1 Statement of Compliance

This trial was designed to reflect the Good Clinical Practice (GCP) principles outlined in ISO 14155:2020. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The trial will be conducted according to the protocol, federal, national, and local laws, regulations, standards, and requirements of the countries where the trial is being conducted. The trial will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this trial by means of the Patient Informed Consent (IC) process, Ethics Board approval, trial training, clinical trial registration, pre-clinical testing, risk benefit assessment, and publication policy.

Investigational sites will not be activated nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency and Ethics Board has been obtained. Additionally, any requirements imposed by a local regulatory agency or Ethics Boards shall be followed, as appropriate. Continuing review by the Ethics Boards will be ongoing throughout the conduct of the trial.

This trial will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110- 85, Section 810(a)).

2 Protocol Summary

2.1 Synopsis

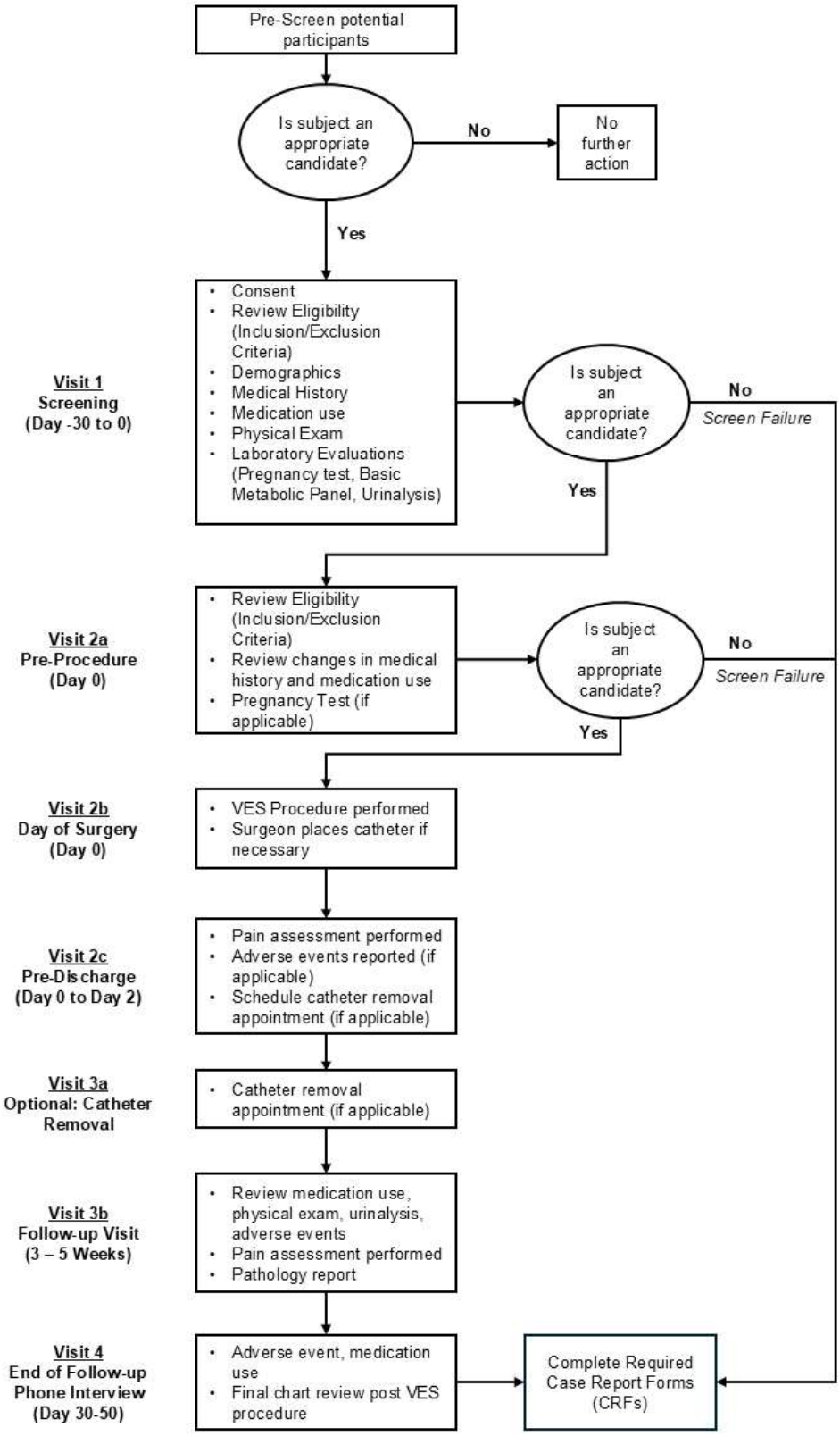
Table 1: VIABLE Clinical Study Synopsis

Title	Virtuoso Improving Anatomic Bladder Lesion Excision (VIABLE) Trial
Study Design	The VIABLE study is a staged study with a Phase I component and a Phase II component. Additional ethical review will be required for Phase II.
Study Objective	The objective of Phase I of this study is to evaluate the feasibility of using the Virtuoso Endoscopy System (VES) to perform safe and effective bladder lesion excisions. The objective of Phase II of this study is to perform a comparative evaluation of the ability of the VES to perform safe and effective bladder lesion excision in comparison to the current standard of care: conventional transurethral resection of bladder tumors (cTURBT).
Study Description	This is a prospective, non-randomized two-phase clinical study. Phase I is a single-center, non-randomized, single-arm study with one operating surgeon. Phase II is a multi-site, non-randomized, single-arm study with multiple operating surgeons.
Study Duration	• The anticipated total duration of each phase of the study is 3 months, which includes conducting bladder lesion removal and/or biopsies via the Virtuoso Endoscopy System with 30 days follow-up for each subject. • The anticipated participant duration is 60 days. This includes a screening visit that can occur up to 30 days prior to the investigational procedure and follow-up for 30 days after the investigational procedure. • Any alternative non-VES procedures performed for bladder lesions within the follow-up period will be recorded for the study but would not extend study follow-up.
Study Institutes and Study Sites	Multiple sites, up to a maximum of five; see VES-251, VIABLE IRB and Institution Document for a list of the sites. The procedure will be performed in an operating room setting.

Enrollment Geography	The subject populations will comply with trial inclusion and exclusion criteria. Patients are expected to be representative and generalizable to bladder resection surgery patients.		
