COVER SHEET

Protocol and statistical analysis plan document

Study Identifier: NCT04202757

Brief Title: Intravenous Plasma Treatment for Parkinson's Disease (yFFP)

Official title: Intravenous young Fresh Frozen Plasma (yFFP)
Investigational Treatment for Parkinson's Disease

Last document revision: Sept. 21, 2021
IRB approval date: Sept. 27, 2021
IRB: Institute of Regenerative and Cellular Medicine

Intravenous young Fresh Frozen Plasma (yFFP®) Investigational Treatment for Parkinson's Disease

Controlled Study YP102018

(Revised Sep. 21, 2021)

1.0 PURPOSE

This study will address a well-known neurological disorder for which there are limited effective treatments and an urgent need to find an efficacious management that could help prevent, or at least slow down the progress of this major public health problem.

- **Parkinson's disease (PD)** is a neurological disorder with evolving layers of complexity. It has long been characterized by the classical motor features of parkinsonism associated with Lewy bodies and loss of dopaminergic neurons in the Substantia Nigra. However, the symptomatology of Parkinson's disease is now recognized as heterogeneous, with clinically significant non-motor features. Similarly, its pathology involves extensive regions of the nervous system, various neurotransmitters, and protein aggregates other than just Lewy bodies. Parkinson's disease seems to result from a complicated interplay of genetic and environmental factors affecting numerous fundamental cellular processes. The complexity of Parkinson's disease is accompanied by clinical challenges, including an inability to make a definitive diagnosis at the earliest stages of the disease and difficulties in the management of symptoms at later stages.

2.0 SCOPE

Sample Size: 20 patients

10 patients will be designated to receive yFFP

10 patients will be designate to receive the placebo - .9% Saline with Riboflavin (Vitamin B2) additive

3.0 DEFINITIONS

FFP: fresh frozen plasma, not necessarily from a young donor

SAE: serious adverse event

SOP: standard operating procedure

yFFP: fresh frozen plasma from a young (18 – 25 year old), sex-identified donor

4.0 RESPONSIBILITIES

Responsible Party –	Principal Investigator:	Dr. Dian Ginsberg The Ginstitute of Functional Medicine 6750 W Loop South, Suite 425 Bellaire, TX 77401 281-569-4289 office
	Co-Investigators:	Dr. Igor Cherches
		Dr. Eddie Patton
	Biostatistician:	Carl Scheffey, PhD
	Trial Manager:	Lynn Maki, RN
	Data Manager:	Patricia Wiginton, RN

5.0 TRIAL STATUS

Current Status: Closed

Closure Date: January 2019

6.0 MATERIALS/EQUIPMENT

- Blood group-specific yFFP
- IV Starter Kit
- IV Catheter
- Plasma Warmer
- .9% Saline Solution
- Fresenius Kabi Blood Bag 200ml
- Riboflavin (Vitamin B2)
- Labels for Placebo

7.0 STUDY DESIGN & METHOD

The study is a prospective double-blind placebo-controlled trial, designed to evaluate the safety and efficacy of intravenous young Fresh Frozen Plasma at 12.5 ml/kg in each of two doses, two days apart (25 ml/kg total).

Patients in the Placebo group will receive infusions of 0.9% Sodium Chloride with Vitamin B2 at a volume rate equal to that of yFFP 12.5 ml/kg in each of two doses, also two days apart.

Consecutive patients are alternately assigned to one of the two treatment study groups, labeled 'yFFP' or 'Saline' group. Because yFFP is in short supply,

the trial manager is free to change the strict alternate allocation sequence, according to the blood types of yFFP available.

Each participant's condition will be classified as mild to moderate. Patients above 2.5 on the Hoehn and Yahr scale will not be eligible for the trial.

The primary outcome is the change in sum of the UPDRS scales 1-3 in the yFFP group compared with the placebo group.

There will be one study site, a secondary care clinic specializing in neurology and infusions (Houston, Texas).

Study will include 20 patients with Parkinson's disease.

