T-DOC® 5 French Clinical Study

STUDY NUMBER:

TDOC5Fr-PEDS-01

STUDY NAME:

T-DOC® 5 Fr Pediatric Clinical Investigation:

A Pivotal Study to Assess the Performance, Safety and Usability of a New 5 French Air-Charged Catheter for Performing Urodynamic Studies on Pediatric Subjects

DOCUMENT:

CLINICAL STUDY PROTOCOL

NCT NUMBER:

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Version 2.02

June 26, 2018

CLINICAL STUDY PROTOCOL

DEVICE:

T-DOC® 5 French Air-Charged Vesical and Abdominal Urodynamic Catheters

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KEY SPONSOR TEAM MEMBERS

Sponsor	Primary Monitor
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CLINICAL STUDY PROTOCOL **PREPARED BY**	PRINT NAME: [redacted] Job function: [redacted] Signature : [redacted] Date:

In signing the box below the approver signifies that they have reviewed the protocol and approve it on the basis that it meets the following requirements

1. *The protocol is consistent with the clinical plan*
2. *Adequacy of sample size and appropriateness of proposed statistical analysis*
3. *Accuracy of device description, efficacy and performance characteristics*
4. *Biological safety of Investigational and control devices and their appropriateness for human use*
5. *Conformance to all applicable regulations*
6. *Adequacy in meeting business needs*

CLINICAL STUDY PROTOCOL **APPROVED BY**	PRINT NAME [redacted] Job function [redacted] Signature Date

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INVESTIGATOR(S)

Principal Investigator [redacted]	**Principle Investigator** [redacted]

PARTICIPATING SITE(S)

[redacted]	[redacted]

INSTITUTION(S) INVOLVED

[redacted]	[redacted]

[redacted]

TDOC5Fr-PEDS-01
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“CONFIDENTIAL INFORMATION"

Will mean all information provided by one party to the other and clearly identified as "CONFIDENTIAL" by the transmitting party at the time of disclosure. If such transmittal occurs orally, the transmitting party will promptly reduce such transmittal in writing, mark and identify it as confidential, and provide such record to the other party.

Specifically excepted from this is all information that

1. was previously known by the receiving party
2. is publicly disclosed except by breach of this AGREEMENT either before or subsequent to the receiving party's receipt of such information
3. is rightfully received by the receiving party without an express obligation of confidence
4. is independently developed by personnel of the receiving party without use of or reliance upon information from the other party
5. is disclosed pursuant to any judicial or government request, requirement or order, provided that the disclosing party takes reasonable steps to provide the other party with sufficient prior notice in order to allow the other party to contest such request, requirement or order.

The receiving party will not disclose CONFIDENTIAL INFORMATION without authorization from the disclosing party. This provision shall remain in effect for five (5) years following completion of this study. COMPANY shall be provided with subject information as allowed

by law and will maintain the confidentiality of all such subject information, unless specifically required to disclose such information by law.

INVESTIGATOR STATEMENT

I fully understand the requirements of this study and my role as Investigator. I agree to participate and to comply with the requirements presented to me by Laborie. I agree to follow the protocol laid out before me and to not deviate from it in any way, except to protect the life or well-being of a subject in an emergency. I also agree to document all the required information as fully as I can.

ACCEPTED BY **PRINCIPAL INVESTIGATOR** [redacted]	PRINT NAME TITLE Signature [redacted]
ACCEPTED BY **PRINCIPAL INVESTIGATOR** [redacted]	PRINT NAME TITLE Signature

TDOC5Fr-PEDS-01

T-DOC® 5 Fr Pediatric Clinical Investigation:

A Pivotal Study to Assess the Performance, Safety and Usability of a New 5 French Air-Charged Catheter for Performing Urodynamic Studies on Pediatric Subjects

Document History

	Version	Date Effective	Changes	Rationale for Change
Creation	1.0	October 5, 2017	-	First release
Amendments	2.0	December 1, 2017	- Section 6.1 (Study Design) updated to explain investigational device test results will be given back to referring physician for test interpretation. - Section 3.3 (Rationale) removed obsolete sentence from previous study design: "As mentioned in Section 3.2 above, the performance of ACC is often compared to water-perfused and this will be addressed under the secondary objective of this study."	SSRI feedback from [redacted] IRB & document editing error
	2.01	April 12, 2018	- Administrative updates: Removed [redacted] from sponsor team. - Changed infusion transducer to optional in page 26. - Corrected "-DOC" to "T-DOC" in page 30.	Internal re-structuring & spelling corrections

			- Corrected page 32 reference Section 4.5 (does not exist) to Section 4.4 - Corrected spelling in page 42 from “soured” to “sourced”, page 44 from “stripend” to “stipend”. - Updated Section 20 (Referenced Documents) to include [redacted] forms.	
	2.02	June 26, 2018	- Fixed spelling mistakes (“bacteruria” to “bacteriuria”) - Formatted table of contents to remove wrong headings - Updated Section 10.5 (Contact Information) - Referred to the Statistical Analysis Plan in Section 12.6 (Analysis Plan)	Administrative changes

This is a clinical research protocol for a pivotal human research study. This study is conducted in accordance with the clinical protocol, Good Clinical Practice, and FDA 21 CFR Parts 50, 812 – Investigational Device Exemptions. This study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Table of Contents

1 List of abbreviations

ACC	Air-Charged Catheter
CRF	Case Report Form
IRB	Institutional Review Board
ERP	Enterprise Resource Planning
FDA	Food and Drug Administration
LUT	Lower Urinary Tract
LUTS	Lower Urinary Tract Symptoms
T-DOC®	Commercial name for the LABORIE air-charged catheters
T-DOC® 5 Fr	5 French version of the T-DOC® air-charged catheter
UDS	Urodynamics
USA	United States of America
VUDS	Video Urodynamics
WFC	Water-Filled Catheter

2 INTRODUCTION

2.1 Clinical Study Summary

Number of Sites	1 – 2
Number of Subjects	A minimum of 10 male and 10 female subjects 12 years of age and younger, with an overall minimum of 28, and maximum of 33 subjects
Objective	The primary objective of this study is to gather clinical data as follows: • To confirm that the T-DOC® 5 French vesical and abdominal catheters are safe and effective for measuring urodynamic pressure in pediatric subjects 12 years of age and younger. The secondary objective of this study is to gather user feedback regarding device performance as follows: • To evaluate the following subjective measures using defined ordinal scales: ease of use, presence of artefacts, stability of the tracing, perceived time savings, ease of voiding around the catheter, presence of use errors, and overall satisfaction.
Inclusion criteria	• Male and Female (Children, 12 years of age and younger) • Subjects who are scheduled and normally indicated for urodynamic testing, for any medically necessary reason as per physician discretion.
Exclusion criteria	• Subjects who suffer from bladder infections (not including subjects with asymptomatic bacteriuria) • Subjects with urethral strictures • Subjects who require the use of a suprapubic catheter
Anticipated Study duration	The proposed recruitment phase following site initiation is 12 weeks (first subject in to last subject out). Subjects will come to the clinic for one visit, their urodynamic procedure, where data pertaining to the safety, efficacy and usability aspects of catheter will be collected. Test duration may be slightly longer than a standard test while assessment of the study materials is being made, and so discomfort and inconvenience associated with an extended test duration may occur.
Follow-up	Subject follow-up will occur 5-7 days following the test to collect information about any adverse events post-test.

Study end point	Once the minimum subject recruitment goal is met, the sponsor will be informed. Sites will have an option to continue recruitment until the maximum is reached, given recruitment does not exceed the allocated timeline. There will be a site monitoring visit where the site will be closed out.

2.2 Primary Hypothesis

Clinicians will rate the T-DOC® 5 Fr vesical and abdominal catheter as safe and effective for measuring urodynamic pressure in at least 95% of enrolled pediatric subjects 12 years of age and younger.

