Pilot Investigation to Evaluate Effectiveness of Shockwave Therapy, Photobiomodulation and Physical Therapy in the Management of Non-insertional Achilles Tendinopathy

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I. BACKGROUND AND SIGNIFICANCE

Non-insertional Achilles Tendinopathy (AT) is a common overuse injury in adults who are both athletes and nonactive.[2] Tendinopathy occurs when there is either a failed healing response or the failure of normal turnover or remodeling response.[3] AT can result in pain and limited movement due to the injury.

In the last few decades there has been an increased prevalence of people running to maintain a healthier lifestyle.[1] With an increase in running, there has been an increase in running-related injuries. Of these running-related injuries, AT contributes to between 6.2% and 9.5% .[1] It's been estimated in some studies that burden of AT may reach 52% lifetime prevalence in runners.[9]

The most common treatment of choice for AT now are exercise loading programs.[2] Eccentric strengthening (ECC), although the current most prominent treatment, may only improve symptoms in approximately 60% of AT patients.[2]

Laser-induced photobiomodulation (PBM) has been shown to increase cell proliferation and metabolism, which may aid in the repair and remodeling process.[3,4] Photobiomodulation therapy (PBMT) has been shown to be effective in a variety of clinical settings depending on wavelength and paraments used.[4] In a meta-analysis and systematic review on plantar fasciitis, it was found that PBMT is effective with exercise and without exercise.[4] Tumilty et al. found that PBMT was effective in the treatment of AT, but it was more effective when paired with exercise sessions, however other studies have shown mixed results.[3]

Extracorporeal shockwave therapy (ESWT) is a process in which energy is delivered to the muscles or tendons to relieve aches and pains.[6] Like PBMT, ESWT is used to treat a variety of musculoskeletal conditions, however it is more expensive and therefore used less often.[5] A recent network meta-analysis showed that in the long term when ECC was combined with ESWT it was effective in treating AT, however there is limited data available on the impacts of ESWT in short term recovery.[2] Notably PBMT was not able to be compared in the analysis due to no published studies meeting criteria for inclusion. There is also limited information available on the best energy settings to be used in treating AT,[2] and therefore more research needs to be done into the impact of ESWT on treating AT.

PBMT and ESWT are effective treatments, and a study on the treatment of other tendons in the body - lateral epicondylitis (tennis elbow) - showed improvement in both the PBMT and the ESWT arms, with ESWT showing a significant difference in increasing handgrip strength.[5] Studies such as this are promising that ESWT and PBMT will be effective in treating other tendon injuries such as AT. This promising result combined with the previous unclarity in the best treatment for AT justifies the need for more research. The sub-section of AT amongst runners has had very limited research and given the high prevalence, is something that should be addressed. Therefore, our study will compare three different treatment arms utilizing SWT, PBMT and traditional physical therapy, and using both questionnaires and measured outcomes we will assess the most effective treatment for AT.

II. SPECIFIC AIMS

The primary aim of this pilot study is to evaluate the **effects** of standard physical therapy compared to treatment with SWT, and a combination of SWT and PBMT (each combined with physical therapy) in the management of Achilles tendinopathy. *We hypothesize runners in each treatment allocation will see improvement in functional outcomes, pain and measures of Achilles tendon structure compared to baseline measures. As SWT and PBMT may change structural properties and modulate pain in tendinopathy, we anticipate greater measures in running function for participants assigned to SWT and PBMT in treatment over physical therapy as sole treatment.*

The secondary outcome will be to evaluate cross-over response. After the initial 3-month randomized control trial, subjects who are not satisfied with results, will be able to select a different treatment arm for the remaining 3 months of the study.

