Clinical Investigational Plan

Study Title: A Multicenter, Prospective, Randomized, Comparison IDE Study between the Pulse Biosciences CellFX® System and Electrodessication (Hyfrecator Electrosurgical) for the Treatment of Sebaceous Hyperplasia (SH) Lesions

Short Title: Comparative Study between CellFX and Electrodessication in SH Lesions

Protocol No: NP-SC-012

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Study Sponsor:

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TABLE OF CONTENTS

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1.0 INTRODUCTION AND BACKGROUND

1.1 Sebaceous Hyperplasia Lesions

Sebaceous hyperplasia (SH) are benign lesions frequently seen by dermatologists in everyday practice. SH lesions commonly manifest as white or yellowish, soft, small papules on the face, such as on the nose, cheeks and/or forehead.[1] These benign SH lesions are more likely to transpire in middle-aged and older individuals but can show up at any age.[2] Although it may be difficult for a non-dermatologist to distinguish the condition from acne, there is a predominant characteristic which sets the two apart. A whitehead or blackhead will usually have lifted centers, but the bumps caused by sebaceous hyperplasia have a slight indentation in the center. These lesions are typically small and cause no pain. Many individuals with oily or combination skin may notice the lesions arise in small clusters or independently.[2]

They occur when hyperactive sebaceous glands produce an excess amount of an oily lubricant called sebum, which pushes up on the skin surface. Sebaceous glands are holocrine glands which are composed of acini attached to a common excretory duct.[2] As sebocytes, cells which form the sebaceous gland, differentiate and mature, they accumulate increasing amounts of lipid and migrate towards the central excretory duct. The mature sebocytes conclude their life cycle at the central duct and fragment, releasing lipid contents as sebum.

Sebaceous glands are androgen sensitive,[1] and, although the amount of sebaceous glands remains roughly the same throughout life, their activity and size vary based on age and circulating hormone levels. Sebocytes contain androgen-metabolizing enzymes such as 5-alpha-reductase type I which metabolize weak circulating androgens into more potent ones, such as dihydrotestosterone.[1,3] Those in turn bind to receptors within sebocytes, triggering an increase in size and metabolic rate of the sebaceous gland. The activity of 5-alpha-reductase has shown to be higher in the scalp and facial skin than in other areas, such that testosterone and dihydrotestosterone stimulate more sebaceous gland proliferation in these regions.[4] As androgen levels dwindle with age, the sebocyte turnover slows down.[1] A decline in circulating androgen results in smaller sebocytes with larger nuclei and decreased lipid content, which migrate slowly through the sebaceous gland.[4] As migration and disintegration of the sebocytes slows, the gland becomes enlarged, with a widened sebaceous duct and an increased number of basal cells. Facial papular sebaceous hyperplasia is thought to be caused by a reduction in the circulating levels of androgen associated with aging.[1]

Various factors increase the probability of developing sebaceous hyperplasia. Individuals with suppressed immune systems and those taking immunosuppressant medication, cyclosporine A, may have a higher risk of developing sebaceous hyperplasia.[2] Individuals may be more likely to develop sebaceous hyperplasia if they have a family history of it. Continual sun damage can also worsen symptoms or cause them to appear early on.[5] Ultraviolet radiation is considered only a cofactor,[3] because sebaceous hyperplasia occasionally occurs on areas of the body where sunlight is not a relevant issue.[5]

The most common reason for having SHs treated or removed is due to patients not liking the cosmetic appearance. Since the lesions will not disappear on their own, dermatologists can remove them for cosmetic reasons and/or because of functional complaints.[2] Some medications and home remedies may reduce the appearance of lesions or reduce sebum production. The purpose of this protocol is to compare NPS technology, using the CellFX® System to Electrodessication for the treatment of SH lesions from the face of healthy adult subjects.

1.2 Current Care

Treatment is usually aimed to remove the SH lesions as well as provide improvement to overall cosmesis of the face. Various modalities are available to improve the appearance of SH lesions; however, long-standing eradication of SH remains difficult.[2] These lesions are a common cosmetic concern but are difficult to treat, as the entire sebaceous gland needs to be destroyed to prevent recurrence[2] and most existing modalities require multiple sessions or applications for complete clearance and/or prevention of recurrence.

Current therapies available for the treatment of SHs include topical and mechanical modalities. Topical therapies include retinoids, facial peels, and antiandrogen medications. Locally destructive or mechanical therapies include laser therapy, photodynamic therapy, cryotherapy, Intralesional electrodesiccation, and excisional surgery. Each treatment depends on the size, location, number, type, age of the patient, risk of scarring and patients' commitment to the therapy. Risk of permanent scarring must be considered when treating benign lesions. Another important consideration using current therapies is post-inflammatory hyperpigmentation (PIH) treatment especially in patients with higher Fitzpatrick skin types like Types III, V, or VI.

1.3 Non-Surgical Approach

Oral Medication

Prescription of medicine with an anti-androgen effect that reduces the production of testosterone and other hormones can be used but are usually kept as a last resort. Examples of these medications are spironolactone or flutamide. Prescription oral retinoids are also available as an option that temporarily shrinks sebaceous glands, but sebaceous hyperplasia lesions return after discontinuing therapy. Isotretinoin (13-cis-retinoic acid) has been used for sebaceous hyperplasia because of its ability to temporarily shrink sebaceous glands.[6,7] Oral isotretinoin has proven effective in clearing some lesions after a few weeks of treatment, but lesions often reappear upon discontinuation of therapy. However, several cases of sustained improvement or clearance after cessation of therapy were reported in 2016, following cumulative doses ranging from 40-60 mg/kg.[6] Studies have shown that it decreases sebaceous gland size and sebum production and may inhibit sebaceous gland differentiation and abnormal keratinization.[7] The most common side effects of oral medication such as isotretinoin include eye irritation, joint pain, nosebleed, rash, skin infection, and tenderness of the bones.

