TITLE: Use of Platelet-rich plasma (PRP) therapy in patients with Brittle Nail Syndrome

IRB Protocol #: 20-07022437
Version Date: 04/14/2023
NCT04941807

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Participating Sites:
Weill Cornell Dermatology - 1305 York Avenue, NY, NY 10021

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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

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

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

List of Abbreviations

WCM	Weill Cornell Medicine
PRP	Platelet-rich plasma
PPP	Platelet-poor plasma
PGIA	Physician Global Improvement Score
PGA	Physician Global Assessment
AE	Adverse events
ADE	Adverse Device Effect
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
NSI	Nail Superficial Abnormality Index

1. Protocol Summary

Full Title: Use of Platelet-rich plasma (PRP) therapy in patients with Brittle Nail Syndrome

Short Title:	Platelet-rich Plasma for Brittle Nail Syndrome
Clinical Phase:	Phase 4
Principal Investigator:	Shari R. Lipner MD, PhD
Study Description:	Brittle nail syndrome is a common condition with no available effective treatments. The purpose of this study is to assess the efficacy and safety of platelet-rich plasma therapy for brittle nail syndrome. 8 of 10 fingernails per participant will be treated with platelet-rich plasma (PRP), while the remaining 2 fingernails will receive injections with platelet-poor plasma (PPP). Efficacy will be assessed at the end of the study by an independent blinded endpoint committee.
Sample Size:	N=10 participants.
Enrollment:	This study will enroll 10 subjects and screen up to 20.
Study Population:	Patients presenting with brittle nail syndrome to the Weill Cornell Medicine, Department of Dermatology, specialized nail clinic.
Enrollment Period:	1 year.
Study Design:	This is a single center study with a PROBE design- Prospective Randomized Open Label Blinded Endpoint Design, i.e. Treatment is open label with respect to patient and investigators but is blinded to the endpoint committee. 10 patients presenting que signs and symptoms of brittle nail syndrome will be included. 8 of 10 nails will be randomized to receive treatment with platelet-rich plasma, and 2 of 10 nails will receive injections with platelet-poor plasma (controls). Each patient will receive 3 treatments and high-quality images will be taken. At the end of the study an independent blinded endpoint committee composed of 3 experts on nail diseases will assess efficacy using the Physician Global Improvement score. Adverse effects associated to treatment will be collected throughout the study.

Description of Sites/ Facilities Enrolling Participants:

