Clinical Investigational Plan

Study Title: A Multicenter, Prospective, Randomized, Comparison IDE Study between the Pulse Biosciences CellFX® System and Cryosurgery for the Treatment of Cutaneous Non-Genital Common Warts

Short Title: CellFX Comparison to Cryosurgery in Cutaneous Non-Genital Common Warts

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PROPRIETARY AND CONFIDENTIAL

TABLE OF CONTENTS

STUDY CONTACTS....5
1.0 INTRODUCTION AND BACKGROUND....6
1.1 Common Warts of Hand and Fingers....6
1.2 Current Care....6
1.3 Non-Surgical Approach....6
1.4 Surgical Approach....7
1.5 Alternative Approach....7
1.6 Study Rationale....9
2.0 STUDY DEVICE DESCRIPTION....10
2.1 Pulse Bioscience CellFX® System....10
2.2 Proposed Indication for Use....12
2.3 Cryosurgical System....12
3.0 PROTOCOL....12
3.1 Study Objectives....12
3.2 Study Design....12
3.3 Randomization....13
3.4 CellFX Procedure....13
3.5 Standard Cryosurgical Procedure....14
3.6 Site Selection....14
3.7 Number of Subjects....14
3.8 Clinical Study Duration....14
4.0 STUDY PROCEDURES....14
4.1 Screening....14
4.2 Subject Selection....15
4.2.1 Inclusion Criteria....15
4.2.2 Exclusion Criteria....15
4.3 Process for Obtaining Informed Consent....16
4.3.1 Process for Obtaining Informed Consent....16
4.3.2 Addition of New Information....16
4.4 Schedule of Events and Evaluations....17
4.5 Screening / Enrollment Procedures....18
4.6. 7-Day Follow-up Visit....18
4.7 30-Day Follow-up Visit (CellFX/Cryosurgical Treatment #2, if required)....19
4.8 60-Day Follow-up Visit (CellFX/Cryosurgical Treatment #3, if required)....19
4.9 90-Day Follow-up Visit....20
4.10 120-Day Follow-up Visit....20
4.11 150-Day Follow-up Visit....21
4.12 Subject Withdrawal....21
5.0 BENEFITS AND RISKS....21
5.1 Benefits....21
5.2 Risks....21
5.3 Mitigation of Risks....21
6.0 STATISTICAL CONSIDERATIONS....22
6.1 Co-primary Endpoints....22
6.1.1 Co-primary Safety Endpoints....22
6.1.2 Primary Effectiveness Endpoint....23

6.1.3 Justification of Non-Inferiority Design and Margin 23
6.1.4 Type I Error Control and Study Success 24
6.2 Secondary Endpoints 24
6.3 Sample Size Determination 26
6.5 Sub-Group Analyses 27
6.6 Missing Data 27
7.0 EXPLORATORY ENDPOINTS 28
7.1 Exploratory Efficacy Endpoint 28
7.1.1 Subject-level clearance of all warts at 30 days post last treatment 28
7.2 Exploratory Safety Endpoints 28
7.2.1 Subject-level wound healing adverse events at 30 days post last treatment 28
7.2.2 Subject-level skin change adverse events at 90 days post last treatment 28
8.0 CLINICAL PHOTOGRAPHY 28
9.0 INDEPENDENT PANEL REVIEW 28
10.0 ADVERSE EVENTS 29
10.1 Adverse Event Definitions 29
10.1.1 Adverse Event (AE): (*ISO 14155:2011 3.2*) 29
10.1.2 Adverse Device Effect (ADE): (*ISO 14155:2011 3.1*) 30
10.1.3 Serious Adverse Event (SAE) *(ISO 14155:2011 3.37)* 30
10.1.4 Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36) 30
10.1.5 Unanticipated Adverse Device Effect (UADE): *(21CFR812.3)* 30
10.2 Device Deficiencies (*ISO 14155:2011 3.15*) 30
10.2.1 Definitions 30
10.3 Safety Reporting Requirements 31
10.3.1 Blinded Live Assessment of Adverse Events 31
10.3.2 Safety Monitor 31
10.3.3 Investigator Responsibilities 31
11.0 STUDY MANAGEMENT (SPONSOR RESPONSIBILITIES) 32
11.1 Sponsor Ethical and Regulatory Considerations 32
11.2 Selection of Clinical Sites 32
11.3 Site Training 33
11.4 Investigator Training 33
11.5 Monitoring of Study Sites 33
11.5.1 Monitoring Methods 33
11.5.2 Periodic Monitoring Visits (Onsite and Remote) 33
11.5.3 Site Close-out Visit 34
11.6 Protocol Deviations 34
11.7 Study Completion 34
11.8 Audits / Inspections 35
11.9 Publication Policies 35
11.10 Data Management 35
11.11 Case Report Forms /Transmission of Data 35
11.12 Data Retention 35
12.0 INVESTIGATOR RESPONSIBILITIES 36
12.1 IRB Approval and Informed Consent 36
12.2 Data Collection and Reporting 36
12.3 Source Documents / Records Retention 37
12.4 Device Accountability 37
13.0 REFERENCES 38

14.0 APPENDICES 39
14.1 Appendix A: Patient Informed Consent 39
14.2 Appendix B: Case Report Forms.....39
APPENDIX A: Patient Informed Consent will be provided as a separate attachment 40
APPENDIX B: Case Report Forms will be provided as a separate attachment.....41

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1.0 INTRODUCTION AND BACKGROUND

1.1 Common Warts of Hand and Fingers

Non-genital warts (verruca vulgaris) are an extremely common, benign, and usually a self-limited skin disease. Infection of epidermal cells with the human papillomavirus (HPV) results in cell proliferation and a thickened, round, raised papule on the skin ranging in size from a pinhead to 10 mm. The appearance of warts is determined by the type of virus and the location of the infection. There are several reasons why some individuals are affected by warts, and other remain trouble free. These include: the type and strength of the viral strain, the health of the exposed person, and the strength of an individual's immune response. Any area of skin can be infected, but the most common sites are the hands and feet. Common warts are most often seen on the hands and present as skin-colored papules with a rough 'verrucous' surface.

1.2 Current Care

Current treatments for common warts involve destruction of the infected cells either chemically or physically and treatment depends on the size, location, number, type, age of the patient, risk of scarring and patients' commitment to the therapy. The clinical management of these warts is challenging, and no current treatment is singularly effective, especially against warts that are recalcitrant. These include non-surgical, pharmacologic, and surgical treatment modalities: topical peeling methods like salicylic acid; immune modulators using contact immunotherapies; intralesional candida antigen or bleomycin; cryotherapy; duct tape occlusion; photodynamic treatment; pulsed dye laser; and general surgical procedures.

1.3 Non-Surgical Approach

Chemical Destruction:

Salicylic Acid

The use of salicylic acid is one of the two most commonly used treatments for warts. Dermatologists prescribe chemical destruction treatments where patients apply an over-the-counter preparation, usually less than 17% salicylic acid or prescription salicylic acid containing up to 70% salicylic acid at home every day. Treatment response rates of 40-84% with an average of 61% have been reported as an effective therapy for non-genital cutaneous warts.[1] Minor skin irritation was reported occasionally in some of the other trials, but generally there were no major harmful effects of topical salicylic acid.[2] A systematic review of local treatments of cutaneous warts by Mitsuishi et al., found evidence that topical treatments with salicylic acid have a therapeutic effect, with a cure rate of 75 percent compared with 34-48 percent in placebo controls.[1,3] Other agents used for chemical destruction are monochloracetic acid, dichloracetic acid, trichloroacetic acid, silver nitrate, glycolic acid and 80% phenol in solution. Complications associated with using chemicals include pain, hyperpigmentation, hypopigmentation, burning sensation and erythema.[4]

Cantharidin

Cantharidin is used as an agent in the clinic by "painting" the wart causing oxidative stress by inhibiting phosphatases 1 and 2A that damages both DNA single- and double-strand breaks and triggers p53 dependent apoptosis.[4] Cantharidin causes a blister to form under the wart. In a week or so, the patient returns to the office and the dermatologist clips away the dead wart.

Immune Modulators

This treatment uses the patient's own immune system to fight the warts. Forms of immune modulators include imiquimod, intralesional immune modulators using Candida antigen or anti-cancer such as Bleomycin; contact immunotherapy, cimetidine, zinc, and retinoids. Because wart proliferation is controlled by the immune system, various methods have been used to stimulate the immunologic response to HPV. This treatment is used when the warts remain despite using other treatments and the ability to treat many lesions simultaneously. One type of immunotherapy involves applying a chemical diphenylcyclopropenone (DPCP). Among these are topically applied inorganic molecules capable of eliciting contact hypersensitivity, such as imiquimod and intralesional interferons[5] to the warts. A mild allergic reaction occurs around the treated warts which stimulates the body's innate response to fight the virus.

Physical Destruction

Liquid Nitrogen Cryotherapy

For common warts in adults and older children, cryotherapy is a standard treatment and can be done in the physician's office. Cryotherapy involves freezing a wart using a very cold substance (usually liquid nitrogen). The liquid nitrogen application usually takes less than a minute and most warts require 1 to 4 treatments, with 1 to 3 weeks between each treatment. Pain from cryotherapy can last up to 3 days. Healing is generally quick (7 to 14 days) with little or no scarring.[6] It can cause dark spots in people who have dark skin. With cryotherapy, it is common for repeat treatments.

Laser

Laser treatment is an option, mainly for warts that have not responded to other therapies. Before laser treatment, the dermatologist may numb the wart with an anesthetic injection.

