## CTTI Quality by Design Project - Critical to Quality (CTQ) Factors Principles Document

Quality in clinical trials may be defined as the absence of errors that matter. Trial quality ultimately rests on having a well-articulated investigational plan (e.g., protocol, analysis and management plans). The trial should have clearly defined objectives and associated outcome measures. However, the likelihood of a successful, quality trial can be dramatically improved through prospective attention to preventing important errors that could undermine the ability to obtain meaningful information from the trial.

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. The document generally assumes that a clinical study will address a relevant scientific question for which there is a legitimate research need and is not intended as a primer on how to design a clinical study.

The Quality by Design Project working group regards the CTQ factors described in this document as generally relevant to the integrity and reliability of conclusions based on study data and to the safety of study participants. While it is recognized that all of the CTQ factors are important, different factors will stand out as critical for different types of trials. That is, trial design and objectives will strongly influence their significance. For example, a randomized controlled trial has inherent strengths that may reduce the need for data quality controls that would be relevant for a different design (e.g., single-arm study). Similarly, the data quality controls employed for a trial evaluating whether a treatment is superior to an active control may differ from those required for a trial designed to establish that the treatment is non-inferior. Therefore, some sections may be more or less relevant depending on trial type, needs of the group, and other variables.

The working group has provided questions to consider for each CTQ factor to support evaluation of the factor's relative importance for a particular trial as well as to inform subsequent evaluation of what events may occur that would be likely to significantly impede the conduct of the study, place trial participants at unnecessary risk, or impede usability of the resulting data (in other words, to become "errors that matter"). These discussions can then be used to develop formal plans to avoid these events (e.g., through tailoring study design or implementation) or mitigate their consequences.

Importantly, this document is not intended to serve as a checklist applicable for every trial, nor be all-inclusive. During protocol development, the study team should carefully evaluate whether there are additional CTQ factors that arise from a specific trial's scientific and operational design or more generally from the development program. Historical data from previous trials with the same investigational product or with a similar design may be useful in identifying additional factors underpinning effective and efficient trial completion. Users should freely adapt the document to best meet the needs of the given clinical situation.

Engaging all stakeholders with study development is an important feature of quality by design. The process of building quality into the study plan may be informed not only by the sponsor organization but also by those directly involved in completion of the study, such as clinical investigators, study coordinators, site staff, and patients. In particular, engagement of patient advocacy organizations (PAO)[1] and clinical investigators may identify barriers to accrual and help ensure that study outcomes are meaningful. In the remainder of this document, we refer to the patient and PAO stakeholders as PPAO.

[1] The CTTI Patient Groups in Clinical Trials project describes best practices of working with advocacy organizations and can be a starting point to helping study teams identify and develop these partnerships. Care must be exercised to ensure that the PAO voice reflects a collective patient perspective as opposed to an individual patient's experience.

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| **Eligibility Criteria** | Carefully designed eligibility criteria ensure that the intended study population is enrolled and that trial participants for whom participation may be harmful are not included. Ambiguity may result in inconsistent application across sites; overly restrictive criteria may limit the real-world applicability of results or impede trial participant recruitment.<br><br>Each criterion should be evaluated in terms of its utility in 1) defining the population, 2) excluding trial participants for whom there are safety concerns, 3) avoidance of confounding of efficacy measures, and 4) identifying contraindicated medications or procedures. If the criterion does not have utility by these measures, the rationale for retaining it should be further considered. | 1. Describe the specific population needed for the trial to evaluate the intended question. If this specific population is not enrolled, will trial results be brought into question?<br>2. Are there trial participant populations that must be excluded from enrollment due to specific safety concerns with administration of the product to that population?<br>3. Evaluate the impact of "getting it wrong" with regard to eligibility. If a trial participant is found to not meet a criterion, what is the impact on the trial?<br>4. Is the trial intended to evaluate effectiveness and safety of the investigational product in a real-world population that would be likely to receive the product after approval?<br>5. What are the commonly accepted criteria for diagnosing and evaluating patients:<br>a. With the disease under study?<br>b. With comorbid conditions that are exclusionary?<br>6. Have PPAO and participating investigators provided imput as to the feasibility of implementing criteria? | 1. Are all criteria relevant to ensuring the specific trial participant population needed for the trial?<br>2. Are additional steps necessary to balance population or ensure subsets (e.g., minorities) are sufficiently enrolled?<br>3. Are there clear and measureable criteria to define the population (e.g., "atrial fibrillation" or "diabetes")?<br>4. Is there a particular criterion critical to trial participant evaluability (e.g., for an enrichment design) or to trial participant safety (e.g., contraindicated medications or procedures)? Who generates/reports data on whether a trial participant meets this criterion?<br>5. Does the protocol elaborate on the desired trial participant population and/or the potential risks of participation, and are these statements reflected in the eligibility criteria?<br>6. What are the considerations with regard to timing of eligibility review vs. enrollment/randomization/ treatment?<br>7. Do any eligibility criteria require involvement of third parties external to the clinical site? What measures will ensure that information is submitted and/or received in a timely manner to permit enrollment?<br>8. Are there device or trial participant characteristics that may make a trial participant ineligible that can only be ascertained after randomization and/or attempted use of the device?<br>9. Are eligibility criteria acceptable to investigators and PPAO? |

