MEDICAL DEVICE SUPPLEMENT to:
CTTI Quality by Design Project – Critical to Quality (CTQ) Factors Principles Document

INTRODUCTION: In 2015, the Clinical Trials Transformation Initiative (CTTI) Quality by Design (QbD) project published the Critical to Quality (CTQ) Factors Principles Document, a guide to support trial development that focused on factors critical to trial quality. *"This document is intended to support proactive, cross-functional discussions and decision making at the time of trial development about 1) what aspects of a trial are critical to generating reliable data and providing appropriate protection of research participants ("critical to quality" [CTQ] factors) and 2) what strategies and actions will effectively and efficiently support quality in these critical areas."*

While the authors of the CTTI project consulted a number of industry and regulatory sources, the Medical Device Innovation Consortium (MDIC) recognized that there are challenges unique to the design of high-quality medical device clinical trials. What follows is a supplement to CTTI's Quality by Design Factors Principles document. It should be used in conjunction with the CTTI document to highlight additional considerations specific to medical device clinical trials. We believe using these documents together will provide medical device company sponsors and researchers with a comprehensive suite of tools to ensure high-quality medical device clinical trial design. This document assumes that issues related to the design of the product itself such as its inherent risks and identification of the most appropriate user will already have been determined.

CTTI Critical to Quality Project FACTOR* (*See References)	**Additional Device-Specific Considerations (in addition to the CTTI considerations)**
PROTOCOL DESIGN	
Eligibility Criteria	***Due to device trial challenges, the efficiency of trial enrollment is a critical component of trial design.*** ▪ Can additional screening criteria be used to maximize efficacy? Can these be obtained consistently across sites? ▪ Is patient population aligned with payers expectations?
Randomization	CTTI CTQ considerations are sufficient. No device-specific considerations to add.
Masking	***Masking is often a challenge in medical device trials because of the involvement of very obvious procedures.*** ▪ For sham procedures, do the sham procedures have the same ritual as treatment procedure so patient is not influenced psychologically or physiologically? ▪ Does the protocol describe the methods to assess the validity of the blind with study participants?
Types of Controls	***Special consideration should be given to the types of controls used in medical device trials, particularly when a sham procedure is used.*** ▪ Is the sham procedure adequate? Does it ensure that both physiological and psychological factors are comparable to the treatment group? ▪ Does the sham procedure deliver any benefit to the subjects? ▪ Is a control group feasible and necessary, treating physician, payers, and statistical perspective?

	▪ Should treatment be offered to control group subjects after unblinding, in particular where control groups are undergoing extensive sham procedure? Consider whether to include subsequent data as part of the analysis.
Data Quantity	***Reasonable data quantity is a challenge as devices are often added to standard of care in clinical trials.*** • What are the necessary data? • What are the critical fields? • What is the minimum acceptable data set? • Should acceptability thresholds be established for data from critical fields? • Can the requirements of imaging, blood testing, and other non-standard of care testing be reasonably met in compliance with the protocol, as data originating from testing beyond standard of care had become increasingly difficult to obtain in today's medical environment? • Are patient care and standard of care treatment taken into consideration in the protocol design to assure collection of all required data and a low percentage of missing data? • Is only relevant medical history collected? Additional history, to support adjudication of adverse events, can be collected on an as-needed basis, provided these data are not necessary for statistical analysis.
Endpoints	***Device study endpoint development may benefit from consideration of patient preferences.*** • Information regarding how to assess patient-centered benefits and risks can be found in the Medical Device Innovation Consortium's (MDIC) project report "A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology" (http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf).
Procedures Supporting Study Endpoints and Data Integrity	CTTI CTQ considerations are sufficient. No device-specific considerations to add.
Investigational Product (IP) Handling and Administration	***Device trials require that product accountability, storage, handling, and disposal be addressed in the protocol.*** • For devices intended to be temporarily implanted, what information is critical to collect for device removal (consider safety, handing, ease of removal, blinding)? • What are the issues for patients that withdraw early from the study or are lost to follow-up regarding explant of the device? Will there be health consequences if not removed? • Has product shelf-life been considered? • Is there a learning curve for the product? If so, consider the need for training cases or roll-in subjects in the study design. • Is training required for use of the investigational product? Consider bench, animal, or cadaver model.

FEASIBILITY	
Study and Site Feasibility	***Site feasibility is particularly important for device trials, as sponsors must assure that the sites have the appropriate facilities to support necessary procedures.*** • Does the site have the appropriate referral base for sufficient patient numbers, for the study and follow-up care? • Does the site have appropriate capabilities (including trained study staff) and equipment for diagnosis, treatment, management, and evaluation of the patients for the new technology? (e.g., MRI or CT for imaging, laboratory on site for testing if needed, nursing skills for patient support) • Can the site provide the necessary additional staffing for the study? (e.g., some interventional studies require a back-up surgical team on call for procedures)
Accrual	***Medical device trials often require that subjects be referred into the site where the product will be used.*** • Have referral patterns for subjects within the research site and in the geographical region been evaluated? (e.g., does the site have a patient database that can be used to identify patients eligible for the type of procedure/device) • Will a patient recruitment company or service be engaged to support the accrual efforts? If so, is their role and access to subject data clearly stated in the informed consent form [if applicable]?"
PATIENT SAFETY	
Informed Consent	***Informed consent for many device trials requires detailed descriptions of the disease or condition being studied for patients to understand the intervention being evaluated.*** Has informed consent been appropriately evaluated to assure the language is understandable to potential subjects? (e.g., describing the aortic aneurysm disease state for a patient taking part in an endograft trial to treat that aneurysm). Use of plain language principles still apply. Additional resources that may be of interest include: • FDA's current thinking on the topic of Informed Consent can be found in the July 2014 draft guidance document "Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors" (http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm) and in the March 2015 draft guidance on "Use of Electronic Informed Consent in Clinical Investigations Questions and Answers Guidance for Industry" (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm436811.pdf). • U.S. Department of Health and Human Services Policy and Guidance on Informed Consent (http://www.hhs.gov/ohrp/policy/consent/)

