Protocol for the clinical study titled

Safety and Effectiveness of Ultrasonic Propulsion of Kidney Stones – a feasibility study

University of Washington Investigator Sponsored study IDE G130085

Clinical Trials NCT02028559

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Revised Clinical Trial Protocol
Safety and Effectiveness of Ultrasonic Propulsion of Kidney Stones – a feasibility study

This is an unblinded, first-in-human, early feasibility study, with one randomized component. conducted within the University of Washington medical system in conjunction with the Department of Urology and the Division of Emergency Medicine, and the Puget Sound Veterans Affairs Health Care system in conjunction with the Division of Urology.

Study Number: P1-01-2013

Device Name: Propulse 1

Study Name: Safety and Effectiveness of Ultrasonic Propulsion of Kidney Stones

Study Location: University of Washington Medical Center (UWMC), Department of Urology
UWMC Emergency Department (ED)
Harborview Medical Center (HMC) ED
UWMC Kidney Stone Center (KSC)
Puget Sound VA Urology Clinics

Changes Implemented: upon approval from FDA

STUDY OBJECTIVES	
Primary	Demonstrate the ability to reposition stones within the human kidney collecting system using the Propulse 1 device.
Secondary	Establish if there is any discomfort associated with the ultrasonic propulsion treatment. Qualify and quantify associated complications from the ultrasonic propulsion procedure. Demonstrate the ability to move stones in a controlled direction. Demonstrate the ability to move both large stones (> 5 mm) and small stones (≤ 5 mm). Demonstrate the ability to move an obstructed stone and an associated reduction in pain and/or hydroneprhosis. Demonstrate a reduction in stone volume

Sponsor: _____ Date: _____
Michael Bailey

Principal Investigator: _____ Date: _____
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1 Protocol

This is a first-in-human, early feasibility study conducted within the University of Washington and Puget Sound VA medical system with one randomized component involving post-lithotripsy subjects.

1.1 Study Population

A total of 259 subjects will be recruited for this study. Subjects will be recruited with the aim of obtaining participants from each of the following populations:

1a) Subjects with non-obstructing stones managed under observation or with medical expulsive therapy (*De Novo* population),
1b) Subjects scheduled for shock wave lithotripsy (SWL) or ureteroscopy (URS) laser lithotripsy, to be treated with the investigational device pre-operatively,
2) Subjects scheduled for URS laser lithotripsy, to be treated with the investigational device during the procedure, (URS population)
3) Subjects with residual stones at follow-up to lithotripsy treatment, (RCT population) and
4) Subjects reporting to the emergency department (ED) or clinic with a symptomatic and/or obstructing stone (Acute population).

Typical stone sizes for population groups 1a and 3 will be ≤ 5 mm. Stones for population groups 1b, 2, and 4 will range up to 20 mm.

Subjects will be recruited with the intent to treat 159 individuals, which includes 42 individuals randomized to the control arm of the RCT population. This leaves the potential for 100 screen exclusions. An estimated distribution of subjects across the treatment populations is provided in Table 1. This study is not restricted to the exact numbers listed in this table as more or fewer screen exclusions may be encountered across the different populations. In addition, this protocol does allow subjects to be recruited into multiple arms and receive multiple investigative treatments. Thus, the total number of treatment cases may exceed 117. However, the total number of individual subjects treated will not exceed 117; the total number of controls will not exceed 42; the total number of enrolled subjects will not exceed 259.

Table 1: Planned Recruitment Information

Subject Population	# Subjects Consented but Screen Fail	# Subjects Control Arm	# Treatment Cases*
FIH	5	0	15
URS	9	0	18
RCT	41	42	42
Acute	30	0	22
De Novo	0	0	5
Dislodging	15	0	20

* The Number of individual subjects treated will not exceed 117. This column exceeds 117 and the consented column exceed 259 because at least 5 subjects have been recruited across multiple study populations and are therefore counted twice.

