Q SUBMISSION: PRE-SUBMISSION MEETING REQUEST

Title of Proposed Trial

Name of Sponsor Investigator, PhD

X Professor, Department

DUKE UNIVERSITY

Date of Submission

# FDA Form 3514

*Link to FDA Form 3514:*

[*http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf*](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf)

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# Purpose

*The overall purpose of the Pre-Sub, including goals for the outcome of the interaction with FDA.*

# Elements of Intended Use/Indications for Use

*You should provide a clear statement of the proposed intended use and indications for use. The intended use statement describes how and by whom the device is to be used and should include the following information:*

* *Measurand (analyte, biological activity, or some other quantity to be measured) or organism to be identified or detected*
* *Whether the test is quantitative, semi-quantitative, and/or qualitative*
* *Specimen type(s) or matrix(-ces) (e.g., blood (include source, e.g., venipuncture, heel or finger stick; donor or patient), serum, plasma (include anti-coagulants), stool, hair, swab (include source, e.g., cervical, nasopharyngeal, throat), urine (include time collected), saliva, cerebrospinal fluid (CSF), sweat, tears, etc.) and any processing required*
* *Conditions for use which describes the setting in which the test is to be performed and the intended user (e.g., prescription use (hospital laboratory, blood donor facility, point of care, physician’s office, home use, workplace) or over-the-counter)*

*The indications for use describes for what and for whom the device is to be used (e.g., target condition, target population and purpose). The following are some examples of information included in the indications for use:*

* *Target condition: a particular disease, disease stage, health status, or any other identifiable condition or event within a patient, or a health condition that should prompt clinical action*
* *Target patient population , for example:*
	+ *Age (e.g., adult, pediatric, specific age limitations)*
	+ *Asymptomatic patients (e.g., screening)*
	+ *Symptomatic patients (e.g., diagnosis or prediction)*
	+ *Already diagnosed patients (e.g., monitoring or prognosis)*
	+ *Recipient of blood or tissue products (e.g., compatibility)*
* *Time and frequency of use (e.g., glucose testing for stability and rapid changes after meals)*
* *Purpose for measurement (e.g., clinical indication – how and why the clinician or the user will use the results of the test)*

# Regulatory History

*List any relevant previous communications with FDA about the subject device including but not limited to any marketing submissions, IDE, 513(g), and/or Q-Sub application numbers relevant to the Pre-Sub. Include submission numbers as appropriate. Include a brief summary of these previous FDA interactions and submissions, including feedback received and resolution of that feedback (or justification of alternative paths) as applicable.*

# Planned Follow-on Submission

*Clearly indicate what type of future submission (i.e. IDE, 510(k), etc.) is the focus of your Pre-Sub questions to help direct FDA’s feedback.*

*Requests for feedback regarding study design for non-significant risk (NSR) or IDE-exempt studies for which the results are not expected to support a future IDE or marketing application (i.e. 510(k), PMA) should use the Informational Meeting instead of a Pre-Sub and may omit this section.*

# Background Information

*Include information on the disease and problem that is being addressed. Please include sufficient background information and supporting documents to allow FDA to develop feedback for the Pre-Sub questions you pose. Keep your submission targeted and focused.*

# Device Description

*Please provide sufficient information regarding the device description, including a detailed technical description of your device including instruments, reagents, components, software, principles of operation, and accessories (if there are changes to a previously cleared or approved device, then you should describe these changes)*

*Additionally, the description may include:*

* *physical, chemical and/or biological processes/principles used by the device to generate device output, if applicable;*
* *physical and biological characteristics of the device output, if applicable;*
* *samples to demonstrate the use of the device (where feasible and appropriate);*
* *explanation of the user interface and/or how the device interacts with other devices or with the user (medical professional and/or patient);*
* *explanation of the materials used in the device;*
* *brief description of the manufacturing process should be included if the manufacturing process may affect safety and/or effectiveness, and may therefore impact FDA’s recommendations regarding device testing; discussion of the mechanism of action and how the device and/or, if applicable, device output is used;*
* *basic scientific concepts that form the basis for the device; and*
* *the generic name of the device as well as any proprietary name or trade name, if applicable*