Weill Cornell Dermatology - 1305 York Avenue, NY, NY 10021

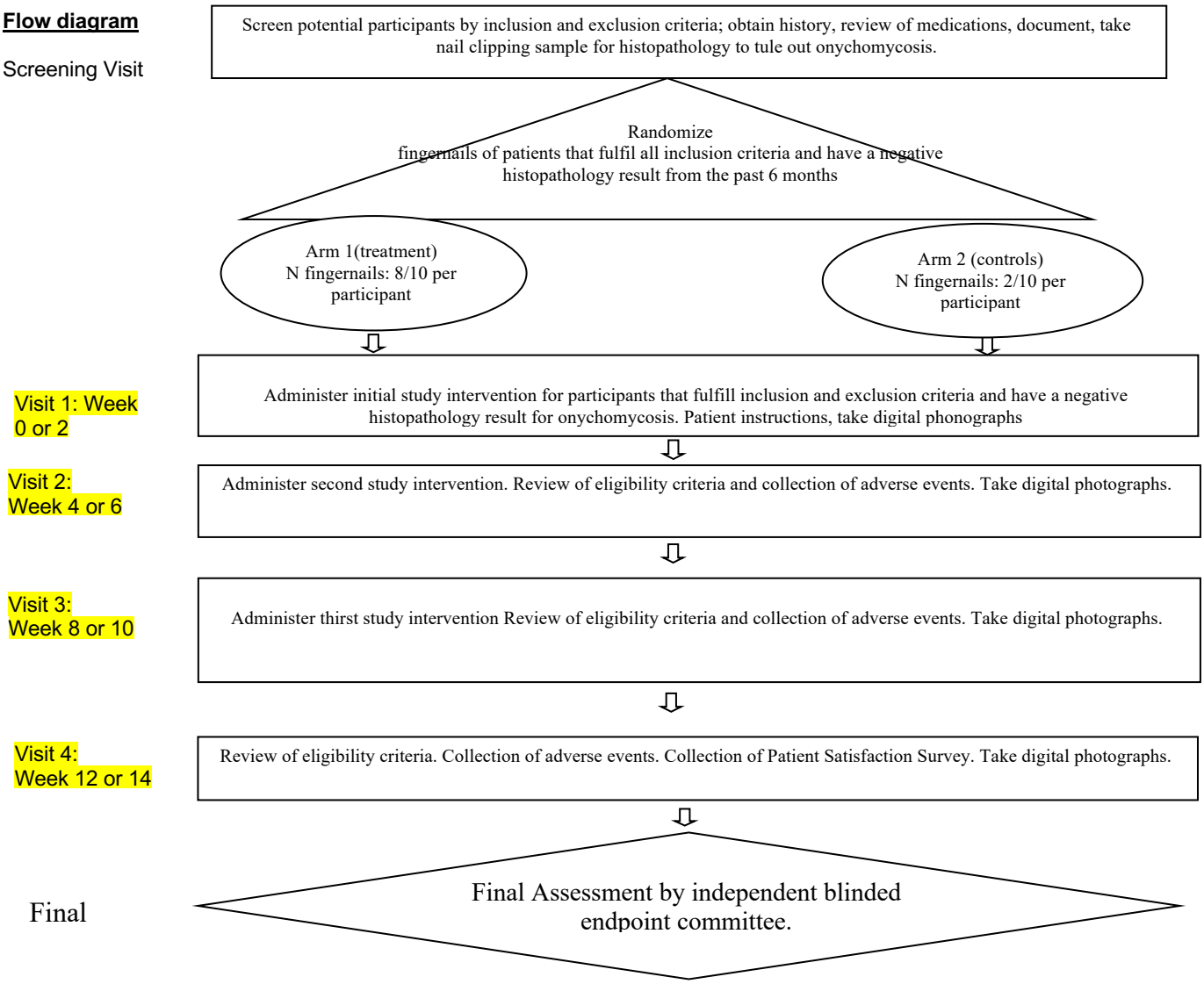
Weill Cornell Dermatology - East Side, 425 E 61st St 4th floor, New York, NY 10065

Study Duration:	October 2022.
Participant Duration:	12 **-** 14 weeks.
Study Agent/Device Name	

Intervention Description:	Platelet-rich plasma (PRP), injected into the proximal nail fold monthly for 3 months. It is defined as a device by the Food and Drug Administration (FDA), and it is a self-contained disposable kit containing two sterile blood separating vacuum tubes, two sleeve filters, various needles and a transferring device.
Primary Objective:	The primary objective of this study is to demonstrate the efficacy of platelet-rich plasma (PRP) injections for brittle nails.
Secondary Objectives:	The secondary objective of this study is to demonstrate the safety and tolerability of PRP injections for brittle nails.
Primary Endpoints:	The Primary efficacy endpoint will be the change in the Physician Global Improvement Assessment (PGIA) of the 8 target nails from baseline to weeks 12 - 14 of follow-up to determine efficacy of PRP injection in the treatment of brittle nail syndrome.
Secondary Endpoints:	Subject reported assessments of nail health will be analyzed using descriptive statistics.

1.1 Schema

Flow diagram



1.2 Study Objectives and End Points

1.2.1 Primary Objectives

The primary objective of this study is to demonstrate the efficacy of platelet-rich plasma (PRP) injections for brittle nails.

1.2.2 Secondary Objectives

The secondary objective of this study is to demonstrate the safety and tolerability of PRP injections for brittle nails.

1.2.4 Primary Endpoints

The Primary efficacy endpoint will be the change in the Physician Global Improvement Assessment (PGIA) of the 8 target nails from baseline to weeks 12 – 14 of follow up to determine efficacy of PRP injection in the treatment of brittle nail syndrome.

1.2.5 Secondary Endpoints

Subject reported assessments of nail health will be analyzed using descriptive statistics.