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| **Randomization** | Randomization, when appropriately executed, addresses selection bias and permits a valid basis for making comparisons between, and drawing statistical inferences about, study groups.The integrity of randomization rests on both sponsor and site-level processes. For example, the sponsor or its designee generates and programs randomization schemes, and must ensure adequate allocation concealment; site staff must administer the treatment to which a trial participant was randomized. | 1. Is the study randomized?<br>2. If the study is randomized, consider:<br>a. Who will generate and implement the randomization schema?<br>b. What is the method by which randomization will occur?<br>c. Are any specific approvals needed to randomize a trial participant?<br>d. Who is permitted to randomize trial participants?<br>e. How and by whom will randomization errors be managed? | 1. Are there ways in which sites could predict treatment? Can these be addressed proactively?<br>2. How will block size be designed to avoid unmasking?<br>3. What controls are necessary and feasible to ensure that randomization occurs as planned (e.g., system is working correctly and algorithm is truly random)?<br>4. Is there the potential for bias to be introduced because the trial participant's condition will be known at the time of randomization but prior to allocation/treatment? How might this be addressed prospectively?<br>5. How will the sponsor and sites ensure in an ongoing manner that trial participants receive the appropriate treatment for their randomized arm while maintaining masking?<br>6. For trial participants who are unmasked to treatment, how will withdrawal of consent between randomization, but prior to treatment, be handled? |

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| **Masking** | Masking may minimize biases that result from differences in management, treatment, assessment of trial participants, or interpretation of results that arise as a result of trial participant, investigator, or study staff knowledge of treatment assignment. Prespecified controls should be considered to prevent unblinding and to deal with potential unblinding events should they occur. Designs that require some staff (whether at the sponsor or site level) to be unmasked while maintaining masking for others present opportunities for inadvertent unmasking and may require additional controls. | 1. What is the impact of unmasking for this study? Does it pose a risk to interpretation of study outcomes?<br>2. Does the study design:<br>a. Require that some site staff members be unmasked while others remain masked?<br>b. Require that some sponsor or contract or academic research organization (CRO/ARO) staff members be unmasked while others remain masked?<br>c. Require study data to be unmasked for periodic interim reviews/analyses (e.g., for a data monitoring committee [DMC] or adaptive design)?<br>If so, the process(es) and responsibilities for maintaining masking in these scenarios should be described. | 1. In what ways could the mask be broken improperly? Are there specific test results (e.g., laboratory data, adverse events) that could unmask site/sponsor personnel?<br>2. What measures does the investigational plan provide to prevent unmasking?<br>3. With partial masking, how will access to treatment assignment knowledge be controlled? Could evaluators be kept masked, even if treating physicians are not? Can the database be structured better to preserve partial masking?<br>4. Specifically, are there procedures and controls to ensure that masking is maintained when:<br>a. An unmasked individual maintains the investigational product supply?<br>b. An unmasked individual must make dosage adjustments?<br>c. There is a double-dummy design?<br>5. Are these measures clearly and consistently described in the protocol and ancillary instructions provided to clinical sites as well as sponsor and CRO/ARO staff?<br>6. What actions are to be taken if unmasking is discovered, and by whom? |