For statistical purposes, this hypothesis will be examined based on the two hypothesis test cases found below. A questionnaire will be presented to the clinician where the clinicians response will be limited to two choices. For example, for the question of safety, the clinician may respond with yes (the device is safe) or no (the device is not safe). Accordingly, a binomial distribution function will be used to evaluate the clinical study results related to the primary hypothesis. Because the alternative hypotheses are directionally based, the null hypotheses will be accepted or rejected based on one-tailed tests. As described in section 4.4 the sponsor team has established that subjects are subjected to no more than minimal risk since an IDE is not required for this study, therefore sample size will be determined based on a desired 95% confidence with 90% reliability.

2.2.1 Primary Hypothesis Test for Safety

H_0: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as safe for measuring urodynamic pressure in 95% of enrolled pediatric subjects

H_α: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as safe for measuring urodynamic pressure in less than 95% of enrolled pediatric subjects

2.2.2 Primary Hypothesis Test for Effectiveness

H_0: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as effective for measuring urodynamic pressure in 95% of enrolled pediatric subjects

H_α: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as effective for measuring urodynamic pressure in less than 95% of enrolled pediatric subjects

2.3 Secondary Hypothesis

At least 80% of trained clinical users shall rate the T-DOC® 5 Fr catheter usability performance as 3 or better (on a scale of 1-5) for the clinical user questionnaire, comparing their experience with use of their currently used urodynamics catheter. The

following hypothesis test case will be used to evaluate clinical study results for the secondary hypothesis.

> H_0: 80% of clinicians or more rate T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better comparing their experience with use of their currently used urodynamics catheter.
>
> H_α: Less than 80% of clinicians rate T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better comparing their experience with use of their currently used urodynamics catheter.

A questionnaire will be presented to the clinician. For this hypothesis, clinicians will respond to the questions on a scale of 1 through 5. Although there are five possible options, responses of 3, 4, or 5 will be tallied as a positive result while responses of 1 or 2 will be tallied as a negative result. Categorizing the data in this manner enables the use of a binomial distribution function for evaluating the clinical study results of the secondary hypothesis. Again, because the alternative hypothesis is directionally based, the null hypothesis will be accepted or rejected based on a one-tailed test. However, because the number of clinicians involved in the study is anticipated to be small (≤ 5), the results will be reported based on an 80% confidence and the calculated reliability permitted by the actual sample size achieved (i.e., count of clinicians). See sections 12.3 Secondary Endpoint and 12.5 Sample Size Determination and Power for further details.

2.4 Exploratory Hypothesis

At least 95% of subjects capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain experienced during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at of 5 or lower, on the Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”).

A Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”) will be presented to the subject.

> H_0: 95% or more of subjects capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain experienced experience during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower, on the Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”).
>
> Hα: Less than 95% of subjects capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain experienced experience during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower, on the Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”).

The subjects will be presented with copies the Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”) and asked to respond to the questions by clinic staff who will record their responses on form TDOC5Fr-PEDS-01-CRF4. Subjects will respond to the question on a scale of 1 through 10. To enable the use of a binomial distribution function for data

analysis of the exploratory hypothesis, responses of 1, 2, 3, 4, or 5 will be tallied as a positive result while responses of 6, 7, 8, 9, or 10 will be tallied as a negative result. Additionally, grouping the data in this manner is assumed to minimize much of the variation caused by the nature of subjective feedback from pediatric subjects. Once more, the alternative hypothesis is directionally based, therefore, the null hypothesis will be accepted or rejected based on a one-tailed test. However, because the number of subjects capable of providing feedback on the Wong-Baker scale is anticipated to be limited (≤ 14), the results will be reported based on a 95% confidence and the calculated reliability permitted by the actual sample size achieved (i.e., count of subjects capable of providing feedback on the Wong-Baker scale). See sections 12.4 Exploratory Endpoint and 12.5 Sample Size Determination and Power for further details.

3 BACKGROUND

3.1 Medical Device

Urodynamic testing makes use of both an intravesical (bladder) and abdominal (rectal) catheter, the aim being to make precise pressure-volume measurements in order to characterize LUT function, identify the causes for symptoms, and quantify related pathophysiological processes (Bauer *et al.*, 2015). UDS is considered in children if the outcome of the test is likely to affect treatment choice, or when a treatment does not lead to an intended outcome. Also, UDS testing is considered when surgical interventions are planned (Bauer *et al.*, 2015). Information is gleaned on storage function (detrusor activity, sensation, compliance, and capacity) and voiding function (outflow obstruction, flow pattern, detrusor contractility and sustainability). Abdominal pressure recordings via a small rectal balloon catheter are necessary to accurately assess changes in abdominal pressure as reflected in intravesical pressure changes (Bauer *et al.*, 2015).

Initially, WFCs were the only urodynamic catheter technology available and only intravesical pressure was assessed (Perez & Webster, 1992). However, with the demand for different ways to better assess LUT dysfunction, multiple catheters types have been developed. Currently, there are four different UDS catheter-based technologies available: WFC, ACC, microtip catheters, and fiberoptic catheters. It is generally known that minimal tracings artefacts and non-physiological changes in pressure are desired for a reliable UDS tracing (Couri *et al.,* 2017). It has been noted that ACC are less likely to be influenced by movement, thus decreasing the occurrence of artefacts (Cooper *et al.,* 2011, Gammie *et al.,* 2014). The Sponsor views this as a great advantage in the pediatric population as movement artefact can be a common issue affecting interpretation of the urodynamic tracing. There are several other advantages and disadvantages of the ACC method but they will not be discussed in this protocol.

The existing T-DOC® 7 French air-charged urodynamics catheter line was first introduced to the market in the early 2000s. The design of which comprises a patent-protected catheter balloon charging mechanism (US6447462/EP1255485) facilitates the pressure transfer medium for recording urodynamic pressure and detection of urodynamic events. The device is provided as a sterile, single (one-time) use catheter. [redacted]

The catheters under review in this clinical investigation are a smaller, 5 French version of the existing 7 Fr design, and are intended for use on both pediatric and adult populations for measuring urodynamic pressures.

The 5 French catheter configuration under assessment will be a combination of one both a vesical (bladder) and rectal catheter: a single sensor vesical (bladder) urodynamics catheter, and an abdominal (rectal) urodynamics catheter.

Table 1. Dimensional changes and operational data comparison between 7 French and 5 French.

	Existing T-DOC® 7 French	**Proposed T-DOC® 5 French**
[redacted]	[redacted]	[redacted]
Pves Balloon Sensor Location	1” from the tip	0.78” from the tip
Pabd Balloon Sensor Location	1” from the tip	0.78” from the tip
[redacted]	[redacted]	[redacted]
Catheter Length	23.5”	23.5”
Flow Rate Specification	Maximum 70mL/min	Maximum 50 mL/min
Sensor Balloon Measurement Error	Maximum 4.0% of applied pressure at 0 – 250 cmH_20 (system level)	Maximum 4.0% of applied pressure at 0 – 250 cmH_20 (system level)*
Operational Pressure Range	0 to 250 cmH_20	0 to 250 cmH_20

**Design feasibility test results indicate <3% balloon measurement error*

3.2 Prior Literature & Studies

The T-DOC® ACCs have been regarded as simple to use, easy to insert, set-up, and zero to atmospheric pressure (Internal Doc #PD-TR-151-01). This has been supported by clinical literature indicating that air-charged catheters are gaining popularity due to their simple handling and set-up (Chapple, MacDiarmid & Patel, 2009). Several studies have been published that examine the accuracy and behaviour of ACCs, both in non-clinical (Cooper *et al.*, 2011, Couri *et al., 2007*), and clinical (Gammie *et al.,* 2016, Digesu *et al.*, 2014) settings. The use of ACCs is often compared to other methods (water-perfused or microtip catheters) like in the literature by Gammie *et al.,* Digesu *et al*. and Cooper *et al.*, however in this study we will not be collecting objective patient data comparing the performance of ACCs vs. WFCs or any other method. Since this is a new investigational device, there is no prior literature examining the safety and effectiveness of the T-DOC® 5 Fr catheter in pediatric patients.

Please refer to Section 5 of the Investigator Brochure (TDOC5Fr-PEDS-01-IB) for a more detailed review of the available prior clinical literature.