Blinding will be achieved by preparing both yFFP and placebo (0.1% Riboflavin in normal saline) solution into identical bags. The Riboflavin is added to achieve indistinguishable color when compared to the yFFP. Labels, barcoded numbers and expiration dates for both the active and saline placebo will be indistinguishable. All infusion bags will be masked.

For the time frame, study day 0 is defined as the day of treatment allocation. Baseline evaluation and laboratory testing will be done then. The first infusion will be scheduled at most two weeks later, and the second infusion will occur two days after the first.

Physician assessments, caregiver surveys and blood tests will be completed at 4-weeks, 12-weeks and 24 weeks, to explore the duration of yFFP - and unspecific treatment effects.

Definition of end of study

The end of the study will be the last participant's final contact at 24 weeks.

The study duration will be eight months from study set-up to analysis and closure. An interim report will be produced at the 12-week point.

Serious Adverse Events (SAE) will be monitored for 14-days after final dose of yFFP or until resolution.

8.0 SECONDARY OBJECTIVES

Secondary objectives: are to achieve a better understanding of this technology including the following:

- Factors predicting a beneficial response
- Effects on additional outcome parameters quality of life, and short-term risk profile

Secondary outcomes will be:

- Adverse events
- Patient laboratory parameters
- Patient Global Impression of change
- Work interference (Stanford Presenteeism Scale)

All other outcomes are exploratory.

9.0 SUBJECT POPULATION

Inclusion criteria

A. Diagnosis of mild or moderate Parkinson's disease, no greater than 2.5 on the Hoehn and Yahr score.
B. Disease duration of 1 to 5 years.
C. Failure to respond (poor efficacy or unacceptable side effects) to drugs recommended for the treatment.
D. Willingness to confirm the use of adequate birth control while on the trial will be required in premenopausal women without evidence for an inability to become pregnant.
E. Willingness to not start any other treatment for Parkinson's disease during the parallel part of the trial.
F. Age 45 years and above.

Exclusion criteria

Any individuals meeting any of the following will be excluded from the study:

A. Other significant disease, which in the view of the study doctor may make assessment of the efficacy of yFFP difficult.
B. Unstable medical conditions.
C. Must weigh at least 45.5 kg. Cannot weigh more than 130 kg.
D. A severe disease state diagnosis
E. Litigation. Patients in litigation will be excluded only if conclusion of that litigation is imminent during the course of the study.
F. If patient is pregnant or breastfeeding.
G. Complete IgA deficiency.
H. Rare contraindications to yFFP therapy as per summary of product characteristics.
I. Receiving yFFP for other reasons.
J. Ongoing drug or alcohol abuse.
K. Psychiatric disorder that could, in the judgement of the site investigator, interfere with successful study participation.

L. Unwillingness or inability to complete the study or an inability to understand the questionnaires being used.
M. Cancer other than basal cell carcinoma within the last 5 years. However, those patients who have received definitive treatment, such as curative surgery more than 6 months ago, with no known recurrence can be included.
N. A history of hypercoagulable or thrombophilic clotting abnormalities.
O. A history of thromboembolic events: ischemic stroke, confirmed myocardial infarction, pulmonary embolism; deep venous thrombosis except where immobility related (for example, after injury or operation).
P. Unstable angina pectoris.
Q. Medications that might react with yFFP such as blood thinners
R. Renal failure or serum creatinine greater than 1.5 times the upper limit of normal at screening.
S. Any medical condition that, in the opinion of the investigator, would make it unsafe for the patient to participate or which would interfere with assessment of the outcome measures.
T. Participation in another interventional trial within 3 months of randomization. Participation in non-interventional studies is not a reason for exclusion.

10.0 SCREENING, RECRUITMENT AND CONSENT

Patients will be identified through the clinical site.

Strategies will be implemented to maximize awareness of the trial in the patient population and increase referrals to the recruiting centers (informative materials will be included as part of the study documents).

Patients will be given the "Patient Information Sheet" to read at least 24-hours before the screening visit, where they will be given the "Informed consent."

At the screening visit, there will be an opportunity for the participants to ask questions of a member of staff trained in all trial procedures, as delegated by the PI. The Principal Presenter or a co-investigator at each site will ensure that the participants meet the inclusion and exclusion criteria at the point of screening.