Inclusion Criteria Population Groups 1 through 3:

- Individuals suspected of having at least one kidney stone. This includes:
  - Patients who are being managed with watchful waiting or medical therapy
  - Patients who recently underwent treatment of their stone with SWL or URS.
  - Patients scheduled for SWL or URS treatment

Inclusion Criteria Population Group 4:

- Individuals suspected of having an obstructing stone. This includes:
  - Patients presenting with renal colic
  - Patients presenting with hydronephrosis or dilation of the ureter

Exclusion Criteria Population Groups 1 through 3:

The following subjects will be excluded from this study:

- Individuals under 18 years of age
- Individuals with stones that are not visible with ultrasound
- Individuals not available for follow-up or unwilling to do follow-up
- Individuals with a coagulation abnormality or taking blood thinners or other anticoagulants at clinically significant levels.
- Individuals with mobility issues who are unable to comfortably lie for up to 30 minutes or roll from their back to their side
- Individuals belonging to a vulnerable group (pregnant, mentally disabled, physically disabled, prisoner, etc.)
- Individuals who have already received four previous ultrasonic propulsion treatments
- Individuals who have received an ultrasonic propulsion treatment within the last month (4 weeks)

Exclusion Criteria Population Group 4:

In addition to all the exclusion criteria listed above for population groups 1 through 3, the following subjects will be excluded from this study:

- Individuals with a suspicion of kidney infection or exhibiting signs of sepsis
- Individuals whom the treating physician considers to be at high risk for serious alternate diagnoses such as acute infectious etiologies (e.g. cholecystitis, appendicitis), aortic aneurysm and rupture, or bowel disorders.
- Individuals who have undergone renal transplant, or individuals who will undergo dialysis.
- Individuals with bilateral hydronephrosis
- Individuals with a single kidney
- Individuals who have already received an ultrasonic propulsion investigative treatment for the same obstructing stone

Subject Discontinuation: Subjects may be discontinued from the study at any time at their request. Subjects may also be discontinued by the study coordinator or physician because of an adverse event or other event related to the subject's health or welfare. Subjects may be discontinued from the study because their stone could not be identified on ultrasound. Subjects discontinued prior to the investigational treatment will still be counted as an enrollment against the total number approved by the FDA.

Stopping Rule: Enrollment will be stopped if there are reports of significant adverse events, such as organ injury, severe pain, or worsening obstruction (e.g., steinstrasse), determined to be related to the device or procedure, requiring increased pain medication or accelerated surgical intervention.

1.2 Study Procedure

Patients suspected of having a stone will be screened for this study. Those who meet the study criteria of the population group for which they belong and indicate initial willingness to participate to the clinical staff will be approached by research staff. The research staff will explain the study and obtain informed consent.

After consent, if the subject does not have recent clinical imaging of their stone(s), the subject will receive imaging to determine eligibility. The imaging could include: a low dose CT, an abdominal x-ray, an ultrasound, or a combination of an ultrasound and abdominal x-ray. All subjects must have clinical imaging, obtained as part of their standard-of-care or as a research activity, indicating stones or fragments are present. Otherwise the subject will be removed from the study.

For patients receiving only watchful waiting or medical expulsion therapy (population 1a), the investigative study may occur the same day as the clinic visit, or be rescheduled on a different day. For the pre-surgery SWL and URS participants (population 1b), the investigative study will occur on the same day as (but prior to) the surgical procedure. For the URS surgical participants (population 2), the study will occur during the surgical procedure. For the post SWL and URS participants, the investigative study will occur after 4 weeks post treatment. The subjects will receive imaging confirmation of a stone fragment. For subjects suspected of having an acute obstructing stone, the study may occur during the same visit or be rescheduled on a different day. The study will take place after management of their pain.

Population Group	Treatment Routine Care	Treatment Investigative Study
1a: Observation/medical expulsive therapy	Pass naturally	As available
1b: Scheduled for SWL	SWL	Day of, but before SWL
1b: Scheduled for URS	URS	Day of, but before URS
2: Scheduled for URS	URS	During URS procedure
3: Post SWL; Post URS fragments	Pass naturally	After 4 weeks as available
4: Obstructing stone	Medical management	As available

The sub-sections below list the routine and investigative protocol pre-, peri-, and post ultrasonic propulsion treatment. The ultrasonic propulsion procedure may be conducted on only one side per session. **For no subject, will the standard-of-care be withheld or delayed for the purposes of this study. All subjects will receive medications as usual.** A urologist (vs ED physician) will be consulted for final approval to recruit ED subjects into the study.

Pre Treatment – Routine Care: As part of routine clinical treatment, subjects may be asked to strain their urine and retain stones. Subjects may also be prescribed medications such as analgesics, alpha blockers, and pain medications to take as needed.