3.3 Rationale

To the study sponsors' knowledge, previous pediatric data has not been published examining the safety, performance or usability of the T-DOC® air-charged UDS catheter technology in the pediatric population, therefore it is necessary to conduct this study in order to collect this data. This study will involve collection of safety and performance data, clinical user feedback, the recording of optimal insertion depth among other metrics, which will feed into use factors and product labelling.

This is considered a pivotal study as these data will be used to comply with the essential requirements from a regulatory perspective. A pilot study is not warranted based on extensive pre-clinical testing (see TDOC5Fr-PEDS-01-IB, Section 4) and the fact that this is not a new technology, nor new diagnostic technique. UDS is a well-established technique in characterizing LUT function in children (Bauer *et al.*, 2015), and the technical performance of ACCs has been proven to be suitable for UDS (Couri *et al.*, 2017). Finally, there will be no control arm, blinding, or treatment/intervention component to this study. This is based on the trial design and the fact that this is a non-comparative study, inclusion of a sham or placebo is not feasible nor necessary, and the device under evaluation is not a treatment or intervention.

Previous literature has indicated that older children and adolescents anatomically can tolerate a 7 French urethral catheter, from approximately the age of 10 according to one expert (Gray 2012). Therefore, for the purposes of our study and to be consistent with an FDA pediatric guidance (U.S. Department of Health and Human Services, 2014), our recruitment will focus on children 12 years of age and younger which will include the Pediatric Subgroups 'Child' (ages 2 to 12 years of age), 'Infant' (>1 month to 2 years) and 'Newborn (neonate)' (birth to 1 month of age) where urodynamics is normally indicated. It is recommended that in children born with

myelomeningocele, a tethered spinal cord, sacral angenesis, or an anorectal malformation, a baseline UDS should be obtained between 3 and 6 months of age and routinely yearly thereafter if the child is at risk for a changing neurological lesion (Drzewiecki & Bauer, 2015). This establishes utility of performing UDS in these very young patients. Utility in newborns suffering from myelomeningocele has also been studied in order to identify those at an early and increased risk of rapid structural deterioration of the urinary tract (Bauer *et al.,* 1984, Sidi, Dykstra & Gonzalez, 1986). For the purposes of this study, decisions regarding timing for prescribing urodynamic testing will be at the discretion of the Investigators.

4 STUDY OBJECTIVES

4.1 Primary Objectives

The primary objective of this pivotal study is to gather clinical data as follows:

- To confirm that the T-DOC® 5Fr vesical and abdominal catheters are safe and effective for measuring urodynamic pressure in pediatric subjects 12 years of age and younger.

4.2 Secondary Objectives

The secondary objective of this pivotal study is to gather user feedback regarding device usability performance as follows:

- To evaluate the following subjective measures using defined ordinal scales: ease of use, ease of insertion, presence of artefacts, stability of the tracing, perceived time savings, ease of voiding around catheter, presence of use errors and overall satisfaction.

4.3 Exploratory Objectives

There are two exploratory objectives for this study. The first is to gather subjective subject feedback from those able to communicate this feedback for exploring whether the newly designed, smaller sized T-DOC® 5 Fr catheters cause undue discomfort based on subjective subject feedback regarding the discomfort and pain level. The second exploratory objective is to gather initial data regarding the effect of several factors (e.g., age, gender, weight, height) on optimal insertion depth of the T-DOC® 5 Fr catheters. These data will be analysed to form a basis for suggesting further hypotheses for later research.

4.4 Assessment of Risks and Adverse Device Effects

Risks to the subject will be no greater than those of a standard UDS test. Subjects may experience temporary discomfort upon insertion of the catheters. Test duration may be slightly longer than a standard test while assessment of the study materials is being made, and so discomfort and inconvenience associated with an extended test duration may occur.

Urodynamic testing exposes subjects to risks of urethral instrumentation which can result in infection, urethral trauma and pain (Winters *et al.* 2012). Other risks can include transient discomfort during or following the procedure, transient dysuria or bleeding (hematuria) following the procedure, or urinary tract infection occurs in 2-4% of subjects (Chapple, MacDiarmid & Patel, 2009). Thus, the clinician must weigh the risks and benefits as to whether the urodynamic test offers additional diagnostic value beyond symptom assessment, physical examination and other diagnostic testing (Winters *et al.,* 2012). The risks of radiation exposure during VUDS should also be weighed against the benefits, and explained to the subject (or subject's guardian), however LABORIE does not manufacture radiation-emitting devices and so we do not offer mitigation against these risks.

In conclusion, the overall residual risks associated with the use of T-DOC® 5 French catheters within this study set-up, are acceptable when weighed against the benefits, and are no different than the risks when using other urodynamic catheter technologies. The sponsor team has also established that subjects are subjected to no more than minimal risk since an IDE is not required for this study (Ref: TDOC5Fr-PEDS-01 - Risk Determination). Lastly, UDS and VUDS are widely-performed procedures on pediatric subjects requiring specialized management for urinary incontinence/retention problems, as recommended by the ICS (Abrams *et al.,* 2013), and is useful in characterizing LUT function, identifying causes of symptoms and quantifying related pathophysiological processes (Bauer *et al.*, 2015).

5 MEDICAL DEVICE

5.1 Description

[redacted] The catheters used in this study will be design verified, sterilized and appropriately labelled before the clinical investigation can begin.

The catheter device models to be evaluated as part of this study include:

1. T-DOC 5 Fr vesical single sensor catheter (yellow)
2. T-DOC 5 Fr abdominal single sensor catheters (blue)

Traceability of investigational study materials will be maintained via the Inventory Control Log (Q905-FRM-17). Traceability of non-investigational materials required for the study will be maintained through sales order shipment tracking using the sponsor's ERP system. Any remaining investigational material stock after study close-out will be returned to the study sponsor at the sponsors' expense.

The T-DOC® 5 French catheters are manufactured using equivalent materials to the existing T-DOC® catheters [redacted], and are verified biocompatible in accordance with the standards EN ISO 10993-5 and -10 and -18 – Biological evaluation of medical devices.

None of the materials being used in this study contain biologically active substances or pharmacological agents.

From a Regulatory standpoint, the following medical device classification rules apply in Europe, the United States and Canada, respectively:

Product Classification Rule

In Summary:

For the European Union, Class IIa

For the United States, Class II as per FDA

For Canada, Class II as per Health Canada Medical Device Regulations

5.2 Purpose & Use

Intended Use: The Urodynamic Catheters are intended for measuring urodynamic pressures. The Urodynamic Catheters are intended to be connected to Urodynamic Analyzer systems using a reusable electronic cable.

Indications for Use: The Urodynamic Catheters are sterile and intended for single use on adult and pediatric patient population requiring urodynamic pressure monitoring through the measurement of bladder, vaginal, urethral and rectal pressures.

NOTE: Recruitment of adult patients is not within the scope of this study. Urodynamic pressure monitoring of vaginal and urethral pressure measurements is also not within the scope.

5.3 Summary of Non-Clinical Safety & Performance Data

The T-DOC® 5 French family of Urodynamic catheters will be tested per ISO 10993 and must meet all biocompatibility requirements for acute tissue contacting devices which includes Cytotoxicity, Sensitization, and Irritation. Furthermore, design verification studies will be undertaken to verify that Level 2 design requirements are met. Please refer to the Investigator Brochure for further details.

5.4 Summary of Clinical Safety and Performance Data

Please refer to Section 5 of the Investigator Brochure (TDOC5Fr-PEDS-01-IB) for detailed review of relevant previous clinical safety and performance data. In all literature presented, the T-DOC® air-charged catheters are safe and effective for measuring urodynamic pressures further justifying the study rationale.

5.5 Risks and Benefits

Please refer also to Section 4.**4** above (Assessment of Risks and Adverse Device Effects), and Section 6 of the Investigator Brochure (TDOC5Fr-PEDS-01-IB).

Risks to the subject will be no greater than those of a standard urodynamics test. Physicians are responsible for determining whether subjects are normally indicated, and who would benefit from urodynamic testing are eligible for recruitment into this study. There is no direct subject benefit for participating other than to gather objective evidence of T-DOC® 5 French air-charged catheter clinical use.

