A Prospective Randomized Multicenter Trial Comparing Performance of Two Intracorporeal Lithotripters for Removal of Large Renal Calculi

The ShockPulse-SE vs. Trilogy Trial

CLINICAL INVESTIGATION PLAN

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Protocol Synopsis

A Prospective Randomized Multicenter Trial Comparing Performance of Two Intracorporeal Lithotripters for Removal of Large Renal Calculi - The ShockPulse-SE vs. Trilogy Trial	
Study Objective(s)	To compare the performance, as measured by the stone clearance rate at time of percutaneous nephrolithotomy, of the ShockPulse-SE Lithotripsy System to the Trilogy Lithotrite.
Study Devices	1. ShockPulse-SE Lithotripsy System with the 3.76 mm probe 2. Trilogy Lithotrite with 3.9 mm probe
Indications for Use	Both devices are cleared for use in the USA for the following indications: 1. The **ShockPulse-SE Lithotripsy System** is intended to be used for fragmentation of urinary tract calculi in the kidney, ureter, and bladder. 2. The **Trilogy** Lithotrite is intended to be used to fragment urinary tract calculi in the kidney, ureter, and bladder.
Device Sizes	1. Shock Pulse-SE 3.76 mm lithotripsy probe 2. Trilogy 3.9 mm Probe
Study Design	Prospective, randomized, multicenter, 2 arm, comparative trial
Planned Number of Subjects	N=100
Planned Number of Investigational Sites / Countries	A total of 3 sites in the USA
Primary Endpoint	Stone clearance rate defined as the kidney stone surface area measured by pre-operative computed tomography (CT) scan divided by the time to remove the targeted stone burden. • Time to remove the targeted stone burden is measured at time the lithotripter unit starts fragmenting the stone to time all fragments are removed from the kidney based on visual inspection. This is prior to final visual inspection of the kidney with a flexible nephroscope.

Additional Endpoints	Additional endpoints include the following: 1. Device malfunctions 2. All complications measured by the Clavien Classification of Surgical Complications 3. Stone free status as defined by the presence or absence of stone material on postoperative CT imaging and at final follow up • Stone free status must be assessed postoperative day 1 by CT scan.
Method of Assigning Patients to Treatment	The patients will be block randomized 1:1 to either stone removal with the Trilogy or the ShockPulse –SE device.
Follow-up Schedule	1. Baseline (Clinic Visit) – within 3 months prior to surgical procedure 2. Procedure (Hospital Visit) • ***Stone free status*** may be assessed at this time by CT scan on Postoperative day 1 3. 6-12 Week Follow-up Visit (Clinic Visit) • ***Stone free status*** may be assessed at this time by KUB scan and/or ultrasound, or CT scan 4. End of Study • End of study will be reached after completion of the 6-12 Weeks Follow-up Visit, subject withdrawal or lost to follow-up, whichever occurs first.
Study Duration	It is anticipated that this study will take 12 months to complete once IRB approval is obtained at all participating locations.

Key Inclusion Criteria	1. ≥ 18 years of age 2. Stone burden ≥ 1.5 cm as measured on preoperative CT scan 3. Patient is scheduled to undergo a percutaneous nephrolithotomy procedure 4. Willing and able to provide informed consent
Key Exclusion Criteria	1. Pregnant 2. Active urinary tract infection 3. Prior shock wave lithotripsy within 3 months of study procedure 4. Multiple percutaneous access sites are anticipated 5. Unable or unwilling to provide informed consent
Statistical Methods	
Primary Statistical Hypothesis	We hypothesize that the Trilogy will increase the stone clearance rate by 25% compared to the Shockpulse-SE
Statistical Test Method	Outcomes between treatment groups will be assessed using a t-test to compare means. Values of $p \leq 0.05$ will be considered significant.
Sample Size Parameters	For simplicity, sample size calculations were performed using a two-sided Student t-test with a power of 90% and a significance level of alpha = 0.05. The primary outcome of interest is the clearance rate of the targeted stone burden. Preliminary in vitro data shows a reduction of approximately 50% in the average lithotripter clearance time of a 1 cm^3 BegoStone for the Trilogy lithotrite compared to the ShockPulse-SE. Given the increased variability of use in vivo and across subjects, a more conservative difference was considered for sample size estimation. Assuming a 25% improvement in clearance rate that results in an effect size of 0.7, a sample size of 44 subjects in each group is required. To account for the possibility of unevaluable data a total of 100 patients, 50 in each group will be enrolled.