III. SUBJECT SELECTION

a. Inclusion/Exclusion Criteria

Inclusion Criteria

Patients will be eligible if they meet the following criteria:

- Patients aged between 18-65 years old with a diagnosis of mid-portion Achilles tendinopathy (including both unilateral and bilateral)
- Running is the pre-injury primary form of physical activity and pre-injury would complete on average 10 miles per week or more of running
- VISA-A <80 at baseline to be eligible

Exclusion Criteria

Exclusion criteria includes:

- Less than 3 months of symptoms
- Primary insertional Achilles tendinopathy
- Diagnosis of rheumatological disease/connective tissue condition, symptomatic arthritis of foot and ankle, a primary running related injury outside Achilles tendinopathy, other contraindications to PBMT or SWT
- Have received SWT within the past 3 months to their Achilles
- Prior injection within 3 months
- Currently enrolled in PT for more than 4 weeks for their condition
- Women who are pregnant or **those who are planning to become pregnant**. This is due to the fact that pregnancy will reduce participants activity after the treatment and the safety concerns related to shockwave treatment.
- Patients with neuropathy affecting sensation to pain
- Patients with a known underlying cardiac disease that could be affected by shockwave therapy
- Patients with known history of Achilles tendon rupture
- Patient currently taking oral steroids or fluoroquinolone antibiotics

IV. SUBJECT ENROLLMENT

a. Recruitment Procedure

We hope to enroll 60 runners into three treatment arms (n=20 in each arm). We will be using a multi-pronged approach to recruit patients:

- Running Clinics
    - Referral from Dr. Tenforde
    - Referrals from other physicians at MGB and Harvard affiliated hospitals
        - A letter and flyer will be provided to other practitioners in the MGB network to ask them to refer our study information to their patients.
- Social Media
- Email Lists
    - Flyers to be sent to different email lists of running clubs
- Hospital advertising
    - Flyers
    - Rally
    - Research Patient Data Registry (RPDR)

b. Procedure for obtaining informed consent

A member of the research study staff will introduce the study to the patient and if they express interest in the study, then they can have the informed consent explained to them. Patients will have as much time as necessary to consult with their family or their physicians before enrolling in the study. If the patient understands and accepts the document, it will be signed, and the subject will be enrolled. No treatment or data collection will be done without informed consent. Consent can be obtained by any member of the study staff who has been trained in Good Clinical Practice (GCP). If a potential study subject is a patient of the PI, Dr. Adam Tenforde, then consent will be obtained by a different trained study staff member to avoid any concern for coercion. Consent may be gained in person or using the MGB online database – REDCap.

V. STUDY PROCEDURE

a. Overall Research Design and Methods

This study has been split into two **parts. Part 1 is the initial randomized control trial, and Part 2 is when the participants can select the treatment they want to receive if they are not satisfied with their initial treatment. In Part 1 patients** will not be blinded to the treatment arm that they receive due to the obvious differences in the treatments.
Participants will also be asked to log their return to running at home using the University of Delaware Return to Sport protocol.[8]

Part 1

Study participants will be randomly assigned to one of three treatment groups, using a block randomization generator **that is implemented into REDCap**. There will be 20 patients per treatment group, no power calculation as this is a feasibility study. The three treatment arms are: physical therapy only, SWT and physical therapy, and a combination of SWT, PBMT and physical therapy. All runners, regardless of treatment group, will be asked to enroll in physical therapy at a location that is convenient to them (and accepts their insurance if applicable) and complete a standard physical therapy program addressing individual strength deficits in both proximal (spine and hip girdle) along with distal (thigh, leg and foot/ankle) muscle groups. To standardize loading program, we will provide all runners with an at-home exercise program designed by Dr. Karin Silbernagel for progressive Achilles tendon loading. This will be

completed alongside the physical therapy they are receiving. Activities including running will be allowed as tolerated following published guidelines by Dr. Silbernagel.[8]
In subjects who have bilateral AT, the leg with the most severe symptoms (determined by the VISA-A) will be chosen as the primary data for the study, however both legs will be treated consistent with the treatment group the subject was randomized into. Outcomes will be obtained for each Achilles tendon, regardless of treatment, using VISA-A at each data collection point. Participants will also be asked to complete a weekly log of running and completing PT exercises.

Part *2*
At the 3-month follow-up, participants who are not satisfied with their outcome will be given the option to choose one of the remaining treatment arms. Regardless of what treatment a patient chooses, if any, there will be one final visit conducted at 6 months for final data collection.