2. Background

2.1 Disease

Brittle Nail Syndrome is a heterogeneous abnormality characterized by roughness of the surface of the nail plate, fragility or raggedness of the distal nail, splitting and peeling. It is most frequent in elderly individuals and affects about 20% of the population with women affected twice as frequently as men. Many patients view brittle nails as a cosmetic problem and a substantial number indicate that these nail abnormalities may be painful, may impair daily activities, and may have a negative impact on occupational abilities. Treatment is challenging for the clinician and is dependent upon cooperation of the patient. Treatment of brittle nails is aimed at restoration and maintenance of a normal degree of nail plate hydration by minimizing exposure to dehydrating chemicals and by use of moisturizers, such as alpha-hydroxy acids. There are currently no consistently effective treatments for this condition.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

Platelet-rich plasma (PRP) is an autologous concentration of platelets, which can release quantities of growth factors and cytokines. As previously reported, such a complex of bioactive agents can promote the healing and restoration of multiple tissues when injured. PRP injections have been used to promote hair growth in dermatology and alleviation of joint instability in orthopedics. PRP injections into the nail matrix may promote the growth nails in patients with brittle nails and offer them better functionality.

2.3 Rationale

Nail Plate (NP) brittleness is a very common nail complaint, with up to 20% of the population

experiencing some form of brittleness in their nails and is much more common for women over 50[1]. Nail brittleness is characterized by nails that split, flake and crumble, become soft and lose elasticity. All the signs of Brittle Nail Syndrome can be present at once or only partially present. Brittle Nail syndrome itself does not cause any pain, however it can cause functional problems due to the inability to use the nail and cosmetic problems, which can distress the patient [2]. Pain can occur due to the splitting of the nail, and in some studies, it correlates to depression in patients [3]. The most common cause of brittle nails is idiopathic, and the mechanism is poorly understood, it may have to do with the water content in the nails [4], but there very few studies in the area. Inflammatory disease such as psoriasis, lichen planus, lichen stratus, alopecia areata, Darier's disease and eczema can also cause secondary Brittle Nail syndrome. When Brittle Nail Syndrome is caused by an inflammatory disease, treatment of the underlying condition can help with Brittle Nail syndrome, however most patients have idiopathic Brittle Nail Syndrome and there is no effective treatment for the condition [5]. Biotin has been suggested as a treatment; however, it is poorly studied and the FDA issued an warning suggesting that biotin can cause interference with laboratory testing [6,9,10]. PRP injections have been used successful in other dermatological conditions such as androgenetic alopecia [7] and non-dermatological conditions like sports-related muscle, tendon and ligament injuries [8]. Platelet-rich plasma (PRP) is an autologous concentration of platelets, which can release quantities of growth factors and cytokines. As previously reported, such a complex of bioactive agents can promote the healing and restoration of multiple tissues when injured. PRP injection into the nail matrix may help promote growth of health nails in patients with idiopathic Brittle Nail syndrome by releasing growth factors and cytokines.

References:

1. Chen, P., et al., Intra-articular platelet-rich plasma injection for knee osteoarthritis: a summary of meta-analyses. J Orthop Surg Res, 2019. 14(1): p. 385.

2. Chessa, M.A., et al., Pathogenesis, Clinical Signs and Treatment Recommendations in Brittle Nails: A Review. Dermatol Ther (Heidelb), 2019.

3. Dicle, O., A. Bilgic Temel, and K.H. Gulkesen, Platelet-rich plasma injections in the treatment of male androgenetic alopecia: A randomized placebo-controlled crossover study. J Cosmet Dermatol, 2019.

4. Gequelim, G.C., et al., Perception of brittle nails in dermatologic patients: a cross-sectional study. An Bras Dermatol, 2013. 88(6): p. 1022-5.

5. Kazakos, K., et al., The use of autologous PRP gel as an aid in the management of acute trauma wounds. Injury, 2009. 40(8): p. 801-5.

6. Lubach, D., W. Cohrs, and R. Wurzinger, Incidence of brittle nails. Dermatologica, 1986. 172(3): p. 144-7.

7. Scher, R.K., Brittle nails. Int J Dermatol, 1989. 28(8): p. 515-6.

8. van de Kerkhof, P.C., et al., Brittle nail syndrome: a pathogenesis-based approach with a proposed grading system. J Am Acad Dermatol, 2005. 53(4): p. 644-51.

9. Lipner SR. Rethinking biotin therapy for hair, nail, and skin disorders. J Am Acad

Dermatol. 2018 Jun;78(6):1236-1238.