Topical Treatments

Superficial SH lesions can be treated by carefully applying topical agents for a set duration of time. Over-the-counter products containing agents such as retinoid (vitamin A) or azelaic acid have been reported to helps with visibly reducing the lesion without completely removing the lesion. If the treated raised SHs are not clear, more topical agent may be applied, as long as the treatment area is not irritated. The most common side effects include itching, stinging, crusting, swelling, redness, and scaling.

Facial Peels

Chemical peels using salicylic, bichloroacetic (BCA), also known as dichloroacetic (DCA), or trichloroacetic (TCA) acids blanch lesions, destroying the tissue. The permanency of this choice depends on the percentage of the acid used, as the complete destruction of the gland is necessary to become a permanent fix. A salicylic peel is a common procedure since its beta hydroxy keratolytic action cleans the surface and breaches deep into the pore, infiltrating oil buildup in order to unclog impactions.[8,9] Its anti-inflammatory benefits help diminish the appearance of the nodules.[8,9] Common side effects may be temporary, and include redness, dryness, stinging or burning, and slight swelling.

Physical Destruction

Liquid Nitrogen Cryotherapy

For common SHs in adults and older children, cryotherapy is a standard treatment and can be performed in the physician's office. Cryotherapy involves exposing an SH lesion to extremely cold temperatures using liquid nitrogen. The application usually takes less than a minute and may require multiple treatment sessions. The sebaceous glands are damaged by controlled cooling at the skin surface, with no nonspecific injury to the surrounding tissues.[1] The direct cooling will disrupt the cellular architecture, membrane integrity, and enzymatic activity in the glands.[1] Once the growth freezes, it tends to fall off within days. Treatment results may vary with this procedure; past research has shown that pigmentary changes are common, as well as erythema, edema, crusting, and blister and/or bulla formation.[1] The pigmentary changes that arise due to treatment is shown to be dependent on the patient's Fitzpatrick Scale ranking.

Laser

Liquid nitrogen cryotherapy and other surgical methods are useful in treating these lesions but are difficult to tolerate in patients who have large numbers of lesions requiring treatment. Sebaceous hyperplasia can be removed using a laser (i.e. with argon, carbon dioxide, or pulsed-dye laser), an intense beam of light that burns and destroys the growth.[3,10] Argon and carbon dioxide lasers act in an ablative manner similar to methods of mechanical destruction.[3] More focused, mid-infrared lasers vaporize water in tissues leading to thermal destruction of the surrounding tissue plus alterations in sebaceous gland structure and function[3]. Prior to laser treatment, the dermatologist may numb the SH lesion with an anesthetic injection. With the help of the laser, the lesion shrinks in size by breaking down the sebum.[10,14] Post laser treatment a crust appears and tends to fall off after a week. Treatments may lead to transient side-effects including infection, erythema, crusting and discoloration. The pigmentary changes that arise post-treatment may be dependent on Fitzpatrick Scale ratings.

Photodynamic Therapy

Due to the well-known accumulation of porphyrins in the sebaceous glands, photodynamic therapy (PDT) may be an effective treatment option.[11] PTD is a light-emitting therapy in which the SH lesions are treated with combined use of 5-aminolevulinic acid and visible light. More specifically, the skin is pre-treated using a photosensitizing, prescription gel (5-aminolevulinic acid (ALA), that reacts with the light source, either IPL or a 405-420 nanometer blue light laser.[11] Generally, this mode of treatment will require several treatment visits, such as 4 sessions at 4-week interval when using the 405-420nm blue light laser.[11] Adverse effects of photodynamic therapy in treating SH were mainly temporary erythema and edema, but some treated lesions underwent burning and blistering before healing.[10]

Electrosurgery

Electrosurgery using intralesional electrodesiccation is an available treatment for common SHs and it involves numbing the growth with an anesthetic prior to using an electric current to destroy the growth. This procedure uses a pencil-shaped metal instrument or needle to destroy or heat the growth via a high-frequency electric current that is applied within the lesion.

Curettage

Curettage involves scraping off the SH with a sharp knife or small, spoon-shaped tool. Curettage may be combined with electrocautery to prevent regrowth of the lesion and it can also be used in conjunction with liquid nitrogen to produce better results than just using liquid nitrogen alone. The general purpose of curettage is to scrape an area free of undesirable tissue.

When the two procedures are combined, first, a curette is used to scrape off undesirable cells down to the level of uninvolved tissue. This is then followed by electrosurgery to widen the region of cell destruction and removal, and to cauterize the wound in order to limit bleeding.

The healing process for such procedures can take a few weeks or longer, depending on the size of the wound and other factors. A scab forms and will generally fall off in a few days. The procedure can cause post-inflammatory hyperpigmentation in the treated area and although electrocauterization provides complete removal, but there is no guarantee that another lesion will not develop nearby. Risk factors include reopening of wounds, scarring, temporary or permanent nerve damage (in regions with extensive nerves), subcutaneous bleeding and/or infections.

1.4 Surgical Approach

Shave Biopsy / Excision

A superficial shave biopsy is a commonly used technique which can be used on raised lesions that are predominantly epidermal without extension into the dermis.[12] A superficial shave removes a thin disk of tissue, typically by scalpel, Dermablade (a double-edged razor blade), or scissors.[12] The shave biopsy provides histologic material for accurate diagnosis and removes the lesion in a cosmetically acceptable manner at the same time.[12] After a shave biopsy is obtained, a curette can be employed to smooth and remove any remaining keratotic material. Sutures are often not necessary and re-epithelialization should occur within a few days.

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 627 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 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 that resolved within days of the procedure.