*Always make sure you use consistent terminology for each component of your device in your submission.*

## Proposed Predicate Devices

*The 510(k) review process focuses on the comparison of a proposed device with a predicate device in terms of indications for use, technological characteristics, and, as appropriate, performance testing. As a result, you should provide a summary of the predicate device(s) you plan to use for your comparison of these characteristics, along with the indication(s) for use and technology of the device you would like to market (i.e., draft of your labeling).*

*For each predicate device you identify, we suggest you provide:*

* *the predicate device trade name, including model, if available;*
* *the 510(k) number under which the predicate device was cleared;*
* *the classification of the predicate device; and*
* *a comparison with the proposed device in terms of indications for use, technological characteristics, and performance testing.*
* *Proposed indication for use*
* *Technology of the device*

Table 1: Potential Predicate Device(s)

| **Predicate Trade Name** | **510(k) Number** | **Classification** | **Intended Use** | **Device Technology** |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |

*Use the 510(k) summary sheet for your proposed predicate to guide the completion of comparison table below. The 510(k) summary of the device should include the intended use, an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material used, and physical properties. You can search for 510(k) devices and their summaries here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm*

Table 2: Comparison Table

| **Device** | **Name** **(Predicate)** | **Name****(New Device)** |
| --- | --- | --- |
| Intended Use |  |  |
| Indications for Use |  |  |
|  |  |  |
| **Materials** |  |  |
|  |  |  |
|  |  |  |
| **Characteristics** |  |  |
|  |  |  |
|  |  |  |
| **Usage** |  |  |
|  |  |  |
|  |  |  |

**Discussion**

*Discuss the information in the comparison table above. Point out the similarities and differences between the new device and the predicate device and comment on whether new questions of safety and effectiveness are raised.*

# Description of How the Device is Planned to be Used in a Real-life Setting

*For novel clinical indications, you should provide a detailed description of how you see your device being used in a real-life setting. You might want to consider diagrams illustrating the clinical management of a hypothetical patient from the proposed target population, including information regarding at what point(s) your device will be used and how information from your device can be used by the user (e.g., physician). It is helpful if you provide a few examples of the use of your device for different patients (with different sets of covariates) from the target population.*

# Risk Anaylsis

*For devices with novel intended uses, you may include an analysis of the impact of false test results on patient management. This information will be useful to aid FDA in determining the appropriate classification of your device. You should present suggested approaches to mitigate the underlying risks as part of the risk analysis.*

# Discussion of Relevant Prior Information

*Please provide an overview of the product development, including an outline of nonclinical and clinical testing already completed. If you intend to include complete copies of literature articles as part of this section, please try to include only those that are relevant to the questions you are asking. Additional articles can be provided in any subsequent marketing application or IDE.*

*Please note that limited bench, animal, or clinical study data may be provided, but only to provide FDA with the needed background information to develop feedback in response to a specific question/proposal (e.g. one page of preliminary feasibility clinical study results are provided when FDA feedback is requested for proposed pivotal study endpoints).*

# Proposed Study Design(s)

*We recommend that you provide a detailed protocol of how you propose to evaluate the analytical and clinical performance characteristics of your device. You may provide descriptions of the studies proposed to support the intended use of your device. In preparation of this section, we recommend that you refer to relevant FDA documents and the standard guidelines, such as the Clinical Laboratory and Standards Institute (CLSI) documents for your device type, as applicable.*

*Specimen Information: As part of your proposed study design you should indicate the types of specimens that you will recommend for testing. The following may be helpful if you wish to gain advice on specimen use in your studies:*

* *A description of the sample collection methods recommended and any specific sample collection devices;*
* *If you propose to utilize more than one sample type, a description of how you propose to evaluate your device performance for the different sample types in your analytical and clinical study designs;*
* *How you plan to assess sample stability, recommended storage conditions, and parameters to demonstrate the quality and integrity of the samples;*
* *How you will utilize fresh, frozen, or otherwise preserved samples in the clinical studies; and/or*
* *A description of sample manipulation or processing steps and accessories required for these purposes.*

