A Randomized Controlled Trial Comparing Platelet Rich Plasma (PRP) to Minoxidil Foam for Treatment of Androgenic Alopecia in Women

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A Randomized Controlled Trial Comparing Platelet Rich Plasma (PRP) to Minoxidil Foam for Treatment of Androgenic Alopecia in Women

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Mayo Center for Regenerative Medicine

Study Product: Platelet Rich Plasma (PRP)

Protocol Number: (IRBe)

Initial version: 6/1/2016 Version **(1)**

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LIST OF ABBREVIATIONS

AGA	Androgenic Alopecia
AE	Adverse Event/Adverse Experience
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IRB	Institutional Review Board
MNX	Minoxidil
PHI	Protected Health Information
PI	Principal Investigator
PRP	Platelet Rich Plasma
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	Minoxidil Foam compared to PRP for Androgenic Alopecia in Women, A Randomized Controlled Pilot Trial
Running Title	PRP for Hair loss in Women
Protocol Number	1
Phase	Pilot
Methodology	Randomized, Controlled, Crossover
Overall Study Duration	12 Months
Subject Participation Duration	12 months
Single or Multi-Site	Single Site
Objectives	Determination of non-inferiority treatment of PRP compared to standard of care MNX in women
Number of Subjects	23
Diagnosis and Main Inclusion Criteria	Female, 18 years or older, Androgenic Alopecia grade I-II by Ludwig classification
Study Product, Dose, Route, Regimen	Platelet Rich Plasma 10cc, Injection by Nappage technique, 3 injections - 1 time every 4 weeks for 3 months
Duration of Administration	12 Weeks (1 time every 4 weeks for 3 months)
Reference therapy	Minoxidil
Statistical Methodology	Wilcoxon signed rank test for comparison of outcomes between treatments and McNemar's exact test for categorical outcome variables

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Androgenic alopecia (AGA) is a common, progressive hair loss disorder affecting both sexes with significant negative impact on social and psychological well-being. The frequency and severity increases with age, and up to 80% of men, and 50% of women are affected by AGA over the course of their lives. (Piraccini 2014) (Varothai) (Bologna - book) While men are more frequently affected, the psychological impact is likely to be high for women where the social impact of hair loss is often devastating. Current medical therapies specifically approved by the US FDA are limited to minoxidil (for men and women) and finasteride (for men only) (Varothai), but variable responses and the need for indefinite use often result in patient fatigue and suboptimal compliance. (Gupta)

Recently, there has been interest in treatments orientated to more biologically regenerative therapies, and consequently there have been numerous studies that have demonstrated successful use for platelet rich plasma (PRP) in treating AGA. (Singhal) (Maria-Angeliki) (Gentile) (Trink) (Gkini) (Cerveli) (Uebel) (Greco) (Takikawa) (Kang) (Betsi) (Sclafani) (Khatu) (Schiavone) PRP contains concentrated platelet cells derived from autologous whole blood that are believed to activate a cascade of growth factors when injected into an area of poor hair growth that stimulates hair growth. (Jain)(Lubkowska) In this proposal we will examine whether PRP therapy provides similar or better hair growing capacity in women compared to the conventional topical application minoxidil.

1.2 Investigational Agent

Platelet Rich Plasma (PRP)

1.3 Clinical Data to Date

PRP is an autologous concentration of human platelets in a small volume of plasma that has a 4-7 times higher platelet concentration than baseline.(Jain) (Lubkowska) (Parsley) Since activated platelets secrete a number of cytokines and growth factors, such as platelet-derived growth factor, epidermal growth factor, transforming growth factor, and vascular endothelial growth factor, (Jain) (Lubkowska) (Parsley) PRP may provide an attractive therapy to promote hair growth in the declining hair follicle.

Recent investigators have explored the use of PRP as a treatment modality for AGA, with most available studies to date showing positive results. (Singhal) (Maria-Angeliki) (Gentile) (Trink) (Gkini) (Cerveli) PRP is attractive as a useful treatment for nonscarring alopecia's such as AGA, because the treatment is safe and adverse effects appear to be negligible. (Singhal) (Maria-Angeliki) (Gentile) (Trink) (Gkini) (Cerveli) However, the effect of PRP on hair growth has been studied primarily in men. Studies that include men and women usually do not analyze the data according to sex or comment on whether sex differences were observed. (Trink) (Takikawa) (Kang) (Betsi) (Sclafani) (Schiavone) (Gkini) Although sex differences are known to exist in the incidence, diagnosis and mechanisms leading to AGA, women are understudied (Farage) (Romanelli). The need to understand hair loss in women is underscored by the growing interest of cosmetic dermatologists and plastic surgeons to use PRP routinely in their aesthetic and rejuvenation practice to reduce/prevent hair loss.