Published data from the initial use of Nano-Pulse Stimulation (NPS) technology for the treatment of sebaceous hyperplasia (SH) conducted under Protocol NP-SH-006[13] (June 28, 2018 through November 29, 2018) in 72 subjects (Fitzpatrick Skin Types I-IV) and 226 primary treated lesions along with 18 retreated lesions at 30-days (n=244) demonstrated greater than 99% investigator rated clearance efficacy with 1 to 2 NPS sessions at 60-days post-last NPS. Efficacy was reported at 91% of treated lesions being rated clear or mostly clear at 60-days post-last NPS with a single treatment. There were no serious adverse events reported. However, in some subjects there were lesion observations of mostly mild post-treatment hyperpigmentation of 45% and skin surface irregularities of 33%. In comparison to the literature, these observations are routinely observed when using treatment modalities like laser with reported hyperpigmentation rates ranging from 30-60%[15-16] and volume irregularity of 24%.[17]

In a second pivotal SH study with dose-response design[18] under Protocol NP-SH-009 (July, 18, 2019 through February, 19, 2020) using much lower energy profiles (30, 60 and 115 mJ/mm^3) as compared to NP-SH-006, showed efficacy rates of 82%, 81%, and 92%, respectively in 116 subjects (Fitzpatrick Skin Types II-IV) and 477 lesions at 60-days post-last NPS. Lower settings more frequently warranted another NPS session, with respective retreatment rates of 27%, 12% and 14%. For lesions treated once, lower settings showed reduced efficacy (54%, 70%, 78%) but also reduced transient PIH rates (14%, 8%, 36% - typically mild) and transient focal surface irregularities (2%, 1%, 10% - also typically mild) that resolved as normal dermis filled in the area where the SH lesion cleared. Overall subject satisfaction was relatively high for all lesions rated clear and mostly clear and treated with the 2.5x2.5mm tip at the two lowest settings with 85% of lesions rated satisfied and mostly satisfied. This study demonstrated the use of low energy settings in a single NPS session to clear a majority of lesions with a low rate of transient skin effects, while a second NPS session achieves greater than 80% clearance.

This new SH comparison study under Protocol NP-SC-012 will evaluate safety and efficacy in a split face design using the CellFX System and pre-defined energy profile for all primary and secondary treatments based on Fitzpatrick Skin Types and tip size. The comparator group will be treated with intralesional electrodesiccation with a needle-shaped electrode for the treatment of SH lesions.

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, Electrodessication (Hyfrecator electrosurgical unit) performed with a non-insulated needle-shaped electrode, for the treatment of SH lesions 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)

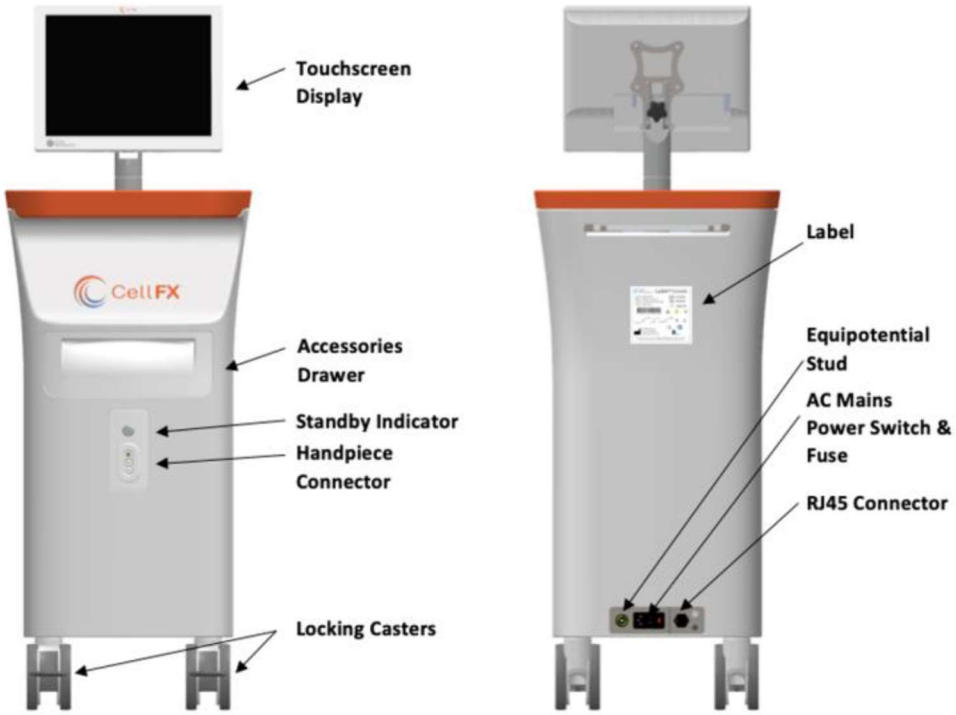


Figure 1: CellFX Console

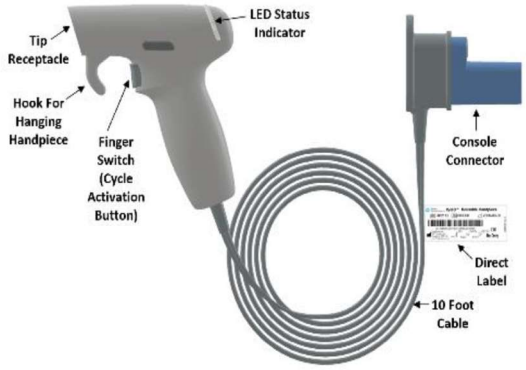


Figure 2: CellFX Handpiece

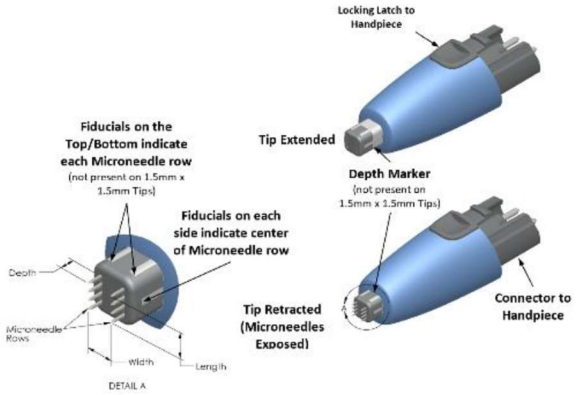


Figure 3: CellFX Tip

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 benign lesions like sebaceous hyperplasia

2.3 Electrosurgical System

The comparator device that will be used in this study is the CONMED Hyfrecator® 2000 which has the ability to connect with a 3/32" shaft non-insulated epilation needle electrode to heat and desiccate SH lesions. All physicians are required to use the same needle electrode (e.g. Segal® Reusable Electrodes, Epilation Needle).