1.4 Surgical Approach

Electrosurgery and Curettage

Electrosurgery (burning) is an available treatment for common warts, filiform warts, and foot warts. Curettage involves scraping off (curetting) the wart with a sharp knife or small, spoon-shaped tool. These two procedures often are used together. The dermatologist may remove the wart by scraping it off before or after electrosurgery.

Excision

The wart may be cut off or surgically excised in combination to using other applications previously mentioned.

1.5 Alternative Approach

CellFX® System

The CellFX System is intended to clear the skin of benign, undesired skin lesions as an alternative to surgery and other more destructive methods for removing non-neoplastic benign lesions. The CellFX System utilizes non-thermal, localized delivery of a timed series of low energy, nanosecond electrical pulses that can trigger regulated cell death. The non-thermal effect on tissue takes place in a very shallow depth of skin directly below the sterile treatment tip. Histology of skin treated with CellFX has demonstrated selective non-thermal effects on cellular structures, including melanocytes, epidermal cells, and sebaceous glands, with no apparent damage to the adjacent acellular dermis.

The device delivers less energy to tissue, but none of these emit thermal energy unlike laser, electro-surgery, or electro-cautery equipment.

PRIOR CLINICAL STUDIES SUMMARY

Twelve (12) clinical studies have been or are currently being conducted using IRB approved non-significant risk protocols and consent with the Nano-Pulse Stimulation (NPS) device. A combined total of approximately 3,125 NPS application cycles have been delivered to over 680 adult subjects. Anatomic locations where NPS has been used include the face, abdomen, truncal, back, arms, legs, hands, and feet. Discomfort in all protocols was managed with localized injected buffered Lidocaine with or without epinephrine. Side effects consisted of relatively minor reactions consistent with routine wound healing. No device or procedure complications and no serious related adverse events were reported. Only minor expected adverse skin effects have been reported and they were resolved within days of the procedure.

Previous Wart Studies Using CellFX System

Nineteen (19) adult subjects were enrolled with the requirement of having a minimum of 2 and up to 5 non-genital, off-face cutaneous warts with one of the warts designated as a sham control. Subjects received an initial NPS treatment and returned for follow-up evaluations at 7-, 30- and 60 days post-last treatment. Each wart was evaluated for size reduction at 30-days for eligibility for retreatment and at 60-days post-last NPS session using a 5-point size scale. At the end of the study, all subjects were asked about their satisfaction with each treated lesion clearance based on a 5-point scale from 1 equaling highly dissatisfied and 5 being satisfied.[7]

Six (6) of the nineteen subjects were male (32%) and 13 were female (68%). Subjects ranged in age from 23 to 71, with an average age of 47. Fitzpatrick skin types were distributed across Type I (5%), Type II (58%), and Type III (37%). Fifty-two percent (52%) of warts were recalcitrant with 69% common warts located on the hands, fingers, and shoulders and the remaining 31% plantar warts. A total of 58 warts were enrolled in the study, 40 treated and 18 controls including one subject having all warts treated without a sham control. Two subjects withdrew early from the study giving a total per protocol population cohort of 37 treated and 16 control warts for evaluating wart reduction and clearance rates at 60-days post-treatment. Fifty-one percent (51%) of treated warts (19/37) received two treatments and 65% (n=20 common and 4 plantar) showed greater than 50% reduction in size with 51% (n=19) rated completely clear at 60-days post-treatment. Three (3) out of 16 sham control warts (18.8%) showed 100% reduction in size, suggesting a possible immune response involved with use of NPS. There were no observations of hypopigmentation and only 3 cases of hyperpigmentation at 60 days. No serious adverse events were reported, however in a few cases local bruising or formation of blood blisters post-treatment were noted that resolved by Day 7 or Day 30. Based on these initial results of achieving a high rate of wart size reduction, inclusive of recalcitrant warts, and with a single NPS session, a pivotal clinical study was initiated to further evaluate energy parameter settings of NPS technology for optimal clinical outcome.[7]

The IRB-approved NSR Protocol# NP-WP-010 pivotal study was designed as a prospective, non-randomized, multicenter study to evaluate the safety and efficacy of the CellFX System with expanding the number of clinical sites to 5 and using larger tip sizes as well as increasing the number of retreatments for investigators to clear cutaneous non-genital warts. Similar to the feasibility study each subject had to have a minimum of 2 warts with one wart serving as the subject's internal control. Additionally, at the 30-day, 60-day and 90-day visits the Investigator had the option to retreat any previously treated wart and were followed for 30 and 60-days post last CellFX treatment (NCT04554394).

A total of 62 subjects and 267 study warts (195 treated and 62 sham controls) with an average of 4.1 warts per subject were enrolled and evaluated at 60-days post last treatment. Forty-two subjects were female (68%) and 20 were male (32%) with an average age of 47.3. Fitzpatrick skin types were distributed across Type I (5%), Type II (44%), Type III (32%) and Type IV (19%). More than 70% of all treated warts were located on the hands, knee, ankle, arm, leg, neck, and torso while the remaining 30% were plantar warts. Pre-treatment with intralesional injection of sodium bicarbonate buffered 1-2% lidocaine with 1:100,000 epinephrine was used to control pain (mean, 1.0ml). Subjects reported a median 4.0 at the time of treatment based on a 11-point visual pain scale, with 47.8% reporting a score of 0 or 1.

Overall efficacy at 60-days post-last treatment showing greater than 90% reduction in size was observed in 77.4% of common (72/93) and 43.8% of plantar warts (14/32). Single treatment efficacy at 60-days post-last treatment showed 81% (51/63) in patients with common warts and 31.6% (6/19) with plantar warts. Subject satisfaction at the end of study was reported in 73.7% (98/133) of subjects being satisfied with final results. As previously described in the wart feasibility study, there were 11 sham control warts (17.7%) showing 100% reduction in size. A total of 31 cases of transient hyperpigmentation (22.8%); 61% mild, 35% moderate, 3% mod/severe and 8 observations of hypopigmentation (5.9%) were observed at 60-days post-last treatment. No serious adverse events were reported however, 9 treatment-related adverse events (6 mild and 3 moderate severity) of transient pain, numbness, or infection were reported. These AEs occurred on the hands (n=5) or plantar area (n=4) and all were resolved with no associated sequela.[8]

This new wart comparison study under Protocol NP-WC-015 will evaluate safety and efficacy using the CellFX System with pre-defined treatment energy profiles for all primary and secondary treatments based on the tip size. The comparator group will be treated with cryosurgery with liquid nitrogen for the treatment of warts.

1.6 Study Rationale

The rationale for this IDE study is to compare the safety and effectiveness of the CellFX System to the comparator group, Cutaneous Cryosurgery performed with direct application with liquid nitrogen for the treatment of cutaneous, non-genital common warts in healthy adult subjects.

2.0 STUDY DEVICE DESCRIPTION

The study device being evaluated is the Pulse Bioscience CellFX® System.

2.1 Pulse Bioscience CellFX® System

The CellFX System consists of an electrical pulse console (similar to devices used to electro-coagulate tissue) combined with a handpiece which is held by the clinician during application of pulses to the skin surface. The handpiece is coupled to a sterile, single patient-use treatment tip.

Once the electrical pulse console is turned on and a predetermined treatment energy setting is selected, a sequence of pre-programmed electrical pulses is administered to an area of skin directly beneath the treatment tip. A common commercially available sterile contact gel may be applied to the skin or treatment tip surface to ensure good electrical contact to the tissue. The three system components are as follows, shown in **Figures 1-3**.

1. CellFX Console including a built-in touch screen for setting selection.
2. CellFX Handpiece (re-usable)
3. Sterile Single Patient-Use CellFX Tip (multiple different tip sizes available)

Figure 1: CellFX Console

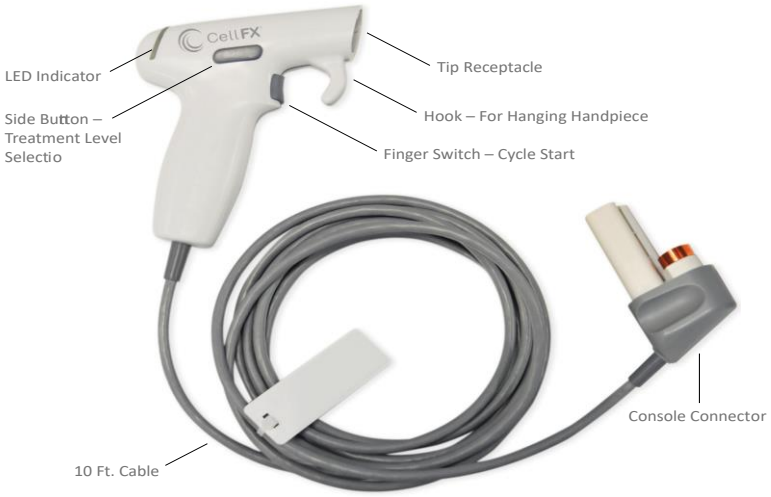

Figure 2: CellFX Handpiece

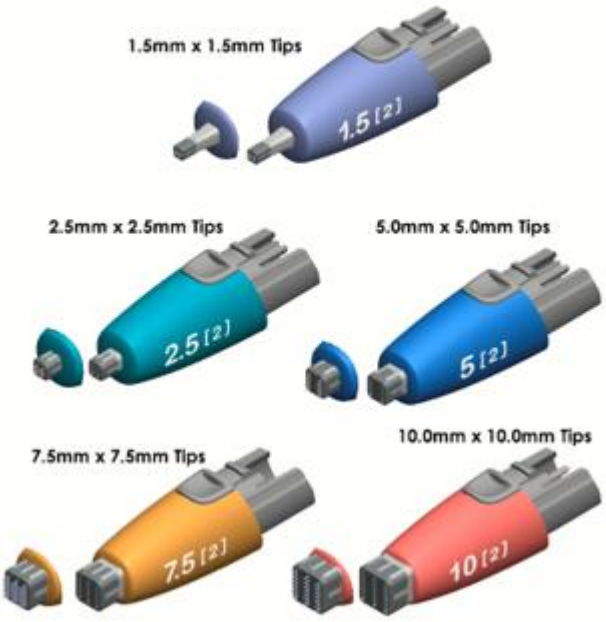

Figure 3: CellFX Treatment Tips

2.2 Proposed Indication for Use

The Pulse Biosciences' CellFX System is investigational in the U.S. and the system is indicated for dermatologic procedures requiring ablation and resurfacing of the skin including the treatment of common warts.