*Analytical Performance: You may submit protocols for analytical validation studies for which you desire FDA feedback. The studies that are necessary to validate the analytical performance of your device may vary depending on the device type (e.g., qualitative, semi-quantitative or quantitative). Many types of analytical performance studies are standardized and follow accepted standard documents such as CLSI documents. It is recommended that you base your studies on such standards, when applicable. The major analytical performance parameters for IVDs may include:*

* *accuracy;*
* *limit of detection;*
* *analytical cut-off of the device;*
* *precision (e.g., repeatability, reproducibility);*
* *matrix comparison;*
* *analytical specificity (cross reactivity and interference);*
* *reagent and sample stability studies;*
* *reference interval;*
* *limit of quantitation;*
* *traceability to standard materials;*
* *linearity;*
* *method comparison; and*
* *high dose hook effect (immunoassays).*

*In any study protocols you propose, we recommend that you indicate for each study: (1) information about the samples used for evaluation and (2) the level of the analyte(s) being measured. You should ensure you clearly describe the proposed study design, the parameters that will be assessed, the acceptance criteria, and the proposed methods for data analysis. If standard guidelines will be followed, we recommend that you specify the guideline used.*

*Method Comparison: For method comparison study proposals, you should include the proposed study design, comparator (predicate or reference method), and proposed analysis method. Method comparison studies usually compare the device performance to the predicate device. However, for certain device types, the predicate device may not be the appropriate comparator; in some cases, a reference method or clinical diagnosis may be a more appropriate comparator. If there is no predicate device for the device under evaluation, you should propose the appropriate comparator and study design, providing scientific justifications for the proposal(s). The method comparison proposal may include:*

* *study design,*
* *study population,*
* *method for sample size determination,*
* *study sample size,*
* *number of testing laboratory sites,*
* *criteria for sample type selection and justification,*
* *method of sample collection and processing,*
* *indication of the number of measurements recorded per individual (as applicable),*
* *description of comparator or predicate device,*
* *detailed testing protocols, and*
* *data analysis protocols (e.g., agreement, regression, and how discrepant or equivocal results will be handled in the analysis).*

*You may wish to include any concerns that you have regarding the selection of the predicate or reference method. If you have identified a predicate device, you may also wish to discuss any potential differences from the predicate that may affect the assessment of your device performance.*

*Clinical Performance: Many IVDs require clinical studies to establish effectiveness. Clinical studies should not be confused with analytical studies that use clinical specimens (i.e., a study that evaluates test measurement parameters compared to those of another method or device). A clinical study is an evaluation of clinical performance, in which patients are enrolled or specimens are collected in accordance with pre-defined inclusion/exclusion criteria. Clinical performance is often stratified by demographic variables (e.g., age, sex). Performance is generally based on a comparison between the device result and clinical presentation or other marker of disease. In some situations other types of clinical performance evaluation may be considered. You may submit protocols for clinical performance studies for which you desire FDA feedback. In this section, you should describe studies designed to support your proposed indication(s) for use. Clinical studies often include evaluating parameters such as clinical sensitivity and specificity, positive and negative predictive values, and clinical cut-offs. Other parameters may be addressed as needed.*

* *Clinical Study Design Elements: You should consider including the following in your study design proposal:*
	+ - *Target condition - brief description of the target condition (diagnosis, stage of illness, signs/symptoms, success of treatment, etc.). Indicate how (criteria, laboratory tests, physical examination) and by whom (i.e., specialist, generalist) the target condition will be determined. Include demographic information and the prevalence of the target condition.*
		- *Intended use population - description of inclusion/exclusion criteria, and how the clinical study population(s) reflect the intended use population(s).*
		- *Matrix type - listing of the sample matrices to be tested in the clinical study. Sample matrices should be consistent with those claimed in the intended use.*
		- *Sample selection - description of sample types used in the study (e.g., fresh, stabilized, prospective, archived, retrospective, etc.). Describe how samples are selected for inclusion in the studies, how they will be stored, and how their integrity and analyte stability will be assessed. If archived samples are used, consider the potential for bias and describe how it will be addressed.*
		- *Study sites - if known, list potential study sites, and their geographical locations. FDA recommends at least three study sites for your clinical studies. Generally, the device should be evaluated at sites representative of those in which the device ultimately will be used.*
		- *Literature - in some cases, you may be able to use published, peer-reviewed literature to support clinical claims. If you are proposing to use literature to support clinical claims, you should clearly outline your reasons for doing so, and be prepared to discuss your proposal with FDA.*
* *Statistical Analysis Plan for Clinical Performance Study: You should consider including the following, as appropriate:*
	+ *Proposed clinical study plan.*
	+ *Explanation of sample size that provides a sound statistical basis for the determination of sample size (N).*
	+ *Proposed plan for how you will analyze data (e.g., identify independent and dependent variables, provide interpretation criteria and your definition of positive, negative, or equivocal results).*
	+ *Description of how you determine and validate the cut-off or reference range.*
	+ *Description of expected results (define or explain calculations; determine equivocal zones and describe if and how discrepant results will be resolved).*
	+ *Expected rate of clinical false positives and false negatives, if known.*
	+ *Description of the success criteria you will use to determine if your device performs acceptably.*