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 Electrodessication (Hyfrecator electrosurgical unit) performed with a non-insulated needle-shaped electrode for removal and treatment of SH lesions in healthy adult subjects.

The following objectives are to evaluate the overall response to CellFX and Electrodessication:

- SH lesion response after treatment vs. the pre-treated appearance of the same lesion
- SH lesion response at various points in time over several weeks following the initial treatments vs. the same pre-treated lesion
- Document the condition of skin in the treatment areas (erythema, swelling, crusting, hyperpigmentation, hypopigmentation, etc.) over the course of various time periods post-initial CellFX and Electrodessication treatment, 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 multicenter, single-blinded, prospective, randomized, comparison IDE study between CellFX System and Electrodessication.

The Principal Investigator will select a sub investigator to be the blinded investigator to classify the healing characteristics and aesthetic appearance of each subject's selected lesions at baseline and treated lesions post treatment and at 7-days, 30-days, and 60-days following the last CellFX

treatment or Electrodessication. This sub investigator will be blinded to the treatment assignment. The subject may not be blinded to the treatment assignment.

Eligible subjects with a minimum of 4 and up to 10 SH lesions meeting the inclusion and exclusion criteria will be enrolled. The SH lesions may be present anywhere on the face except the scalp, nose and within the orbital region of the face. The subject must have at least two SH lesions on each side of the face. Subjects will be randomized to receiving the two treatments in a split-face design with CellFX being used on only one side of the face and Electrodessication on the other side. A minimum of two lesions must be treated with CellFX and a minimum of two lesions must be treated with Electrodessication per subject. Selected lesions for each treatment modality must be clearly separated in distance from each other so that lesion treatment and side effects can be assessed by the blinded site investigator.

All selected and qualifying study lesions will receive at least one CellFX or Electrodessication treatment. Each subject will be evaluated by the blinded site investigator at 7-days, 30-days, and 60-days post-initial CellFX and Electrodessication treatments. At the 30-day follow-up visit, if any lesion is rated 1-4 on the Global Aesthetic Improvement Scale (GAIS), the lesion must receive an additional treatment. In case of a second treatment, the subject will be evaluated by the blinded site investigator at 30-days and 60-days post-retreatment. Photography of the study lesions will be captured along with the blinded site investigator assessments at all visits.

Note:
Eligible lesions 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, the subjects can only receive one additional treatment or up to a maximum of two CellFX or Electrodessication treatments.

3.3 Randomization

All enrolled subjects will be randomized to receive the two treatments in a split-face design with CellFX being used on only one side of the face and Electrodessication on the other side. Randomization will be implemented through the Electronic Data Capture (EDC) system. The randomization assignment will include the type of treatment and which side of the face to treat first. For example: 1) First Treatment = CellFX and 2) Side of Face = Right. All randomized subjects will be included in the intent-to-treat 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 5.0 mm x 5.0 mm in length and width and 2.0 mm in depth. 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” on the face 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 and Fitzpatrick Skin Type

Tip Size (L x W, mm)	Fitzpatrick Skin Type	1st Treatment Level mJ/mm³	Re-Treatment Level mJ/mm³*
1.5 x 1.5	I-II	190	150
1.5 x 1.5	III	150	150
2.5 x 2.5	I-II	60	30
2.5 x 2.5	III	30	30
5.0 x 5.0	I-II	45	30
5.0 x 5.0	III	30	30

**If a lesion was rated as 1-4 on the GAIS scale at the 30-day follow-up visit due to a mistargeted lesion that was confirmed by a photograph taken immediately post CellFX procedure, it is recommended to use the first treatment level energy settings.*

3.5 Standard Electrodessication Procedure

Electrodessication will be standardized across all investigational sites. Investigators will perform the Electrodessication procedure with a Segal® Hyfrecator Needle and will use the same local anesthetic to numb the skin. Laser or curettage post Electrodessication will be prohibited. Pulse Biosciences will provide a training video on how to perform the Electrodessication procedure to the treating site investigators.

3.6 Site Selection

The study will be conducted at up to 5 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 60 subjects at up to 5 sites will be enrolled.

3.8 Clinical Study Duration

It is anticipated that the enrollment of subjects in this study will take approximately 2-3 months in duration. All subjects included in this clinical investigation will return for follow-up visits at 7-days, 30-days, and 60-days, post first CellFX or Electrodessication treatment. For subjects who received a second CellFX or Electrodessication treatment, at the 30-day follow up visit, will return for one additional follow-up visit at 90-days from their initial treatment date. The total study duration will be 6 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 at least one procedure (e.g. CellFX or Electrodessication)

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 21 and no older than 80 years of age.
2. Subject has a Fitzpatrick Skin Type I, II, or III.
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 follow-up visits.
5. Subject is willing to have SH lesions treated in a single treatment session and understands that their lesion(s) may undergo a second treatment session at a subsequent visit.
6. Subject must have a minimum of four SH lesions and up to 10 SH lesions to be treated and the subject must have at least two SH lesions located on each side of the face.
7. For study purposes, the SH lesions must be no greater than 2 mm in height and must not exceed 5 mm x 5 mm at their largest dimension. The subject's lesions cannot be located within the eye orbit, nose, or scalp.
8. Subject consents to have photographs taken of the SH lesion(s).
9. Subject agrees to refrain from using all other lesion removal products or treatments (e.g. retinols, retinoids, and exfoliating products) to the treated SH lesions or any new SH lesions during the study period.
10. Subject agrees to refrain from prolonged sun exposure during the study period.