2.3 Cryosurgical System

The comparator device that will be used in this study is the standard of care procedure using liquid nitrogen to treat warts. The liquid nitrogen procedure uses a single freeze thaw cycle, with warts placed in contact with a metal probe (spray tip) held at liquid nitrogen temperature until a 2 to 3 mm halo is visible around each wart. All physicians are required to use the same Cryosurgical System.

3.0 PROTOCOL

3.1 Study Objectives

The primary objective of this study is to compare the safety and effectiveness of the CellFX System to Cryosurgery for the clearance of cutaneous non-genital common warts on all areas of the body, excluding the scalp, nose, within the orbital region of the face, plantar or periungual area in healthy adult subjects.
The following objectives are to evaluate the overall response to CellFX and Cryosurgery:

- Wart response after treatment vs. the pre-treated appearance of the same lesion
- Wart response at various points in time over several weeks following the initial treatments vs. the same pre-treated wart
- Overall wart clearance (generally accepted as complete clearance of warts from the treated area)
- Comparisons of reduction from baseline in wart size of treated warts
- Document the condition of skin in the treatment areas over the course of various time periods post-initial CellFX and Cryosurgery, and
- Document all safety related issues that may be considered as adverse side effects or serious adverse events

3.2 Study Design

This study is designed as a prospective, multicenter, single-blinded, randomized comparison IDE study between CellFX System and Cryosurgery. The Principal Investigator will select a sub-investigator to be the blinded investigator to classify the healing characteristics and wart clearance and/or reduction assessment of each subject's selected warts at baseline, post treatment and at 7-days, 30-days, 60-days, and 90-days following the last CellFX treatment or Cryosurgical procedure. This sub investigator will be blinded to the treatment assignment. The subject may not be blinded to the treatment assignment. The Principal Investigator can choose to be the blinded investigator and select a sub investigator to be the treating investigator.

Eligible subjects with a minimum of 2 and up to 8 warts meeting the inclusion and exclusion criteria will be enrolled. If the subject has more than 8 warts, the subject is excluded from the study. Warts may be present anywhere on the face except the scalp, nose and within the orbital region of the face. Plantar warts are also excluded. Subjects will be randomized to receive either a CellFX treatment or Cryosurgery. Selected warts for each treatment modality must be clearly separated in distance from each other so that wart treatment and side effects can be assessed by the blinded site investigator.

All eligible warts will receive at least one CellFX or Cryosurgical treatment. Each subject will be evaluated by the blinded site investigator at 7-days, 30-days, 60-days, and 90-days post-initial CellFX and Cryosurgical treatments. At the 30-day or 60-day follow-up visit, if any wart is classified as "not resolved" , the wart must receive an additional treatment. In case of a second or third retreatment, the subject will be evaluated by the blinded site investigator at 30-days, 60-days, and 90-days post-retreatment. Photography of the warts will be captured along with the blinded site investigator assessments at all visits.

Numbness (diminished/altered sensation) Assessment: The treating investigator will conduct a "light touch" exam to all treated areas at baseline, 7 days and 30 days post initial treatment and 30 days post retreatment(s). Light touch is tested with a cotton wisp, feather, and/or even light finger touch. The subject will be asked how one area feels compared to another.

Note 1:
Eligible warts that should be treated and do not receive a retreatment will be considered a protocol deviation. The reason(s) for not receiving an additional treatment will be collected on the electronic case report form (eCRF). These subjects will remain in the study and will be included in the ITT population.

Additionally, subjects can only receive two additional treatments or up to a maximum of three CellFX or Cryosurgical procedures.

Non-Treated Wart Criteria: Data will be collected on ineligible or non-treated warts for all enrolled subjects. Non-treated warts are defined as flat, periungual, subungual, mosaic, plantar, filiform and/or common warts that are excluded due to anatomic location. Photography of the non-treated warts will be captured at baseline and the last study visit.

3.3 Randomization

All enrolled subjects will be randomized according to the total number of warts and will receive either CellFX or Cryosurgery. Randomization will be implemented through the Electronic Data Capture (EDC) system and will be stratified by the total number of eligible warts (2-4 warts or 5-8 warts). The randomization assignment will include the type of treatment and all randomized subjects will be included in the intent-to-treat (ITT) analysis.

3.4 CellFX Procedure

The intended CellFX treatment device is described as the CellFX® System using the skin contacting component referred to as the "tip" ranging in sizes from 1.5 mm x 1.5 mm to 10.0 mm x 10.0 mm in length and width and may range from 1.0 to 3.0 mm in depth depending on the wart location and size. Each tip will be used with pre-determined energy settings displayed on the CellFX Console and are provided in **Table 1.** These energy settings do not exceed the maximum safe ranges of settings previously tested in clinical studies. A local anesthetic will be used to manage potential treatment discomfort during the CellFX treatment. All subjects will be monitored for muscle "twitching" during each CellFX treatment and the subjects will be asked whether they felt any muscle "twitch" during the treatment.

Table 1: Energy Settings per Tip Size

Tip Size (L x W, mm)	Treatment Level mJ/mm³
1.5 x 1.5	575
2.5 x 2.5	345
5.0 x 5.0	155
7.5 x 7.5	85
10.0 x 10.0	85

3.5 Standard Cryosurgical Procedure

Cryosurgery will be standardized across all investigational sites. Investigators will perform the Cryosurgical procedure using the Brymill Cry-Ac B700 Liquid Nitrogen Sprayer. Laser or curettage post Cryosurgery will be prohibited. Pulse Biosciences will provide a training video on how to perform the Cryosurgical procedure for training non-blinded treating investigators.

3.6 Site Selection

The study will be conducted at up to 10 clinical research sites. The sites will be selected based on the appropriate patient population, board certified dermatologist, and sufficient resources to support this IDE study.

3.7 Number of Subjects

Up to 150 subjects at up to 10 sites will be enrolled.

3.8 Clinical Study Duration

It is anticipated that the enrollment of subjects in this study will take approximately 3-4 months in duration. All subjects who only receive one treatment will return for follow-up visits at 7-days, 30 days, 60-days, and 90-days or up to a total of 5 study visits. For subjects who receive additional CellFX or Cryosurgery retreatments, at the 30-day or 60-day follow up visit, will return for additional follow-up for 90-days post last treatment or up to a total of 6 or 7 study visits. The total study duration will be approximately 9 months.

4.0 STUDY PROCEDURES

4.1 Screening

Recruitment will be conducted via direct communication by the investigator and/or his/her designated staff, advertisement and/or office ads. The Informed Consent discussion and signature process will be conducted by the investigator and/or designated staff. No study-specific assessments will be performed prior to obtaining consent.

A Screen Failure will be defined as a subject who did not meet one or more of the following criteria:

- Did not meet all of the inclusion and/or exclusion criteria

- Did not sign informed consent
- Did not receive a randomization assignment
- Did not undergo the randomized treatment procedure (e.g. CellFX or Cryosurgery)

A screen failure will not be assigned a subject ID and information on this subject will not be entered in the electronic database. Information will be transcribed on the enrollment/screen failure log.

4.2 Subject Selection

4.2.1 Inclusion Criteria

Candidates for this study must meet **ALL** the following criteria:

1. Subject is at least 18 and no older than 80 years of age.
2. Subject has a Fitzpatrick Skin Type I, II, III or IV.
3. Subject gives voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained.
4. Subject must comply with study procedures including all follow-up visits.
5. Subject is willing to have warts treated in a single treatment session and understands that their warts may undergo multiple treatment sessions at subsequent visits.
6. Subject must have a minimum of 2 warts and up to 8 warts to be treated.
7. Subject with a clinical diagnosis of common warts located on hands and fingers or other body areas that are not located on the scalp, nose, within the orbital region of the face, plantar, genital or periungual area.
8. For study purposes, the warts must be no greater than 3 mm in height and must not exceed 10 mm x 10 mm at their largest dimension.
9. Each wart must appear alone and discrete and not appear in clusters.
10. Each wart must have been present for at least 4 weeks.
11. Subject consents to have photographs taken of the warts.
12. Subject agrees to refrain from taking an antihistamine including those used for gastric symptoms(e.g.,Loratadine, Desloratadine, Cetirizine, Fexofenadine, Levocetirizine, Azelastine, Ranitidine, Cimetidine, Famotidine, and Nizatidine) up to 48 hours before enrollment and each scheduled follow-up visit, to facilitate an adequate wash-out period.
13. Subject agrees to refrain from using all other wart removal products or treatments (e.g. topical medication including over-the-counter medications) during the study period.