Physical Therapy Only Arm
After enrollment, participants will be assigned the home exercise program from Dr. Silbernagel and physical therapy with a therapist of their choice, instructions will include addressing any other lower extremity impairments known to contribute to Achilles tendinopathy including proximal strengthening program.[10,11] The treatment protocol from Silbernagel et al. (2017)[7] is described below:

Phase 1: Week 1 – 2 *(perform exercises every day)*
- Pain-monitoring model information and advice on exercise activity
- Circulation exercises (moving foot up/down)
- 2-legged toe raises standing on the floor (3 sets × 10-15 repetitions/set)
- 1-legged toe raises standing on the floor (3 × 10)
- Sitting toe raises (3 × 10)
- Eccentric toe raises standing on the floor (3 × 10)

Phase 2: Week 3 – 5 *(Perform exercises every day)*
- 2-legged toe raises standing on edge of stair (3 × 15)
- 1-legged toe raises standing on edge of stair (3 × 15)
- Sitting toe raises (3 × 15)
- Eccentric toe raises standing on edge of stair (3 × 15)
- Quick-rebounding toe raises (3 × 20)

Phase 3: Week 3 – 12 *(Perform exercises every day and with heavier load 2-3 times/week)*
- 1-legged toe raises standing on edge of stair with added weight (3 × 15)
- Sitting toe raises (3 × 15)
- Eccentric toe raises standing on edge of stair with added weight (3 × 15)
- Quick-rebounding toe raises (3 × 20)
- Plyometric training

Phase 4: Week 12 – 6 months *(Perform exercises 2-3 times/week)*
- 1-legged toe raises standing on edge of stair with added weight (3 × 15)
- Eccentric toe raises standing on edge of stair with added weight (3 × 15)
- Quick-rebounding toe raises (3 × 20)

Patients when working with their physical therapist, may be at different stages in their rehabilitation, continued physical activity/sport may be performed without a negative effect on recovery if the guidance on pain level and perceived exertion scale laid out by Dr. Silbernagel is

followed. Patients do not need to stop their activities as long as the activity is modified according to the pain monitoring model, and recovery days are adjusted accordingly.

Shockwave (SWT) Arm:
The shockwave arm will receive shockwave treatment in addition to the physical therapy program from Dr. Silbernagel. They will receive one treatment a week and one telephone check-in a week for three weeks. Dr. Tenforde, the PI, will perform the SWT on all study participants, using the OrthoPlus Ultra 100/radial D-Actor. This Extracorporeal Pressure Activation Treatment (EPAT) device will be used at a radial shockwave of 3000 counts treatment settings of 15 Hz minimum 2 bars with a focus applicator head at mid-portion of Achilles using clinical focusing technique, and 3000 counts at 15 Hz minimum 2.5 bars using broad oscillator to myotendinous region and over symptomatic areas of gastrocnemius and soleus. Maximal settings will be 4 bars and initial treatment will start at 500 strikes at 1.5 bars for each treatment head to allow participant to be comfortable as we start shockwave sessions. The research coordinator will conduct the telephone calls to check-in on physical therapy exercise compliance and response to each treatment.

SHW and PBMT Arm
This treatment arm will receive both SWT and PBMT in addition to the physical therapy program from Dr. Silbernagel. The SWT will be performed by PI, Dr. Tenforde, and the PBMT will be performed by either the PI or a trained member of the study staff. Training for the PBMT will be conducted by a local LightForce representative. They will receive PBMT using the LightForce® XPi 25W device with the Smart Hand Piece technology, which has a built-in accelerometer in the hand piece that controls the speed of light delivery to the treatment area. The therapy is delivered through a flexible optical fiber threaded through the hand piece, which contains a rolling glass massage ball. PBMT will be delivered at 10 J/cm^2 and applied in a serpentine pattern to the calf from the fold in the back of the knee to the bottom of the foot and the sole of the foot including the arch. A member of the study team will calculate the treatment area according to a standard protocol (appendix I), and calculate the treatment time.
Patients will receive PBMT twice a week for three weeks, and SWT will be combine once a week for three weeks.

b. Visit Details

After consent has been obtained, patients will be randomly allocated to one of the three treatment arms. The expectations for the visits for the different study arms are outlined below:

Table 1: Outlined visits from three different study arms

	Physical Therapy only	**Shockwave**	**PBMT & Shockwave**
T0: Baseline	Subject screening & enrollment*		
Part 1	Subject to be randomly assigned a treatment arm		