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| **Types of Controls** | The acceptability of the control (if used) in the study may affect the willingness of trial participants to participate in the study and the interpretation of perceived value and reliability of the study's conclusions by different stakeholders (e.g., patients, regulators, payers). | 1. Consider the type(s) of control(s) to be used in the study (e.g., placebo/sham procedure, standard of care, historical) and the rationale for selection.<br>2. Is there clinical equipoise? Do PPAO and treating physicians agree that there is clinical equipoise?<br>3. Is a control group feasible, especially from the PPAO and treating physician perspective?<br>4. Identify controls that may be preferred by different stakeholders (regulators, payers, PPAO). | 1. Based on the type of control, what opportunities for bias might be introduced? If historical controls are used, are study designs sufficiently similar so that resulting data may be considered comparable?<br>2. If a placebo control is planned, does the investigational plan provide explicit plans for minimizing risk to the study population on the control arm (e.g., "early escape")?<br>3. From where will the control be obtained, and what steps can be taken to ensure an adequate and timely supply?<br>4. Is the standard of care provided to control groups, at a minimum, equivalent to well-established and commonly employed local treatment?<br>5. Is there also "usual care" in additional to protocol-defined arms, and is this described clearly in the protocol/investigational plan?<br>6. Are there specific treatments that may not be used per protocol that might otherwise be part of "usual care"?<br>7. Does the investigational plan clearly describe plans for treatment failure? Are crossovers permitted? |

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| **Data Quantity** | There are a variety of viewpoints and interests involved in designing a trial. The minimum data set that is sufficient to address study endpoints and meets the needs of various stakeholders should be that which is collected (data parsimony). | 1. What data points are critical to addressing the question(s) posed by the trial?<br>2. How will these critical data points be generated, collected, and reported?<br>3. What is the distinction between exploratory endpoints and primary and secondary endpoints?<br>4. Does the need for exploratory data endpoints unduly burden data collection?<br>5. Have PPAO and participating investigators provided input as to which data points are the most important to them? | 1. Can each data point be classified as trial participant classification, endpoint, or safety related? If not, what is the justification for collection?<br>2. Are the methods for the data collection and reporting clearly described?<br>3. Are all data described in the protocol captured in the case report form (CRF) or other data collection tool (e.g., electronic health record, electronic data capture [EDC], or electronic patient-reported outcomes [ePROs]), and vice versa?<br>4. Are there critical data generated or maintained by third parties (e.g., central laboratories, electronic health records, ePROs) that must be integrated into the study database? What opportunities for error are there?<br>5. What is the tolerance for error in collection of data points?<br>6. For which data points can a greater error rate be tolerated (e.g., exploratory endpoints) and for which is there a more limited margin for error?<br>7. Could any exploratory endpoints be eliminated to simplify data collection and reporting, and overall burden on the investigational site?<br>8. Have site personnel given feedback on CRFs and proposed timing of assessments? |

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| **Endpoints** | Clearly defining study endpoints and describing how endpoint data are to be collected and reported will support consistent trial implementation across sites and prevent errors that may interfere with analysis and bring into question study conclusions. In defining endpoints, prospective attention should be given to the degree of objectivity in assessment of endpoints, the potential for simple external verification (e.g., death certificates, central and/or bioanalytical laboratory data), and potential for unbiased adjudication or review of endpoint data. | 1. Is/are the endpoint(s) commensurate with the scientific question/objectives of the study?<br>2. Will the endpoint have a clinically meaningful impact on patient care or provide a unique building block for future research?<br>3. Are standardized and generally accepted endpoint definitions and methods to ascertain endpoints available?<br>4. If there are multiple primary endpoints, verify and describe how each is necessary to address/directly link to the scientific question posed by the study.<br>5. Consider the characteristics of the primary endpoint(s), including<br>• How is the endpoint defined?<br>• Is it assessable?<br>• How and by whom will the endpoint(s) be ascertained (e.g., investigator, centrally, third party uninvolved in the study)?<br>• If the endpoint is to be adjudicated, what were the criteria to determine that adjudication was necessary?<br>• Is the endpoint objective (e.g., pregnancy, death) or subjective (e.g., pain score)?<br>• Is the endpoint event-driven?<br>6. Have patient-reported outcomes (PROs) been considered as an endpoint? What are the risks and benefits of their use?<br>7. If composite endpoints are to be used, these should be clearly defined. | 1. Does the primary endpoint address the study aims? Is it accepted by PPAO, regulators, payers, and clinicians?<br>2. Are assessments related to the endpoint complex and/or subject to variable interpretation?<br>3. If it is a "soft" endpoint, is there the potential for bias to be introduced? How and by whom? What might minimize this potential for bias?<br>4. What measures are necessary to ensure appropriate endpoint ascertainment and reporting, particularly if an endpoint occurs external to the site?<br>5. If a third-party adjudicator is involved:<br>• In what aspects of the adjudication process would a failure undermine evaluability?<br>• By whom and by when will adjudication rules and required training be developed and delivered?<br>• How will the team ensure that events are appropriately sent for adjudication?<br>• Are adjudicators masked to treatment assignment? If so, by what method?<br>6. For event-driven endpoints, how will the study team monitor the rate of reporting of key study outcomes?<br>7. If the event rate is below a specified threshold, are there remedial measures that will be taken to preserve the power or integrity of the study?<br>8. If the study is not blinded, are there special considerations for using PROs?<br>9. For composite endpoints, is it reasonable to anticipate that the effect on the components wil be similar or might important signals on some components be obscured by the lact of effect (or an opposite effect) on others? |