# Specific Questions

*The Pre-Sub should include specific questions regarding review issues relevant to a planned IDE, a clinical investigation, or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements) to allow FDA and the submitter to focus their efforts on issues most relevant to the project moving forward. You may wish to describe your perspective on the questions you provide FDA to inform FDA’s review.*

*The number of questions and extent of feedback requested in a single Pre-Sub should be carefully considered to ensure that FDA has sufficient time to provide an in-depth response to each question. In general, FDA has found it difficult to address more than 3-4 substantial questions in a single Pre-Sub.*

*In FDA’s experience, questions that lead to productive Pre-Sub interactions share the following characteristics:*

* *Questions request specific feedback on a provided proposal (e.g., an animal model is proposed, including rationale, and FDA feedback is requested on the acceptability of the animal model)*
* *Questions have considered and include reference to applicable guidance documents, standards and previous discussions with FDA (e.g., chemical characterization testing is proposed with citations to relevant biocompatibility guidance document and standards as well as feedback FDA provided in previous Pre-Sub interactions)*
* *Questions clearly articulate a desired outcome including indications for use or labeled uses (e.g., FDA feedback is requested on clinical study endpoints, inclusion criteria, and follow up duration given that the study is intended to expand the currently approved indications for use from prescription use only to over the counter use)*
* *Questions are timed to inform future device development and submission preparation (e.g., prior to conducting fatigue testing, a submitter requests feedback regarding proposed pre-conditioning procedures)*
* *Questions do not request decisions regarding approval or clearance of a future IDE, CW, IND, or marketing submission; that is, a question should not ask “Will an IDE that includes results from the proposed testing be approved?”*
* *Questions do not provide data unless necessary as supportive context for a specific proposal; that is, a question might provide limited bench, animal or clinical study data, but only to provide FDA with the needed background information to develop feedback in response to a specific proposal (e.g., one page of preliminary feasibility clinical study results are provided when FDA feedback is requested for proposed pivotal study endpoints)*
* *Questions do not ask FDA to design a study or indicate how a submitter should proceed; that is, a question should not ask “What should my clinical study design be?”*
* *Questions do not request formal regulatory determination; that is, a question should not ask “Is my device a Class II medical device to be regulated under CFR 892.2050?”*

*The following are examples of questions, provided by review topic category, expected to lead to productive Pre-Sub interactions:*

*Regulatory Strategy Questions*

* *Are there concerns with the predicate device proposed?*
* *Can we obtain FDA's feedback and guidance on pursuing a De Novo request for classification pathway given that there is not a currently marketed device that we believe could serve as predicate under the 510(k) pathway?*
* *Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that additional clinical data is not needed to support a future 510(k)?*

*Indications for Use/Intended Use Questions*

* *Does FDA have any concerns with our proposal to label the described device as over the counter?*
* *Does FDA agree with the proposed definition of drug-resistant hypertension provided in the draft indications for use statement?*
* *Does the Agency agree with the proposed size range offered for the new device, based on the intended use?*

*Clinical Study Questions*

* *Does FDA have any comments on the provided OUS study protocol regarding its ability to support a future HDE?*
* *Does FDA agree with the revised clinical study designs, statistical analysis and acceptance criteria included in this Pre-Sub supplement?*
* *Are the primary and secondary analyses appropriate for the Indications for Use for the monitoring indication proposed?*