A recent review of the available literature regarding PRP treatment for hair loss identified 14 articles describing the use of PRP, 12 of which were used for AGA. (Maria-Angeliki) This systematic review considered 7 studies to be of moderate quality, 4 of low quality and 3 of very low. Of the 7 trials of moderate quality, all reported a statistically significant increase in the number of hairs and hair density following PRP therapy, indicating a positive response to treatment. The predominant criticisms of the trials to date are the lack of a consensus protocol regarding the exact concentration of PRP, dose, frequency, depth of injections, and number of required sessions. Variability in evaluation methods also limits accurate comparison between the studies (i.e., global photographs, phototrichograms, dermascopic images, hair pull test, and manual counting were all reported as measurement tools). In addition, these studies predominantly used men. Very little published data exists for PRP use in women with AGA. The studies that did include women examined very low numbers and/or did not analyze results according to sex so that it is not possible to evaluate whether PRP therapy is safe and efficacious in women. (Trink) (Takikawa) (Kang) (Betsi) (Sclafani) (Schiavone) (Gkini) Nonetheless, PRP appears to be a useful treatment for AGA, particularly in men, and there is an urgent need for randomized controlled studies with standardized measurement techniques and reproducible protocols to study clinical efficacy. Considering the widespread use of PRP in cosmetic clinics among women and the lack of data on the effect of PRP on hair regeneration in women there is a great need to perform a controlled trial in women. In future studies we would like to examine whether PRP is equally effective in men and women and to examine its mechanism of action.

1.4 Dose Rationale and Risk/Benefits

We will dose PRP in a manner similar to previous trials. (Gentile, Trink, Cerveli) Fresh PRP will be harvested from the individual and their own PRP administered at three time points, once every 4 weeks for a totally treatment time of 12 weeks. Minoxidil will be used according to FDA and manufacturer instructions daily for 12 weeks.

Risks associated with PRP therapy include possible pain, redness, and/or irritation at the site of injections for up to 2-3 days post injection. Published human data indicate no significant adverse events related to injection of PRP into the skin and previous authors utilizing similar protocols reported no infection, fever, hematoma, tissue hypertrophy, or major adverse events among the subjects. (Singhal) (Cerveli) (Gentile) (Trink) (Gkini) Known possible risks for Minoxidil include chest pain, rapid heartbeat, faintness, dizziness, sudden or unexplained weight gain, swelling of the hands or feet, scalp irritation or redness, changes in hair color and texture, and unwanted facial hair growth.

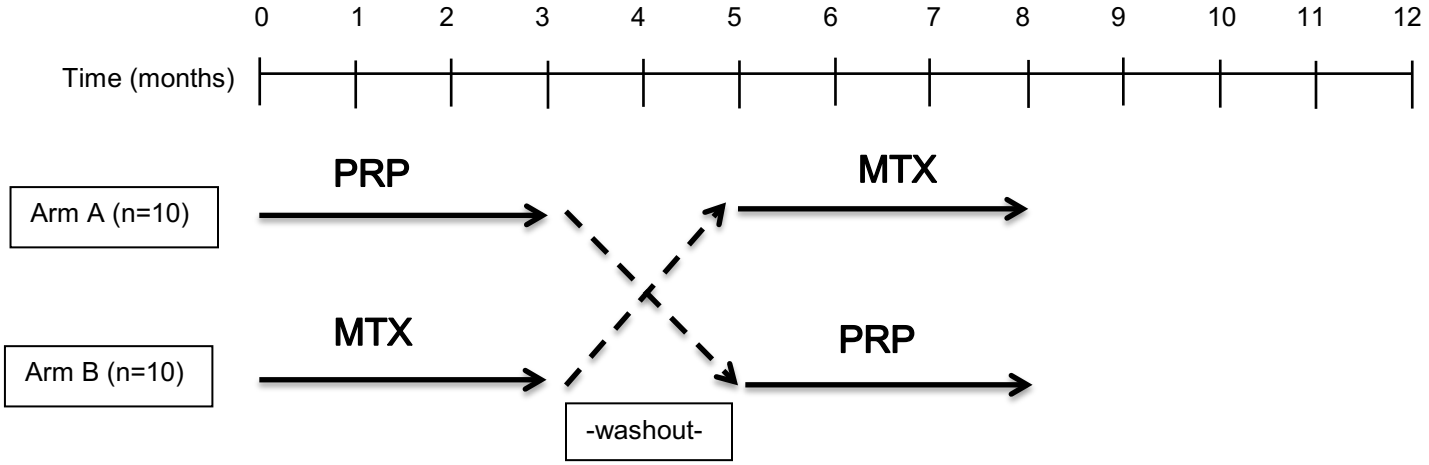
2 Study Objectives

The overall goal of this study is to develop regenerative cell therapy for use in female patients with AGA. The primary objective of this proposal is to conduct a pilot study on the efficacy of using PRP to treat this type of hair loss in females.