Pre Treatment – Investigative Subject Populations 1-3: Research staff will review the subject's chart prior to their clinic visit to determine patient eligibility and to assess for prior history of stones and the corresponding intervention. Potential participants may be contacted via phone prior to their clinic visit to introduce the study. With the patient's permission, consent forms may also be emailed to the subject in advance. Once consented, if not already available, clinical imaging will be ordered to confirm stone presence. Subjects may or may not be screened in advance with ultrasound. The subject will be asked to fill out a pain questionnaire pre and post of the screening exam if they occur on a separate time or day from the investigative study. Contact email or phone number, and home address will be recorded for follow-up and patient availability for follow-up confirmed.

Pre Treatment – Investigative – Subject Population 4: Research or clinical staff will review the subject's chart to determine patient eligibility and to assess for prior history of stones and the corresponding intervention. Research staff will also verify the patient's condition has been managed sufficiently for informed consent. Potential participants will then be approached by the research staff to assess interest in participating in the study. Consented subjects will undergo a dipstick urinalysis or microscopic urinalysis to rule out patients with infection. Contact email or phone number, and home address will be recorded for follow-up and patient availability for follow-up confirmed.

Study Treatment – Investigative – All Subjects: The investigational examination is expected to take 30 minutes to 1 hour and will be performed by either a certified sonographer or physician identified as an investigator for this study and previously trained on the device. The study will take place after consultation with at least one urologist and with at least one physician in attendance.

a) Prior to the ultrasound study, participants will complete a baseline pain questionnaire.
b) A photo of the subject's skin in the region where the probe will be positioned will be taken.
c) Participants will undergo a diagnostic ultrasound examination by a certified physician or sonographer with the investigational device. The sonographer and physician will verify the stone is visible on ultrasound and near the location identified on the most recent diagnostic imaging, if available.

d) Audio and video of the exam will be recorded. Select images of the kidney anatomy and stone will also be captured using the screen capture functionality of the investigational software. A second photograph of the skin in the region where the probe was positioned will be taken between the screening examination and stone pushing.
e) Participants will undergo stone pushing with the investigational device. The operator will begin with low output and increase the output as necessary. The subject will be directly asked if they experienced any sensations with each of the first three pushes. The subject will be advised to report if they feel any change in sensation with the remainder of the study – they will no longer be asked directly. A maximum of three pushes should be attempted from a single probe position and focus. If the stone does not relocate, the operator should alter the angle of approach by (first) rotating the probe to a new angle of approach, (second) repositioning the probe, and (last) repositioning the subject for a more optimal transducer to stone angle (i.e. so as to not push the stone against the tissue wall.)
f) The study staff will monitor the real-time ultrasound image during each burst applied. If echogenicity related to cavitation within the tissue is observed, the treatment will be paused for 1 minute. The treatment will resume at a reduced dose level. This procedure will be repeated as echogenicity related to cavitation in the tissue is continued to be observed. If the treatment setting is reduced to 50 W/cm^2 and cavitation is still observed, the study will be stopped.
g) Select ultrasound images extending over the duration of the Push and a listing of the system settings, including the target location and Push power, will be recorded automatically to the system hard drive. The output voltage, patient position, stone position, and result of the Push burst will also be recorded manually. There are three potential types of motion for each push pulse, 1) no motion, 2) moved but trapped within a confined space, such as a calyx, 3) translation of the stone to a new location. A fourth option that can be recorded is U) unintended Push. This occurred occasionally with the animal studies through accidental activation of the touch screen.
h) With Probe 1 (C5-2 transducer) a maximum of 120 Push bursts will be delivered in a single session and a maximum of 40 Pushes will be delivered to a single location. With the SC-X probe, a maximum on-time of 5 minutes will be delivered in a single session. If the operator switches probes, the sum of the percentage of the limits of use for either probe cannot exceed 100% (e.g., 90 pulses with the C5-2 probe is 75% of the total 120, so 25% of the 5 minute total, or 1 minute 15 s total ON time could be used with SC-X.)
i) Participants will immediately undergo a second diagnostic ultrasound exam to confirm the location of the stone after treatment. Audio and video of the exam will be recorded and select images of the kidney anatomy and stone will also be captured.
j) A third and final photograph of the skin in the region where the probe was positioned will be taken at the conclusion of the investigational study.
k) Participants will complete a second questionnaire at the completion of the exam addressing any discomfort or pain they may have felt related to the procedure.

l) The subject may be provided with a strainer to collect stones during the three week follow-up period. In some investigational procedures passing a stone is unlikely and not relevant to the study so no strainer will necessarily be provided. The subject may also be provided with a medical diary sheet to record their medication use during the three week follow-up period. The diary is a copy of clinical research form 6B.
m) The subject may be provided with subsidized parking pass for the duration of the research study.
n) The subject may be provided with bottled water throughout their stay for the research study to help with hydration.