*Labeling Questions*

* *Does FDA agree with the proposed test plan in support of MR Conditional labeling for 1.5T scanners with an exclusion zone between the neck and groin?*
* *We intend to label our device for re-use if the attached cleaning instructions are followed. The test plan to support this label is provided in Attachment B. Does FDA agree with this plan?*

*Reprocessing, Sterilization & Shelf Life Questions*

* *Does FDA have any comments about the methods described in the Microbiology protocol "Microbiology Study Protocol" included in Appendix 3?*
* *Does FDA concur that accelerated testing outlined in Appendix 2 conducted to represent 1 year shelf life is sufficient for an IDE with real time testing provided in the PMA?*
* *To address FDA's deficiency regarding our sterilization validation, we propose using Small Lot Release in accordance with Annex E of ISO 11135-2014. Does FDA have objections?*
* *Does FDA agree with our recommendation to low level disinfect the cannula device between uses?*

*Benchtop Performance Testing Questions*

* *Does FDA agree with the provided justification for the proposed worst case comparison testing?*
* *In the event that the prospective collection does not meet the protocol’s intended number of specimens of a given type, we propose to use retrospective, characterized (banked) specimens to ensure these numbers are achieved. Is this approach acceptable to FDA?*
* *We have provided a justification of the worst-case testing volume that will be used, and provided an analysis of the sensitivity of the test, as requested. Does FDA find this justification and analysis adequate to support using the methodology described in our testing protocol? If not please provide further guidance.*
* *Does the Agency agree with our approach to use the average of valid measurements of the five replicate measurements?*
* *We have provided a response to FDA's question about sample sizes used in the in vitro test, along with a justification based on a power analysis. Is this plan acceptable? If not please provide further guidance.*

*Animal Study Questions*

* *Does FDA concur that the revised GLP Study design is sufficient to address potential device risks and support initiation of a pivotal clinical trial?*
* *Is our alternative approach to an animal study appropriate?*
* *Please advise if FDA believes that additional animal studies outside of those already conducted (and described in this submission) are recommended to support a future marketing application.*
* *Does the agency agree that the proposed animal study is designed to provide a sufficient assessment of the local tissue and systemic response?*
* *Is the animal model proposed appropriate based on the proposed intended use?*
* *Are the proposed animal study endpoints and follow up schedule appropriate?*

*Biocompatibility Questions*

* *We propose to conduct the biocompatibility testing identified in Tables 7-9 on only the largest model dialyzer. Does FDA concur with the testing protocol?*
* *We propose to conduct chemical characterization (described in Appendix 1) in lieu of chronic implantation testing. Please provide any comments on the acceptability of this approach.*
* *Is our justification for not conducting carcinogenicity studies adequate?*
* *Is our alternative test method to the material-mediated sensitization testing, which does not use a traditional rabbit model but an in vitro alternative, acceptable?*

*Software/Firmware Questions*

* *Does FDA agree that our software/instrument is a moderate level of concern and that the level of documentation that will be included in an upcoming marketing submission is consistent with FDA’s recommendations provided in FDA’s guidance entitled “Guidance for the Content of Premarket Submission for Software Contained in Medical Devices?”43 as part of the upcoming device submission?*
* *Does FDA expect any further data validating functional operation of alerts and alarms in real or simulated circumstances beyond that recommended in FDA’s guidance entitled "Guidance for the Content of Premarket Submission for Software Contained in Medical Devices?"44 If so, can FDA give us additional guidance on what they might like to see?*
* *Does FDA agree that the software documentation defined in Section 4.2 of this Pre-Sub does not need to be included in the PMA supplement for the device as it was previously reviewed and approved in other PMA supplements (i.e., the PMA supplement will reference previously submitted information)?*

*Human Factors Questions*

* *Does the agency have comments on our proposed human factors engineering process?*
* *Is the attached use-related risk analysis plan adequate? Does the agency agree that we have identified all the critical tasks?*

*Does the agency agree with our proposed test participant recruitment plan for the human factors validation testing?*