Introduction

Large and complex renal calculi, defined as those with a maximum diameter of ≥ 1.5 cm, can be removed from the upper urinary tract by percutaneous nephrolithotomy but the stones usually require fragmentation in order to remove them through the access site. There are a number of commercially available intracorporeal lithotripters used to fragment or break kidney stones to allow elimination including pneumatic, ultrasonic, and combination devices. Each technology has its own relative advantages and disadvantages.

New versions of intracorporeal lithotripter devices have been introduced with improvements meant to address prior functional limitations such as probe clogging or breaking and cumbersome hand piece design.

The Trilogy lithotrite is the newest generation device stone fragmentation device from Boston Scientific. The Trilogy device uses unique technology to efficiently fragment and remove stone material, superior to other devices on the market based on preliminary bench testing. From Olympus, the ShockPulse-SE Lithotripsy System (Cybersonics, Erie, PA, USA is a constant ultrasonic wave energy lithotripter with intermittent shock wave (ballistic/mechanical) energy. The ShockPulse-SE has a single probe design with an OD of 3.76 mm which allows for larger sized stone fragments to be vacuumed from the urothelium. The larger, single lumen also allows for a high flow rate to reduce probe clogging events. The end result is faster stone clearance rates based on in vitro studies (company brochure).[2]

The objective of this study is to compare the performance, as measured by the stone clearance rate at time of percutaneous nephrolithotomy, of the ShockPulse-SE Lithotripsy System to the Trilogy lithotrite when used for large complex renal calculi.

2. Device Description

The Trilogy has been FDA cleared for fragmentation of urinary tract calculi in the kidney, ureter, and bladder. Trilogy is a combined piezoelectric/pneumatic device capable of fragmenting calculi and aspirating stone debris. The novel technology in Trilogy has been demonstrated in bench testing to more quickly disintegrate stones compared to other devices. The following components are included in the Trilogy System:

REF	Description	
Trilogy Parts	Trilogy Lithotrite	
	M0068402010	Swiss LithoClast® Trilogy Console
	M0068402030	Swiss LithoClast® Trilogy Handpiece Kit
	M0068402050	Swiss LithoClast® Trilogy Foot Switch
	M0068403590	Trilogy Reusable Torque Wrench
	M0068401890	Quick Guide
	M0068401810	Stone Catcher Holder
	M0068401800	HDMI-VDI cable (10m)
	M0068401820	Filling Bottle
	M0068401830	Bottle of Demineralized Water (2.5l)
	M0068401850	Power Cord (US - 6m)
	M0068401860	Swiss LithoClast® Trilogy System IFU
	M0068403540	3.9mm x 350mm Trilogy Probe Kit
	M0068403550	3.9mm x 440mm Trilogy Probe Kit
	M0068402980	Stone Catcher for Trilogy

The ShockPulse-SE Lithotripsy System has been FDA cleared fragmentation of urinary tract calculi in the kidney, ureter, and bladder. The ShockPulse-SE System is an electromechanical device capable of fragmenting calculi and aspirating stone debris. The novel technology in the ShockPulse-SE Lithotripsy System uses a single transducer and proprietary ShockPulse technology to generate both low-frequency mechanical impacts and high-frequency ultrasonic energy which quickly disintegrates stones. The following components are included in the ShockPulse System:

REF	Description	
SPL-S	ShockPulse-SE Lithotripsy System	
	SPL-T	ShockPulse Lithotripsy Transducer
	SPL-CSL	ShockPulse Lithotripsy Cleaning Stylet - Large
	SPL-W	ShockPulse Lithotripsy Wrench
	SPL-PC	ShockPulse Lithotripsy Power Cord
	SPL-G	ShockPulse Lithotripsy Generator

	SPL-NC	ShockPulse Lithotripsy Nose Cone
	SPL-IFU	ShockPulse Lithotripsy Instructions for Use
	SPL-PDBX376	ShockPulse Lithotripsy Probe, Sterile Single Use, 3.76 mm (3/Box)

Study Objectives

To compare the performance, as measured by the stone clearance rate at time of percutaneous nephrolithotomy, of the ShockPulse-SE Lithotripsy System to the Trilogy Lithotrite.

Study Endpoints

Primary Endpoint

Stone clearance rate defined as the kidney stone surface area measured by preoperative computed tomography (CT) scan divided by the time to remove the targeted stone burden.

Time to remove the targeted stone burden is measured at time the lithotripter unit starts fragmenting the stone to time all fragments are removed from the kidney based on visual inspection. This is prior to final visual inspection of the kidney with a flexible nephroscope.

Additional Endpoints

1. Device malfunctions
2. All complications measured by the Clavien Classification of Surgical Complications

Stone free status as defined by the presence or absence of stone material on postoperative day 1 CT imaging

This study is a post-market, prospective, randomized, multicenter, 2-arm, comparative trial.

