio or television advertisement; referral by a clinician or other specifically for this research)? Version 2 - PROTOCOL # 0145-23-FB Page 20 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 21 of 27 No B. Will the investigator make the initial contact with the potential subject to tell him/her about the research (for example, by contacting existing or past previous patients or research participants; or by contacting prospective subjects thru school records, or thru support groups or other Interest Groups; or thru use of the Hospital Opt-In Database)? Yes 1. How will prospective subjects be identified? Patients that meet the study criteria will be identified in the UNMC COD clinic during normal clinical treatment. 2. Will potential subjects be screened for eligibility prior to informed consent? No 3. How will potential subjects be approached and invited to participate? Eligible patients will be asked if they want to participate in the study. a. Describe the process of initial contact Patients that would otherwise be presenting to the clinic for extraction and grafting will be invited to participate in the study. b. Who will make the initial contact? One of the investigators or collaborators. c. Does that person have ethical access to information about potential

subjects? Yes i. Describe All investigators and collaborators are responsible for supervising dental students in patient care in the clinic where potential subjects are treated, therefore direct contact with potential subjects and their records is part of that supervision. C. Will this study be listed in the clinical trial registry at www.clinicaltrials.gov? Yes 1. Provide the NCT#. NCT application has been submitted, awaiting NCT#. Will inform the IRB when it comes Version 2 - PROTOCOL # 0145-23-FB Page 21 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 22 of 27 through. 2. Identify who holds the NCT# ♦ PI Sponsor OBTAINMENT OF INFORMED CONSENT 26. Waiver or Alteration of Informed Consent A. Is a complete waiver or alteration of consent requested? No 27. Waiver of Signed Consent Is a waiver to obtain signed consent requested? No 29. Process of Informed Consent A. When will the prospective subject/parent(s)/guardian(s)/LAR be approached relative to their/the subject's actual participation in the study? Prospective subjects will be approached after it has been determined that they have a nonrestorable anterior or premolar tooth that needs extraction and they have expressed interest in replacing the tooth with a dental implant. Subjects will be referred to the graduate periodontal clinic where they will be approached by study personnel (periodontal resident) about their interest in participating in the study. B. Where will informed consent be obtained, and how will the environment be conducive to discussion and thoughtful consideration? Informed consent will be obtained in a private room in the Cruzan Center for Dental Research. C. Who will be involved in the process of consent and what are their responsibilities? The investigators will explain the research, ask questions to be certain that the subject understands the procedure, and answer any subject questions. Additionally, investigators will also ask questions to ensure that subjects understand their rights as research subject D. Is there any limitation on the amount of time allotted to the process of consent? No E. How will the process of consent be structured for subjects who are likely to be more Version 2 - PROTOCOL # 0145-23-FB Page 22 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 23 of 27 vulnerable to coercion or undue influence? All subjects approached about this study will already have made the decision to extract the tooth and have expressed interest in implant replacement of that tooth. Additionally, they will already have been counseled on the process of extraction, grafting and implant placement; including the costs and time required for successful treatment. Investigators acknowledge concerns regarding the potential subject misinterpreting the study as standard of care, or having his/her decision regarding participation influenced by concerns about disappointing or offending his/her care provider by having the introductory and informed consent conversations completed by study personnel who are not familiar to the subject. The subject will not have had previous contact with study personnel, thus minimizing the concern about disappointing or offending his or her provider. Additionally, extreme care will be taken during discussion/description of the study with the subject to highlight that the removal of soft tissue is not standard of care for routine extraction and