10. John JJ, Lipner SR. Consumer Perception of Biotin Supplementation. J Cutan Med Surg. 2019 Nov/Dec;23(6):613-616

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

PRP therapy has not been studied for nail disease in the past. Risks associated with the use of PRP therapy in the context of hair restoration and skin aging are mostly mild and transient. They include pain, erythema, bruising/ecchymosis, edema, tenderness, scarring, bleeding or infection at the injection site.

2.4.2 Known Potential Benefits

Platelet-rich plasma (PRP) is an autologous concentration of platelets, which can release quantities of growth factors and cytokines. Such a complex of bioactive agents can promote the healing and restoration of multiple tissues when injured. PRP injections have been used to promote hair growth in dermatology and alleviation of joint instability in orthopedics. PRP injections into the nail matrix may promote the growth nails in patients with brittle nails and offer them better functionality.

2.4.3 Assessment of Potential Risks and Benefits

There are currently no consistently effective treatments for brittle nail syndrome. Risks associated with platelet-rich plasma (PRP) therapy for hair restoration and skin aging have been shown to be mostly mild and transient. If PRP is shown to be effective for brittle nail syndrome in this study, patient's quality of life and functionality may significantly improve.

3. Study Design

3.1 Overall Design

This is a single center evaluation of 10 patients with signs and symptoms of brittle nails. Patients will be consented and 8/10 fingernails will be treated with PRP and 2/10 fingernails will be used as controls. Computer software will be used to randomly generate a randomization table for each participant. Randomization for each participant will be done on the same day of their first treatment, after all inclusion and exclusion criteria, including a negative histopathology report for onychomycosis are fulfilled. Blood will be drawn from a vein in the patient's arm into a 11 ml Eclipse PRP Tube. The blood is processed using a centrifuge machine from eclipse medical. After centrifugation, the platelet poor portion will be separated from the platelet-rich portion. The proximal nail folds are cleansed with alcohol. Using a 1ml syringe and 30g needle, 0.1-0.2 ml of platelet-rich plasma is injected into 8 proximal nail folds (treated nails), while 2 proximal nail folds (untreated nails) are injected with platelet-poor plasma. The study patients will be treated with PRP injections monthly for 3 months. Study patients may not have used any medications on the nails 3 months prior to the study or nail polish 1 month prior to the study. The patient must abstain from using any medication, moisturizers, oils, or nail polishes during the study period. The primary efficacy

endpoint will be the individual physician observed Physician Global Improvement Score (PGIA), which encompasses observed improvement of lamellar splitting, transverse splitting, ridges and longitudinal grooves, longitudinal splitting, and nail thickness of target nails. This is a PROBE design- Prospective Randomized Open Label Blinded Endpoint Design, i.e. Treatment is open label with respect to patient and investigators but is blinded to the endpoint committee. High quality images will be obtained utilizing a Canon camera and reviewed by an independent blinded endpoint committee (3 dermatologists with expertise in nails disease Dr. Richard Scher, Dr. Matilde Iorizzo, and Dr. Bianca Maria Piraccini) for PGIA (Physician Global Improvement Assessment. If necessary due to poor image quality (e.g. light source not properly deployed), exposure correction post-imaging may be applied to images that are deemed unsatisfactory. The present study Is not funded, Eclipse Medical provided the required PRP kits, including the sterile tubes.

PGA (Physician Global Assessment) Score:
The Principal Investigator will utilize the Physician Global Assessment (PGA) score for screening purposes during the screening/baseline visit to determine eligibility. The PGA will be comprised of five components: lamellar splitting, transverse splitting, ridging and longitudinal groove, longitudinal splitting, and nail thickness. Lamellar splitting, which represents onychoschizia, is defined as distal furrows or splits encompassing the distal nail plate involving the complete free edge of the nail plate. The second component, transverse splitting, is described as horizontal splitting from the free edge of the nail plate- with at least 2 or 3 horizontal splits of the distal nail plate. The third component, ridging and longitudinal grooves, is defined by at least 50% of the nail plate showing deep ridges and corresponding grooves. The fourth component, longitudinal splitting, which represents onychorrhexis, is defined as at least one deep longitudinal split of the entire nail plate. The fifth component, nail thickness, is defined by a clearly visible change in nail thickness. The presence of each of these components during the screening/baseline visit will represent 1 point on a scale. The inclusion criterion requires patients to have a score of at least 2 out of a maximum of 5 points.
The components used in the PGA assessment have been based on the scoring system used by Van der Kerkhof et. Al in their study, “Brittle nail syndrome: A pathogenesis-based approach with a proposed grading system”. In this study, a grading system of 0-3 was used for each component, with 0-none, 1-mild, 2-moderate, 3-severe. The scale used for screening in the present study mirrors the moderate (score of 2) criteria used in the study by van der Kerkhof et. Al.