It is important to note the American Urological Association (AUA) has identified two clear categories of subjects who may benefit from urodynamic studies (Winters *et al*., 2012): (1) those in whom information beyond that obtained by a history, physical examination and basic tests is necessary in order to make an accurate diagnosis and direct therapeutic decisions, and (2) those whose LUT condition may have the potential to cause deleterious and irreversible effects on the upper urinary tracts. Marked functional and anatomic abnormalities can be present even in the absence of concomitant proportionate symptoms, particularly in subjects with neurologic disease.

In conclusion, the overall residual risks associated with the use of T-DOC® 5 French catheters within this study set-up, are acceptable when weighed against the benefits. The sponsor team has also established that subjects are subjected to no more than minimal risk since an IDE is not required for this study (Ref: TDOC5Fr-PEDS-01 - Risk Determination). Lastly, Urodynamics is already a widely performed procedure on pediatric subjects requiring specialized management for urinary incontinence issues, as recommended by the ICS (Abrams *et al.,* 2013), and is useful in characterizing LUT function, identifying causes of symptoms and quantifying related pathophysiological processes (Bauer *et al.*, 2015).

6 STUDY DESIGN

6.1 Description

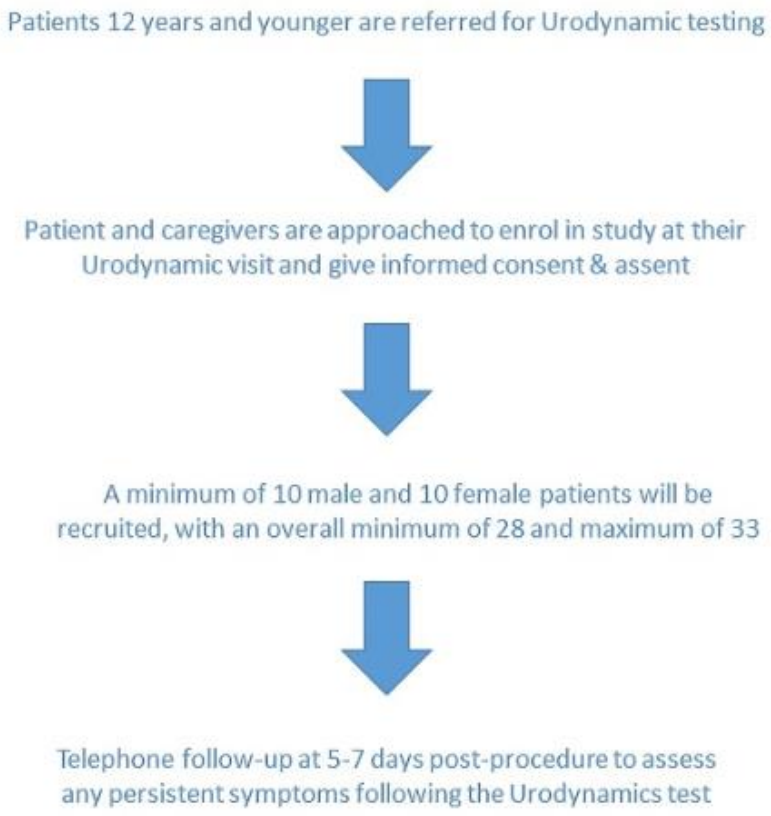
This pivotal study will be conducted where a minimum number of subjects will undergo a conventional urodynamic study (VUDS or non-VUDS) using the investigational device that will be conducted according to Good Urodynamic Practices (Rosier *et al*., 2016). There is no need

for any repeat catheterization or urodynamics testing using an approved (non-investigational) urodynamics catheter. Urodynamic test results using the investigational device will be provided back to the referring physician for test interpretation. Given positive test results for the investigational device design verification and manufacturing process validation in accordance with ISO 13485, the sponsor has no reason to suspect device safety and performance will be any different as compared to the currently marketed T-DOC® 7 French catheter. Therefore, to reiterate, the urodynamics pressure data collected using the investigational device will be used in the referring physician's test interpretation for each participant enrolled, unless there is reason to believe the test should be repeated. This can happen under normal (non-investigational) circumstances if the test was inconclusive (Abrams, 2006).

Further subject data collected will include age, medical history, height, weight, adverse events during or immediately following the test and 5-7 days follow-up, catheter insertion depth etc., as objective evidence on each patients CRF. There will be no control arm, blinding, or treatment/intervention component to this study.

In order to evaluate prospective product claims, a usability questionnaire will also be completed (one per clinical user, defined as an individual trained and certified to perform UDS). The study aim is to enlist 5 clinical users across 1-2 sites. Five users will allow for 85% of use errors to be detected (U.S. Department of Health and Human Services, 2016). A minimum of 1 physician should be utilized.

The following schematic diagram gives a high-level overview of the study design and subject flow-through:



6.2 Duration

The expected duration of each subject's participation is one clinic visit to receive their already prescribed urodynamics test. Once ethics board approval is received, site training and initiation is expected to take 1-2 weeks, whereas the estimated duration of active recruitment for this study is estimated at 3-4 months. Database lockout and study report completion is estimated at 2 months after the last subject is recruited.

7 SUBJECT SELECTION

7.1 Inclusion Criteria

- Male and Female (Children and infants, 12 years of age and younger)
- Subjects who are scheduled and normally indicated for urodynamics testing, for any medically necessary reason as per the physician.

7.2 Exclusion Criteria

- Subjects who suffer from bladder infections (not including subjects with asymptomatic bacteriuria)
- Subjects with urethral strictures
- Subjects who require the use of a suprapubic catheter

7.3 Vulnerable Populations

Subjects inherently represent a vulnerable population group, and so consideration for anatomical and physiological differences from adult subjects will be taken into consideration. The major premise of this study is that the T-DOC® 5 French catheter is smaller in size, and is therefore better suited for subjects with a smaller anatomy.

7.4 Recruitment Plans

The target enrolment is a minimum of 28 subjects up to a maximum enrolment of 33 subjects. A minimum of 10 male patients and 10 female patients shall be recruited so that insertion depths and any usability issues identified with one or both genders can be reliably identified.

Subjects who are visiting the urodynamics clinic for their medically-indicated urodynamics test will be approached regarding participation in this study. It is estimated that recruitment will be 3 subjects per week, therefore it should take approximately 9-12 weeks to recruit 28-33 subjects. Recruitment will be monitored through scheduled meetings with the site co-ordinator. If the subject and legal guardian sign the informed consent, this will be treated as the point of enrolment.

7.5 Informed Consent Process

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the subject and parents/guardians of all pertinent aspects of this clinical trial, including the written information giving a favourable opinion by the IRB. New information in regard to the study will be provided to the subject by the Site.

Prior to a subject's participation in the clinical trial, the written Informed Consent Form should be signed, name filled in and personally dated by the subject's parent/guardian, and by the person who conducted the informed consent discussion. Additionally, the subject's assent should be collected. A copy of the signed and dated written Informed Consent Form & Assent will be provided to the subject/guardian. The date of informed consent and assent should be recorded on the subject's CRF.

The Informed Consent Form & Assent used by the Investigator for obtaining the subject's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB for approval/favourable opinion.

The Informed Consent process will follow the ethical procedures as outlined in 21 CFR Part 50 – Subpart D – Additional Safeguards for Children in Clinical Investigations. The IRB will determine whether there is no more than minimal risk to the child in determining whether one or both parents must provide their consent. Provisions will be made for soliciting assent of the child wherever possible.

The study sponsor does not foresee any circumstances where emergency enrolment would occur due to the device indication (it is not used in emergency situations), and the fact that patients being recruited are attending their urodynamics appointment as a pre-scheduled visit.

7.6 Subject Withdrawal

Subjects may withdraw voluntarily from the study or the investigator may terminate a subject's participation (see below). The Investigator will notify the sponsor when a subject is withdrawn from the study (and if possible why), and this will be recorded on the subject's CRF. Subjects who withdraw from the trial will be allowed to be replaced by another subject.

7.7 Suspension or premature termination

The study may be terminated prematurely if the Sponsor or the Investigator feel that the equipment is not producing results as expected which could be due to inappropriate operator handling or faulty equipment. The Investigator and/or sponsor would determine termination by observing unanticipated problems, design defects or evidence of noncompliance, or serious and/or continuing noncompliance which could affect any of subject safety, device performance or integrity of study data.