3 Study Design

3.1 General Design

The study will be a randomized control trial following a crossover design to compare PRP to MNX in females.



Subjects will be recruited from the clinical practice of the Department of Dermatology, Mayo Clinic Florida. 23 females with AGA grades I-II based on the Ludwig Classification. (Ludwig)

Patients will be randomized into a PRP then MNX (Arm A) or MNX then PRP group (Arm B). Both treatments will be administered for 12 weeks with a 2 month washout period in between treatments. Hair density and adverse events will be assessed using Phototrichograms, Macroscopic Photos, physical exams and patient questionnaires. All patients will be followed for efficacy and adverse events at 3 month intervals until 1 year after enrollment.

3.2 Primary Study Endpoints

1) Hair growth related to each of the two treatment arms.
2) Morbidity related to PRP scalp administration.

3.3 Secondary Study Endpoints

1) To collect PRP samples to study the molecular mechanisms of PRP and hair growth

3.4 Primary Safety Endpoints

1) Documentation will include levels of pain at injection sites, any evidence of adverse reaction in the skin (e.g., swelling, erythema, warmth) and any other concerns expressed by patients.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Only female patients are eligible
2. Patients must be 18 years of age or older
3. Patients must have Androgenic Alopecia Grade I-II by Ludwig Classification

4. Patients must have been on stable birth control for the past month if premenopausal.
5. Patients are able and willing to provide written informed consent after the nature of the study is fully explained

4.2 Exclusion Criteria

1. Patients with clinically abnormal hematology, serum chemistry, or screening laboratory results as reviewed by the Principal Investigator
2. Patients who have undergone topical and systemic therapies for hair loss 3 months prior to the procedure
3. Patients who have used any cosmetic product meant to address hair loss 3 months prior to enrollment
4. Patients taking anti-rheumatic disease medication (including methotrexate or other anti-metabolites) within the 3 months prior to study entry.
5. Patients previously having undergone hair transplant surgery prior to study entry
6. Patients who are pregnant or currently breast-feeding children as Rogaine for Women is contra indicated for these women
7. Patients who have taken spironolactone in the 3 months prior to study participation
8. Patients with systemic, rheumatic or inflammatory disease or who are immunosuppressed
9. Patients with ongoing infectious disease, including HIV and hepatitis
10. Patients with clinically significant cardiovascular, renal, hepatic, endocrine disease, cancer, or diabetes
11. Patients participating in a study of an experimental drug or medical device within 30 days of study entry
12. Patients with history of platelet disorders, bone marrow aplasia
13. Patients with a history of sepsis, or cancer must have been disease free for the past 5 years.
14. Patients taking antiaggregating therapy
15. Patients on anticoagulant therapy
16. Patients with tendency to keloid formation
17. Patients with uncompensated diabetes
18. Patients with active skin disease or skin infection at intended treatment areas

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited from the clinical practice of the Department of Dermatology, Mayo Clinic Florida. Patients seeking treatment for Androgenic Alopecia will be offered standard conservative medical therapy for their disease as part of routine dermatological treatment. As an alternative, patients will be informed of the study protocol, and offered the option to enroll if they meet the study eligibility criteria.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may withdraw from the study at any time for the following:

- Subject safety issues
- Subject decision to withdraw from the study (withdrawal of consent)
- Subject's decision to pursue other therapeutic regimens, either surgical or non-surgical

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though a subject has withdrawn from the study, it may be important to collect some follow-up or survival data on subjects throughout the protocol defined follow-up period. Such data are important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study for subject safety reasons attempts will be made to obtain permission to collect follow up information whenever possible. Patients will be analyzed by intention to treat principles without some of the follow-up data as necessary.

5 Study Drug

5.1 Description

1. PRP – Autologous Platelet Rich Plasma isolated from blood collected from each patient at each treatment time point.

2. **Minoxidill 5% Topical Foam** - Manufacturers Description: Indications: To regrow hair on top of the scalp. Active Ingredient: Minoxidil 5% w/w (without propellant) Inactive Ingredients: butane, butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, isobutane, lactic acid, polysorbate 60, propane, purified water, SD alcohol 40-B, stearyl alcohol (Rogaine for Women).