Study Population	This study will enroll subjects 22 years and older with bladder lesions that require removal and/or biopsy for diagnosis, who meet all the inclusion criteria and none of the exclusion criteria.		
Sample Size	In Phase I, the target number of surgical procedures is 6. In Phase II, target enrollment is 30. If there are no VES or protocol changes that impact the validity of the data between Phase I and Phase II, it is acceptable to utilize the patient population from Phase I to contribute to the 30 patients required for Phase II. Phase I must include at least 2 female patients. At least 7 patients total enrolled in the study (Phase I + Phase II) must be female.		
Primary Endpoints	**Primary Endpoint**	**Timeframe**	**Safety/Effectiveness**
	Detrusor muscle presence in the pathologic specimen after VES procedure	Postoperative	Effectiveness
	Adverse events	Intraoperative	Safety
	Adverse events	Postoperative	Safety
Secondary Endpoints	**Secondary Endpoints**	**Timeframe**	**Safety/Effectiveness**
	Rate of conversion to standard cTURBT equipment	Intraoperative	Safety/Effectiveness
	Rate of en bloc lesion excision with VES	Intraoperative	Effectiveness
	Complications (Clavien-Dindo)	Intraoperative	Safety
	Significant bladder perforation requiring intervention	Intraoperative	Safety
	Urethral injury	Intraoperative	Safety
	Transfusion rate	Intraoperative	Safety
	Estimated blood loss	Intraoperative	Safety
	Obturator nerve reflex	Intraoperative	Safety
	Mortality	Intraoperative	Safety
	VES surgery procedural time	Intraoperative	Effectiveness
	Presence of clear, evaluable margins in excised specimen	Postoperative	Effectiveness
	Time of catheterization	Postoperative	Safety
	Time of hospital stay	Postoperative	Safety
	Complications (Clavien-Dindo)	Postoperative	Safety
	Significant bladder perforation requiring intervention	Postoperative	Safety
	Urethral injury	Postoperative	Safety
	30-day reoperation rate	Postoperative	Safety
	30-day hospital readmission rate	Postoperative	Safety

	30-day mortality	Postoperative	Safety
Description of Study Device	The VES provides two dexterous, miniature instrument tools at the tip of a rigid endoscope. It is a digital electromechanical surgical device. The surgeon controls the miniature instruments from a workstation under constant visual feedback. The Virtuoso Endoscopy System is designed to enable high-quality removal and/or biopsy of bladder lesions. In standard bladder resection (cTURBT) and/or biopsy procedures performed currently today, only one straight tool is available at the tip of a rigid endoscope in the form of either a straight laser fiber, resectoscope loop, or biopsy forceps. The VES system provides an instrument for retraction and/or biopsy and an instrument for directing energy during lesion removal or biopsy.		
Study Schedule	Subjects will undergo a screening and enrollment process up to 30 days prior to the procedure and will be followed for 30 days post procedure. For more details on all activities, see the Schedule of Activities in Section 2.3.		