This study does not include blinding and so a process for accessing and unblinding subjects and Investigators is not required.

8 MANAGEMENT OF MEDICAL DEVICE

8.1 Description

The following devices and equipment will be required for each patient. Those indicated by asterisk are to be sourced and provided by the site:

- Laborie Urodynamics processor already in use
- Computer/laptop with Laborie UDS-120 urodynamics software already loaded and in use by each site
- Infusion transducer (optional)
- Uroflowmetry/Urocap device configured with the Urodynamics processor and computer for pressure-flow studies, already in use by each site (optional)

- T-DOC® transducer cables:
    - Pabd (blue) – Abdominal channel reusable cable
    - Pves (yellow) – Bladder channel reusable cable
- One (1) air-charged T-DOC® 5 Fr abdominal single sensor catheter per subject
- One (1) air-charged T-DOC® 5 Fr radiopaque or non-radiopaque single sensor catheter per subject
- EMG cable (optional component at the discretion of the site)
- EMG patches (optional component at the discretion of the site)
- Laborie Urodynamics pump tubing infusion line per subject (must be Laborie part number: TUB500)
- 1000 mL beaker* (whatever is currently in use at the site)
- One (1) sterile saline bag per subject*
- One (1) bottle omniopaque / contrast fluid per subject (VUDS only)*
- Tape*
- Lubricant*
- Gloves*
- Any other supplies deemed necessary for conducting a Urodynamic study*

The study agreement will further specify the equipment and disposables that will be required and provided by Laborie.

8.2 Regimen

N/A – there is no treatment regimen required as part of this study.

8.3 Assignment to Groups

Once enrolled, subjects will be stratified to male and female subjects (defined as gender at birth), and to ensure minimum enrolment targets are met. This includes:

- A minimum of 10 male subjects
- A minimum of 10 female subjects

8.4 Preparation and Handling

The Urodynamics system and air-charged catheters will be prepared, and maintained by the physician. Catheters should be stored between -25°C to +50°C.

8.5 Packaging and Labelling

Investigational device labelling will appear on all investigational materials under FDA 21 CRF Subpart 812.5. A copy of the investigational label is shown the Investigator's Brochure.

8.6 Device Accountability

All devices used directly for testing subjects must be recorded using the device LOT number on the subjects CRF form.

8.6.1 Laborie to Study Site:

All investigational devices or equipment transferred between Laborie and the study site must be recorded through the Inventory Control Form. This includes postal deliveries and any deliveries made in person by Laborie. Any equipment or devices that are not used and are returned to Laborie must be recorded on the Inventory Control Log Template as well. When the devices have been received by Laborie, it is their responsibility to ensure that all inventory both at Laborie and the study site correlate. All investigational device accountability will be recorded through the Inventory Control Form.

8.6.2 Study Site Usage:

All devices used directly for testing subject samples must be recorded on the Inventory Control Form. All devices used by the study site that are not directly used for the testing of subject samples must be recorded on the Inventory Control Form. This includes any devices used for training or demonstration or any devices which are noted to be defective when opened.

8.7 Concomitant Treatment

This study will not make use of any concomitant treatments nor will the subject samples interact with any medical treatment or medications.

8.8 Subject Compliance Monitoring

Not applicable in this study.

9 ASSESSMENT OF INVESTIGATIONAL DEVICE

9.1 Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To confirm the T-DOC® 5Fr vesical and abdominal catheters as a safe and effective means of measuring urodynamic pressure in pediatric subjects 12 years of age and younger.	The primary endpoint will be measured by recording the clinician safety and effectiveness rating for each patient on their CRF. The clinician will indicate whether the T-DOC® 5 Fr vesical and abdominal catheters are safe and effective for measuring urodynamics pressure in at least 95% of patients enrolled.	Given the intended use of the device, and the fact that there is no single or combination of objective measures generated from the urodynamics test that can establish the safety and effectiveness, it is justified to obtain clinician feedback via a binomial response whether the device was safe and/or effective for measuring urodynamic pressure.
Secondary		
To evaluate the usability of the device by collecting subjective feedback using defined ordinal scales: ease of use, ease of insertion, presence of artefacts, stability of the tracing, perceived time savings, ease of voiding around catheter, presence of use errors and overall satisfaction.	The usability performance endpoint will be captured in a questionnaire format. At least 80% of trained clinical users shall rate the T-DOC® 5 Fr performance as 3.0 or better (on a scale of 1-5) on the study outcome questionnaire.	When evaluating the usability of a device, the Sponsor feels its appropriate to use a subjective ordinal scale response while evaluating human and device usability factors.
Tertiary/Exploratory		
To explore whether the newly designed, smaller sized T-DOC® 5 Fr catheters causes undue	This exploratory endpoint will be measured by collecting patient feedback (within the abilities of	Given the patient population, use of the Wong-Baker face

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
discomfort based on subjective subject feedback regarding the discomfort and pain level, for those able to communicate such feedback	the child) regarding the level of discomfort and pain experienced during their Urodynamic test using the Wong-Baker visual analogue scale. 95% of patients capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain at 5 or lower, on the Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”).	pain scale is a proven tool in evaluating pain ratings in children and can be used for children as young as 3 years old (Hockenberry, Wilson & Rodgers, 2016).
To explore the effect of several factors (e.g., age, gender, weight, height) on optimal insertion depth of the T-DOC® 5 Fr catheters.	Subjects’ age, gender, weight, and height will be recorded on TDOC5Fr-PEDS-01-CRF1. These data will be analysed to determine a subject stratification approach to be used in examining further hypotheses for later research regarding optimal insertion depth.	The sponsor would like to collect this information, due to a lack of available published data.

9.2 Methods of Assessment

A T-DOC® 5 French air-charged catheter will be used to assess and record bladder and abdominal pressures which are in turn used by the clinician to identify urodynamic events. These measurements will be recorded using a LABORIE urodynamics system. The resulting interpretations regarding safety, effectiveness, and usability will be made by the physician overseeing the subject’s case. Patients capable of providing feedback regarding their level of discomfort experienced during the procedure with the T-DOC® 5Fr vesical and abdominal catheters will be presented with copies of the Wong-Baker scale from 0 (“No Hurt”) to 10 (“Hurts worst”) and asked questions by clinic staff who will record their responses on form TDOC5Fr-PEDS-01-CRF4. Subjects will respond to the questions on a scale of 1 through 10.

All study outcome data captured will be compiled and analysed by the LABORIE study team to determine if the endpoints were successfully achieved based on whether the null hypotheses were accepted or rejected.

10 SUBJECT SAFETY

10.1 Definitions

10.1.1 Adverse Events:

Any untoward medical occurrence in a subject, whether or not related to the investigational medical device.

10.1.2 Adverse Device Effect:

Any adverse event related to the use of an investigation medical device.

10.1.3 Device Deficiency:

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

10.1.4 Serious Adverse Event:

An adverse event that:

1. Led to a death;
2. Led to a serious deterioration in health of a subject, user, or others that:
    a. Results in a life-threatening illness or injury;
    b. Results in a permanent impairment of a body structure or body function;
    c. Requires in subject hospitalization or prolongation of existing hospitalization;
    d. Results in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function;
3. Led to foetal distress, foetal death or a congenital abnormality/birth defect.

10.1.5 Unanticipated Adverse Device Effect:

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 investigation protocol or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.1.6 Unanticipated Serious Adverse Device Effect (USADE):

Serious adverse device effect which by nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.2 Data Collection

Adverse events, device deficiencies, serious adverse events, and unanticipated adverse device effect shall be recorded on the CRF.

10.3 Reporting

All serious adverse events and unanticipated adverse device effects occurring during the investigation will be reported as soon as possible, but no later than 10 working days after the Investigator/Laborie first learns of the effect. This information will be submitted to Laborie/investigator and the IRB.