4.2.2 Exclusion Criteria

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

1. Subject has an implantable electronic medical device.(i.e., pacemaker, implantable cardioverter defibrillator)
2. Subject has an active infection or history of infection in designated test area within 90 days prior to first treatment.
3. Subject is not willing or able to sign the Informed Consent.
4. Subject is known to be immune compromised.
5. Subject is prone to developing hypertrophic scars or to be a keloid producer.
6. Subject has allergies to Lidocaine or Lidocaine-like products.
7. Subject is employed by the sponsor, clinic site, or entity associated with the conduct of the study.
8. 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.
9. Use of any other investigational drug, therapy, or device within the past 30 days of enrollment or concurrent participation in another research study.

10. Subject was previously treated with CellFX for SH lesions.
11. Subjects with a personal or family history of Muir-Torre Syndrome or with a history of multiple family members with colon cancer
12. Subjects with Basal Cell Nevus Syndrome

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 from 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 after 1st TX**	**Visit 3 30-days after 1st TX**	**Visit 4 60-days after 1st TX**	**Visit 5* 90-days after 1st TX**
	Day -0	Visit Range ±3 days	Visit Range ±7 days	Visit Range ±7 days	Visit Range ±7 days
Informed Consent	✔				
Demographics, Medical HX, Fitzpatrick Skin Type	✔				
Randomization	✔				
1st TX (CellFX + Electrodessication)	✔				
2nd TX (CellFX and/or Electrodessication)			✔ If applicable		
Photographs of pre and post treated SH Lesions	✔	✔	✔	✔	✔
Wound Healing Characteristics	✔	✔	✔	✔	✔
Lesion Clearance Assessment			✔	✔	✔
Pain Score/Assessment for muscle twitching: Treated SH Lesions	✔		✔		
5 Point Investigator and Subject Global-Aesthetic Improvement Scale (GAIS)**			✔***	✔	✔
6 Point Subject Satisfaction Scale (SSS)/ 5 Point Recommendation Scale**				✔	✔
Adverse Event Assessment	✔	✔	✔	✔	✔
Study Exit				✔	✔

**The 90-day visit is only for subjects that received a second treatment at the 30-day visit.*

*** The three scales (GAIS, SSS, and 5-point recommendation scale) are completed one time by the subject (e.g., 60 days post last treatment).*

****The GAIS is performed by the blinded site investigator at 30-days and 60-day post last treatment.*

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 and Electrodessication treatment, the subject will be considered enrolled and each enrolled subject will be assigned a unique Study Identification Number.

4.5.3 CellFX Treatment / Electrodessication Treatment

- Up to 10 clinically diagnosed SH lesions that meet the study criteria will be selected by the treating investigator and prior to assigning lesions the subjects should have baseline photos taken.
- The site will log onto the Captivate EDC system. The randomization assignment will include the type of treatment and which side of the face for CellFX and Electrodessication.
- A template may be used to determine which treatment tip size will be used for each lesion – sizes range between 1.5 mm x 1.5 mm and 5.0 mm x 5.0 mm. The identified lesions will be numerically labeled.
- The blinded site investigator will then perform a baseline lesion(s) assessment.
- Photographic images of each selected lesion will be taken prior to using local anesthesia/numbing.
- Local anesthesia/numbing will be applied to all selected study lesions.
- Each lesion randomized to CellFX will be treated with pre-determined energy settings; each lesion randomized to Electrodessication will be treated as defined in **Section 3.5**.
- The subject will be asked to rate his/her pain immediately after each lesion treated with the CellFX and Electrodessication procedures by using a numerical rating score.
- The subjects will be asked whether they felt muscle twitching immediately after each lesion treated with CellFX.
- Post procedure lesion assessment will be performed by the blinded site investigator.
- Photographic images of each selected lesion will also 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.

4.6. 7-Day Follow-up Visit

- Photographic images of each of the study lesions will be taken with pre and post lesion markings.
- All lesions will be clinically assessed by the blinded site investigator.
- Any adverse events will be identified and documented.

4.7 30-Day Follow-up Visit (Optional CellFX/Electrodessication Treatment #2)

- Photographic images of each of the study lesions will be taken with pre- and postlesion markings.
- All lesions will be clinically assessed by the blinded site investigator and rated using GAIS scale and the 4-point lesion clearance scale.
- If any lesion is rated 1-4 on the GAIS scale, a second treatment with CellFX or electrodessication will be performed to the previously treated lesion.

In case of a second CellFX or Electrodessication treatment:

- Local anesthesia/numbing will be applied to each lesion designated for retreatment.
- Each lesion designated for a CellFX retreatment will be treated using pre-determined energy settings.
- Each lesion designated for Electrodessication retreatment will be performed as outlined in protocol **Section 3.5** .
- The subject will be asked to rate his/her pain immediately after each lesion treated with CellFX and/or Electrodessication treatments by using a numerical rating score.
- The subjects will be asked whether they felt muscle twitching immediately after each lesion treated with CellFX.
- Post procedure lesion assessment will be performed by the blinded site investigator.
- Photographic images of the retreated lesions will also 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.

4.8 60-Day Follow-up Visit

- **This is Final Study visit for any subject for whom all lesions were treated only one time.**
- Photographic images of each of the study lesions will be taken with pre and post lesion markings.
- All lesions will be clinically assessed by the blinded site investigator and rated using the GAIS scale and the 4- point lesion clearance scale.
- 5-point Investigator-and-Subject-Global-Aesthetic-Improvement-Scale
- 6-point subject satisfaction scale
- 5-point subject scale related to recommendation of procedure(s)
- Any adverse events will be identified and documented.

4.9 90-Day Follow-up Visit

- **This is Final Study visit for any subject for whom lesion(s) were retreated at the 30-day follow-up.**
- Photographic images of each of the study lesions will be taken with pre and post lesion
- markings.
- All lesions will be clinically assessed by the blinded site investigator and rated using the GAIS scale and the 4-point lesion clearance scale.
- 5-point Investigator-and-Subject-Global-Aesthetic-Improvement-Scale
- 6-point subject satisfaction scale

- 5-point subject scale related to recommendation of procedure(s)
- Any adverse events will be identified and documented.