Withdrawal Criteria and Trial Participant Retention	CTTI CTQ considerations are sufficient. No device-specific considerations to add.
Signal Detection and Safety Reporting	***Trials of therapeutic approaches utilizing new medical devices may identify unique safety issues not previously experienced in the patient population.*** • Does the protocol provide a means to capture unexpected events? • Is the reporting process capable of identifying their source and highlighting them? • Does the device meet the requirements for UDI and do the methods for detection and analysis utilize these data?
Data Monitoring Committee (DMC)/Stopping Rules (if applicable)	CTTI CTQ considerations are sufficient. No device-specific considerations to add.

Training	***Training is particularly important in medical device clinical trials as the procedure itself affects patient outcomes.***
	• Has appropriate training been developed and evaluated to assure the trial can be conducted as designed?
	• Is the level of detail in the product training sufficient given the risk of the product?
	• Has the protocol appropriately identified which individuals need to be trained on specific aspects of trial conduct?
	  o This is particularly relevant for implanted devices and devices that require programming by either the site or sponsor personnel.
	• Does the trial design assure consistency in the use of the product?
	  o For example, for devices that are implanted in a surgical manner will there be proctors, certifications needed to be in surgery room, etc.
	• Are there personnel outside of designated study personnel that will require product training (e.g., cath lab staff)?
	• How will product training/proctoring transition from a pre-market environment to the post-market environment?
	• What are the requirements for a trainer? Can certified site personnel train other site personnel?
	• Should a product-use learning curve be taken into account in the analysis of the data? (See Statistical Analysis section)

Data Recording and Reporting	***Special considerations are necessary in data handling for open label device studies.*** • What are the best ways to protect/restrict information related to the randomized arm (e.g., implant information, adverse events) of open label trials? • How will device / implant issues that need to be quickly identified for re-training be handled? • How will data from blinded trials be reported to CEC / DMC or other open label groups? • How will reporting of Unanticipated Adverse Device Effect be handled?

Data Monitoring and Management	***Monitoring considerations may include monitoring procedures for multiple institutions for the same individual patient.*** • Has risk-based monitoring been included in the protocol design? • What procedures are in place to access data outside of the primary research center if necessary (e.g., implanting institution for device accountability and validation of implanting information, follow up physician locations, rehab facilities)?
Statistical Analysis	***Device trial SAPs are often complicated by unknowns at trial initiation and need to be adjusted during the trial.*** • Are all of the issues related to subgroups and their analysis been addressed in the SAP? Post-hoc analyses create unique problems for the evaluation of device safety and efficacy due to potential bias. • How will early cross-over of subjects be addressed? • How will poolability of the data be evaluated? • How will Type 1 errors be addressed? • How should any learning curve for the device be managed in the SAP?
STUDY REPORTING	
Dissemination of Study Results	***Incidental findings from subject evaluations present unique issues related to dissemination of these results to subjects/families. Diagnostic studies present unique issues in terms of time to disclosure of such results.*** • When and how should incidental findings from evaluations that are not related to the primary purpose of the study be disseminated? • Who will disseminate incidental results to the study subjects?
THIRD PARTY ENGAGEMENT	
Delegation of Sponsor Responsibilities	***Sponsors of medical device trials frequently delegate many aspects of trial design, conduct and monitoring to third parties, often more than one.*** • Is there a statement that clarifies sponsor and Clinical Research Organization (CRO) responsibilities? • Have differences in the Standard Operating Procedures of the Sponsor and CROs been reviewed for conflicts and gaps? • Does the contract specify how future decisions and agreements between the Sponsor and CROs will be made? (e.g., parties could agree to document a scope change in the project file)
Collaborations	***Conducting clinical trials utilizing multiple product types raises challenges for all aspects of the clinical trial design, execution, and evaluation.*** • When working with sponsors with experience focused on other regulated products, have the differences between requirements and protocol considerations been fully evaluated?

	• Is there clarity on which Sponsor or other Third Party holds and manages the protocol, the IDE application or other regulatory approvals/clearances and responsibilities?

Glossary & Acronyms: Device-specific terms

- CRF: Case Report Form
- CEC/ DMC: Clinical Events Committee/ Data Monitoring Committee
- IDE: An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. (http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/default.htm)
- PMA: Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. (http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/)
- SAP: Statistical Analysis Plan
- Sham Procedure: (a) surgical incision but not operation performed; (b) Implant of a device but no therapy delivered.
- UDI: Unique Device Identifier
- 510K: A 510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR §807.92(a)(3)) that is not subject to premarket approval. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm)

References

Clinical Trials Transformation Initiative, "Critical to Quality (CTQ) Factors Principles Document," 2015, http://www.ctti-clinicaltrials.org/files/QbD_toolkit/Principles%20Document_finaldraft_19MAY15.pdf