Patients will be telephoned within 2 days, and maximally 4 days after baseline testing to confirm eligibility to participate.

Screen failures may be rescreened ONLY where there is a short-term reason for ineligibility, such as non-availability for study visits due to planned holidays or an ongoing acute illness.

A screening log will be kept at site to document details of patients invited to be screened for participation in the study. For patients who decline or are ineligible, this will document any reasons available for nonparticipation (where provided). The log will ensure potential participants are only approached once.

The original signed consent form will be retained in the investigator site file, with a copy in the participant's medical notes, and a copy provided to the participant. The participant will specifically consent to their GP being informed of their participation in the study.

The right to refuse to participate without giving reasons will be respected.

11.0 STUDY MEDICATION

Placebo

Matching placebo infusions will be supplied by the Spectrum Plasma Blood Bank for the infusion. These will be identical in appearance to the active infusions - they will be indistinguishable by color and labeling of the infusion.

yFFP infusion

The experimental intervention is 12.5 ml/kg intravenous Spectrum Plasma yFFP, per each of two infusions (25 ml/kg total), in combination with ongoing normal standard treatment.

For reported side effects of Spectrum Plasma yFFP infusion, please refer to AABB Circular of Information.

Contraindications include:

Absolute contraindications to the use of yFFP are documented intolerance to plasma or its components or selective deficiency of immunoglobulin A (IgA).

Relative contraindications are Heart failure or pulmonary edema.

Additional Cautions

Patients should avoid citrus and highly acidic fruits (example: strawberries, blueberries, loganberries, cranberries, currants, gooseberries, pineapple etc.) before and for a day after their last infusion, as patient may experience a reaction due to citrate.

Selection and timing of dose for each participant

Solutions will be available in 200 ml Spectrum Plasma yFFP infusion bags or matching placebo bags. Both bags will be masked prior to infusion.

In exceptional circumstances, where a randomized patient does not attend for the first infusion on day 1, delay of the first infusion up to day 5 is acceptable.

Data collection timelines remain the same, regardless of when infusions are received. Any patient who has not received his/her trial infusion by day 5, that is, before day 6, will be withdrawn and not given trial medication.

All patients who receive ≥80% of the target dose will be included in the per-protocol analysis.

yFFP or placebo will be infused intravenously at an initial rate of not more than 2 ml/minute for 15 minutes. If well tolerated, the rate of administration may be increased to 10-15 ml/minute for the remainder of the infusion.

Infusion rate adjustments can be made if patients experience mild adverse clinical effects, reducing to 2 ml /minute in the first instance and further if required, while aiming for sufficient time to complete the entire infusion in a single day.

The dosing is based on the patient weight, clinicians should refer to this table before administering the study drug

Weight range Min (in kg)	Weight Range Max (in kg)	Volume to be Administered (in ml)	Bags (200 ml) to be dispensed	Bags – Infusion 1	Bags - Infusion 2
45.5	55.4	1,400	7	4	3
55.5	65.4	1,600	8	4	4
65.5	75.4	1,800	9	5	4
75.5	85.4	2,200	11	6	5
85.5	95.4	2,400	12	6	6
95.5	105.4	2,600	13	7	6
105.5	115.4	2,800	14	7	7
115.5	125.4	3,200	16	8	8
125.5	135.4	3,400	17	8	9

12.0 PACKAGING AND LABELING OF INVESTIGATIONAL MEDICINAL PRODUCT

Medicinal product will be supplied by Spectrum Plasma in Fresenius Kabi individual 200 ml bags, containing--yFFP and 23-27 ml dextrose solution of citric acid, or 0.1% Riboflavin in normal saline as a control solution. Each bag will be blinded during administration by the study site.

Packaging and labeling will be completed in accordance with FDA regulations and Current Good Manufacturing Practice (CGMP). Spectrum Plasma is a FDA-AABB & CLIA registered, audited and accredited blood bank that will supply the investigation with FDA approved [21CFR640.30] plasma exclusively collected from

healthy, 18-25 year old sex-identified volunteer donors in full compliance to AABB and State of Texas regulations. yFFP is a registered trademark of Spectrum Plasma, Inc.