The Nail Superficial Abnormality Index (NSI):
The surface of the nails is divided into four quadrants, and each quadrant is scored for four parameters, namely, pitting, discoloration, longitudinal ridging and horizontal ridging. The presence or absence of any of these four parameters is scored as 1 or 0, respectively. Thus, the maximum possible score for a nail is 16 and minimum is 0.

Adverse Events and Reporting
Adverse events (AE) assessment will be ongoing throughout the study. All adverse events shall be reported by the clinical Investigator to the IRB as described below.

Adverse Device Effect (ADE)
Any sign, symptom, or disease in a study subject that occurs during the course of a clinical trial that is determined by the investigator to have a causal relationship or possible causal relationship with the device under investigation.

Serious Adverse Event (SAE)
Any untoward medical occurrence in a subject, regardless of whether the event is related to the device that:

a. results in death;
b. results in a life-threatening illness or injury;
c. results in a permanent impairment of a body structure or body function;
d. requires in-subject hospitalization or prolongation of existing hospitalization
e. requires a medical or surgical intervention that was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
f. If exposed prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
g. Does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be reported within 24 hours of knowledge of the event to the IRB.

Unanticipated Adverse Device Effect (UADE) Any serious adverse effect on health and safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Investigator shall be responsible for determination of the causal relationship of all adverse events to the device and/or procedure. The Principal Investigator is responsible for monitoring the safety of the subjects enrolled.

Any serious adverse events will be reviewed and analysed by the Principal Investigator as soon as the event occurs and will be documented in the subject's binder.

INVESTIGATIONAL DEVICE SUPPLY
PRP (medical device) will be supplied by Eclipse Medical.

3.2 Scientific Rationale for Study Design

This is a PROBE design- Prospective Randomized Open Label Blinded Endpoint Design, i.e. Treatment is open label with respect to patient and investigators but is blinded to the endpoint committee. 8/10 Fingernails per participant will be randomized to receive treatment with platelet-rich plasma and the remaining 2 nails will receive injections with platelet-poor plasma. Potential problems with the control group include nonuniform results due to the lack of response for the 2 nails receiving injections with platelet-poor plasma.

3.3 Justification for Dose

The nail matrix, located at the proximal nail fold, functions as the nail growth center. We hypothesize that injecting 0.1-0.2 ml of platelet-rich plasma in this area will promote nail growth. On the other hand, injecting platelet-poor plasma, which lacks bioactive agents compared with the platelet-rich section, should not promote nail growth.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit. The end of the study is defined as completion of the last visit or procedure.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of brittle nail syndrome in all 10 fingernails who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Patients who have been diagnosed with brittle nails
2. Must understand and voluntarily sign an informed consent form
3. Must be male or female and aged 18-95 years at time of consent
4. Must be able to adhere to the study visit schedule and other protocol requirements
5. A nail clipping with histopathology that is negative for the presence of dermatophyte infection
6. Patient must present with at least a score of 2 on the PGA scale.

4.3 Exclusion Criteria

1. Inability of the patient to provide written informed consent for any reason.
2. Subject has psoriasis, lichen planus, dermatophyte infection or other confounding abnormalities that are severe enough to result in a clinically abnormal fingernail
3. Use of any medication within 90 days prior to start of study
4. Inability to abstain for nail polishes, nail gels during the study period
5. Subject is pregnant or planning pregnancy.