4.2.2 Exclusion Criteria

Candidates will be excluded from the study if **ANY** of the following apply:

1. Subject with more than 8 visible warts in total anywhere on the body.
2. Presence of genital or anal warts will exclude subject participation in study, including treatment of warts on other areas.
3. Periungual, subungual, mosaic, plantar, or filiform warts will not be treated in the study. However, presence of these wart types in addition to warts that meet inclusion criteria will not exclude a participant from the study.
4. Subject has an implantable electronic medical device.(i.e., pacemaker, implantable cardioverter defibrillator)
5. Subject has an active infection or history of infection in designated test area within 90 days prior to first treatment.
6. Subject is prone to Koebnerization or has any of the following conditions (e.g., psoriasis, vitiligo, lichen planus, or an autoimmune disorder of the skin)
7. Subject is not willing or able to sign the Informed Consent.

8. Subject is known to be immune compromised.
9. Subject has allergies to Lidocaine or Lidocaine-like products.
10. Subject is a member of a vulnerable population including pregnant women and individuals employed by the Sponsor, clinic site, or entity associated with the conduct of the study.
11. Have any condition or situation which, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study.
12. Use of any other investigational drug, therapy, or device within the past 30 days of enrollment or concurrent participation in another research study.
13. Subject was previously treated with CellFX for warts.

4.3 Process for Obtaining Informed Consent

Prior to undergoing any study-specific tests or procedures, the subject must sign and date the site's current and approved Institutional Review Board (IRB) informed consent form in order to be eligible for study participation. The informed consent must contain all elements required by 21 CFR Part 50 and ISO 14155:2011/AC:2011 and comply with the ethical principles of the Declaration of Helsinki.

4.3.1 Process for Obtaining Informed Consent

The patients will be informed by the Investigator or Investigator's designee that they are free to refuse participation in this research study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

The Investigator or the Investigator's designee will inform patients that their medical records will be subject to review by the sponsor or appropriate regulatory bodies. This information will be used during the analysis of the results of the clinical study, but the patients' identities will be treated as confidential. Patients will be assigned a unique study subject code that will not reveal the patients' identity, and this code will be used on all data and data collection forms during the study period. The Investigator will explain the conditions of the study, giving the patient sufficient time to ask questions and to consider whether to participate. Eligible patients who agree to participate will be asked to sign and date an IRB-approved informed consent. If the patient agrees, an IRB-approved consent form will be provided to the patient for signature and date. One copy shall be returned to the Investigator and filed in the patient's case history; the other copy is for the patient to keep.

4.3.2 Addition of New Information

Pulse Biosciences, Inc. will revise the written informed consent form whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the Investigator for approval by the IRB. After approval of the IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to the repeated. Please follow the central IRB guidelines on the process of re-consenting subjects.

4.4 Schedule of Events and Evaluations

Schedule of events and evaluations required for this study are provided in **Table 2**.

Table 2: Schedule of Events

Study Activity/ Procedure	Visit 1 Enrollment 1st TX	Visit 2 7-days Post-1st TX	Visit 3 30-days Post-1st TX	Visit 4 60-days Post-1st TX	Visit 5 90-days Post-1st TX	Visit 6 120-days Post-1st TX	Visit 7 150-days Post-1st TX
	Visit Range	±3 days	±10 days	±10 days	±10 days	±10 days	±10 days
	Consent / Wart Eval / Tx 1	Wart Eval	Wart Eval / Tx 2	Wart Eval / Tx 3	Wart Eval / Final Visit Subject Satisfaction	Wart Eval Final Visit Subject Satisfaction	Wart Eval Final Visit Subject Satisfaction
Informed Consent	✔						
Demographics, Medical HX, Fitzpatrick Skin Type, Baseline Wart Size	✔						
Photographs of Non-treated Warts	✔				✔	✔	✔
Subject Randomization	✔						
1st TX (CellFX or Cryosurgery)	✔						
2nd TX (CellFX or Cryosurgery)			✔ If required				
3rd TX (CellFX or Cryosurgery)				✔ If required			
Photographs of Pre and Post Treated Warts	✔	✔	✔	✔	✔	✔	✔
Wart Healing Characteristics	✔	✔	✔	✔	✔	✔	✔
Assessment of Numbness in the Treated Area	✔	✔	✔	✔*	✔*		
Wart Clearance/Resolution			✔	✔	✔	✔	✔
Wart Reduction Assessment		✔	✔	✔	✔	✔	✔
Pain Score/ Assessment for muscle twitching: Treated Warts	✔		✔	✔			
6 Point Subject Satisfaction Scale (SSS)					✔	✔	✔
Adverse Event Assessment	✔	✔	✔	✔	✔	✔	✔
Study Exit					✔	✔	✔

*Numbness assessment will be performed at Visit 4 for those subjects who are retreated at the 30 day follow up visit.
*Numbness assessment will be performed at Visit 5 for those subjects who are retreated at the 60 day follow up visit.

4.5 Screening / Enrollment Procedures

The following evaluations are required at the time of the subject screening/baseline visit.

4.5.1 Activities prior to or on same day as study enrollment

- Evaluation for Inclusion/Exclusion criteria.
- Collect Demographic information and medical history including but not limited to age, gender, race, ethnicity, dermatologic conditions, and Fitzpatrick skin type.
- Sign the consent form prior to any study activities.
- Receive a copy of the signed consent form.

4.5.2 Definition of Enrollment

Once the subject has been consented, randomized, and has received a CellFX or Cryosurgery procedure, the subject will be considered enrolled and each enrolled subject will be assigned a unique Study Identification Number.

4.5.3 CellFX / Cryosurgical Procedures

- Up to 8 clinically diagnosed warts that meet study criteria will be selected by the treating investigator prior to assigning warts or taking baseline enrollment photos
- The treating investigator will conduct a numbness assessment on the selected warts that will be treated
- Photographic images will be collected on all non-treated warts
- The site will log onto the Captivate EDC system. The randomization will include the type of treatment (CellFX or Cryosurgery) that the subject will be assigned
- A template may be used to determine which CellFX treatment tip size will be used for each wart – sizes range between 1.5 mm x 1.5 mm and 10.0 mm x 10.0 mm. Each wart will be numerically labeled using the Canfield two dot system
- The blinded site investigator will perform the baseline/enrollment wart(s) assessment (wart healing characteristics)
- Photographic images of each wart will be taken prior to using local anesthesia/numbing
- Local anesthesia/numbing will only be applied to warts treated with CellFX
- Each subject randomized to CellFX will be treated with pre-determined energy settings; each subject randomized to Cryosurgery will be treated as defined in **Section 3.5**
- The subject will be asked to rate his/her pain immediately after each wart treated with the CellFX and Cryosurgical procedure by using a numerical rating score
- The subjects will be asked whether they felt muscle twitching immediately after each lesion treated with CellFX
- Immediately post-procedure, a wart healing characteristics assessment will be performed by the blinded site investigator
- Photographic images of all treated warts will be taken post-treatment
- A light bandage and/or any physician recommended dressing may be applied before the subject leaves the clinic
- Any adverse events will be identified and documented with a live assessment by the blinded site Investigator

4.6. 7-Day Follow-up Visit

- Photographic images of treated warts will be taken with pre- and post- wart markings
- The blinded site investigator will perform wart(s) assessments (wart healing characteristics and wart reduction)

- Assessment of numbness in the treated area will be performed by the treating investigator
- Any adverse events will be identified and documented with a live assessment by the blinded site investigator

4.7 30-Day Follow-up Visit (CellFX/Cryosurgical Treatment #2, if required)

- Photographic images of all treated warts will be taken with pre- and post- wart markings
- All warts will be clinically assessed by the blinded site investigator (wart healing characteristics, wart clearance and wart reduction assessments)
- Assessment of numbness in the treated area will be performed by the treating investigator

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- If any wart is classified as "not resolved", a second treatment with CellFX or Cryosurgery will be performed to the previously treated wart(s)

In case of a second CellFX or Cryosurgical treatment is required:

- Local anesthesia/numbing will be applied to each wart designated for a CellFX retreatment
- Each wart designated for a CellFX retreatment will be treated using pre-determined energy settings
- Each wart designated for Cryosurgical retreatment will be performed as outlined in protocol **Section 3.5**
- The subject will be asked to rate his/her pain immediately after each wart treated with CellFX and/or Cryosurgery by using a numerical rating score
- The subjects will be asked whether they felt muscle twitching immediately after each lesion treated with CellFX
- Immediately post-procedure, a wart healing characteristics assessment will be performed by the blinded site investigator
- Photographic images of all retreated warts will be taken post-treatment
- A light bandage and/or any physician recommended dressing may be applied before the subject leaves the clinic
- Any adverse events will be identified and documented with a live assessment by the blinded site investigator

4.8 60-Day Follow-up Visit (CellFX/Cryosurgical Treatment #3, if required)

- Photographic images all treated warts will be taken with pre- and post-wart markings
- All warts will be clinically assessed by the blinded site investigator (wart healing characteristics, wart clearances and wart reduction assessments)
- Assessment of numbness in the treated area will be performed by the treating investigator (only for those subjects who received a retreatment at the 30-day follow-up visit)

- If any wart is classified as "not resolved", a third treatment with CellFX or Cryosurgery will be performed to the previously treated wart(s)

In case of a third CellFX or Cryosurgical treatment is required:

- Local anesthesia/numbing will be applied to each wart designated for a CellFX retreatment
- Each wart designated for a CellFX retreatment will be treated using pre-determined energy settings
- Each wart designated for Cryosurgical retreatment will be performed as outlined in protocol **Section 3.5**
- The subject will be asked to rate his/her pain immediately after each wart treated with CellFX and/or Cryosurgery by using a numerical rating score
- The subjects will be asked whether they felt muscle twitching immediately after each lesion treated with CellFX
- Immediately post-procedure, a wart healing characteristics assessment will be performed by the blinded site investigator
- Photographic images of all retreated warts will be taken post-treatment
- A light bandage and/or any physician recommended dressing may be applied before the subject leaves the clinic
- Any adverse events will be identified and documented with a live assessment by the blinded site investigator

4.9 90-Day Follow-up Visit

- **This is the Final Study visit for any subject for whom all wart(s) were only treated one time**
- Photographic images of all treated warts will be taken with pre and post wart markings
- All treated warts will be classified as "resolved" or "not resolved" by the blinded site investigator
- Wart healing characteristics and wart reduction assessment will be performed by the blinded site investigator
- Assessment of numbness in the treated area will be performed by the treating investigator (only for those subjects who received a retreatment at the 60-day follow-up visit)
- 6-point subject satisfaction scale (for those subjects exiting the study)
- Photographic images will be collected on all non-treated warts (for those subjects exiting the study)
- Any adverse events will be identified and documented with a live assessment by the blinded site investigator

4.10 120-Day Follow-up Visit

- **This is Final Study visit for any subject who have undergone only 2 treatments and/or the last treatment performed at the 30-day follow-up**
- Photographic images of all treated warts will be taken with pre and post wart markings
- All treated warts will be classified as "resolved" or "not resolved" by the blinded site investigator
- Wart healing characteristics and wart reduction assessment will be performed by the blinded site investigator

- 6-point subject satisfaction scale (for those subjects exiting the study)
- Photographic images will be collected on all non-treated warts (for those subjects exiting the study)
- Any adverse events will be identified and documented with a live assessment by the blinded site investigator

4.11 150-Day Follow-up Visit

- **This is Final Study visit for any subject for whom wart(s) were retreated at the 60-day follow-up**
- Photographic images of all treated warts will be taken with pre and post wart markings
- All treated warts will be classified as "resolved" or "not resolved" by the blinded site investigator
- Wart healing characteristics and wart reduction assessment will be performed by the blinded site investigator
- 6-point subject satisfaction scale
- Photographic images will be collected on all non-treated warts
- Any adverse events will be identified and documented with a live assessment by the blinded site investigator

4.12 Subject Withdrawal

A study subject has the right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitles. A withdrawn subject will be treated according to standard of medical care and will not be replaced.

5.0 BENEFITS AND RISKS

5.1 Benefits

There are no guaranteed benefits from participation in this study. Participation in the study offers another dermatological approach to accomplish the same clinical effect as the typical treatment devices currently used to treat patients with warts. The information learned from this study may contribute to the ultimate use of a safer and more effective device and the availability of the device to treat benign lesions as an alternative for use in future patients.

5.2 Risks

For detailed information on the risks of the devices used in the study procedure, including a complete list of warnings, precautions, and potential adverse events, please refer to the Instructions for Use (IFU) for the Pulse Bioscience CellFX® System.

5.3 Mitigation of Risks

As with any dermatological procedure, appropriate safety precautions will be followed. Risks observed or theoretical adverse events have been mitigated through the Instructions for Use, physician training, and patient selection in the study protocol.

All efforts will be made to minimize these risks by:

- Site Selection
- Patient Population that represents the demographics of the U.S. with a uniform

distribution of Fitzpatrick Skin Types I, II, III and IV
- Ensuring compliance to the protocol and IFU
- Study monitoring
- Safety processes-protocol adverse events reporting requirements

6.0 STATISTICAL CONSIDERATIONS

Further details of planned analyses can be found in the statistical analysis plan (SAP).

6.1 Co-primary Endpoints

Clinical acceptance of treatment with the CellFX System for common warts requires non-inferior clearance response (effectiveness), non-inferior healing processes and non-inferior rates of adverse skin changes (safety) versus cryosurgery. Because these features are critically important for treatment acceptability, this study is designed with 3 co-primary endpoints. The endpoints must demonstrate non-inferiority for the study to be considered successful. [11]

All 3 co-primary endpoints are assessed with wart as the unit of analysis, but the analyses will be adjusted for within-subject correlation. The co-primary safety endpoints are the proportion of warts with adverse events related to wound healing (scabbing, swelling, crusting, blister, scar or ulcer) at 30 days after the last treatment and adverse skin changes (the presence of hyperpigmentation, hypopigmentation or scarring) at 90 days post last treatment. The co-primary effectiveness endpoint is the proportion of warts classified as “resolved” at 30 days post last treatment.

6.1.1 Co-primary Safety Endpoints

The wound healing safety endpoint is the presence or absence of a wound healing safety event at 30 days from the last CellFX or Cryosurgical treatment as assessed by the blinded site investigator. The wound healing safety event is defined as the presence of scabbing, swelling, crusting, blister, scar or ulcer. The timing of the evaluation of this endpoint is wart specific as some warts may not require multiple treatments with CellFX or Cryosurgery. Warts will be categorized as having a primary safety event if any component (scabbing, swelling, crusting, blister, scar or ulcer) is present at the follow-up visit 30 days after the last treatment.

The statistical hypotheses to be evaluated for the wound healing primary safety endpoint are:

H_0: $p_{CellFX} - p_{Cryo} \geq 15\%$ at 30 days post last treatment, versus

H_A: $p_{CellFX} - p_{Cryo} < 15\%$ at 30 days post last treatment

Where p_{CellFX} and p_{Cryo} are the proportion of warts with a composite wound healing safety event (scabbing, swelling, crusting, blister, scar or ulcer) in each treatment group. The null hypothesis will be rejected if the upper bound of the 2-sided 95% confidence interval for the difference in proportions ($p_{CellFX} - p_{Cryo}$) is less than 15%. This approach is equivalent to a 1-sided test with a 2.5% type I error rate.

The skin change safety endpoint is the presence or absence of a skin change safety event at 90 days from the last CellFX or Cryosurgical treatment as assessed by the blinded site investigator. The skin change safety event is defined as the presence of hyperpigmentation, hypopigmentation, or scarring. The timing of the evaluation of this endpoint is wart specific as some warts may not require multiple treatments with CellFX or Cryosurgery. Warts will be

categorized as having a skin change safety event if any component (hyperpigmentation, hypopigmentation, or scarring) is present at the follow-up visit 90 days after the last treatment.

The statistical hypotheses to be evaluated for the skin change primary safety endpoint are:

H_0: $p_{CellFX} - p_{Cryo} \geq 15\%$ at 90 days post last treatment, versus

H_A: $p_{CellFX} - p_{Cryo} < 15\%$ at 90 days post last treatment

Where p_{CellFX} and p_{Cryo} are the proportion of warts with a composite skin change safety event (hyperpigmentation, hypopigmentation, or scarring) in each treatment group. The null hypothesis will be rejected if the upper bound of the 2-sided 95% confidence interval for the difference in proportions ($p_{CellFX} - p_{Cryo}$) is less than 15%. This approach is equivalent to a 1-sided test with a 2.5% type I error rate.

6.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is wart clearance, defined as "resolved" versus "not resolved" at 30 days following the last CellFX or Cryosurgical treatment (30 days post-last treatment) based on the classification of the blinded site investigator. The timing of the evaluation of this endpoint is wart specific as some warts may not require more than 1 treatment with the CellFX System or Cryosurgery. The investigator, blinded to treatment assignment, will classify each wart as "resolved" or "not resolved".

The primary effectiveness analysis will be a comparison between CellFX and Cryosurgical treatment groups based on 30-day post treatment clearance rate, defined as the proportion of warts classified as "resolved". This binary outcome classifies warts as completely clear versus not completely clear. The 30-day time-point was selected to reduce the impact of spontaneous wart resolution unrelated to treatment.

The statistical hypotheses to be evaluated for the primary efficacy endpoint are:

H_0: $p_{CellFX} - p_{Cryo} \leq -15\%$ at 30 days post last treatment, versus

H_A: $p_{CellFX} - p_{Cryo} > -15\%$ at 30 days post last treatment

Where p_{CellFX} and p_{Cryo} are the proportion of warts classified as "resolved" in each treatment group. The null hypothesis will be rejected if the lower bound of the 2-sided 95% confidence interval for the difference in proportions ($p_{CellFX} - p_{Cryo}$) is greater than -15%, which is equivalent to a 1-sided test with a 2.5% type I error rate.

6.1.3 Justification of Non-Inferiority Design and Margin

The selection of a non-inferiority design for this study is based on the choice of an active comparator (cryosurgery), the acceptability of the design to subjects seeking treatment for common warts, and feasibility considerations[11]. Although cryosurgical treatment for warts was found to have numerically higher efficacy compared to placebo[15], the many variations in timing, frequency and delivery of cryosurgery preclude a meta-analysis-based margin derivation for the technique selected for this study. Safety outcomes are inconsistently reported in publications, and no estimates of the composite endpoint of skin changes proposed for this study was available. Thus, non-inferiority margins of 15% were selected based on clinical judgement for the primary safety and effectiveness endpoints. Clinical justifications for this non-inferiority margin

for safety include existing CellFX safety data that demonstrate no serious adverse events, and a comparable safety profile compared to the predicate devices for this indication with the suggestion of faster healing. Clinical justifications for a 15% non-inferiority margin for effectiveness include consistency of treatment and ease of use with the CellFX system.