13.0 LABEL DESIGN FOR PRIMARY AND SECONDARY PACKAGING

IV bags will incorporate a masking structure that allows the placebo and yFFP to remain blinded to clinical staff and participants. Both the primary container (bag) and the secondary packing of the IV bags will be masked in an identical manner.

Example masking of the primary container (bag) and the secondary packing of the investigational medicinal product and the placebo.

14.0 PRESCRIPTION OF THE MEDICINAL PRODUCT

Medication will be prescribed by an authorized study physician according to the protocol, using a trial-specific prescription. The volume to be dispensed per patient will be calculated according to patient weight (dosing-schedule Table) and the site investigator will dispense the required number of bags.

Participants will be informed of potential adverse reactions and advised to seek medical help and contact the research team, if required.

Patients will carry cards with an emergency 24-hour emergency phone number.

Documentation of prescribing and dispensing study medication shall be maintained for study records in the patient file and a copy of all documents will be sent to the Trial Manager.

A specific prescription must be submitted to the Spectrum Plasma Blood Bank no later than the day prior to the patient's infusion.

15.0 DISPENSING AND DISTRIBUTION OF THE MEDICINAL PRODUCT

The study drug will be stored in a secure area with limited access within each site in the original shipping container until just prior to the infusion to ensure product temperature is maintained at -18°C or colder.

Supplies of study medications dispensed post-allocation will be blinded by the Spectrum Plasma Blood Bank and shipped according to centers SOP regardless if product is placebo or yFFP.

16.0 ADMINISTRATION OF THE MEDICINAL PRODUCT

If site prefers to run a slower infusion than described above, this will not be considered a protocol violation.

Patients may be offered diphenhydramine orally prior to starting the infusion.

Patients must be under continuous nurse observation during the infusion; in cases where no reduction of the infusion rate is required, the average infusion duration for a participant of 75 kg to 90 kg body weight is about 1.5 to 2 hours.

In the event that patients do not receive their entire first infusion, either due to having to stop early because of time constraints arising from long infusion duration with a low rate, or because side effects are intolerable even with the lowest infusion rate, they should still be offered the second infusion. Details of the amount infused should be recorded in the notes section of the infusion form.

Where the infusion cannot be tolerated, and the patient wishes to not receive additional infusion, the patient is withdrawn from further infusion, but follow-up data will be collected until the end of the study.

17.0 SAFETY MONITORING

The blood tests listed below in Section 18.0 will be done at baseline and at 4,12, and 24 weeks. Additional blood monitoring is only required for the protocol in response to adverse events.

18.0 ROUTINE HEMATOLOGY

Routine hematology includes the following:

- White blood cell and differential count (eosinophils, basophils, neutrophils, lymphocytes and monocytes)
- Red blood cell and indices (PCV, MCV, MCH, MCHC)
- Hemoglobin
- Platelets

- Serum IgA
- Serum IgM
- Serum IgG.
- C-reactive Protein

Biochemistry

Routine biochemistry includes:

- Sodium
- Potassium
- Urea
- Serum creatinine
- ALT, AST, GGT, Bilirubin.

19.0 PREGNANCY

Pregnancy status will be verified using blood pregnancy testing at baseline for female patients of childbearing potential and urine pregnancy testing at visit --- if patient is receiving yFFP.

20.0 ALLOCATION

Identification and allocation of patients

A patient identification number will be assigned after consent has been signed.

Patients will be allocated to placebo or yFFP (ratio 1:1) by Trial Manager.

21.0 BLINDING

In the event of an urgent need to unblind treatment, call the Trial Manager.

If unblinding occurs, details including patient study number, the date performed, people involved, and the reason for the unblinding, shall be recorded by the administering nurse and retained.

If clinically indicated, the participant will be withdrawn from the medication.

Accidental unblinding's will be dealt with on a case by case basis if and when they arise. The patient's data should continue to be collected according to the visit schedule, even in the event of unblinding or withdrawal from study medication, unless the patient refuses.

22.0 STUDY DATA

Database

Source data will be entered by authorized staff onto a password protected Excel spreadsheet. All data entered will be QA-verified against the source documents.