4.4 Lifestyle Considerations

During this study, participants are asked to:

- Abstain from using any medication, moisturizers, oils, or nail polishes during the study period. Participants that do not fulfill this criterion will be excluded from the study.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a <specify modifiable factor> may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Patients attending Weil Cornell Medicine, Department of Dermatology, specialized nail clinic run by PI Dr. Shari Lipner, with signs and symptoms of brittle nail syndrome will be targeted. 10 participants will be included in the study and approximately 20 patients will be screened. All participants will be enrolled in one of two U.S. locations:

Weill Cornell Dermatology - 1305 York Avenue, NY, NY 10021

In the present study, participants will not be compensated or provided any incentives.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial event

	Screening visit	Visit 1: Wk 0 or 2	Visit 2: Wk 4 or 6	Visit 3: Wk 8 or 10	Visit 4: Wk 12 or 14	Off Study[d]
Agent Administration		X	X	X		
Informed consent	X					
Demographics	X					
Medical history	X					
Physical exam	X	X	X	X	X	X
Concurrent medications	X	X	X	X	X	

Obtain nail clipping sample	X					
Adverse event evaluation		X	X	X	X	
Digital photographs	X	X	X	X	X	
Patient satisfaction survey					X	
Efficacy assessment						X

6.1.1 Screening Visit (visit 1)

Screening visit

During the screening visit, all inclusion and exclusion criteria will be reviewed. Obtaining patient consent, history and review of medications will take place. A nail clipping will be obtained for those patients that have not had a negative histopathology result for onychomycosis within the past 6 months. If the patient has had a previous nail clipping within the past 6 months, that will suffice. Therefore, for some patients Visit 1 can take place on the same day of the Screening Visit, while for others Visit 1 will take place on week 2 (after a negative histopathology result for onychomycosis is received).

6.1.2 Treatment Phase

The 10 fingernails of each participant will be randomly assigned to treatment with platelet-rich plasma or platelet-poor plasma (placebo) treatment groups in a 8:2 ratio using a computer-generated randomization scheme developed by the data manager.

Study Visits
Visit 1: Week 0 - 2

Subjects who fulfill all inclusion and exclusion criteria, and sign informed consent are eligible to enroll and begin Visit 1 procedures that same day. For those patients that do not have a negative histopathology result for onychomycosis within the past 6 months, a nail clipping is obtained during screening visit and visit 1 procedure will take place in week 2 assuming the patient fulfill all inclusion and exclusion criteria.

Visit 1 Procedures:

- Patient Instructions
- Take High resolution digital photographs
- Randomization of participants that fulfilled all inclusion and exclusion criteria
- First Injection of PRP

Visits 2 and 3: Week 4 - 6 (±7 days) and Week 8 - 10 (± 7 days)
The following procedures will be performed on these visits:

- Second and third injections of PRP

- Review of eligibility criteria including review of concomitant medications/cosmetics
- Collection of adverse events
- Take High resolution digital photographs

Visit 4: Week 12 – 14 (± 7 days)
Collection of adverse events

- Take High resolution digital photographs
- Collection of Patient Satisfaction Survey

6.1.3 Follow-up Phase

After visit 4 (week 12 - 14) is completed, the independent blinded endpoint committee will judge improvement of brittle nail syndrome based on high quality digital photography taken throughout the study.

7. Study Intervention

7.1 Study Intervention/Device Description

Platelet-rich plasma kit it is defined as a device by the Food and Drug Administration (FDA).

7.2 Availability

Platelet-rich plasma kit and centrifuge machine is an investigational device supplied to investigators by Eclipse Medical.

7.3 Acquisition and Accountability

Agent Inventory Records/Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents/device received from Eclipse Medical on a Drug Accountability Record Form (DARF) or Device Log.

7.4 Formulation, Appearance, Packaging, and Labeling

Platelet-rich plasma kit is a self-contained disposable kit containing two sterile blood separating vacuum tubes, two sleeve filters, various needles and a transferring device.

7.5 Product Storage and Stability

Sterile tubes and centrifuge machine should be stored in temperature between 41°F – 100°F. PRP should be applied to the same patient from whom the blood was drawn.

7.6 Preparation

Blood will be drawn from a vein in the patient's arm into a 11 ml Eclipse PRP Tube. The blood is processed using a centrifuge machine from eclipse medical. After centrifugation, the platelet poor portion will be separated from the platelet-rich portion.

7.7 Dosing and Administration

The proximal nail folds are cleansed with alcohol. Using a 1ml syringe and 30g needle, 0.1-0.2 ml of platelet-rich plasma is injected into 8 proximal nail folds (treated nails), while 2 proximal nail folds (untreated nails) are injected with platelet-poor plasma. The same volume will be administered during each study visit.

7.7.1 Dosing Delays/Dose Modifications

Table 2.