4.10 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 surgical devices currently used to treat patients with SH lesions. 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 and non-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, and III
- 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 SH lesions requires both non-inferior improvement in lesion appearance (effectiveness) and non-inferior rates of adverse skin changes (safety) versus Electrodessication. Because both features are critically important for treatment acceptability, this study is designed with 3 co-primary endpoints (1 related to appearance and 2 related to adverse skin changes). All 3 endpoints must demonstrate non-inferiority be considered successful.[19] These co-primary endpoints are: (1) rate of pigmentary changes and scarring at 60 days post last treatment, (2) rate of skin textural changes at 30 days post last treatment and (3) rate of improvement in aesthetic appearance. All 3 co-primary endpoints are assessed at a lesion level, but the analyses will be adjusted for within-subject correlation. The pigmentary changes and scarring primary safety endpoint is the proportion of lesions with the presence of hyperpigmentation, hypopigmentation or scarring at 60 days post last treatment. The skin textural change primary safety endpoint is the proportion of lesions with the presence of crusting, flaking, or other skin textural change. The primary effectiveness endpoint is the proportion of lesions classified as responders on the Global Aesthetic Improvement Scale (GAIS).[22]

6.1.1 Primary Safety Endpoints

The first primary safety endpoint is the presence or absence of hyperpigmentation, hypopigmentation or scarring at 60 days from the last CellFX or Electrodessication treatment as assessed by the blinded site investigator. The timing of the evaluation of this endpoint is lesion specific as some lesions may not require a second treatment with the CellFX System or Electrodessication. Lesions will be categorized as having this safety event if any component (hyperpigmentation, hypopigmentation, or scarring) is present at the follow-up visit 60 days after the last treatment.

Clinical justifications for the 15% non-inferiority margin for the primary safety endpoints include the avoidance of electrosurgical smoke plume, which may be harmful to patients and providers,[20] as well as existing safety data that demonstrate no serious adverse events. Safety data show a comparable safety profile for CellFX compared to the predicate devices for this indication, with the suggestion of faster healing.

The statistical hypotheses to be evaluated for the pigmentation and scarring primary safety endpoints are:

H_0: $p_{CellFX} - p_{Electro} \geq 15\%$ at 60 days post last treatment, versus
H_A: $p_{CellFX} - p_{Electro} < 15\%$ at 60 days post-last treatment

Where p_{CellFX} and $p_{Electro}$ are the proportion of lesions with any of these events (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 absolute difference in proportions ($p_{CellFX} - p_{Electro}$) is less than 15%. This approach is equivalent to a 1-sided test with a 2.5% type I error rate. To be clinically meaningful, the absolute difference should not exceed 7.5%.

This second safety endpoint is the presence or absence of skin textural changes (scaling, flaking etc.) at 30 days from the last CellFX or electrodessication treatment as assessed by the blinded site investigator. The timing of the evaluation of this endpoint is lesion specific as some lesions

may not require a second treatment with the CellFX System or electrodessication. Lesions will be categorized as having this safety event if any skin textural change is present at the follow-up visit 30 days after the last treatment.

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

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

Where p_{CellFX} *and* $p_{Electro}$ are the proportion of lesions with scaling, flaking or other skin textural changes in each treatment group. The null hypothesis will be rejected if the upper bound of the 2-sided 95% confidence interval for the absolute difference in proportions ($p_{CellFX} - p_{Electro}$) is less than 15%. This approach is equivalent to a 1-sided test with a 2.5% type I error rate. To be clinically meaningful, the absolute difference should not exceed 7.5%.

Because multiple lesions are treated within subjects, the difference in proportion and 95% confidence interval will be calculated using generalized estimating equations (GEE).[21] The dependent variable is the presence or absence of a safety event for each lesion at 60 days post last treatment, with randomized treatment strategy included as a fixed effect. A repeated term for subject will be included to account for the within-subject correlation. An exchangeable working correlation matrix will be used to reflect a common correlation across lesions within subject.

6.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is response measured by the Global Aesthetic Improvement Scale (GAIS) at 60 days following the last CellFX or Electrodessication treatment (60 days post-last treatment). GAIS score will be assessed by three independent observers, blinded to treatment assignment, who will classify the response for each lesion based on photographs taken at baseline and 60 days post last treatment. The 3 observers will assign a score based on the 5-level GAIS scale described in this section. For analysis purposes, the lesion will be classified as a responder if 2/3 blinded observers assign a score of 4 or 5, and as a non-responder if 2/3 blinded observers assign a score of 1, 2 or 3. The timing of the evaluation of this endpoint is lesion specific as some lesions may not require a second treatment with the CellFX System or Electrodessication. The GAIS scale[22] describes aesthetic changes as follows:

GAIS Rating	Description
5=Much Improved	Marked improvement in appearance from the initial condition, touch-up treatment(s) is not indicated
4=Improved	Obvious improvement in appearance from the initial condition, but a touch-up or re-treatment is indicated
3=No Change	The appearance is essentially the same as the original condition
2=Worse	The appearance is worse than the original condition
1=Much Worse	The appearance is much worse than the original condition

The primary effectiveness endpoint is lesion-level GAIS response, defined as a score of 5 (“Much Improved) or 4 (“Improved) versus non-response defined as a score of 3, 2 or 1 (“No Change”, “Worse”, “Much Worse”) for at least 2/3 blinded observers. This dichotomization of the GAIS scale has been used to define response in several previous cosmetic procedures.[23-26]

The 15% non-inferiority margin for the primary effectiveness endpoint is justified by consistency of treatment and ease of use with the CellFX system. Outcomes for standard of care Electrodessication procedures depend heavily upon operator skill and experience. Furthermore, electrodesiccation involves destruction of the entire gland but can lead to sequelae such as scarring and discoloration. Therefore, depending on the number of lesions and the cosmetic concerns of the patient, it may be necessary to avoid such interventions.[27] In contrast, the CellFX system is designed to be a straightforward procedure that is reproducible among providers with fewer sequelae.