T1: week 1 visit 1	VISA-A, ProMIS-29, UWRI, patient goals Ultrasound, heel raises & hopping test	Treatment 1 VISA-A, ProMIS-29, UWRI, patient goals Ultrasound, heel raises & hopping test	PBMT & SW treatment VISA-A, ProMIS-29, UWRI, patient goals Ultrasound, heel raises & hopping test
T2: week 1 visit 2	telephone check-in	telephone check-in	PBMT treatment only
T3: week 2 visit 1	telephone check-in	Treatment 2	PBMT & SW treatment
T4: week 2 visit 2	telephone check-in	Telephone check-in	PBMT treatment only
T5: week 3 visit 1	telephone check-in	Treatment 3	PBMT & SW treatment
T6: week 3 visit 2	telephone check-in VISA-A, ProMIS-29, UWRI	telephone check-in VISA-A, ProMIS-29, UWRI	PBMT treatment only VISA-A, ProMIS-29, UWRI
T7: 6 week follow up	telephone check-in VISA-A, ProMIS-29 & UWRI	telephone check-in VISA-A, ProMIS029 & UWRI	telephone check-in VISA-A, ProMIS-29 & UWRI
T8: 3 month follow up	VISA-A, ProMIS-29, UWRI, patient goals, patient satisfaction**, new treatment selection** Ultrasound, heel raise & hopping test	VISA-A, ProMIS-29, UWRI, patient goals, patient satisfaction, **new treatment selection** Ultrasound, heel raise & hopping test	VISA-A, ProMIS-29, UWRI, patient goals, patient satisfaction, **new treatment selection** Ultrasound, heel raise & hopping test
Part 2	Participants to choose treatment and follow visit schedule as listed above		
T9: 6 month follow up	Patient satisfaction, ultrasound, heel raises & hopping test	Patient satisfaction, ultrasound, heel raises & hopping test	Patient satisfaction, ultrasound, heel raises & hopping test

*At baseline subjects will be screened for their eligibility using the inclusion and exclusion criteria described on page 2 of this document. To determine pregnancy female patients will be asked if they are pregnant**, planning to become pregnant,** or not **pregnant**. MGB guidelines state that when using non-iodizing radiation if a woman states she is not pregnant, no pregnancy test is required.

Due to the nature of COVID-19, in-person visits, check-ins, and questionnaires, can be rescheduled +/- 14 days within each of the outlined study timepoints.

Physical Therapy

In part 1 the physical therapy only arm will only have to complete 2 in-person visits, baseline and the 3 month follow up, but they will receive two calls a week for the first three weeks to ensure consistency with the other treatment arms, and the virtual 6 week follow-up. The number of visits they will have to complete in part 2 will depend on which treatment arm the subject selects, but they will be required to come in at least once to complete the 6 month follow-up. The study will start when they enroll in the study and start the Dr. Silbernagel's protocol.

Shockwave
The shockwave group will have 3 in-person visits and 3 virtual visits in part 1, and then at least one visit in Part 2 for the 6 month follow up. The number of visits required in part 2 will depend on what treatment the subject chooses at the 3 month check in.

Shockwave + Photobiomodulation therapy
The PBMT and SWT treatment arm requires 6 in person visits in part 1 (3 for PBMT alone and 3 for PBMT & SWT), 1 virtual visit (6 week follow up) and at least 1 visit in part 2. The number of visits in part 2 will depend on which treatment the subject chooses at T8 (see table 1).

Study Visits for all treatment arms:
An overview of the questionnaires and measurements that will be taken at various time points, regardless of treatment arm, are described in table 2.