Scale and Duration

A total of 100 subjects will be enrolled and treated at 3 study sites across the USA. Each subject will be followed for approximately 6-12 weeks after the study procedure. It is anticipated for the entire study to last approximately 12 months.

***All sites will perform 10 independent PCNL cases, outside of the study period, using the Trilogy lithotrite to become accustomed with the device prior to enrolling patients.**

Treatment Assignment

The patients will be block randomized 1:1 to either stone removal with the Trilogy or the ShockPulse–SE device. All randomization will occur at the central study site via computer randomization by the statistician to limit selection bias.

Justification for the Study Design

This study will compare performance of two devices for the treatment of large renal calculi. The study has been designed as a prospective, multi-centric, randomized, comparative study. The intent of this design is to minimize bias and to allow for statistical comparison of the two treatment groups.

Subject Selection

Study Population and Eligibility

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be considered for inclusion in theis study.

Inclusion Criteria

1. ≥ 18 years of age
2. Stone burden ≥ 1.5 cm as measured on preoperative CT scan
3. Patient is scheduled to undergo a percutaneous nephrolithotomy procedure
4. Willing and able to provide informed consent

Exclusion Criteria

1. Pregnant
2. Active urinary tract infection
3. Prior shock wave lithotripsy within 3 months of study procedure
4. Multiple percutaneous access sites are anticipated
5. Unable or unwilling to provide informed consent

Subject Accountability

Point of Enrollment

A subject will be considered enrolled in the study if they meet all eligibility criteria and after the subject signs and dates the informed consent form (ICF). No study-related procedures can take placed until the ICF is signed.

Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to study device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include:

- Physician discretion
- Subject choice to withdraw consent
- Lost to follow-up
- If the subject dies due to any cause

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment.

If any treated study patient is unable to return to the study center after treatment, efforts will be made to obtain complete follow-up information from the patient's primary physician. The reason for a patient's failure to return for the necessary follow-up visits or for a patient's discontinuance from the study must be determined and recorded in the case report forms (CRF).

All applicable CRFs up to the point of subject withdrawal must be completed. Subjects who are "lost to follow up" should have documented attempts to contact them.

Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. Data collected up to the point of subject withdrawal may be used for study analysis.

Study Methods

Data Collection

The schedule of data collection is illustrated in Table 2.

Procedure/Assessment	Screening/Baseline (Clinic Visit)	ShockPulse-SE or Trilogy Procedure (Hospital Visit)	Follow-up Visits	
			6-12 Week Visit[3] (Clinic Visit)	Unscheduled Visit[2] (Clinic Visit)
Visit Window	***Within 90 Days Prior to Procedure***			
Informed Consent Form	**X**			
Selection Criteria	**X**			
Randomization	**X**			
Demographics	**X**			
CT Scan& Stone Information	**X**			
Medical History	**X**			
Pre-operative Physical Exam and Laboratory Data	**X**			
Lithotripsy Procedure		**X**		
Stone Free Status		**X[1]**	**X[1]**	
Post-operative Stone and Laboratory Data		**X**		
Device Malfunctions		**X**		
Adverse Events		**X**	**X**	**X**

[1] Stone Free Status must be assessed on POD 1 by CT. [2] Unscheduled Visits may be performed between protocol specified visits as deemed appropriate by the investigator.[3] End of study will be reached after completion of the 6-12 Week Follow-up visit, subject withdrawal, or lost to follow-up, whichever occurs first.

Informed Consent

All subjects taking part in this clinical study must undergo the informed consent process. Subjects must be allowed adequate time to review the consent, raise questions, and make a voluntary decision to participate in the clinical study. Each subject must sign and date the IRB approved informed consent form before any clinical study-related procedures are performed. A copy of signed informed consent form will be provided to the subject for his/her records. A subject's participation in the clinical study begins with the signing and dating of the informed consent form.