5.2 Treatment Regimen

Patients will be randomized into a PRP then MNX (Arm A) or MNX then PRP group (Arm B). Patients randomized to Arm A will receive injections of PRP using the nappage technique (Sivagnanam) every 4 weeks for a total of 3 treatments over 12 weeks. Patients will then have a 2 month (8 week) washout period lasting until the end of month 4. Starting on month 5 they will receive crossover treatment with Minoxidil by applying the 5% foam once daily following manufacture instructions (Rogaine For Women) for a total of 3 months after which they will be followed until 1 year after enrollment. Patients randomized to Arm B will apply Minoxidil topical foam once daily following manufacture instructions for a total of 3 months followed by a two month (8 week) washout period. At the 5 month mark, the patients in Arm B will receive crossover treatment with PRP harvested and administered in the same manner as the patients in Arm A. At the end of the PRP treatment patients in Arm B will be followed until 1 year after enrollment.

5.3 Method for Assigning Subjects to Treatment Groups

Assignment of treatments will be randomized using dynamic allocation.

5.4 Preparation and Administration of Study Drug

PRP will be harvested and prepared in the Mayo Jacksonville Dermatology practice. 20 mLs of blood will be collected from patients using standard venipuncture technique. Collected blood will be processed using a standard dual spin centrifugation protocol resulting in approximately 10.5 mLs of PRP. The 10 cc of PRP will be injected with a 30-gauge needle using the nappage technique (Sivagnanam) over the affected part of the scalp, approximately 1/10 cc / injection site. At the investigators discretion scalp may be numbed with Gebauer's Pain Ease Nonflammable Medium Stream Spray Instant Topical Anesthetic or Impax Lisocaine and Prilocaine Cream, USP 2.5%. The remaining 0.5 mL of PRP will be collected for future research purposes.

5.5 Prior and Concomitant Therapy

Subjects will not be allowed any concomitant therapy for hair loss treatment.

No prior hair replacement / treatment surgeries.
No topical and systemic therapies for hair loss 3 months prior to study enrollment.

6 Study Procedures

- **a.** At baseline all patients will undergo a clinical exam, assessments of hair density using phototrichograms, macroscopic photographs, patient questionnaires and labs including CBC, ferritin, thyroid function, testosterone, TSH and pregnancy test for premenopausal women. All patients will also have a small area shaved at the center of the treatment area, as well as a small tattoo injection to allow for follicle counting via the computerized software.
- **b.** At 3 months, 5 months, 8 months and 12 months, patients will have repeat clinical exams and phototrichograms, macroscopic photographs and complete patient questionnaires.
- **c.** At 12 months, repeat serum tests (CBC, ferritin, thyroid function, testosterone, TSH) will be performed.
- **d.** Adverse events will be assessed at each visit (3, 5, 8 and 12 months post enrollment) as well as 1 week after each injection of PRP.
- **e.** Shampoo and conditioner will be standardized with the study supplying Free & Clear brand products to the patients free of charge for the duration of the study.
- **f.** Pre-menopausal patients will undergo a second pregnancy test before beginning the cross-over treatment.

6.1 PRP vs Minoxidil Study Calendars

Arm A – PRP then MNX

Procedure	Baseline	Week 1	Week 4	Week 5	Week 8	Week 9	Month 3/ Week 12	Month 5/ Week 20	Month 8/ Week 32	Month 12/ Week 48
Consent	X									
Clinical Exam	X						X	X	X	X
Labs	X							X*		X
Phototrichograms & Macroscopic Photos	X						X	X	X	X
Questionnaire	X						X	X	X	X
PRP Injections	X		X		X					
Minoxidil Treatment Daily								X		
Adverse Events		X	X	X	X	X	X	X	X	X
Clinical Assessment of Injection Sites		X		X		X				
Collection of Research Samples	X		X		X					

*- pre-menopausal patients will have a second pregnancy test at the end of the washout period before beginning the cross-over treatment.

Arm B – MNX then PRP

Procedure	Baseline	Month 3/ Week 12	Month 5/ Week 20	Week 21	Week 24	Week 25	Week 28	Week 29	Month 8/ Week 32	Month 12/ Week 48
Consent	X									
Clinical Exam	X	X	X						X	X
Labs	X		X*							X
Phototrichograms & Macroscopic Photos	X	X	X						X	X
PRP Injections			X		X		X			
Minoxidil Treatment Daily	X									
Questionnaire	X	X	X						X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Clinical Assessment of Injection Sites				X		X		X		
Collection of Research Samples			X		X		X			

*- pre-menopausal patients will have a second pregnancy test at the end of the washout period before beginning the cross-over treatment.