6.1.4 Type I Error Control and Study Success

Study success requires the demonstration of non-inferiority for the primary safety and efficacy endpoints.[11] Thus, no type I error adjustment for multiple testing is required. No formal hypotheses will be tested for secondary endpoints.

6.2 Secondary Endpoints

Details of the planned analyses for secondary endpoints can be found in the statistical analysis plan. No formal hypotheses will be tested for secondary endpoints. The ITT population will be used for all analyses of secondary endpoints.

1. Wart Resolution Determined by Photographic Review
   Wart resolution will be assessed by three independent observers, blinded to treatment assignment, who will classify the response for each wart based on photographs taken at 30 days post last treatment. The 3 observers will classify each wart as "resolved" or "not resolved" described in **Section 6.1.2**. The wart will be classified as "resolved" if 2/3 blinded observers classify the wart as "resolved", and as "not resolved" if 2/3 blinded observers classified the wart as "not resolved". The difference in proportion of warts classified as "resolved" will be assessed using the GEE model as described in the statistical analysis plan with the photo review endpoint replacing the endpoint derived from the blinded site investigator classification.
2. Wart Resolution after Single Treatment
   The proportion in each treatment group and the difference in proportion classified as "resolved" between CellFX and Cryosurgery assigned by the blinded site investigators at 30-days post initial treatment (as opposed to the efficacy endpoint, which is 30 days post last treatment) will be assessed using the GEE model described in the statistical analysis plan with the 30 day endpoint classified by the blinded site investigator.
3. Wart Resolution at 60 Days Post Last Treatment
   The proportion in each treatment group and the difference in proportion classified as "resolved" between CellFX and Cryosurgery assigned by the blinded site investigators from baseline to 60-days post last treatment will be assessed using the GEE model described in the statistical analysis plan with the 60 day post last treatment endpoint based on the blinded investigator classification as "resolved" or "not resolved".
4. Within Subject Effectiveness
   The ratio of cleared warts (classified as "resolved") to all treated warts will be calculated at 30 days post last treatment. The proportion of subjects with complete clearance of all warts (ratio 1) will be calculated for each treatment group, as well as the proportions with > 50% and > 75% of treated warts cleared.
5. Change in Wart Size
   The mean difference in reduction from baseline in wart size of treated warts at 30 days post last treatment will be calculated using a mixed model for repeated measures, with treatment, number of warts stratification and baseline size included as fixed effects. An exchangeable correlation matrix will be used to adjust for within-subject correlation. Least-square mean change, difference, and 95% confidence intervals will be calculated from this model.

6. Wart Resolution Over Time
   The rate of wart resolution of the treated warts over time and up to 90 days post last treatment will be calculated.

7. Lesion Observations
   Lesion observations at 7-days, 30-days, 60-days, and 90-days post last treatment between CellFX and Cryosurgery. Lesion evaluation includes the following:
   - Blister Formation
   - Bruising
   - Crusting
   - Erythema
   - Hyperpigmentation
   - Hypopigmentation
   - Scabbing
   - Scarring
   - Swelling or Edema
   - Ulceration

   The rate of each event individually and a composite of any of these events will be calculated for each treatment using the GEE model described in the statistical analysis plan, along with the 95% confidence interval as described for the primary safety endpoint.

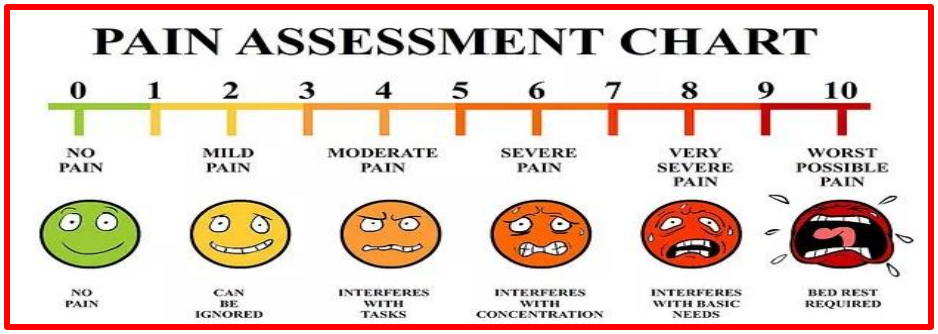
8. Satisfaction with Treatment
   A 6-point Treatment Satisfaction Scale will be used to measure subject's satisfaction with the treatment of each wart.

Table 3: Treatment Satisfaction Scale

Rating	Description
6	Very Satisfied
5	Satisfied
4	Somewhat Satisfied
3	Somewhat Dissatisfied
2	Dissatisfied
1	Very Dissatisfied

   The proportion with each response will be summarized. An analysis will be performed using the binary endpoints of satisfied ("Very Satisfied" or "Satisfied") versus not satisfied ("Somewhat Satisfied", "Somewhat Dissatisfied", "Dissatisfied", "Very Dissatisfied") to compare satisfaction across treatment groups. As with treatment-level clearance, the counts and proportions of warts categorized as satisfied will be reported. A GEE model to estimate the treatment difference in the proportion of warts with satisfactory treatment will be performed using the methods described in the statistical analysis plan.

9. Acute Pain Assessment
   Face Pain Scale with an assigned numerical rating between 0 (smiling) and 10 (crying) will be used to assess pain immediately after the CellFX and Cryosurgical treatments at Day 0, and Days 30, or 60, if applicable. The face pain scale will be assessed immediately after each wart treatment. Please see pain scale chart on the next page.



The number and percent will be tabulated for each level of pain for first, second, or third treatments separately. A histogram of scores will be produced. If the scores are not markedly skewed, mixed models using score as a continuous dependent variable and treatment as a fixed covariate (adjusted for within-subject correlation) will be used to compare the least-square mean difference in pain scores across treatment groups. A model including all treatments and adjusted for treatment number (initial, first retreatment, second retreatment) may be performed for comparison, convergence permitting.

6.3 Sample Size Determination

Power for the primary endpoints was assessed and calculated using the formula for standard non-inferiority designs[12] and then inflating the total number of warts required to account for correlation within subjects.[13] Several assumptions were estimated using a previous study of warts.[8] An average of 3 eligible warts per subject was assumed, based on the median number of observed common warts.

The efficacy response rate (classified as “resolved” versus “not resolved”) was approximated using the complete clearance rate for common warts, yielding an estimated CellFX clearance rate at 30 days post last treatment of 75.5%. The within-subject correlation for this endpoint was estimated to be 0.3. The composite wound healing safety event at 30 days post last treatment was estimated to be 37.6%, and the within-subject correlation was estimated to be 0.55. The composite skin change safety event rate at 90 days post last treatment was estimated to be 32.5%, and the within-subject correlation for this endpoint was estimated to be 0.55. For cryosurgery, the 30 day post last treatment clearance rate was estimated to be 70%[14,10] and the 90 day post last treatment safety event rate was estimated to be 40% (based on 29% hypopigmentation reported and 11% hyperpigmentation assumed).[15] The wound healing safety event rate for cryotherapy was assumed to be 43%. The within-subject correlation for warts was assumed to be identical for CellFX and cryosurgery. No type-1 error adjustment is needed to account for multiple endpoints as the effectiveness response rate and safety event rate are co-primary. In order to maintain at least 88% power to test the primary hypotheses using 15% non-inferiority margins, approximately 97 warts (33 subjects) would be required in each arm. After accounting for within-subject correlation, at least 63 subjects (189 warts) are needed in each arm. To account for approximately 15% loss to follow-up, a total of 150 subjects will be enrolled.

6.4 Populations for Analyses

The primary analysis dataset for study outcomes will be the intent-to-treat (ITT) population wherein data from all randomized warts will be analyzed based on the intended randomization assignment. The intent of this protocol is to apply up to 3 sessions of each treatment, but no warts will be

excluded from the ITT population based on the number of treatments actually received. The primary efficacy analysis will be performed using the ITT population. A modified intent-to-treat population will include all warts that received at least one treatment, and the primary efficacy analysis will also be calculated for this population for comparison. The modified ITT population will be the analysis population for the primary safety endpoint.

Study outcomes will also be analyzed using a per-protocol (PP) population. The PP population includes all subjects who had no pre-specified inclusion and exclusion violations, received either CellFX or Cryosurgery, and repeated the treatments per protocol for any warts classified as "not resolved" at the 30-day and/or 60-day visit.

6.5 Sub-Group Analyses

Primary and secondary endpoints will be evaluated for the ITT and PP populations, as well as analyzed in strata based on the following sub-groups:

- Number of treated warts (2 to 4 or 5-8)
- Age
- Prior treatment for treated warts
- Gender
- Clinical Site
- Treatment Energy Level
- Size of CellFX Treatment Tip
- Total Energy Density
- Number of Treatments

These analyses are meant to assess consistency of treatment effects only, and this study is not powered for inference within subgroups.

6.6 Missing Data

All possible efforts will be made to minimize missing data in this study. Based on previous studies, any missing data that does occur is likely due to missed follow-up visits, so all study warts for subjects with a missed visit will have missing endpoints. The timing of the co-primary effectiveness and wound healing events at 30 days should minimize missed visits related to study fatigue. The generalized estimating equation model can yield valid results when data are missing completely at random, and the sensitivity analysis using a mixed model can yield valid results when data are missing at random. Additionally, the sensitivity of the final results to missing data for the skin change safety outcome will be examined by comparing the primary outcomes to the results using a longitudinal model with both the 30-day, 60-day and 90-day post treatment results, and a tipping-point analysis will be performed for the endpoints at 90 days to determine whether the missing data could change the inference compared to the primary models.