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

H_0: $p_{CellFX} - p_{Electro} \leq -15\%$ at 60 days post last treatment, versus
H_A: $p_{CellFX} - p_{Electro} > -15\%$ at 60 days post last treatment

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

Because multiple lesions are treated within subjects, the 95% confidence interval will be calculated using GEE.[21] The dependent variable is GAIS response each lesion at 60 days post last treatment, and randomized treatment strategy will be included as a fixed effect. A repeated term for subject will be included to account for the within-subject correlation. An exchangeable working correlation matrix will be used to reflect a common correlation across lesions within subject.

6.1.3 Type I Error Control and Study Success

Study success requires the demonstration of non-inferiority for the primary safety and efficacy endpoints.[19] Thus, no type I error adjustment for multiple testing is required. No formal hypothesis will be tested for secondary endpoints. In addition, the point estimate for the response rate for the primary effectiveness endpoint among lesions treated with CellFX must be greater than 60%.

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. Secondary endpoints collected in this study are as follows:

1. The investigator, blinded to treatment assignment, will classify the aesthetic change for each lesion using photographs taken at baseline as a reminder of baseline condition. The score will be assigned based on the in-person observation at 60 days post last treatment according to the GAIS scale[22]. A GEE model similar to the model described in **Section 6.1.2** will be performed to assess differences in the investigator-assess response rate.
2. Difference in proportion with GAIS improvement between CellFX and Electrodessication based on score assigned by blinded site investigators from baseline to 30-days post-last treatment.
3. Wound healing characteristics at 7-days, 30-days, and 60-days post-last treatment between CellFX and Electrodessication. Wound healing includes evaluation of the following:
    - Hyperpigmentation
    - Hypopigmentation

- Erythema
- Crusting
- Scabbing
- Flaking
- Scarring
- Other surface irregularities

The rate of each event individually and a composite of any of these events will be calculated for each treatment and time-point. Differences in proportion and 95% confidence interval as described for the hyperpigmentation, hypopigmentation or scarring endpoints will be calculated using GEE, convergence permitting.

4. The **GAIS Scale** will be used to measure aesthetic improvement for each treated lesion site (left, right).[23-26]

   The proportion with each response will be summarized. An analysis will be performed using the same response definition as for the primary efficacy outcome (see **Section 6.1.2**) to compare investigator and subject perception of change across treatment groups.

5. A **6-point Subject Satisfaction Scale** will be used to measure subject's satisfaction with the overall treatment of their SH lesions by treated lesion site (left, right):

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.

6. A **5-point Recommendation Scale** will be used to measure the subject's likelihood of recommending the treatment procedure used on each treated lesion site (left, right) to a significant other, relative or friend.

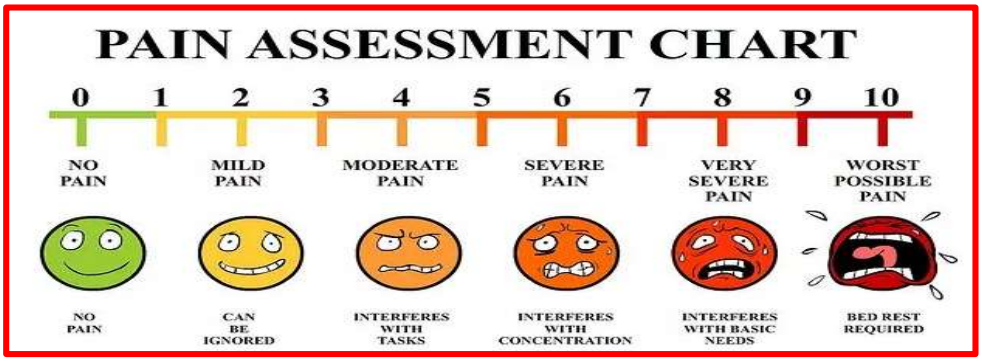
Rating	Description
5	Highly Likely
4	Likely
3	Neutral
2	Unlikely
1	Highly Unlikely

   The frequency of each response will be tabulated by treatment. The proportion with responses of "Highly Likely" or "Likely" will be tabulated and compared across treatments.

7. **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 Electrodessication treatments at Day 0 and 30 days, if applicable. The face pain scale will be assessed immediately after each lesion treatment (left, right). Please see pain scale chart below.

The number and percent will be tabulated for each level of pain for first and second treatments separately, and GEE 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.



6.3 Sample Size Determination

Power for the co-primary endpoints was assessed using a bootstrap simulation. To accurately model within-subject correlation across lesions, the safety and efficacy outcomes for subjects with at least 4 lesions in a previous study (SH-009) were sampled with replacement. An assumed mapping was created between the clearance scale used in that study (**Section 6.7**) and the GAIS scale: lesions rated as "Clear" with hypopigmentation rated as "None" or "Mild" were classified as GAIS responders. Among lesions rated as "Mostly Clear" with hyperpigmentation rated as "None", a binary random variable derived from a standard normal distribution was used to categorize 88% of these as GAIS responders with the remaining 12% categorized as non-responders. All other combinations of clearance and hypopigmentation were classified as non-responders. The resulting distribution of lesions had a GAIS response rate of 73%, which reflects discounts for both conversion to a different scale and a slight reduction in efficacy due to visibility differences in photo review compared to live assessment. Both primary safety outcomes (skin texture changes at 30 days post last treatment and pigment changes or scarring at 60 days post last treatment) were also calculated for each lesion.