10.4 Foreseeable Events

For a complete Risk Management Report please refer to the Risk Management File. The residual risks have been deemed acceptable and the benefits overweighs the risks. Please also refer to Section 4.4 above Assessment of Risks and Adverse Device Effects

10.5 Contact Information

In the event of a serious adverse event and serious adverse device event please contact:

[redacted]

10.6 Follow-Up

If an adverse event occurs, any follow-up intervention prescribed is at the discretion of the Investigator, and the site must notify Laborie of the outcome of the follow-up. The study safety endpoint will be measured by capturing adverse event data both during the study visit, and at 5-7 days post-test follow-up.

11 STUDY PROCEDURE

11.1 Visit Schedule

Evaluation	Screening & Clinic Visit	Follow-up
	Day 1	Day 5-7
Informed Consent & Assent	X	
Inclusion Criteria	X	
Exclusion Criteria	X	
Record any Adverse Events	X	X

Questionnaire for Operator (once minimum 3 subjects completed)		X

11.2 Screening for Eligibility

Subject's may be screened for eligibility for this study by referencing the inclusion criteria. No special testing is required in order to determine eligibility.

11.3 Day 1 (Screening & Clinic Visit)

1. Determine if the subject is eligible for this study.
2. Conduct Informed Consent and Assent discussion with the subject and guardian and sign where required.
3. Collect medical history and record in case report form (TDOC5Fr-PEDS-01-CRF2).
4. Collect and record other patient details as required on TDOC5Fr-PEDS-01-CRF1 [weight (lbs), height (',"), date of birth, sex, etc].
5. Site personnel will explain what will happen during the urodynamics test to the subject/parent or caregiver.
6. Site personnel will prepare urodynamics equipment, study materials, other sterile disposables and supplies as required for the urodynamic study and record catheter lot number information on TDOC5Fr-PEDS-01-CRF1.
7. Follow the investigational device instructions for use for placing the catheters. Record insertion depth once catheter is in place on TDOC5Fr-PEDS-01-CRF1.
8. Conduct urodynamic study according to Good Urodynamic Practice recommendations, including regular cough checking to ensure good pressure transmission and catheter positioning wherever possible (Rosier *et al.,* 2016).
9. If within capabilities of the child, and if their condition allows, complete TDOC5Fr-PEDS-01-CRF4 – Subject Questionnaire.

11.4 Day 5-7 (Follow-Up)

1. Site personnel will telephone the subject's guardian/caregiver and inquire about any adverse events that occurred after Visit 1 that may or may not be persistent. Record the call details on the subjects' CRF (TDOC5Fr-PEDS-01-CRF1).

NOTE: If an adverse event occurs during this study, any follow-up intervention prescribed is at the discretion of the Investigator. Each subject will be contacted 5-7 days post-test in order to record the occurrence of any adverse events. Any subject with persistent symptoms post-test shall be followed until such a time it is resolved, and the site must notify Laborie of the

outcome of the follow-up. This information should also be recorded on the subjet's CRF (TDOC5Fr-PEDS-01-CRF1).

11.5 End of Study (EOS)

At the conclusion of the urodynamics test, the subject is no longer required to undergo any further study-related procedures, with the exception of a 5-7 day telephone follow-up.

Once a clinical user has performed a minimum of 3 urodynamic studies and the related tasks under this protocol, they are then eligible to complete the Usability Questionnaire (TDOC5Fr-PEDS-01-CRF3).

Once a site has completed its' target recruitment, the sponsor (Laborie) will schedule a time to close-out the site, either in person or by telephone as per Section 14.1. All study related files will be collected and reviewed for completeness. Final arrangements will be discussed regarding payment at this point in time. The EOS is considered the point when all subjects have been followed-up and data collection completed.

12 STATISTICAL CONSIDERATIONS

12.1 Primary Endpoint

In order to satisfy the primary endpoint, each subject CRF will include a binomial question regarding clinician acceptance of the device as being both safe and effective. According to the risk determination outlined in section 4.4 Assessment of Risks and Adverse Device Effects, no more than minimal risk is foreseen for the subject by participating in this study. Given this, the allowable Type I error (α) will be 5% (1-confidence), such that the clinician will grade the device as being safe and effective for 95% of subjects enrolled in this study. Whereas the corresponding Type II error is estimated at 10% (reliability). As stated earlier, safety and effectiveness will be evaluated separately via the following sets of hypotheses:

12.1.1 Primary Hypothesis Test for Safety

H_0: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as safe for measuring urodynamic pressure in 95% of enrolled pediatric subjects

H_α: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as safe for measuring urodynamic pressure in less than 95% of enrolled pediatric subjects

12.1.2 Primary Hypothesis Test for Effectiveness

H_0: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as effective for measuring urodynamic pressure in 95% of enrolled pediatric subjects

H_α: Clinicians rate T-DOC® 5 Fr vesical and abdominal catheter as effective for measuring urodynamic pressure in less than 95% of enrolled pediatric subjects

In both cases, analysis of the clinical results will be performed as outlined below based on a binomial distribution. In general, the probability mass function of a binomial random variable X is:

$$f(x)= (\binom{n}{x} p^x (1-p)^{n-x})$$

In this study, n represents the number of patients accepted into the trial; x represents the number of procedures for which clinicians rate the device as safe or effective (as the case may be); and p = 0.95 (as stated in the null hypothesis that 95% of the time clinicians rate the device as safe or effective as the case may be).

Because the alternative hypotheses are directionally based, the null hypotheses will be accepted or rejected based on one-tailed tests. If the numbers of patients accepted into the trial is 28 as expected (see section 12.2 Sample Size Determination & Power), the test statistic, for both one-tailed tests with an α =.05, will be:

$$P(true\ X \leq\ x) = \binom{28}{x} 0.95^x (1-0.95)^{28-x} \leq\ 0.05$$

Solving for x in the case of 28 patients results in the null hypothesis being rejected when 24 procedures or fewer are rated as safe and accepted when 25 or more procedures have been rated safe. The actual results will be tabulated based on the actual number of patients excepted into the study.

12.2 Secondary Endpoint

To satisfy the secondary (usability) endpoint, a categorical response variable using a defined ordinal data scale will be used. At least 80% of clinical users, who have performed three or more procedures with subject device, shall rate the T-DOC® 5 Fr catheter usability performance as 3.0 or better (on a scale of 1-5) for the clinical user questionnaire, comparing their experience with use of their currently used urodynamics catheter. For this endpoint, eligible clinicians will respond to the questions on a scale of 1 through 5. To enable analysis based on a Binomial Distributions, responses of 3, 4, or 5 will be tallied as a positive result while responses of 1 or 2 will be tallied as a negative result. However, because the number of clinicians who perform three procedures or more with the T-DOC® 5 Fr vesical and abdominal catheter during this study is anticipated to be small (≤ 5), the results will be reported based on the confidence of 95% (based on the assumed minimal risk level described in section 4.4) and the calculated reliability permitted by the actual sample size achieved (i.e., count of eligible clinicians). The following hypothesis test case will be used to evaluate clinical study results.

H_0: 80% of clinicians rate T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better compared to their experience with their currently used urodynamics catheter.

H_α: Less than 80% of clinicians rate T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better compared to their experience with their currently used urodynamics catheter.

The probability mass function of a binomial random variable X stated above will again be used to analyse the questionnaire data. For the secondary endpoint, n represents the number of clinicians who performed three or more procedures with the T-DOC® 5 Fr vesical and abdominal catheter; x represents the number of procedures for which the eligible clinicians rate the device usability performance as 3 or better compared to their experience with their currently used urodynamics catheter; and p = 0.8 (as stated in the null hypothesis that 80% of the time clinicians rate the device usability performance as 3 or better compared to their experience with their currently used urodynamics catheter).

Again, because the alternative hypothesis is directionally based, the null hypotheses will be accepted or rejected based on a one-tailed test. For example, if the numbers of clinicians eligible to complete a questionnaire is 5, the test statistic, for the one-tailed tests, with an α =.05 will be:

$$\mathrm{P}(\text{true X} \leq x) = \binom{5}{x} 0.8^x (1-0.8)^{5-x} \leq .05$$

Again, if it is assumed that 5 clinicians respond to the questionnaire, the reliability level would be 55% (see Section 12.5 Sample Size Determination and Power). Solving for x based on this assumption would then result in the null hypothesis being rejected when 1 or fewer clinicians rate the T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better compared to their experience with their currently used urodynamics catheter and accepted when 2 or more clinicians rate the T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better compared to their experience with their currently used urodynamics catheter.