Screening (Clinic Visit):

The following data will be captured during the Screening Visit:

- Informed consent process
- Inclusion / exclusion criteria
- Randomization
    - All randomization will occur at the central study site via computer randomization by the statistician to limit selection bias

Baseline (Within 90 Days Prior to Procedure) (Clinic Visit):

The following data will be captured during the Baseline Visit:

- Demographics
- CT scan
- Stone burden
- Stone size (cm)
    - Axial x Coronal
- Targeted stone surface area (mm2)
    - This measurement is determined by outlining the CT image of the stone using a digital system such as PACS)
- Previous treatment of targeted stone
- Medical history
- Pre-operative physician exam
    - Height, weight, and BMI
- Pre-operative laboratory data
    - Serum creatinine (mg/dl)
    - Hemoglobin (g/dl)
    - Hematocrit (%)
    - Na (mEq/l)
    - Urine culture

ShockPulse-SE or Trilogy Procedure (Hospital Visit):

The following data will be captured during the Lithotripsy Procedure Visit:

Intraoperative Data:

- Date of surgery
- Device accountability
  - The lot number of the disposable devices used shall be captured.
- Type of Anesthesia
  - General
  - IV Sedation
  - Regional
- ASA Level
  - 1: A normal, healthy patient
  - 2: A patient with mild systemic disease
  - 3: A patient with severe systemic disease
  - 4: A patient with severe systemic disease that is a constant threat to life
- Number and location of access sites for lithotripsy procedure
- Total procedure time as measured in minutes from induction of anesthesia to end of anesthesia
  - **Please ensure these time points exists in the subject's source documentation**
- Time to clearance of targeted stone burden as measured in minutes
  - Start time: When the investigator begins to use the lithotriptor on the targeted stone
  - Stop time: When the investigator has cleared all fragments and prior to final inspection of the kidney with the flexible nephroscope
  - **Please ensure these time points exists in the subject's source documentation**
- Use of other intracorporeal lithotripsy devices including laser
- Settings utilized for each lithotripter device
- Stone Free Status
  - Assessed by CT scan performed postoperative day 1.
- Estimated blood loss (EBL)
- Device malfunctions
- Adverse events

2.1.1. Post-operative Data:

- Length of hospitalization measured in days
- Need for blood transfusion
- Assessment of nephrostomy tube
- Adverse events
- Stone Free Status
  - Date of imaging study should be provided.
- Stone analysis
- Stone culture results
- Post-operative laboratory data
  - Serum creatinine (mg/dl)
  - Hemoglobin (g/dl)
  - Hematocrit (%)

- Na (mEq/l)

6-12 Week Follow-up Visit (Clinic Visit):

The following data will be captured during the 6-12 Week Follow-up Visit:

- Stone Free Status
  - Date of imaging study should be provided. Either a CT or KUB and/or Ultrasound is required prior to or during the 6-12 Week Follow-up Visit.
- Adverse events

Unscheduled Visit (Clinic Visit):

Unscheduled visits may be performed between visits required by the protocol as deemed necessary by the investigator. Data for unscheduled visits will be captured on the Adverse Event case report form (CRF).

End of Study

End of study will be reached after completion of the 6-12 Week Follow-up visit, subject withdrawal, or lost to follow-up, whichever occurs first.

Source Documents

Source documents are the patient records maintained at the study site. In most cases, the source documents will be the physician's or hospital's patient chart. In some cases, the source documents may be electronic. In both cases, the information captured in the CRF must match the information in the chart or electronic source document.

Statistical Considerations

Endpoints

Primary Endpoint

Stone clearance rate.

Hypothesis

It is hypothesized that the Trilogy will reduce the stone clearance rate by 25% compared to the Shockpulse-SE.

Additional Endpoints

Additional endpoints include the following:

1. Device malfunctions

2. All complications measured by the Clavien Classification of Surgical Complications
3. Stone free status as defined by the presence or absence of stone material on postoperative imaging
    - Stone free status must be assessed prior POD #1 by CT scan.

Analysis Sets

The Intent-To-Treat (ITT) dataset will consist of all patients who were randomized and is defined by all subjects being grouped by their initial randomization, regardless of the actual treatment received.

The Per Protocol (PP) dataset will consist of all randomized subjects who underwent their assigned treatment and full outcome assessment.

The Safety Analysis (SA) dataset consists of all subjects who received any amount of treatment on protocol.

Sample Size

For simplicity, sample size calculations were performed using a two-sided Student t-test with a power of 90% and a significance level of alpha = 0.05. The primary outcome of interest is the clearance rate of the targeted stone burden. Preliminary in vitro data shows a reduction of approximately 50% in the average lithotripter clearance time of a 1 cm3 BegoStone for the Trilogy lithotrite compared to the ShockPulse-SE. Given the increased variability of use in vivo and across subjects, a more conservative difference was considered for sample size estimation. Assuming a 25% improvement in clearance rate that results in an effect size of 0.7, a sample size of 44 subjects in each group is required. To account for the possibility of unevaluable data a total of 100 patients, 50 in each group will be enrolled.