implant preparation. F. Will non-English speaking subjects be enrolled in this research? Yes Describe the plan to conduct the process of informed consent in the language of the subject/parent(s)/guardian(s)/LAR The process of informed consent in the language of the subject includes utilization of interpretation services via video (Language Link) or in-person interpreter. G. How will it be determined that the subject/parent(s)/guardian(s)/LAR understood the information presented? The investigator will question the subject concerning his/her understanding of all elements of the informed consent. This will include having the subject describe what will be done to them along with the risks 31. Information Purposely Withheld Will any information be purposely withheld from the subject during the research or after completion of the research? No RESOURCES 33. Describe the resources available to safely conduct this study at each study sites specified in Section I.7. 1. Funding for all research-related expenses have been secured through departmental Version 2 - PROTOCOL # 0145-23-FB Page 23 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 24 of 27 funds. 2. Research procedures will be conducted in the Cruzan Center for Dental Research at the UNMC College of Dentistry. 3. Laboratory space for the GCF tests will be available in the laboratory of one of our investigators (RR). 4. Emergency equipment and personnel services are routinely available in the periodontal clinic during operation, during which all patient-based procedures will be performed. LITERATURE REVIEW 34. References Provide a full listing of the key references cited in the background (Section II.3). The references should clearly support the stated purpose of the study. Araujo, M.G. and J. Lindhe, Dimensional ridge alterations following tooth extraction. An experimental study in the dog. J Clin Periodontol, 2005. 32(2): p. 212-8. Chappuis, V., M.G. Araujo, and D. Buser, Clinical relevance of dimensional bone and soft tissue alterations post-extraction in esthetic sites. Periodontol 2000, 2017. 73(1): p. 73-83. Fickl, S., et al., Tissue alterations after tooth extraction with and without surgical trauma: a volumetric study in the beagle dog. J Clin Periodontol, 2008. 35(4): p. 356-63. Ghanaati, S., et al., Evaluation of the tissue reaction to a new bilayered collagen matrix in vivo and its translation to the clinic. Biomed Mater, 2011. 6(1): p. 015010. Jung, R.E., et al., Radiographic evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial. J Clin Periodontol, 2013. 40(1): p. 90-8. Jung, R.E., D.W. Siegenthaler, and C.H. Hammerle, Postextraction tissue management: a soft tissue punch technique. Int J Periodontics Restorative Dent, 2004. 24(6): p. 545-53. Kotsakis, G., et al., Flapless alveolar ridge preservation utilizing the Version 2 - PROTOCOL # 0145-23-FB Page 24 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 25 of 27 "socket-plug" technique: clinical technique and review of the literature. J Oral Implantol, 2014. 40(6): p. 690-8. Morelli, T., et al., Three-Dimensional Volumetric Changes After Socket Augmentation with Deproteinized Bovine Bone and Collagen Matrix. Int J Oral Maxillofac Implants, 2020. 35(3): p. 566-575. Sclar, A.G., Preserving alveolar ridge anatomy following tooth removal in conjunction with immediate implant placement. The Bio-Col technique. Atlas Oral Maxillofac Surg Clin North Am, 1999. 7(2): p. 39-59. Thoma, D.S., et

al., Clinical and histologic evaluation of different approaches to gain keratinized tissue prior to implant placement in fully edentulous patients. Clin Oral Investig, 2018. 22(5): p. 2111-2119. Version 2 - PROTOCOL # 0145-23-FB Page 25 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 26 of 27 SECTION III SUBMISSION DEADLINE A. Full Board Review: The IRB meets twice monthly, on the first and third Thursday of the month, with the exception of January and July when the IRB meets only on the third Thursday of the month. No more than 15 applications (e.g., initial review of a new study, re-review of a tabled study) will be reviewed at each meeting. All reviews are performed on a firstcome first-served basis. The IRB meeting schedule and deadline dates can be found on the IRB website at www.unmc.edu/irb. B. Expedited Review Applications that qualify for expedited review have no submission deadline and can be reviewed independent of the IRB meeting schedule. Call the Office of Regulatory Affairs for assistance in determining if your study meets the requirements for expedited review. ADDITIONAL REVIEW REQUIREMENTS Final IRB approval and release of studies is contingent upon approval by the following UNMC committees or departments. Check the appropriate boxes: UNMC and NM - Pharmacy & Therapeutics (P&T) Committee (Required for studies involving drugs) Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) (Required for studies involving cancer) Institutional Biosafety Committee (IBC) (Required for studies involving the use of gene transfer and vaccines) Investigational Device Review Committee (IDRC) Review by the IDRC is required for all protocols involving the use of investigational or marketed devices Billing Grid (Required for all studies involving billing for hospital/clinic services) Coverage Analysis (Departments requiring this analysis have been specified by the Organization) Conflict of Interest (COI) Management Plan (Required for all studies with declared COI by study personnel) Sponsored Programs Administration (SPA)/UNeHealth grants and contracts Pathology approval for collection of tissue samples required for this study Radiation Committee Approval Other Review ♦ None of the above organizational requirements apply to this study Version 2 - PROTOCOL # 0145-23-FB Page 26 of 27 Institutional Review Board (IRB) IRB PROTOCOL # 0145-23-FB Page 27 of 27 SECTION IV COVID-19 Human Subjects Research Safety Plan For studies involving face-to-face encounters, the research team under the responsibility of the principal investigator will agree to comply with the following safety measures: 1. Masking of the researcher(s) during a face-to-face encounter 2. Cleansing of any surface and/or equipment utilized before and after a subject encounter 3. The Biosafety Officer (jenna.mckenzie@unmc.edu) will be notified if obtaining saliva, nasal, sputum or stools samples to ensure safe collection, handling, and processing plan is in place 4. Suggest addressing the current health of the subject before commencing faceto-face research via questions below: Have you or anyone in your household tested positive or had a fever, chills, cough, shortness of breath, diarrhea, nausea, vomiting, recent loss of taste or smell, tiredness or fatigue, or muscle aches? If yes, the monitor will not be allowed on campus. Have you recently traveled to an

area with a widespread outbreak or had close contact with a person known to have COVID-19, MERs-CoV or Ebola? Have you traveled outside of the country within the past month? If so, where did you travel and when did you return? Have you had a recent SARS-COV-2 antibody test or nasal swab and if so when and what were the results? ♦ I acknowledge this requirement. Powered by TCPDF (www.tcpdf.org) Version 2 - PROTOCOL # 0145-23-FB
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