The study will cease immediately if the participant requests that the study end or if the participant experiences significant pain and/or discomfort. If at any point the participant expresses some level of discomfort, the source of the discomfort will be identified, recorded, and resolved if possible. The operator will use the usual safety procedures for operating a clinical diagnostic ultrasound instrument, including using the ALARA principle.

Exceptions for the URS participants receiving treatment during the surgical procedure.

a) The subject will not complete a baseline pain questionnaire because the investigation procedure will be completed with the subject under anesthesia.
d) The subject will not be asked if they feel any sensation related to the push as they will be under anesthesia.
d) The subject will not be moved to any new scanning positions once the URS guide is inserted.
g) The subject will not be given a post-study pain questionnaire since they will not be awake and accessible for several hours (after recovery). This is not a relevant timeline for obtaining this information; the questionnaire should be delivered immediately following the procedure.

<u>Additions for participants with an obstructing stone</u>

- A urine culture will be ordered for all subjects undergoing treatment to evaluate for the definitive presence of infection in follow-up.

<u>Follow up – Routine Care:</u> As part of the routine treatment patients may be asked to strain their urine and retain stones. Patients may also be prescribed alpha blockers to facilitate stone passage, as well as pain medications to take as needed. Surgical (SWL and URS) participants will also be seen for an ultra-low-dose CT, plainfilm KUB and/or renal ultrasound exam post treatment, as standard care.

<u>Follow up – Investigative –Subjects Undergoing Ultrasonic Propulsion or Enrolled in a Control Group:</u> Research staff will contact the patients each week for three weeks and review their charts each week for the longer of a) 90 days or b) follow-up imaging has been completed to

assess for acute colic events, stone passage, and/or additional interventions/adverse events. Subjects will be asked to record the date of any stone passage since the investigational study. Pain medication taken by the participant will be recorded and converted to Morphine equivalents. With the exception of subjects who underwent the investigational study prior to their surgical treatment, all subjects will be scheduled for follow-up visit if it is not already prescribed as part of their routine care. The subject will be scheduled either for a low dose CT, plainfilm KUB, ultrasound, or a combination of KUB and ultrasound as follow-up. In the case of multiple study treatments, the subject will undergo only 1 follow-up CT; ultrasound and/or plainfilm KUB will be used for any additional follow-up requirements. A certified letter will be sent to any subjects lost to the three week follow-up or post-study imaging visit. The letter will be sent if the subject cannot be reached within four weeks following the study.

In addition, specifically for participants with an acute obstructing stone, subjects will be telephoned with the results of the urine culture test when infection is indicated. This may occur through standard-of-care or by the research team.

For those subjects with residual fragments recruited into the long-term clinical follow-up study, subjects will be contacted semi-annually for up to 3 years and charts reviewed semi-annually for up to 5 years following the investigative study. A subject is considered to have completed the study once the 5-year period has passed or if the subject undergoes a kidney stone procedure as part of their standard-of-care stone management on the same side as enrolled for this study. The reasons why subjects exit either the treatment or control group of the study will be recorded. Potential reasons include treatment failures, lost to follow up, withdrawal, end of study, and death. Subjects who exit the study for surgery resulting from the residual fragments will be adjudicated as treatment failures.

A second blinded physician, radiologist, sonographer, or equally qualified individual will be used to review the ultrasound images and confirm representative documented stone movement.

1.3 Study Analysis

Safety will be determined by the frequency and severity of any adverse events. Effectiveness of the device will be measured by the % of stones moved and average distance of stone motion. The frequency of stone motion in the desired direction (i.e. toward the UPJ or away from the UPJ) will also be assessed. For the observation/medical expulsive therapy population (1a) and stone fragment population (3), the time between treatment and any reported stone passage will be an additional effectiveness parameter. For the obstructing stone population (4), change in pain status and hydronephrosis status, in addition to time between treatment and any reported stone passage, will be additional effectiveness parameters. Sub-categories will include the average number of pushes and the average treatment time.

<u>Safety of ultrasonic propulsion:</u> Safety is a difficult parameter to establish, particularly for the obstructing stone population who are already experiencing symptoms and subjects receiving SWL and URS treatment, since both these procedures my result in potential confounding

complications (see Table 2). In addition, all patients, at any time, could experience complications associated with the natural passage of a stone, such as renal colic, irrespective of having received our investigational treatment.