7.0 EXPLORATORY ENDPOINTS

The primary outcomes are wart-level endpoints that account for within-subject correlation. The exploratory endpoints are patient-level calculations of these endpoints, which lack sufficient statistical power for formal hypothesis tests.

7.1 Exploratory Efficacy Endpoint

7.1.1 Subject-level clearance of all warts at 30 days post last treatment
The number and percent of subjects with all warts "resolved" at 30 days post last treatment and the number of subjects with at least 1 wart "not resolved" at 30 days post last treatment will be calculated.

7.2 Exploratory Safety Endpoints

7.2.1 Subject-level wound healing adverse events at 30 days post last treatment
The number and percent of subjects with any wound healing event in any wart (composite of scabbing, swelling, crusting, blister, scar or ulcer) and no wound healing events in any wart at 30 days post last treatment will be calculated.

7.2.2 Subject-level skin change adverse events at 90 days post last treatment
The number and percent of subjects with any skin change event in any wart (scar, hypopigmentation or hyperpigmentation) and no skin change events in any wart at 90 days post last treatment will be calculated.

8.0 CLINICAL PHOTOGRAPHY

The Canfield Handheld 2D Imaging System and the Canon SL2 camera with ranging lights and MM Scale will be provided by the photography vendor, Canfield Scientific, Inc. (Parsippany, NJ) to document Investigator selected warts at enrollment, post treatment and at 7-days, 30-days, 60-days, and 90- days following the last CellFX treatment or Cryosurgical procedure. All consenting subjects' study photographs will be captured using the equipment, supplies, and guidelines provided by Canfield to have consistent visual representation of the AD appearance during the study treatment. Images will be captured, viewed, and uploaded using Canfield Capture software which automatically checksums, encrypts, packages, and transfers the data to a secure, validated, and compliant web server hosted by Canfield. Detailed instructions for all aspects of the photography procedures will be supplied separately in the investigator user manual to be provided by Canfield.

9.0 INDEPENDENT PANEL REVIEW

To meet the requirements of the secondary endpoint, an Independent Panel will evaluate the treatment response from each study device. In order to enhance objectivity and reduce potential for bias, the Panel shall be independent of the Sponsor as well as the study sites/investigators.

The Panel is made up of three clinicians with pertinent expertise in dermatology who are not participants in the study and who do not have any other real or potential conflicts of interest. The Panel will be provided photographs of all treated warts at baseline and 30 days post last treatment and will be trained on specific criteria used to classify the response to treatment as noted in study **Section 6.1.2**.

An Independent Panel review will be conducted by Canfield Scientific based on prior standard methodology.

10.0 ADVERSE EVENTS

Pulse Biosciences will classify each reported Adverse Event according to ISO 14155:2011. All protocol specific AEs, whether device-related or not, will be recorded on the AE case report form and reported. Data to be collected will include the description of the AE, onset, and resolution dates (or whether the AE is ongoing), severity, management/treatment, outcome, and determination of the relationship to the device and/or procedure. All AEs related to a treated wart should be reported and classified by the blinded site Investigator and to be followed by the treating Investigator to determine the relationship of the AE to the device or the study procedure.

All AE information will be collected at each study visit from enrollment through 90 days following the last CellFX and Cryosurgical procedures. All AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes, and the overall clinical outcome has been ascertained).

When reporting AEs/SAEs, the Investigator should include the following information:

- Description of event
- Onset of event
- Duration of event
- Severity
- Relationship to device or procedure
- Action taken
- Subject outcome

Severity describes the intensity of an event and will be assessed as:

- **Mild**: The AE does not interfere in a significant manner with the subject's normal functioning level.
- **Moderate**: The AE produces some impairment of function but not hazardous to health.
- **Severe**: The AE produces significant impairment of function or incapacities and/or it is a hazard to the subject.

Relationship to device or procedure will be assessed as:

- **Unlikely**: There is no indication that the AE was caused by the investigational or standard of care device.
- **Possibly**: It cannot be excluded that the AE was caused by the investigational or standard of care device.
- **Likely**: A causal relationship between the investigational or standard of care device and the AE is at least a reasonable possibility; i.e. there is evidence or argument suggesting a causal relationship.

10.1 Adverse Event Definitions

10.1.1 Adverse Event (AE): (*ISO 14155:2011 3.2*)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
***For the purposes of this protocol, only dermatologic AEs will be reported to the Sponsor**.

10.1.2 Adverse Device Effect (ADE): (*ISO 14155:2011 3.1*)
Adverse event related to the use of an investigational medical device
NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

10.1.3 Serious Adverse Event (SAE) *(ISO 14155:2011 3.37)*
Adverse event that
a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.
NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

10.1.4 Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36)
Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event

10.1.5 Unanticipated Adverse Device Effect (UADE): *(21CFR812.3)*
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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2 Device Deficiencies (*ISO 14155:2011 3.15*)

10.2.1 Definitions
Device Deficiency is an Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

NOTE*:* Device deficiencies include malfunctions, use errors, and inadequate labelling.

Device Malfunction is a failure of the study device to perform in accordance with its intended purpose when used in accordance with the instructions for use or study protocol.

10.3 Safety Reporting Requirements

The following sections will summarize the safety reporting requirements for the Sponsor and site Investigators. The NP-WC-015 IDE study will also include an early safety assessment on the first 20 subjects treated with CellFX.

10.3.1 Blinded Live Assessment of Adverse Events

The Blinded Investigator from each of the clinical research sites will conduct a live safety assessment on all enrolled subjects at each study visit. The blinded investigator will ensure that all adverse events that are related to the stopping rules in **Section 10.3.2.1** are reported to the Sponsor within three calendar days.

10.3.2 Safety Monitor

The Sponsor will select an independent Safety Monitor to oversee dermatological adverse events. The First 20 subjects who are treated with CellFX will have their data analyzed when they complete the 30 day follow up visit or 30 days post initial treatment. A table describing the 30 days status of the subjects will be prepared. Adverse events will be presented as the percentage of subjects who experience an event, the number of events and the event rate per 30 days. The photographic images of the dermatological adverse events will also be presented to the Safety Monitor.

10.3.2.1 Stopping Rules

a) Full dermal thickness ulcer in any subject, of any duration;

b) Any depth ulcer or erosion lasting ≥30 days, in more than 2 of the first 20 subjects treated with CellFX or more than 10% of subjects treated after the first 20 subjects; and

c) Scab or crust that is so severe at the 30 day visit that it would preclude additional treatment that day, in more than 2 of the first 20 subjects treated with CellFX or more than 10% of subjects treated after the first 20 subjects.

10.3.3 Investigator Responsibilities

The Investigator is responsible for reporting adverse events, including device malfunctions and device deficiencies as defined in the protocol. **Table 4** summarizes the time sensitive requirements for reporting adverse events and device deficiencies. The Sponsor is the contact person for these reporting requirements.

Table 4: Investigator Responsibilities for Submitting Adverse Events to the Sponsor

Type of Adverse Event	Reporting Timeframe
*Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE) and dermatological events as described in section 9.3.2.1	As soon as possible, but in no case later than 3 calendar days after the clinical site first learns of the event or of new information in relation with an already reported event
**Serious Adverse Events (SAE)	As soon as possible, but in no case later than 3 calendar days after the clinical site first learns of the event or of new information in relation with an already reported event
Adverse Device Effects (ADE)	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the event or of new information in relation with an already reported event
All other AEs	Submit in a timely manner after the clinical site first learns of the event

Type of Adverse Event	Reporting Timeframe
**Device Deficiency with SADE potential	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the deficiency or of new information in relation with an already reported deficiency
All other Device Deficiencies	Submit in a timely manner after the clinical site first learns of the deficiency

*The Sponsor will report the results of an evaluation of an unanticipated serious or serious adverse device effect to the FDA and all reviewing IRBs and investigators within 10 working days after the Sponsor first received notice of the adverse effect per 21 CFR 812.150.

**It is the responsibility of the investigator to inform their IRB of serious adverse events and device deficiencies as required by their IRB guidelines.

11.0 STUDY MANAGEMENT (SPONSOR RESPONSIBILITIES)

11.1 Sponsor Ethical and Regulatory Considerations

As the Sponsor of this clinical study, Pulse Biosciences has the overall responsibility for the conduct of the study, including assurance that the study meets US federal and local regulatory requirements appropriate to the conduct of the study and is conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The study sponsor will adhere to sponsor general duties as described in ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, and CFR Part 812, 50, 56, 54 and the World Medical Association Declaration of Helsinki.

To maintain confidentiality, all evaluation forms, reports, and other records will be identified by a unique subject identification code (ID number). All study records will be kept in a locked file cabinet and clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

General Duties

Pulse Biosciences will ensure that the application is submitted to the appropriate regulatory authorities, obtaining copies of IRB approvals and ensuring documentation of IRB approvals prior to the shipping of devices, ensuring proper clinical site monitoring, ensuring patient informed consent is obtained, providing quality data that satisfies regulations and informing the Investigators and IRBs of unanticipated adverse device effects, events, and deviations from the protocol as appropriate.

11.2 Selection of Clinical Sites

The primary requirements of site and Investigator selection and continued participation in the Trial include adequate experience, commitment to safety, consistency in adherence to the protocol, and patient volume. The clinical site must have facilities that are capable of processing patients in the manner prescribed by the protocol.

The study sponsor, Pulse Biosciences, and its designees will select qualified Investigators, ship, or deliver devices only to participating Investigators, obtain signed study agreements, and provide Investigators with the information necessary to conduct the study.