Table 2: Overview of questionnaires and measurements required regardless of treatment arm

	Questionnaires							Measurements	
Visit	VISA-A	ProMIS-29	UWRI	Patient goals	Treatment preference	Patient satisfaction	Return to sports worksheet collection	Ultrasound	Heel raise & hopping test
Baseline	x	x	x	x	x			x	x
3-week follow-up	x	x	x				x		
6-week follow up	x	x	x				x		
3-month follow-up	x	x	x	x	x	x	x	x	x
6-month follow up	x	x	x	x	x	x	x	x	x

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected

Questionnaires:

- Symptoms severity specific to Achilles will be **VISA-A**

    - The VISA-A is currently the only valid and reliable measure to assess function and pain in AT (validity, *P<0.01*; test-re-test reliability, *r = 0.98*) (2*)
- ProMIS-29 will be used to capture other aspects of non-disease specific measures of health-related domains (physical, mental and social health).
- The University of Wisconsin Running Injury and Recovery Index (**UWRI**) will measure aspects unique to the running population.
- Visual analog scale of pain
- To quantify patient choice and motivation for treatment, an unvalidated survey will be obtained to determine patient goals of enrollment in study and reason for selecting a different intervention.
- Patient satisfaction with treatment
- **Participant demographics**
    - **Age at enrollment**
    - **Gender**
    - **Fitzpatrick skin type**
    - **Self-identified race and/or ethnicity**
    - **Marital status**
    - **Military status**
    - **Exclusion Criteria**
    - **BMI calculated from height and weight**
    - **Achilles tendon surgical history**
- **Expected AE interview forms**
    - **Achilles specific (one for each limb at week 1 check in, week 2 check in, 3 week follow-up, 6 week follow-up, 3 month follow-up, and 6 month follow-up)**

Ultrasound: Ultrasound measures will be assessed at baseline, 3 months and 6 months. Measures of interest include cross-sectional area, degree of thickening within the tendon at site of maximal circumference and maximal pain, and presence and number of neovessels on color flow doppler.
Function: Quantitative function in heel raises to fatigue will be measured at baseline, 3 months and 6 months on both affected and unaffected limb. We will also ask the participants to complete 20 hops and rate their pain using a visual analog scale (0 to 10).
Return to running: We will be asking participants to record their return to running, following Drs. Silbernagel & Crossley[8] protocol. In order to log this, they will track the date, exercise and pain level using the University of Delaware training diary.[8]

b. Study Endpoints

Objective Endpoints

- Ultrasound endpoints
- Calf raises

Subjective Endpoints

- Questionnaires

c. Statistical methods

For the statistical analysis of both the primary outcome, VISA-A, and secondary outcomes, PROMIS-29, UWRI, VAS, ultrasound measurements, and functional tests, we will use the

Shapiro-Wilk test to for normality in the data. For the continuous data we will use the t-test and ANOVA test if the data is normally distributed, and we will use the Mann-Whitney U test and Kruskal-Wallis analyze the data that is not normally distributed. For the binary data we will use the chi^2 or Fishers test to compare the data.
In the first phase of the study, the randomized control trial, we will use a multivariable linear regression, controlling for: sex, BMI, age, medical condition (thyroid disease and diabetes) and prior oral steroid and/or fluoroquinolone use. In phase 2 after the elective cross-over, we will use the models described above as repeated measure models.
Interim analysis will be performed after 30 participants are enrolled to review for safety and tolerance to treatment.

VII. RISKS AND DISCOMFORTS

Physical Therapy
There are no expected risks or discomforts associated with the physical therapy, however physical therapy involves exercises designed to address causes of movement impairment, similar response to exercising muscles such as soreness and pain may be experienced. This is minimized by supervision by trained physical therapy using best practices to guide treatment.

Shockwave
The OrthoPlus Ultra 100 is a Class I FDA approved device with minimal risk. It is a low energy device and no severe events have been reported.
Reported discomforts of shockwave include bruising, swelling and rarely, tissue damage. Pain response is expected due to device treatment over sites of injury and use of process of clinical focusing; we will monitor each patient and adjust treatment settings to ensure pain is tolerable during the treatment.

Photobiomodulation
The risks associated with PBMT are minimal. Mild discomfort may be experienced during the treatment, the treatment should not be “hot”, but participants should notify the study team member if they feel any uncomfortable warming. Individuals with neuropathies or difficulty distinguishing changes in skin temperature are at higher risk. Protective eyewear will be provided and must be worn by the participant and study team member during operation of the laser to protect your eyes from accidental laser exposure. No serious adverse events have been reported using this treatment.