AGENT(S)	DOSE	ROUTE	VISIT
PRP, PPP	0.1-0.2 ml	Intramatricial	1
PRP, PPP	0.1-0.2 ml	Intramatricial	2
PRP, PPP	0.1-0.2 ml	Intramatricial	3

7.8 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication chart throughout the course of the study and saved in subject binder, if applicable.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment may continue for 3 cycles or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject’s condition render the subject unacceptable for further treatment in the judgment of the investigator.

Study Termination Guidelines: A subject’s follow-up in the study will end after one of the following applies:

- Subject’s voluntary withdrawal
- Subject lost to follow-up
- Subject death
- Completion of all scheduled study follow-up appointments
- Any other rules specific to your study

7.10 Duration of Follow Up

Subjects will be followed 4 weeks after their last treatment. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

Computer software will be used to randomly generate a randomization table. 8/10 fingernails will be randomly allocated to treatment with PRP and the remaining 2 fingernails will receive injections with PPP. Randomization for each participant will be done on the same day of their first treatment, after all inclusion and exclusion criteria, including a negative histopathology report for onychomycosis are fulfilled. For the present study, treatment will be open label with respect to patient and investigators but is blinded to the endpoint committee. High quality images will be obtained utilizing a Canon camera and reviewed by an independent blinded endpoint committee (3 dermatologists with expertise in nails disease Dr. Richard Scher, Dr. Matilde Iorizzo, and Dr. Bianca Maria Piraccini) for PGIA (Physician Global Improvement Assessment.

7.12 Study Intervention/Follow-up Compliance

During the baseline visit (standard of care visit), participants will be asked to schedule their follow-up study visits. In addition, patients will receive a call prior to their scheduled visit in order to confirm attendance.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. Participants will be excluded if they have/develop psoriasis, lichen planus, dermatophyte infection or other confounding abnormalities that are severe enough to result in a clinically abnormal fingernail. Have used any medication within 90 days prior to the start of the study. Use of nail polishes or gels during the study period. The subject gets pregnant or is planning pregnancy.

8.1 Discontinuation of Study Intervention

Discontinuation from PRP does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason(s) for discontinuation, take digital photographs, assessment of concomitant medications.

8.2 Participant Discontinuation/Withdrawal from the Study

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

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive PRP.
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for one or more scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit up to 7 days after the 4 weeks from the previous visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and if possible, 1 email). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not applicable

9.1 Laboratory Correlative Studies

9.1.1 Title – Laboratory Correlative Study #1
9.1.1.1 Collection of Specimen(s)
9.1.1.2 Handling of Specimen(s)
9.1.1.3 Shipping of Specimen(s) (if multicenter)
9.1.1.4 Site(s) Performing Correlative Study (if multicenter)

9.2 Special Studies

9.2.1 Title – Special Correlative Study #1
9.2.1.1 Assessment
9.2.1.2 Method of Assessment
9.2.1.3 Timing of Assessment

10. Measurement of Effect

PGA (Physician Global Assessment) Score:
The Principal Investigator will utilize the Physician Global Assessment (PGA) score for screening purposes during the screening/baseline visit to determine eligibility. The PGA will be comprised of five components: lamellar splitting, transverse splitting, ridging and longitudinal groove, longitudinal splitting, and nail thickness. Lamellar splitting, which represents onychoschizia, is defined as distal furrows or splits encompassing the distal nail plate involving the complete free edge of the nail plate. The second component, transverse splitting, is described as horizontal splitting from the free edge of the nail plate- with at least 2 or 3 horizontal splits of the distal nail plate. The third component, ridging and longitudinal grooves, is defined by at least 50% of the nail plate showing deep ridges and corresponding grooves. The fourth component, longitudinal splitting, which represents onychorrhexis, is defined as at least one deep longitudinal split of the entire nail plate. The fifth component, nail thickness, is defined by a clearly visible change in nail thickness. The presence of each of these components during the screening/baseline visit will represent 1 point on a scale. The inclusion criterion requires patients to have a score of at least 2 out of a maximum of 5 points. An independent blinded endpoint committee will assess change from baseline based on the PGA.

10.1 Response Criteria

Change in the PGA from baseline.

10.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.3 Progression-Free Survival

Not Applicable.