Database passwords, data handling and confidentiality/format of records

Database access will be strictly restricted through passwords to the authorized research team.

All participant contact/screening and recruitment data will be stored on spreadsheets on DropBox, which will have restricted access from password protected computers. Accrual data will be anonymized and collated by the Trial Manager. No identifiable data will be transferred.

At the end of the study, essential documentation will be archived in accordance with sponsor and local requirements. The retention of study data will be the responsibility of the Principal Investigator.

23.0 ON-SITE/CENTRAL MONITORING

The Trial Manager will conduct on-site/central monitoring.

The Statistician may identify data fields that should be checked against the source data during site monitoring visits, where there are data queries, the research nurses will be responsible for resolving the queries.

The QA will review responses before closing the query.

24.0 STATISTICAL CONSIDERATIONS

Data analysis will be performed using a password-protected computer independent of study sponsor or clinical sites.

25.0 STATISTICAL ANALYSIS

A comprehensive statistical analysis plan will be developed and agreed upon with the trial's oversight committees. Section 26 contains a tentative outline for the statistical analysis of the UPDRS scores.

26.0 EFFICACY

Primary analysis

The sum of UPDRS subscales 1-3 will be considered as a summary of disease severity. For the various patients, differences between the baseline sums and sums at 24 weeks give summaries of disease severity change over the course of the study. The population of yFFP differences will be compared with the population of differences for the placebo patients. Past studies have found that sums of

UPDRS scores are normally distributed. An initial comparison between yFFP and placebo will then be afforded by a simple t-test. In view of the small sample size and the categorical nature of the data, other analyses will be explored. Those additional analyses may include a permutation test or other bootstrap methodology.

Secondary analysis

Changes in the three UPDRS subscales 1-3 will also be analyzed separately. Additional analysis will be performed as dictated by data exploration. End scores may be modeled as a function of initial scores and lab tests. The possibility of using the 12-week scores in a longitudinal model will be considered.

27.0 SAMPLE SIZE CALCULATION

The sample size was calculated based on available participant populations.

FFP has long been an approved medication in the US. This study addresses the potential benefits of FDA approved [21CFR640.30] Plasma exclusively collected from 18 – 25 year old volunteer donors.

28.0 COMPLIANCE AND WITHDRAWAL

Subject compliance

Compliance will be measured by attendance at infusion visits and tolerance of entire prescribed infusion.

Treatment cessation

Patients who develop an unexpected new condition precluding further participation will be withdrawn from receiving further infusions.

29.0 WITHDRAWAL OF PARTICIPANTS

Study drug must be discontinued for the following:

1. The participant decides he/she no longer wishes to continue

2. Withdrawal is recommended by the Investigator or another clinician (for example, intercurrent illness during course of study or side effects from study drug)

3. The trial is terminated at the request of the Co-Investigator

Patients will be discontinued for the following:

Patient is randomized, but never receive any medicine (that is, the first infusion is never started - this is also termed 'non-compliance')

Participants have the right to withdraw from the study at any time and for any reason without providing a reason. The investigator also has the right to withdraw participants from the study if they consider that it is in the best interests of the participant. Should a participant decide to withdraw from the study, he/she will be asked to volunteer a reason for withdrawal but are at liberty not to state a reason.

Should a participant withdraw from study drug only, efforts will be made to continue to obtain follow-up data with the permission of the patient. Subjects who withdraw from treatment early will be encouraged to return to the study site for follow-up, providing that consent is not withdrawn.

30.0 DATA MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

This protocol has been developed by clinicians.

Day to day management of study will be the responsibility of the Co-Investigator with the assistance of the Trial Manager.

Dr. Dian Ginsberg:	Principal Investigator
Dr. Igor Cherches:	Co-Investigator
Dr. Eddie Patton:	Co-Investigator
Lynn Maki, RN:	Trial Manager (TM)
Patricia Wiginton, RN:	Data Manager (DM)

The TM will arrange telephone conferences and provide weekly recruitment email updates during recruitment and status reports.

The TM & DM will organize a meeting for all Investigators (and for key staff working on the study) to sign the protocol, and to agree on the content and undergo training on SOPs before the start of recruitment.