For each simulation, subjects were selected from SH-009 with replacement. Half of the lesions for each selected subject were randomly assigned to each treatment, which assumes equal efficacy and safety across treatments. The GEE models for the primary safety and primary efficacy outcome were used as described in **Sections 6.1.1** and **6.1.2** . The proportion of simulations for which the 95% CI for the difference in proportions excluded the critical values for the hypotheses in **Sections 6.1.1** and **6.1.2** was calculated. This analysis (based on 10,000 simulations) demonstrated that 240 lesions (approximately 48 subjects) would provide at least 80% power for the coprimary endpoint hypothesis tests. To account for error in estimation of the mapping between lesion clearance and GAIS, a target of 260 lesions (approximately 52 subjects) with follow-up at 60 days after the last treatment was set for adequate power. Assuming 10% loss to follow-up, up to 60 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 lesions will be analyzed based on the intended randomization assignment. The intent of this protocol is to apply up to 2 sessions of each treatment, but no lesions 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 lesions 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 endpoints.

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 both CellFX and Electrodessication, and repeated the treatments per protocol for any lesions that were not clear at the 30-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:

- Age
- Prior treatment for treated SH lesions
- Gender
- Fitzpatrick score (I/II vs III)
- Clinical Site
- Treatment Energy Level
- Size of CellFX Treatment Tip
- Total Energy Density
- Secondary 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. However, based on previous studies, any missing data that does occur is likely due to missed follow-up visits. Since each subject receives both treatments, differential follow-up by treatment is unlikely to be systematic. However, the sensitivity of the final results to missing data will be examined by comparing the primary outcomes to the results using a longitudinal model with both the 30-day and 60-day post treatment results, and a tipping-point analysis will be performed for the endpoints at 60 days to determine whether the missing data could change the inference compared to the primary models.

6.7 Exploratory Analysis

6.7.1 Lesion Clearance

The Lesion Clearance Scale will be used by blinded site investigators to classify the degree of lesion clearance at 30 and 60 days post last treatment. A 4-point scale (0,1,2,3) will be used to characterize each lesion as “Clear”, “Mostly Clear”, “Partially Clear”, or “Not Clear”.

Lesion Clearance Scale			
CLEAR	MOSTLY CLEAR	PARTIALLY CLEAR	NOT CLEAR
0	1	2	3

The number and proportion at each level of response will be tabulated, and the proportion of lesions with clearance response will be compared across treatment groups using a model similar to the primary effectiveness outcome (**Section 6.1.2**). Clearance response is defined as scores of 0 or 1 ("Clear" or "Mostly Clear") versus non-response defined as scores of 2 or 3 ("Partially Clear" or "Not Clear"). This endpoint is collected for comparison to previous trials, which used the Lesion Clearance Scale.

6.7.2 Subject-Level Safety Events at 30 Days Post-Last Treatment

Subjects will be classified based on the presence or absence of hyperpigmentation, hypopigmentation or scarring at 30 days after the last treatment. Subjects will be counted once per treatment (that is, per randomized side of face) based on whether any lesion treated with electrodessication or CellFX experiences hyperpigmentation, hypopigmentation or scarring at 30 days after the last treatment. The number and percentage of subjects in each of the following categories will be tabulated:

- Subjects with no events for either treatment
- Subjects with an event in at least 1 CellFX-treated lesion but no events in any electrodessication-treated lesion
- Subjects with an event in at least 1 electrodessication-treated lesion but no events in any CellFX-treated lesion
- Subjects with events in both electrodessication and CellFX-treated lesions

This tabulation will be performed using the ITT population, but lesions will be classified as treated with CellFX or electrodessication based on the actual treatment received for each lesion.

6.7.3 Subject-Level GAIS Response at 30 Days Post-Last Treatment

Subjects will be classified based on whether all treated lesions respond to treatment (defined as a score of '4' or '5' on the GAIS scale) at 30 days after the last treatment. Subjects will be counted once per treatment (that is, per randomized side of face) based on whether all lesions treated with electrodessication or CellFX respond to treatment at 30 days after the last treatment. The number and percentage of subjects in each of the following categories will be tabulated:

- Subjects with at least 1 lesion failing to respond in each treatment
- Subjects with GAIS response for all CellFX-treated lesions but failure to respond for any electrodessication-treated lesion
- Subjects with GAIS response for all electrodessication-treated lesions but failure to respond for any CellFX-treated lesion
- Subjects with GAIS response for all lesions treated with electrodessication and CellFX-treated lesions

This tabulation will be performed using the ITT population, but lesions will be classified as treated with CellFX or electrodessication based on the actual treatment received for each lesion.

7.0 CLINICAL PHOTOGRAPHY

The Sponsor will use Canfield Scientific, Inc. to provide photography equipment and services to the study sites. Three close-up photographs (left, right and frontal) at each study visit will be taken with the VISIA-CR system. In order to ensure consistent serial clinical photography is achieved during the study, all subject photographs will be reviewed (monitored) on an ongoing basis. Digital images will be transferred to Canfield via the secure website.

8.0 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 study lesions at baseline and 60 days post last treatment and will be trained on specific criteria used to classify the response to treatment as noted in **Section 6.2**.

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

9.0 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 the lesion site(s) 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 from enrollment through 60 days following the last CellFX and Electrodessication 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.

9.1 Adverse Event Definitions

9.1.1 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__.

9.1.2 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

9.1.3 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.

9.1.4 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

9.1.5 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.

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

9.2.1 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.

9.3 Safety Reporting Requirements

Table 3 summarizes the time sensitive requirements for adverse events and device deficiencies. The Sponsor is the contact person for these reporting requirements.

Table 3.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)	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 (dermatologic only)	Submit in a timely manner after the clinical site first learns of the event
**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.

10.0 STUDY MANAGEMENT (SPONSOR RESPONSIBILITIES)

10.1 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.

10.2 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.

10.3 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.

10.4 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 Electrodessication procedure for this study.

Canfield Scientific, Inc. will provide training to the sites on the VISIA-CR system.

10.5 Monitoring of Study Sites

10.5.1 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.

10.5.2 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.

10.5.3 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.

10.6 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.

10.7 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.

10.8 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.

10.9 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.

10.10 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.

10.11 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.

10.12 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.).

11.0 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.

11.1 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.

11.2 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.

11.3 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.

11.4 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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13.0 APPENDICES

13.1 Appendix A: Patient Informed Consent

13.2 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