10.4 Other Response Parameters

Please see section **12.5 Secondary Endpoints.**

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group-based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the

requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

For study design, please see section **3. Study Design.**

Endpoints

The Primary efficacy endpoint will be the Physician Global Improvement Assessment (PGIA), which will be compared between follow-up point (week 12 - 14) and baseline point for nails with PRP injection, and between follow-up point (week 12 - 14) and baseline point for nails without PRP injection. The power analysis estimated that with approximately 44 nails with PRP injection enrolled in the study, a score change of 0.5 from baseline to week 12 – 14 can be detected through paired two-sided t-test with 90% power at 0.05 significant level for PRP group. The calculation assumed a standard deviation of 1 in scores. PGA is a novel tool that there is not enough reference to assume an accurate standard deviation, so the sample size estimation was also performed on a range of sd assumption. With assumption of sd in range of 0.5 to 1, 13 to 97 nails would be needed for the PRP injection group to detect a score change of 0.5 from baseline to week 12 - 14 through paired two-sided t-test with 90% power at 0.05 significant level.

Sample size estimation summary given different settings of standard deviation and meaningful changes

	sd=0.5	sd=1	sd=1.5
Difference = 1	5	13	26
Difference = 0.5	13	44	97

Secondary
Subject reported assessments of nail health will be analyzed using descriptive statistics.

12.2 Sample Size/Accrual Rate

With a total of 10 participants, 80 fingernails will be included in the treatment group, and 20 fingernails in the control group.

12.3 Stratification Factors

Not applicable.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

Please see **section 12.1 Study design/Endpoints**

12.4.2 Analysis of Secondary Endpoints

Please see **section 12.1 Study design/Endpoints**

12.5 Interim Analysis

Not applicable.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with PRP and PPP.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least 3 treatments.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

PRP has not been studied for nail diseases in the past. Adverse events associated with the use of PRP therapy in the context of hair restoration and skin aging are mostly mild and transient. They include pain, erythema, bruising/ecchymosis, edema, tenderness, scarring, bleeding and infection at the injection site.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Not applicable.

13.1.6 Events of Special Interest

Any other confounding disease found in the histopathology analysis of the nail clipping during the screening phase will be communicated to the subject.

13.1.7 Reporting of Pregnancy

Discontinuation of study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER-only Biologic INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologic Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.2.3 Reporting of SAE to Eclipse Medical

Institution will send Eclipse Medical copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory

authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within 30 business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities. Copies should be faxed directly to Eclipse Medical at (866)-558-0415.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

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

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

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

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

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

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature,

severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

14.1.2 Unanticipated Problem Reporting

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

15. Data and Safety Monitoring Plan (DSMP)

In this section, please include a written plan of the measures that will be taken to ensure the safety of clinical research subjects and protect the validity and integrity of research data. The following questions should be addressed as a part of the DSMP and must be incorporated into your WCM eIRB application:

- Include a description of the proposed monitoring entity (i.e. WCM DSMB, Independent Medical Monitor) and rationale for choosing the specified monitoring entity. If you are using an independent medical monitor or study monitoring committee/group, please specify their qualifications.
- Describe the data/events that will be captured and submitted to the monitoring entity. Specify what data will be collected during the course of the study to assess both safety and efficacy.
- Describe what adverse events may cause the subject to terminate protocol treatment. Specifically, describe treatment stopping rules for an individual subject.
- How will adverse events and unanticipated problems be reported to the monitoring entity and with what frequency?
- How often will the monitoring entity review data/events (i.e. annually, semi-annually, etc.)?
- Describe the complete study stopping rules (criteria for study suspension and potential study termination) statistical considerations. If there are no defined stopping rules, please provide a rationale. Also, state any specific triggers for action.
- All dose escalation trials are required to define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial and defining the Maximum Tolerated Dose.
- How will the monitoring entity’s comments/review be disseminated? (e.g. Submitted to the IRB at the time of continuing review and submitted to participating sites upon receipt of review comments.)

16. References

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4. Gequelim, G.C., et al., Perception of brittle nails in dermatologic patients: a cross-sectional study. An Bras Dermatol, 2013. 88(6): p. 1022-5.

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10. John JJ, Lipner SR. Consumer Perception of Biotin Supplementation. J Cutan Med Surg. 2019 Nov/Dec;23(6):613-616