Alternatively, a second calculated confidence and reliability level combination could be 80% and 70%, respectively, based on 5 clinicians responding to the questionnaire. In this case, if the numbers of clinicians eligible to complete a questionnaire is 5, the test statistic, for the one-tailed tests, with an α =0.2 (i.e., 1-confidence level) will be:

$$\mathrm{P}(\text{true X} \leq x) = \binom{5}{x} 0.8^x (1-0.8)^{5-x} \leq .2$$

Solving for x would result in the null hypothesis being rejected when 2 or fewer clinicians rate the T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better compared to their experience with their currently used urodynamics catheter and accepted when 3 or more clinicians rate the T-DOC® 5 Fr vesical and abdominal catheter usability performance as 3 or better compared to their experience with their currently used urodynamics catheter.

Due to the minimal risk of the device as stated in section 4.4, the study team has opted to use a combination of levels where the confidence level is stated as 95% (i.e., $\alpha = 0.05$), and the reliability (power) of the test will be calculated, though it will likely be significantly reduced.

The actual results will be tabulated based on the actual number of clinicians who respond to the questionnaire.

12.3 Exploratory Endpoint

12.3.1 Exploratory Hypothesis Test for Discomfort/Pain

To satisfy the first exploratory endpoint (subject experience), a categorical response variable using the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst") will be used. The stated exploratory endpoint is that 95% of patients capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain of 5 or lower, on the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst"). To enable analysis based on a Binomial Distributions, responses of 1, 2, 3, 4, or 5 will be tallied as a positive result while responses of 6, 7, 8, 9, or 10 will be tallied as a negative result. Additionally, grouping the data in this manner is assumed to minimize much of the variation caused by the nature of subjective feedback from pediatric subjects. A confidence level of stated as 95 % (i.e., $\alpha = 0.05$) has been selected based on the risk determination that no more than minimal risk is foreseen for the subject by participating in this study (4.4 Assessment of Risks and Adverse Device Effects). As stated earlier, the following hypothesis test case will be used to evaluate the exploratory clinical study results.

> H_0: 95% or more of subjects capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain experienced experience during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower, on the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst").
>
> $H\alpha$: Less than 95% of subjects capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain experienced experience during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower, on the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst").

The subjects will be presented with copies the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst") and asked to respond to the questions by clinic staff who will record their responses on TDOC5Fr-PEDS-01-CRF4. As with the previous endpoints, the alternative hypothesis is directionally based, therefore, the null hypothesis will be accepted or rejected based on a one-tailed test. Because the subjects range in age from 2-12 years, the number of subjects capable of providing feedback on the Wong-Baker scale is anticipated to be limited (≤ 14). Similar to the secondary hypothesis, the study team has opted to use a combination of levels where the confidence level is stated as 95% (i.e., $\alpha = 0.05$), and the reliability (power) of the test will be calculated, based on the sample size achieved (i.e., count of subjects capable of

providing feedback on the Wong-Baker scale). See section 12.5 Sample Size Determination and Power for further details.

The probability mass function of a binomial random variable X as stated for the primary and secondary endpoints will again be used to analyse the subjects' questionnaire data. For the exploratory endpoint, n represents the number of subjects capable of providing feedback on the Wong-Baker scale; x represents the number of subjects who rate their discomfort/pain experienced during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower on the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst"); and p = 0.95 (as stated in the null hypothesis that 95% of subjects capable of providing feedback on a Visual Analogue Scale, will grade their discomfort/pain experienced experience during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower).

Again, because the alternative hypothesis is directionally based, the null hypotheses will be accepted or rejected based on a one-tailed test. For example, if the numbers of subjects capable of responding to the questionnaire is 10, the test statistic, for the one-tailed tests, will be:

$$P(\text{true } X \leq x) = \binom{14}{x} 0.95^{x}(1-0.95)^{14-x} \leq 0.05$$

Again, if it is assumed that 14 subjects respond to the questionnaire, the reliability level would be approximately 80% (see Section 12.5 Sample Size Determination and Power). Solving for x, with the assumed count of subjects would result in the null hypothesis being rejected when 12 or fewer subjects capable of providing feedback on a Visual Analogue Scale, grade their discomfort/pain experienced experience during the procedure utilizing the T-DOC® 5 Fr vesical and abdominal catheter at 5 or lower, on the Wong-Baker scale from 0 ("No Hurt") to 10 ("Hurts worst").

The actual results will be tabulated based on the actual number of subjects who respond to the questionnaire.

12.3.2 Exploratory Data Collection regarding influencing factors on insertion depth

To satisfy the second exploratory endpoint, subject data including gender, age, height, weight, adverse events during or immediately following the test and 5-7 days follow-up, catheter insertion depth will be collected as objective evidence on each patient's CRF, where insertion depth is considered the response variable and assumed to be influenced by gender, age, height, weight and/or BMI. Adverse event data will be factored into the assessment of the adequacy of the individual insertion depth used during the subject's procedure.

The collected data will be reported using graphical tools for central tendency and dispersion of insertion depths based on gender, age, height, weight, and BMI. The goal of reporting data in this manner is to facilitate the identification of a natural subject stratification approach for use in later research regarding optimal insertion depth.

Based on the stated data collection and analysis approach, the anticipated outcome of this endpoint, and the fact that the subject population is not being controlled for age, height, or weight, this study exploratory objective is being evaluated as a case-series observational study. Accordingly, sample size will not be pre-determined based on pre-ordained confidence and reliability statements.

12.4 Sample Size Determination & Power

Sample size calculations were and will be performed in accordance with Binomial Distribution theory (except for the second exploratory objective), utilizing the following formula:

$$n = \frac{ln(1 - confidence\ level)}{ln(reliability)}$$

Where *n* is the number of samples (e.g., patients, clinicians), and *ln* is natural log. In the case of the primary endpoint, the desired confidence level and reliability have been stated as 95% and 90% respectively. Hence the minimum required number of samples for the primary endpoint is 28 as shown below.

$$n = \frac{ln(1-0.95)}{ln(0.90)} = 28$$

In addition, the study sponsor will allow up to 33 subjects (20% additional) during the allowable recruitment time period given the minimum recruitment goals are met (see Section 6.1 for and Section 7.1 for stratification and recruitment requirements). The additional subjects will ensure that the desired confidence and reliability levels are met should any data or subjects be disqualified due to technical errors or if any subject requests to exit the study.

In the case of the secondary endpoint, the confidence level has been stated to be 80% and the reliability statement will be calculated based on the actual number of clinicians who respond to the questionnaire. For instance, if 5 clinicians respond to the questionnaire, and an $\alpha = 0.20$ (i.e., (1- confidence level)) is maintained, the reliability of this test will drop to approximately 73%.

In the case of the first exploratory endpoint, the confidence level has been stated to be 95% and the reliability statement will be calculated based on the actual number of subjects who respond to the questionnaire. For instance, if 14 subjects respond to the questionnaire, and an $\alpha = 0.05$ (i.e., (1- confidence level)) is maintained, the reliability of this test would be approximately 80%.

In all cases, test statistics will be calculated based on the actual number of samples achieved.

12.5 Randomization / Blinding

Randomization and/or blinding is not utilized in this study based on study design.

12.6 Analysis Plan

All subjects enrolled will be considered in the final analysis. Data will be analysed as discussed in Section 12.1 above. A Statistical Analysis Plan containing the details of the analyses and hypothesis testing will be finalized prior to database lock.

If any CRFs are found to be incomplete, the study monitor will follow-up as to the reasoning why. If for some reason a clinical user is unable to complete their questionnaire, the questions they have completed will be included in the analysis. Data will be monitored as the study progresses, please refer to Section 7.7 for details about suspension or premature termination.

12.7 Deviations

In any event there are deviations from the original statistical plan they will be described and justified in the final report.

12.8 Early Stopping

An interim data analysis will be conducted once 30 subjects have been recruited in order validate the product design meets the user requirements.