VIII. POTENTIAL BENEFITS

a. Potential benefits to the subjects

Medical/Physical benefits
The aim of this study is to improve recovery of AT, it is expected that all treatment arms will help AT recovery, some treatments potentially quicker that other, more traditional treatment options.
Compensation

All patients will be eligible to receive PBMT or SWT without cost. The cost of medical assessment or prescribed physical therapy will be paid by patient through traditional health insurance.
Patients will be able to receive checks up to $150 in renumeration for completing the study. They will receive their payment at the end of the study, if they withdraw early, they will be compensated for the visits that they did complete as broken down below:

- Enrollment and completion of 6-week follow-up: $50
- 3-month follow-up: $50
- 6-month follow-up: $50

b. Potential benefits to society

Taking part in this study will include a sense of contributing to the benefit of other through participating in medical research.

IX. MONITORING AND QUALITY ASSURANCE

a. Data and safety monitoring

The principal investigator (PI) will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data. All those responsible for data collection and storage will be aware of and comply with all regulatory requirements related to Adverse Events (AE). If a person becomes ill or is injured as a direct result of study, medical care will be made available. All adverse events (and device events) will be followed to resolution and reported to the MGB IRB. Documentation of the presence of any side-effect, adverse event and unexpected device events will be completed at every visit and will be reported in accordance with AE reporting guidelines of the MGB IRB. Persons will be encouraged to contact the investigator or a member of his staff at any time between visits concerning adverse events or worsening of symptoms. An event that is deemed serious by the principal investigator will be recorded in the person's study binder and will be handled in an expeditious manner. If at any time during the study, the PI judges that the risk to subjects outweighs the potential benefits, the PI shall have the discretion and responsibility to recommend that the study be terminated.
Data will be shared with the Geneva Foundation via REDCap. This data will include de-identified common demographic variables, including: biological sex, marital status, year of birth, self-identified race and/or ethnicity, **Fitzpatrick skin type,** military status (civilian vs other aspects of prior or current military service), and injury location.

b. Plan for review of adverse events

An Adverse Event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.
All AEs that occur after the subject signs the consent form will be documented as an AE. The Investigator will ensure that all events that occur during the study period are recorded. All AEs will be followed until resolution or until, in the Investigator's judgement, that are chronic and

stable. In an emergency situation appropriate medical measures will be taken to stabilize the subject.

Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires in subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is another medically important condition.

Adverse Event Severity Assessments

The guidelines outlined in CTCAE v4 will be used for severity assessments. (Note – the term "severe" is a measure of intensity and that a severe AE is not necessarily serious).

AE Severity Grading Scale

Severity Grade	Description
Mild (1)	Awareness of sign, symptom, or event, but easily tolerated; does not interfere with usual daily activities or tasks.
Moderate (2)	Discomfort enough to cause interference with usual daily activity. It may warrant therapeutic intervention.
Severe (3)	Incapacitating; inability to perform usual activities and daily tasks; significantly affects clinical status; requires therapeutic intervention.
Life-threatening (4)	Emergency treatment required life-threatening, death.

Each AE will be categorized as "serious" or "not serious" based on the definition of an SAE.

Adverse Event Causality Assessments

Adverse events will be assigned a relationship (causality) to the treatments. The PI will be responsible for determining the relationship between the treatment and the AE. The type of event will help assess the likelihood that an AE is related to the treatment. Relationship of AEs to study products will be classified as follows:

- **Not Related**: No relationship exists between the AE and the treatment. The event is attributed to a pre-existing medical condition or an intercurrent event unrelated to the study device and procedures.
- **Possibly Related**: Follows the treatment, but may have been developed as a result of an underlying clinical condition or treatments/interventions unrelated to the study.
- **Probably Related**: Follows the treatment, but is unlikely to have developed as a result of the subject's underlying clinical condition or other treatment or other interventions.

- **Definitely Related**: Follows the treatment and the physical evidence shows a convincing relationship to the treatment.
- **Unknown**: Follows the treatment, but unable to determine the relationship to the treatment.

Serious injury is defined to be an injury or illness that results in permanent impairment of a body function or permanent damage to a body structure, **or** necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure that occurs during the course of the trial beginning after informed consent has been executed and extending until 30 days after the final study visit.

Partners IRB must be notified within 5 working days/ 7 business days of SAE discovery.

The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

X. REFERENCES

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