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| **Procedures Supporting Study Endpoints and Data Integrity** | Conduct of key procedures, collection of critical data, and effective monitoring of trial participant safety depend on consistent conduct of study procedures. Resources should be focused on preventing opportunities for errors in critical study procedures supporting collection and reporting of critical data directly related to study endpoints and in study procedures necessary to ensure adequate monitoring of trial participant safety. | 1. Can the investigational product technically do what you are aiming for clinically?<br>2. What procedures are critical to collecting reliable data for analysis of study endpoints? Which are non-critical?<br>3. How necessary is it for these procedures to be conducted absolutely consistently across sites or in a highly specific manner or window?<br>4. What procedures do not significantly impact data analysis or trial participant safety (i.e., where error or inconsistency in conduct can generally be tolerated)? | 1. Can study processes and data collection be simplified to ensure consistency across sites in collection and reporting of critical data?<br>2. What errors in conducting protocol-defined assessments would constitute important protocol deviations (i.e., are "errors that matter" in terms of study analyses or trial participant safety monitoring)?<br>3. Are there critical handoffs or steps in data collection in which errors cannot be tolerated? What mechanisms can be implemented to prevent errors in these steps?<br>4. Do "errors that matter" cluster in any specific area or procedure, permitting resources to be focused on their prevention and management? Are these errors readily detectable, permitting swift action?<br>5. Do some data (i.e., endpoints or serious adverse events) need to be recorded more rapidly to support an adaptive design or for DMC monitoring?<br>6. Are there redundant process controls that could be eliminated in processes or steps where errors can be tolerated?<br>7. Are time windows for collection of study endpoints clearly specified? How will observations out of window be handled? What about multiple observations in a single window? |

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| **Investigational Product (IP) Handling and Administration** | Appropriate controls must be in place to ensure equivalent consistency between IPs from manufacturing through administration. In addition, evaluation of both the efficacy and safety effects of an intervention requires confirmation that the assigned intervention was received as prescribed in the investigational plan. | 1. Describe the IP, including any special considerations for its handling and use in this trial.<br>2. Evaluate any specific safety concerns associated with the use of the product and describe how these have been identified and managed in prior investigational or marketing experience.<br>3. What IP use data are integral to evaluating trial results? Why are these data critical?<br>4. For implantable devices, what information about the implant procedure is critical to trial analysis, results, and reporting?<br>5. For diagnostic trials, how will appropriate handling of specimens be verified?<br>6. If the protocol calls for dosage adjustments of IP or control product, are the directions and procedures for making dosage adjustment(s) clear and is the responsible entity (e.g., interactive voice response system directed, site staff) clearly defined? | 1. Given the trial design and stage of product development, what measures are in place or needed to ensure that study trial participants received the assigned IP, as well as to ensure that only study trial participants received the IP?<br>2. Are there potential risks of IP use error? How will these be identified and reviewed, and appropriate action taken?<br>3. What aspects of IP use error do not impact study analysis and reporting?<br>4. What level of detail is necessary with regard to IP accountability?<br>5. Do any aspects of IP use potentially pose problems for the sites at which the study may be conducted?<br>6. Are there specific storage and handling considerations for the IP (e.g., limited stability, restricted distribution product, battery life)? In what aspects of storage and handling can errors be tolerated?<br>7. What assessments are necessary to support ongoing safety evaluations? Does the investigational plan contain/clearly describe these?<br>8. How will device malfunctions be recorded and reported?<br>9. How will trial participants for whom initial IP use is unsuccessful be treated? In the event of multiple attempts, when is the treatment considered to begin? |