A second investigators' meeting will be held at the end of 12 weeks to review the results. A final meeting will be held at the conclusion of the study at 24 weeks.

The Co-Investigators will be responsible for the day-to-day study conduct at site. This includes establishing and carrying out the trial at his/her center in accordance national and local law and public health regulations and FDA.

They will ensure that all site-specific documentation is complete and correct; and that all staff involved in the trial are compliant with regulations, and that they are appropriately trained in those aspects relevant to their role in the study while being familiar with the trial protocol.

Co-Investigators are also responsible for managing recruitment on target and collecting and submitting accrual and outcome data in a timely manner; responding in timely fashion to requests from the sponsor for information; providing and responding promptly to SAEs and agreeing to monitoring audit visits by Quality Assurance as required.

Central and site monitoring of study conduct, and data collected will be performed by the Trial Manager on behalf of the Sponsor. Full details will be documented in a monitoring plan, agreed upon with the study sponsor. The main areas of focus will include:

- Consent
- Serious adverse events
- Essential documents
- Drug accountability and management.

All monitoring findings will be reported and followed up with appropriate persons in a timely manner.

31.0 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The investigators agree to provide full access to all source data, study data and materials to the sponsor for purposes of monitoring, audit or inspection.

32.0 PHARMACOVIGILENCE

Refer to AABB Circular of Information

33.0 UNEXPECTED ADVERSE REACTIONS

Adverse event reporting will be in compliance with FDA. Most adverse drug reactions that occur in this study, whether serious or not, will be expected treatment-related side effects as FFP has a well-established side-effect profile and approximately 20% of all blood plasma transfused is from 18-25 year old donors (yFFP).

FFP can cause adverse reactions such as:

- Chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and mild back pain, which may occur occasionally.

- Increase in serum creatinine level and/or acute renal failure have been observed.
- Very rarely, thromboembolic reactions, such as myocardial infarction, stroke, pulmonary embolism, and deep vein thromboses have occurred.

Details of further spontaneously reported adverse reactions include the following:

- Cardiac disorders: angina pectoris (very rare)
- General disorders and administrations site conditions: rigors (very rare)
- Immune system disorders: anaphylactoid shock (very rare), hypersensitivity (very rare)
- Blood pressure decreased (very rare)
- Musculoskeletal and connective tissue disorders: back pain (very rare)
- Respiratory, thoracic and mediastinal disorders: Dyspnea NOS (very rare); or
- Vascular disorders: shock (very rare).

The adverse events reported above are expected in the sense that they are possible known side-effects of the study medication, but all reported instances of both serious and non-serious adverse events will be reported in this study.

During the trial, investigators will be made aware of any updates to the summary of product characteristics (SPC) but the protocol need not be amended every time there is a change unless it directly affects the study conduct. The source of accurate information regarding the active medication must always be the SPC and not the study protocol, and the above information is provided to reflect the situation at study start only.

34.0 PROTOCOL SPECIFICATIONS

For purposes of this protocol

1. Any serious adverse events will be recorded throughout the duration of the trial until 14 days after cessation of study drug or until resolution.
2. Non-serious adverse events will be recorded throughout duration of trial until 14 days after cessation of study drug.
3. Serious adverse events exclude any pre-planned hospitalizations not associated with clinical deterioration.

35.0 RECORDING AND REPORTING SERIOUS ADVERSE EVENTS OR REACTIONS

All adverse events and all serious adverse events should be recorded. Depending on the nature of the event, the reporting procedures below should be followed.

Any questions concerning adverse event recording/reporting should be directed to the Trial Manager in the first instance.

36.0 NON-SERIOUS ADVERSE EVENTS

All non-serious adverse events will be recorded on the "Patient infusion log". Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, or severe):

Mild: Discomfort is noticed, but there is no disruption of normal daily activities.

Moderate: Discomfort is sufficient to reduce or affect normal daily activities.

Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

Relation of an AE to treatment should be assessed by the investigator/delegate (must be a clinician) on-site. Investigators will be responsible for managing all adverse events according to local protocols, as the study blood product is already approved for use in other indications.