A method for evaluating complications associated with the investigational study is listed in the bullet points below. Adverse events (AEs) that occur during or after the study will also be subdivided into procedure AEs and device AEs. Procedure AEs are defined as morbidity / mortality events that may occur no matter what device is used. Examples include heart rate changes during treatment, anesthesia issues, discomfort from lying on an exam table, or for this case, intermittent urinary obstruction and other pain events associated with kidney stones. Examples of device AEs include irritation where the probe was in contact with the skin or an AE that occurs as a result of a software issue.

- The number and level of procedural and device AEs identified during and after the investigational procedure will be established.
- The number and severity level of the AEs will be compared with potential occurrences with routine care.
- Medication use will be reported for each subject. The results will be compared against the baseline level of pain medication used by the general stone population that falls within the same treatment group.
- Short-term complications (within 90 days) identified from follow-up contact and medical chart reviews will be recorded including type and frequency. The results will be compared to the types and frequency of complications expected in stone patients on average.
- The presence and degree of hydronephrosis will be compared between the research study visit and follow-on clinical visit. The result will be compared to stone patients on average.

Effectiveness of ultrasonic propulsion: The pre- and post- ultrasound images, video data, and manual data recorded during each push pulse will be used to evaluate stone motion. The motion associated with each push will be categorized based upon the following criteria: 1) no motion, 2) moved but trapped within a confined space, such as a calyx, 3) translation of the stone to a new location, or U) unintended activation of the Push pulse. The distance achieved for motion #3 and an estimate of the total distance moved for the entire treatment will also be determined. Lastly, the anatomical position of each stone will be identified. From these data, quantitative measurements can be made as to the effectiveness of the clinical device in moving stones. The analysis can be made over all subjects, but also broken down based on group, stone location, or stone size groupings.

- % occurrence of each motion level achieved per total number of pushes
- % occurrence of each motion level achieved as a function of anatomical location.
- Average distance moved for motion levels 3
- Total distance moved per stone

- For subjects enrolled in the long term study, % occurrence of clinical stone events and length of time to those events from the investigative study.

Stone Passage: Stone passage will be identified either from the subject urine screen, chart review, or post-treatment imaging compared to pre-treatment imaging. If the stone was captured and sent for stone analysis, the size and type of stone will also be documented.

- The number of ultrasonically treated stones that passed (spontaneously without additional surgical procedures) will be reported.
- If available, the time between the investigational ultrasonic intervention and stone passage will be recorded.

Metrics for Success: The following metrics will be used as a measure of success for an individual study.

- By any measure, the stone moved more than 2 mm.
- The treatment procedure was tolerable to the patient.
- No complication requiring intervention beyond that typically experienced with routine care.
- Decrease in pain, hydronephrosis, or absence of emergency intervention in the 3-week post study follow-up period.

TABLE 2. REPORTED COMPLICATIONS EXPERIENCED UNDER ROUTINE CARE

GROUP	FREQUENCY	COMPLICATION
Post SWL	***> 20% of patients***	
	● Most treatments	Hematuria (blood in urine)[1]
	● Most treatments	Skin redness at shock wave entry site[1]
	● 40% - 45%	Pain / renal colic (abdominal, back, or groin pain caused by stones) [1,2]
	1 – 20% of patients	
	● 2% - 20%	Cardiac arrhythmia[1]
	● 1% - 7%	Urinary tract infection[1]
	● 2% - 10%	Urinary obstruction / steinstrasse [1]
	● occasionally	Skin bruising at shock wave entry site[1]
	● occasionally	Fever (> 38 °C)[1]
	● occasionally	Nausea / vomiting[1]
	< 1% of patients	
		Hematoma (clinically significant blood pool)- perirenal or intrarenal)[1]
		Renal injury[1]
		Sepsis[2]
Post URS (with stent)*	***> 20% of patients***	
		Voiding symptoms (e.g. urinary urgency, frequency, dysuria, bladder pain)[4]
		Pain; renal colic[4]
		Hematuria[4]
		Nausea / Vomiting[5]
		Constipation / Diarrhea[5]
	1 – 20% of patients	Ureteral damage (e.g. perforation, mucosal erosion)[3]
		Urinary tract infection / Sepsis[3]
		Fever (> 38 °C)[3]
	< 1% of patients	
		Renal injury
		Avulsion (tearing or separation of the ureter)[3]
Medical Therapy	3-28%	Symptomatic elimination of fragments[6,7]
	7-26%	Need for intervention[6,7]

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