11.3 Site Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor designee. The Investigator is responsible for ensuring that his/her staff conduct the study according to the protocol. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present a formal training session to study site personnel which will review the Instructions for Use of the device, the Investigational Plan, instructions on data collection, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor or designee through the regular site monitoring.

11.4 Investigator Training

The Sponsor will provide appropriate Investigator training on the use of the CellFX System, Handpiece, and Treatment Tips. Training will take place prior to the initiation of the clinical investigation. Training will address topics including indications for use of the device, management of complications, and instructions to subjects. Training will be documented for each physician on a training log, signed by both the physician and training representative.

All treating investigators will be required to watch a training video on how to perform the Cryosurgical procedure for this study.

Canfield Scientific, Inc. will provide training to the sites on the photography equipment and services as described in **Section 8.0**.

11.5 Monitoring of Study Sites

11.5.1 Monitoring Methods

Monitoring functions for this study will be conducted by Pulse Biosciences. The study will be monitored to ensure that the protocol, applicable regulations, and Good Clinical Practice Guidelines are followed. The study monitor will ensure that the rights and well-being of subjects are protected, and the clinical trial data are accurate, complete, and verifiable. Specific monitoring requirements are detailed in the study specific Monitoring Plan.

Prior to subject enrollment, the Sponsor will obtain the essential regulatory documents required to initiate the study. The Sponsor will be responsible for the review and approval of the following essential documents:

- Current Protocol Revision
- Investigator Agreement
- IRB approval letter for the protocol and consent form
- IRB approved consent form
- IRB membership roster or assurance number

Copies of file documents will be maintained by the Sponsor.

11.5.2 Periodic Monitoring Visits (Onsite and Remote)

Periodic monitoring visits will be made at the investigational site throughout enrollment of the clinical study to assure that the Investigator obligations are fulfilled, and all applicable regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable; the protocol and investigational plan are being followed, the IRB/HREC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and

timely reports have been made to the Sponsor and the IRB, device and device inventory are controlled and the Investigator is carrying out all agreed activities. The monitor will verify accuracy of CRF or EDC completion against source documents maintained at the site.

During monitoring visits, the Monitor will perform a review of study eligibility, Inclusion/Exclusion criteria, informed consent, all reports of device malfunction, all events meeting criteria for serious adverse event reporting as well as safety and efficacy endpoints.

Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits.

The monitor will ensure that Investigators are aware of the regulatory requirement to maintain information in the study subject's medical records which corroborate data collected on the CRF or EDC system. To comply with these regulatory requirements, the following information will be maintained and made available as required by the sponsor and/or regulatory inspectors:

The monitor will compare key variables (demographics, inclusion/exclusion criteria, and safety) on the CRFs or EDC database with each subject's source documents. Any discrepancies will be noted and resolved.

11.5.3 Site Close-out Visit

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits and the CRFs or EDC and queries have been completed), the Sponsor will notify the site of closeout and a study closeout visit will be performed. All CRFs, unused study devices, and any unused study materials will be collected and returned to the Sponsor. The Monitor will ensure that the Investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

11.6 Protocol Deviations

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the Investigational Plan or the Investigator Agreement.

Deviations shall be reported to the Sponsor regardless of whether medically justifiable, pre-approved, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the provided protocol deviation form. Non-subject specific deviations will be reported to the sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.
Good Clinical Practice (GCP) regulations require that Investigators maintain accurate, complete, and current records, including documents showing the dates and reasons for each deviation from the protocol.

11.7 Study Completion

The study is considered completed after all subjects have undergone all of their protocol required follow-up visits, all eCRFs have been submitted, all queries have been resolved, and all action items have been closed. All unused study materials and study devices will be collected and returned to Pulse Biosciences or appropriately discarded as per instruction. After study closure, a final report will be completed.

11.8 Audits / Inspections

Pulse Biosciences, national/international regulatory authorities and IRBs may conduct initiated audits or inspections at the study sites during the course of, or after completion of the study. The Investigator shall allow access to the original medical records and provide all requested information.

11.9 Publication Policies

Publications based on the results of the study will follow the process outlined in the Investigator Agreement. The study will be registered on www.clinicaltrials.gov.

11.10 Data Management

Pulse Biosciences will be responsible for database creation and validation. Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data from the analysis for each subject will be determined by appropriate clinical and statistical personnel. All exclusions related to either safety or efficacy will be documented in subject listings.

11.11 Case Report Forms /Transmission of Data

All required data for this study will be collected via web-based electronic data capture (EDC) system and entered in electronic Case Report Forms (eCRFs). A unique study identifier will be assigned to each study subject. The database will contain only the study identifier to identify the subject.

Required data will be recorded on the appropriate electronic Case Report Forms at the time of or as soon as possible after the subject visit. This will enable timely monitoring visits.

Any data discrepancies identified during data review or a monitoring visit will be queried by Pulse Biosciences and must be resolved by the site staff and Investigator in a timely manner.

11.12 Data Retention

Pulse Biosciences will maintain copies of correspondence, data, shipment of devices, adverse device effects, Investigator agreements and other records related to the clinical study. All study records and reports will remain on file at the sites for a minimum of 2 years after completion of the Study and will further be retained in accordance with local guidelines as identified in the clinical study agreement. Study records are to be discarded only upon notification by the study Sponsor. The Investigator must contact the study Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be contacted if the Investigator plans to leave the investigational site. All required data for this study will be collected on standardized CRFs or an electronic data capture system. All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The Principal Investigator consents to visits by the staff of the Sponsor and its authorized representatives and the U.S. Food and Drug Administration or any other local governmental body to review the study subjects' medical records including any test or laboratory data that might have been recorded on diagnostic tests media (e.g., photographs, etc.).

12.0 INVESTIGATOR RESPONSIBILITIES

The role of the Principal Investigator is to implement and manage the conduct of the clinical study at their site, as well as ensure data integrity and the rights, safety, and well-being of the participating subjects.

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice. The Investigator will provide current copies of the study protocol to all Sub-Investigators or other site personnel responsible for study conduct.

Upon completion or termination of the study, the Investigator will submit a final written summary to the IRB. The summary should be submitted to the Sponsor within three (3) months of study completion or termination. The Investigator will provide the Sponsor with copies of all IRB/HREC actions regarding the study.

12.1 IRB Approval and Informed Consent

The clinical study must be reviewed and approved by the IRB before subject enrollment may begin. All proposed changes to the investigational plan must be reviewed and approved by Pulse Biosciences. Prior to shipment of study devices, a signed copy of the IRB Committee approval letter identifying the clinical study must be submitted to Pulse Biosciences, signifying study approval. Investigators are responsible for obtaining and maintaining approval of the study by the IRB.

Written informed consent is mandatory and must be obtained from all subjects prior to performing any study procedures in this clinical study. Pulse Biosciences will provide the site with a Sponsor approved consent template. Each site is expected to modify the template, if necessary, to meet their facilities requirements. Modified ICF templates must be reviewed by the Sponsor prior to submission to their IRB.

Informed consent must be obtained and shall inform the subject as to the objective and procedures of the study and possible risks involved. The subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. The clinical study informed consent must be used in addition to any institutional standard consent form for participation in clinical research. The institutional standard subject consent form does not replace the study consent form.

It is the responsibility of the investigator to obtain both an authorization for patient health information and study consent.

The IRB approved Informed Consent Forms must be retained at the site along with the other investigational case report forms or source documents. A signed copy of the consent form must be given to each subject enrolled in the study.

12.2 Data Collection and Reporting

Case report forms or source documents will be used to record demographic, procedural, and follow-up data, as well as any adverse events which may occur during the study period. The AEs and incidence of morbidity and mortality will be reviewed with Investigators to assess the safety of the device and the procedure.

The Investigator must comply with the safety reporting requirements specified in (**Section 9.3**)

Qualified study staff at each clinical site will perform primary data collection drawn from source-document (hospital or clinic chart) reviews. The Monitor will perform clinical monitoring, including review of CRFs, source documents and/or Electronic Data Capture (EDC) system with verification of study eligibility, informed consent process, scheduled follow-up visits and AEs to the source documentation.

12.3 Source Documents / Records Retention

The investigator shall maintain accurate, complete, and current records relating to the investigator's participation in an investigation including records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, progress notes of the physician, the individual's hospital or clinic chart(s), and the nurses' notes. Such records shall include:

1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each subject shall document that informed consent was obtained prior to participation in the study.

2. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

Investigator files containing all records and reports of the investigation should be retained for a minimum of 5 years after the completion or termination of the investigational study or until two years after they are no longer needed to support product approval. They may be discarded upon notification by Pulse Biosciences. To avoid any error, the Investigator should contact Pulse Biosciences before destroying any records and reports pertaining to the study to ensure they no longer need to be retained.

12.4 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all study devices. When the enrollment is complete, the Investigator shall return any unused devices to the Sponsor. At the completion of the study, all devices shall be returned to the Sponsor. The Investigator’s copy of the Device Accountability Log must document devices that have been returned to the sponsor.

The device accountability log will include records of receipt, use or disposition of a device that relate to:

1. The type and quantity of the device, the dates of its receipt, and the lot number.
2. The names of all persons who received, used, or disposed of each device.
3. Why and how many device(s) were returned to the Sponsor, or otherwise disposed of.

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14.0 APPENDICES

14.1 Appendix A: Patient Informed Consent

14.2 Appendix B: Case Report Forms

APPENDIX A: Patient Informed Consent will be provided as a separate attachment

APPENDIX B: Case Report Forms will be provided as a separate attachment