37.0 SERIOUS ADVERSE EVENTS

All Serious Adverse Events (SAEs) shall be recorded and reported on the serious adverse event form and sent to the Co-Investigator and Trial Manager within 24 hours of learning of its occurrence. The initial report can be made by completing the "Report of Adverse Transfusion Form" and faxing or emailing to Trial Manager. A record of this notification (including date of notification) must be clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available.

Relationship of the SAE to the treatment should be assessed by the investigator/delegate (must be a clinician) at that site, as should the expected or unexpected nature of any serious adverse reactions. As this is a blinded study involving a placebo and biologics product, seriousness, causality and expectedness should be evaluated as though the patient was on the blood product.

All SAEs-reporting responsibilities to FDA will be that of the Sponsor, with the support of the clinical sites. The Sponsor will report SAEs to the regulatory authority Food and Drug Administration (FDA).

SAEs that are fatal or life-threatening must be reported as soon as possible and no later than 12 hours after the Co-Investigator is first aware of the reaction, and

Sponsor will report to FDA within 24 hours of first becoming aware. Any additional relevant information must be reported within a further 7 days.

SAEs that are not fatal or life-threatening must be reported within 3 days to the sponsor.

The Principal Investigator will provide a final report of all SAEs (expected and unexpected), which will be distributed to the Sponsor.

All investigators will be informed of all SAE's assessed as fulfilling criteria as possibly, probably or definitely related to the study intervention and unexpected per the SPC. This will be regardless of medication administered in order to avoid the risk of inadvertently unblinding investigators, unless this information is needed for medical management of patients.

The Trial Manager MUST be informed of all SAEs within 24 hours of learning of its occurrence. A record of this notification (including date of notification and acknowledgement of receipt) must be clearly documented to provide an audit trail.

The Trial Manager will forward the report to the Sponsor in compliance with regulatory requirements.

38.0 PREGNANCY

Should a trial participant become pregnant during the trial, she will be immediately withdrawn from study treatment, and the pregnancy will be followed up until outcome. The need to unblind will be considered on a case-by-case basis. Pregnancy will be reported as a serious adverse event. Data collection at the planned scheduled follow-up timeline must continue, unless the patient is unwilling to provide further data.

39.0 ETHICS AND REGULATORY ISSUES

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the Texas Medical Board.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures. Participants will be provided with a copy of the completed consent form for their records.

The participating Investigators have participated and signed off on this protocol.

40.0 FINANCE AND INSURANCE

The Carolina Longevity Institute is the sponsor of this study and will be the largest source of funding. Spectrum Plasma will provide medication (placebo & yFFP) free of charge.

The investigators have liability for clinical negligence that harms individuals towards whom they have a duty of care. No provision has been made for potential liability for issues arising from negligence in study design. There are no arrangements for non-negligent compensation.

41.0 PUBLICATION POLICY

The data will be the property of the sponsor and co-sponsors. Publication will be the responsibility of the Principle Investigator. Co-Investigators, Sponsor and contributing participants have the right to publicize the results from the study. All manuscripts abstracts or other modes of presentation will be reviewed by the Principle Investigator prior to submission. No reference will be made to any particular study subject. Results of the study will also be reported to the Sponsor/Funder in the required format.

Participants will be informed about their treatment allocation at the end of the study, along with a summary of the results, once the primary paper has been finalized for submission for publication.

42.0 AUTHORS' CONTRIBUTIONS

Dr. Dian Ginsberg is the current Principal Investigator and oversees the Trial Manager. Dr. Igor Cherches and Dr. Eddie Patton are Co-investigators for the trial and contributed to the protocol. Patricia Wiginton is the Data Manager and Research Coordinator and, along with Lynn Maki, the Trial Manager, oversees the recruitment process for all sites. Carl Scheffey is the Biostatistician and contributed to the protocol. All authors contributed to the manuscript. All authors read and approved the final manuscript.

43.0 APPLICABLE REFERENCES

21CFR 210, 211, 600,601, 606,607, 610, 630, 640, 660, 820.

42 CFR 493

AABB Standards for Blood Banks & Transfusion Services

https://www.webmd.com/parkinsons-disease/default.htm

End Document