There are currently no criteria for stopping the study early on statistical grounds, however please refer to Section 7.7 for details about suspension or premature termination.

13 DATA HANDLING & RECORD KEEPING

13.1 Direct Access

The Investigator/Institution will permit trial-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to the source data/documents as needed.

13.2 Confidentiality & Security

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the study, including, but not limited to, the Study Protocol, the CRFs, the Instructions for Use and the results obtained during the course of the study, is confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Study Protocol and other necessary documentation to the Ethics Committee (IRB) is expressly permitted, the IRB members having the same obligation of confidentiality.

The Sub-Investigators, if employed, shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Usability Study.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Study, to the exclusion of any use for their own or for a third party's account.

All data to Laborie will be confidential and all subject identifiers will be blacked out before being sent to Laborie. Documents will be kept in a secure location and all digital information will be kept following HIPAA and local government regulations.

13.3 Data Handling

A list of individuals will be maintained who are authorized to make any changes to the data. Data will be reviewed by the Sponsor (outside of monitoring personnel), and requests for clarification and/or corrections will be made through the monitor. Once the review is conducted, the database will be considered clean and ready for analysis. Missing values will remain missing, i.e. no attempt will be made to input missing values and only observed values will be used in data analyses and presentations.

13.4 Case Report Form (CRF) & Source Documents

All study staff will be trained on the protocol requirements and questionnaire completion. It is the responsibility of the Investigator to maintain adequate and accurate questionnaires and CRFs designed by Laborie to record all observations and other data pertinent to the clinical investigation. All questionnaires and CRFs should be completed in their entirety in a neat, legible manner to ensure accurate integration of data. Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person on the questionnaire. Source document worksheets for recording data will be created as agreed upon by the sponsor or the site as required. Data from the source documents should be entered into the CRF after each subject's visit. The anonymized urodynamic data files (DTA files) are requested by the sponsor for each patient, to confirm the quality of the tracing. A unique subject code will be assigned to each subject based on the site number (100) and sequential subject number (i.e. 100-001). The investigator is responsible for maintaining subject identifying information. CRF's will be treated as source data in the event that the original information is entered in the CRF first (and no source document worksheet is utilized for that data point).

13.5 Record Retention

An investigator or sponsor shall maintain the records required by 21 CFR Part 812.140 during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no

longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. All essential documents from the Investigator will be kept in the Investigator binder. All sponsor essential documents will be kept in the study master file. The investigator and sponsor shall also maintain a record of their location of the respective essential documents. If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

13.6 Performance Monitoring

Monitors will periodically check questionnaire data to ensure all fields are entered as far as possible and inquire as to whether any usability issues are being encountered as the study progresses.

14 MONITORING, AUDITING, AND INSPECTING

14.1 Study Monitoring Plan

The Investigator agrees to provide reliable and accurate data, and all information requested by the study protocol (with the help of any questionnaire, other appropriate instruments) in an attributable, legible, contemptuous, original, accurate, and complete form according to the instructions provided and to ensure direct access to source documents to Sponsor representatives. Any changes to the sourced data shall be traceable and not obscure the original entry.

The Sponsor of this Study is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of this study protocol with regards to ethics, protocol compliance, integrity and validity of the data recorded on the CRF and questionnaires. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and subject compliance with study protocol requirements, and any emergent problems. During these monitoring visits, the following, but not exhaustive list of points will be scrutinized with the Investigator: subject informed consent, subject recruitment and follow-up, Adverse Event documentation and reporting, outcome events documentation and reporting, Investigational Product allocation, Investigational Product accountability, and quality of data.

14.2 Auditing and Inspecting

For the purpose of ensuring compliance with the study protocol, Good Clinical Practice and regulatory requirements, the Investigator should permit inspection by applicable regulatory body authorities. This investigation will not include audits conducted by the Sponsor.

The Investigator agrees to allow the inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor. The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the inspections.

15 DEVIATIONS

All departures from the approved protocol shall be documented by the Investigator. All deviations will be recorded on the subject CRF, and a deviation report will be sent to Laborie and the ethics board, as required. Timelines for notification will be subject to ethics board standard operating procedures. Deviations will be reviewed and signed off by the sponsor. If deviations are observed/reported that significantly affect or have the potential to significantly affect human subject protection or reliability of the trial results, then LABORIE will conduct a root cause analysis and implement appropriate corrective and preventative actions.

16 AMENDMENTS

If there are any changes to the protocol during the application of the study or during the length of the clinical study in progress, the IRB will be notified for review. During an ongoing study if an amendment is made to the protocol the amended protocol will be sent to the applicable institution within the timelines required. The Investigator should not implement any deviation from, or changes to the clinical protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB of an amendment, except when necessary to eliminate an immediate hazard(s) to a clinical study subject. In some instances, an amendment may require a change to the Informed Consent Form. The investigator must

receive an IRB approval/favourable opinion concerning the revised Informed Consent Form prior to implementation of the change.

17 STUDY ADMINSTRATION

17.1 Funding Source and Conflicts of Interest

Laborie will be the sponsor and the financial details are covered in the Investigator Agreement.

17.2 Subject Stipends or Payments

Subjects will be offered a $40 USD stipend for their participation in the study to offset the cost of parking and/or meals required during their clinic visit.

The Sponsor has covered this study by means of an insurance covering bodily injury or property damage arising out of the clinical trial. The certificate of insurance evidencing the coverage, insurance company, policy number and the sum insured are provided in the Study's File.

17.3 Committees

A Data Monitor Committee will not be utilized in this study based on the evaluation of the level of potential risks.

17.4 Study Timetable

PROPOSED STUDY TIMELINE	TOTAL DURATION (WEEKS)	ACTUAL DATES
PROPOSED START DATE (Planning)	**8**	**JULY 10, 2017**
PROPOSED SITE TRAINING & INITIATION PHASE	**1**	**NOVEMBER 20, 2017**
PROPOSED RECRUITMENT (1st subject in to last subject out)	**12 - 14**	**NOVEMBER 27, 2017**
PROPOSED DATABASE LOCKOUT	**4**	**MARCH 16, 2018**
PROPOSED STUDY REPORT COMPLETION	**4**	**MARCH 30, 2018**
TOTAL (WEEKS / MONTHS)	**34 / 8 1/2**	
ESTIMATED COMPLETION (QUARTER)	**Q2 FY2018**	**APRIL 2018**

18 ETHICS AND REGULATORY APPROVAL

This study will not begin until the appropriate approvals from the IRB have been obtained. Any additional requirements imposed by the IRB will be followed. This study will be conducted in

compliance with all international laws and regulations, and national laws and regulations of the countries in which the usability study is performed, as well as any applicable guidelines.

19 PUBLICATION POLICY

The results of the study may be submitted for publication, whether peer-reviewed or marketing materials. Publication rights and details are covered in the Investigator Agreement, there may be other authors involved in the creation of the publication.

20 REFERENCED DOCUMENTS

20.1 Informed Consent Documents

- TDOC5Fr-PEDS-01-AF1 – Pediatric Assent Form [redacted]
- TDOC5Fr-PEDS-01-ICF1 – Informed Consent Form [redacted]
- TDOC5Fr-PEDS-01-AF3 - Pediatric Assent Form [redacted]
- TDOC5Fr-PEDS-01-ICF3 - Informed Consent Form [redacted]
- TDOC5Fr-PEDS-01-AF2 - Pediatric Assent Form [redacted]
- TDOC5Fr-PEDS-01-ICF2 - Informed Consent Form [redacted]
- TDOC5Fr-PEDS-01-HA - HIPAA Authorization [redacted]
- TDOC5Fr-PEDS-01-HA - HIPAA Authorization [redacted]

20.2 Investigator's Brochure

- TDOC5Fr-PEDS-01-IB T-DOC 5 French Investigator's Brochure

20.3 Case Report Forms:

- TDOC5Fr-PEDS-01-CRF1 - Case Report Form 1
- TDOC5Fr-PEDS-01-CRF2 - Case Report Form 2
- TDOC5Fr-PEDS-01-CRF3 - Case Report Form 3
- TDOC5Fr-PEDS-01-CRF4 - Case Report Form 4

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