Statistical Methods

All demographic data will be summarized using descriptive statistics (for continuous measures; mean, standard deviation, median, min and max and for categorical measures; count and percent) and tabulated by treatment group. Distributions of continuous measures will be investigated and if found to be significantly non-normal appropriate transformations will be sought. Demographics will be compared between groups using Student t-tests and Fisher's exact tests, as appropriate. If any demographics measures are found to be unbalanced between groups, they will be considered as possible covariates when analyzing the primary outcome.

The primary outcome, clearance rate, will be calculated by dividing the stone surface area by the clearance time. To compare the clearance rate between groups a mixed effects model will be used including treatment group as a fixed effect and site (hospital) as a random effect. Any demographics that were found to be unbalanced between groups may also be included in the model as covariates.

Device malfunctions will be recorded and summarized by treatment group. The proportion of cases experiencing device malfunctions will be compared between groups using Fisher's Exact test. All subject complications will be recorded and summarized using the Clavien Classification of Surgical Complications. The proportions of subjects experiencing complications will also be compared between groups using Fisher's Exact test. The number (and percent) of patients found to be stone free at 6-12 weeks post-op will be summarized and compared between groups using Fisher's Exact test.

The main analysis of the primary endpoint will be performed on the ITT dataset. Supportive analyses may be performed on the PP dataset. All reporting and analysis of adverse events and complications will be done using the SA data set.

Control of Systematic Error/Bias

To minimize selection bias there will be a single randomization schedule managed at the lead investigative site. Upon subject enrollment, all participating sites will contact the main site for experimental group randomization. The randomization will be a permuted block randomization that will help ensure a reasonable balance of group assignment throughout the study enrollment period.

Number of Subjects per Investigative Site

The maximum number of subjects for any single site is 85.

Data Management

Data Collection, Processing, and Review

Subject data will be recorded in a limited access, secure, web-based electronic data capture (EDC) system called REDCap. REDCap is designed to comply with HIPAA regulations. REDCap is not 21 CFR Part 11 compliant; however, this data will not be submitted to the FDA as it is part of a post-market study comparing two commercialized devices for their cleared intended uses.

The conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the

study subjects in compliance with regulatory guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product.

Data Safety Review

Individual Investigators will conduct continuous review of data and patient safety. Summaries submitted to the lead site should include review of data, the number of patients, significant adverse events as described in the risks, and responses observed. A combined summary for all sites will be submitted half way through enrollment (50 subjects) and at the completion of enrollment (100 subjects) for review by the DSMC.

Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB) of the revised protocol must be obtained prior to implementation.

Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

Device/Equipment Accountability

The study devices/equipment shall be securely maintained, controlled, and used only in this clinical study.

Compliance

Statement of Compliance

This study will be conducted in accordance with ICH Guidelines, Good Clinical Practices ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB authority has been obtained. Any additional requirements imposed by the IRB shall be followed, if appropriate.

Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.

- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

Institutional Review Board/Ethics Committee

The protocol and informed consent document must have the approval of a properly constituted committee ("Institutional Review Board" / "Ethics Committee") responsible for approving clinical trials. The signed IRB/EC approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol title, and date of approval, and informed consent document). A copy of the approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

Potential Risks and Benefits

Anticipated Adverse Device Effects

The following adverse events (AEs) are considered anticipated during percutaneous nephrolithotomy procedures and are reflected in the commercial instructions for use (IFU) for each lithotripsy device:

- Infection
- Bleeding
- Damage to the kidney or surrounding organs
- Other adverse events associated with anesthesia

Each participating site is responsible for recording AEs and classifying them based on the below Clavien Classification system:

Clavien Classification of Surgical Complications

All adverse events that occur intra-operatively or within the 30 day postoperative period will be assessed using the Clavien Classification of Surgical Complications:

Grade I: Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions.

Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for Grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic or radiological intervention.

Grade IIIa: Intervention not under general anesthesia

Grade IIIb: Intervention under general anesthesia

Grade IV: Life-threatening complication (including CNS complications) requiring IC/ICU management.

Grade IVa: Single organ dysfunction (including dialysis)

Grade IVb: Multi-organ dysfunction

Grade V: Death of a patient

Suffix "d": If the patient suffers from a complication at the time of discharge the suffix "d" (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator, or IRB/ EC in this Study may discontinue participation in the study or withdrawal approval of the study, respectively. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

Abbreviation	**Definition**
AE	Adverse Event
CA	Competent Authority
CRF / eCRF	Case Report Form / Electronic Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
EBL	Estimated Blood Loss
EC	Ethics Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	Internal Organization for Standardization
ITT	Intent-to-Treat
KUB	Kidney, Ureter, and Bladder

NEMA	National Electrical Manufacturers Association
OD	Outer Diameter
PP	Per Protocol
SA	Safety Analysis
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
USA	United States of America