7 Statistical Plan

7.1 Sample Size Determination

A total of 23 patients will be enrolled in this study. This sample size will be sufficient in order to gain valuable data to be used in the design of a future, larger study. Given the pilot/feasibility nature of the study, no formal power calculations were performed.

7.2 Statistical Methods

Data Analysis – Given the design, all statistical analysis will be focused on the difference in outcomes, and differences in outcomes compared to baseline, for each treatment within individual patients. For continuous or ordinal outcome variables, we will use a Wilcoxon signed rank test for comparison of outcomes between PRP and Minoxidil, while for categorical outcome variables we will use McNemar's exact test for these. Continuous outcome measures will be summarized using the sample mean, standard deviation, median, minimum, 25th and 75th percentiles, and maximum. Categorical variables will be summarized with number and percentage. 95% confidence intervals (CIs) will be estimated where appropriate. P-values of 0.05 or less will be considered as statistically significant, however the results of these tests will be interpreted with the low power of this pilot study in mind; more emphasis will be placed on graphical and descriptive summaries than on the results of statistical tests. No adjustment for multiple testing will be made owing to the exploratory, pilot nature of the study. Given the prospective nature of the study, we expect to encounter little if any missing data. However in the event of missing data, no attempt to impute this missing data will be made in this pilot study; missing data will be treated as missing.

Descriptive Statistics

We will summarize continuous variables using the sample mean, standard deviation, median, minimum, 25th and 75th percentiles, and maximum. We will summarize categorical variables with number and percentages. Ordinal variables will be summarized using the sample median, minimum, 25th and 75th percentiles, and maximum, as well as with number and percentage.

Handling of Missing Data

Given the prospective nature of the study, we expect to encounter little if any missing data. However in the event of missing data, no attempt to impute this missing data will be made in this pilot study; missing data will be treated as missing.

Multiplicity

No adjustment for multiple testing will be made owing to the exploratory, pilot nature of the study. P-value of 0.05 or less will be considered as statistically significant.

Primary Hypothesis:

We hypothesize that PRP administration for AGA will be safe and without significant complications for the patient. AGA will be comparable in efficacy or superior to conventional treatment with MNX.

The primary endpoints of the study, occurrence of adverse reactions and morbidity, are both dichotomous categorical variables. As such, the proportion for which these outcomes occur will be estimated along with 95% CIs. These proportions will be compared between treatments using McNemar's exact test

Interim Analysis

No interim analysis will be performed in this pilot study.

7.3 Subject Population(s) for Analysis

All-treated population: Any subject randomized into the study that received study drug.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e., unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

or other events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is 12 months after enrollment. The adverse event monitoring period will end at the end of the follow-up period. If an event is reported after this time it would not be considered study related.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if it was exhibited as a severe reaction i.e. swelling, that required hospitalization or additional clinical intervention.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

All adverse events will be documented as required under 21 CFR part 1271. Depending on the nature and seriousness of the adverse reaction, the IRB will be notified according to the Mayo Clinic IRB policy. If An SAE occurs it will also be reported to the FDA as per regulations

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or separate worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and/or log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.4 Stopping Rules

Study enrollment and treatment procedures will be suspended in the event that 3 successive subjects experience a Serious Adverse Event within the first 3 months after treatment. The study would only be resumed after a thorough review of the incidents and any corrective and preventative actions have been put in place along with consultation between the study team and the IRB.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Data Handling

Data will be collected and entered by the study coordinator assigned to the project, and stored into a REDCap database.

9.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

Hard copy data such as consent forms will be stored in locked file cabinets; electronic data will be stored in secure web-based database (REDCap) that will be designed with the help of the statistician.

9.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data Management

Study data will be managed in a study specific REDCap system

Data Security and Confidentiality

The REDCap system has built in systems for control of access, data integrity and audit trails. Access and confidentiality are controlled in a manner similar to other institutional systems.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for whichever is longer;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR

2. As outlined in the Mayo Clinic Research Policy Manual "Access to and Retention of Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

The study specific DSMP will be submitted to the IRB as a separate document in the IRB application.

This study will be monitored on a routine basis during the conduct of the trial. The Mayo Clinic Office of Research Regulatory Support will assist in coordination of the clinical monitoring for the trial as a service for the sponsor-investigator. Clinical trial monitoring requires review of the study data generated throughout the duration of the study to ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

Mayo Center for Regenerative Medicine accelerated research Intramural funding.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

12.3 Subject Stipends or Payments

No subject payments or reimbursement will be offered.

13 Publication Plan

The Principal Investigator will be responsible for manuscript preparation and submission to a suitable orthopedic journal for publication of results.

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