2.2 Schema


Pre-Screen potential participants
Is subject an appropriate candidate?
No
No further action
Yes
Visit 1
Screening
(Day -30 to 0)
Consent
Review Eligibility (Inclusion/Exclusion Criteria)
Demographics
Medical History
Medication use
Physical Exam
Laboratory Evaluations (Pregnancy test, Basic Metabolic Panel, Urinalysis)
Is subject an appropriate candidate?
No
Screen Failure
Yes
Visit 2a
Pre-Procedure
(Day 0)
Review Eligibility (Inclusion/Exclusion Criteria)
Review changes in medical history and medication use
Pregnancy Test (if applicable)
Is subject an appropriate candidate?
No
Screen Failure
Yes
Visit 2b
Day of Surgery
(Day 0)
VES Procedure performed
Surgeon places catheter if necessary
Visit 2c
Pre-Discharge
(Day 0 to Day 2)
Pain assessment performed
Adverse events reported (if applicable)
Schedule catheter removal appointment (if applicable)
Visit 3a
Optional: Catheter Removal
Catheter removal appointment (if applicable)
Visit 3b
Follow-up Visit
(3 – 5 Weeks)
Review medication use, physical exam, urinalysis, adverse events
Pain assessment performed
Pathology report
Visit 4
End of Follow-up Phone Interview
(Day 30-50)
Adverse event, medication use
Final chart review post VES procedure
Complete Required Case Report Forms (CRFs)

6 Study Population

6.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1) The subject is 22 years or older.
2) The subject is eligible and fit for transurethral bladder lesion removal and/or biopsy and has an appropriate indication to go through this surgery.
3) The subject is willing and able to provide written informed consent and comply with the study protocol.
4) The subject can undergo general anesthesia per anesthesiologist assessment.
5) The subject's planned aggregated bladder lesion(s) excision specimens are smaller than 3 cm.[1]

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) The subject has acute untreated urinary tract infection or urosepsis.
2) The subject has a documented nickel allergy or nickel sensitivity.
3) The subject is confirmed to be or suspected to be pregnant.
4) The subject is receiving anticoagulants and is unable or not willing to cease the medication for the investigational procedure.
5) The subject belongs to a vulnerable group (prisoner, etc.)
6) The subject has a urethral abnormality, implant, or previous surgery which would conflict with the procedure.
7) The subject has undergone a transurethral bladder resection procedure in the past 6 months.
8) The subject has a history of radiation treatment within the pelvis.
9) Bladder tumor base maximal dimension is greater than 3 cm.
10) Bladder tumor detected during intravesical therapy.
11) Previous histological diagnosis different than non-muscle invasive bladder cancer.
12) Presence or prior history of upper urinary tract malignancy.
13) Eastern Cooperative Oncology Group performance status greater than or equal to 3.
14) American Society of Anesthesiologists physical status classification of IV or above.
15) History of bleeding disorder, coagulation abnormality, or use of anticoagulants.
16) The presence of other active malignancy.
17) Life expectancy <1 yr.

6.3 Subgroup Considerations

6.3.1 Sex-Specific Considerations

Clinically meaningful differences in treatment effect are not expected across sexes. This expectation is consistent with United States guidelines related to bladder cancer treatment. The American Urological Association and Society of Urologic Oncology do not recommend different treatment approaches for male/female patients [26]. However, since bladder cancer occurs more frequently in males than in females (see

[1] Clarifying language was added to this inclusion criterion. The intent of this inclusion criterion is to prevent attempted removal of specimens that are unlikely to be removed successfully through the endoscope in a single piece – 3 cm is a well-known size limit [16]. The term "aggregate" is intended to account for clustered tumors that could be removed en bloc, where the specimen size may be significantly larger than the individual tumor sizes. For avoidance of doubt, multiple excisions – each of which are less than 3 cm – are acceptable even if the sum of excisions sizes exceeds 3 cm.