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| **Study and Site Feasibility** | As the success of a study is largely dependent on the implementation of the investigational plan by investigator sites, it is important to assess the feasibility of successful completion of the study at potential sites. Consideration should be given to what kind of site is required based on the particular study design. Typical areas considered include access of the site to the study target population, whether site staff are qualified to conduct the study, and whether the site has adequate resources to conduct the study, especially if the experimental arm involves a change in procedure from standard care.<br><br>Expanding this inquiry beyond traditional measures can highlight important issues with trial feasibility, such as:<br>• Inconsistency across countries in standard of care vs. protocol-defined procedures.<br>• Important differences in study staff expertise.<br>• Potential critical differences in characteristics of the patient population.<br>• Disparate access to trial participant data.<br><br>Identifying such issues early in protocol development may permit the protocol or other aspects of the investigational plan to be modified in order to minimize their impact. | 1. Describe the countries and regions in which the trial is planned. Consider both the countries/regions in which the trial will initially be conducted and those that might be added to bolster enrollment. If the trial could not be conducted in these regions, would there be an impact on the trial completion or conclusions?<br>2. Discuss the standard of care for the therapeutic area/indication in the different countries/regions in which the trial will be conducted.<br>3. Are established research networks for the therapeutic area available?<br>4. Evaluate the level of clinical experience with the trial interventions that will be needed at the clinical sites.<br>5. Describe the site-level infrastructure, resources, and any specific certification or training necessary to carry out the planned study visits and procedures and to collect and report data in a timely manner.<br>6. Will the protocol design be pretested with investigators, site staff, and/or PPAO during development?<br>7. Consider the reimbursement issues that impact conduct of the study at the site:<br>a. Will unmasking of the control arm become an issue to secure reimbursement for trial participants in the control arm?<br>b. Will use of the investigational product in the post-marketing setting affect reimbursement? | 1. Is the standard of care in the regions in which a trial is planned commensurate with the protocol requirements?<br>2. Are there countries or regions in which the planned study visits, procedures, and data collection will not be feasible? If so, why? Does the regulatory body have conditions about how many trial participants may be enrolled from various regions?<br>3. Do any of the regions/countries in which the trial is planned pose specific concerns related to:<br>a. Data privacy laws (e.g., data collection or follow-up of drop-outs)?<br>b. Import/export requirements for investigational products?<br>c. FCPA/UK Bribery Act issues?<br>4. If there is not an opportunity to field-test the protocol design with investigators, site staff, and PPAO, how will the general feasibility assessments be assessed?<br>5. Do any data from prior performance for the proposed sites, countries, or regions suggest the potential for difficulty in collecting or reporting critical data?<br>6. Is selected patient population appropriate for phase/level of risk in the protocol?<br>7. What is the skill level and experience of non-research staff interacting with the trial participant during study participation? How might that affect outcomes?<br>8. What is the site's level of experience and reliability at specimen handling and storage?<br>9. Does the research team have institutional support to engage in the research (i.e., are there institutional demands on the investigator's time |

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| | | | that prevents him/her from conducting the study)? |
| **Accrual** | A study may be well designed scientifically but still fall short or even fail, if the appropriate number of trial participants cannot be accrued. Factors considered during feasibility may enhance the likelihood that the study will accrue sufficient trial participants to address the intended objectives posed by the protocol. | 1. Describe the enrollment needed by site and overall to complete the study.<br>2. Determine if historical data are available regarding enrollment and site performance, including:<br>a. Recent data (if available) regarding enrollment for similarly designed trials.<br>b. Whether the anticipated patient population will be available in the regions in which the study is planned.<br>3. Are there competing trials for this patient population? What impact might this have on any pre-specified sample sizes for subgroups of trial participants?<br>4. Are existing patient advocacy groups or support networks available that can be used to generate interest and support around the trial? Consider involving these groups from the time of initial protocol development. | 1. How will each investigator demonstrate the potential to recruit sufficient research participants?<br>2. Are there any sites, countries, or regions in which anticipated recruitment is not based on empirical data?<br>3. Given the anticipated patient population, are the planned study visits and procedures feasible or likely to pose an impediment that may limit recruitment?<br>4. Are there external factors (e.g., competing trials or seasonal variations in prevalence of disease process under study) that might affect accrual rates? |

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| **Informed Consent** | The clinical investigator has a responsibility to ensure that trial participants' participation in research is informed and voluntary, and that new information that may affect trial participants' willingness to continue in the study is communicated in a timely manner. Informed consent is an ongoing process, and the consent document should be the basis for a meaningful exchange between the investigator (or designee) and the trial participant. | 1. What are the key elements of the informed consent process for this study?<br>2. Have various stakeholders, especially PPAO and treating physicians, been involved in the development of the informed consent document?<br>3. Does the consent document employ plain language principles, including description of symptoms rather than disease state (e.g., fatigue rather than anemia)?<br>4. How does the consent process (vs. the document) fit within the study processes?<br>5. Describe the study population. Is there the potential for:<br>• Vulnerable trial participants?<br>• Trial participants with impaired cognition or diminished capacity to consent, either initially or over time?<br>• Emergency situations in which obtaining consent prospectively may not be feasible? | 1. Are key elements of the consent process for the study reflected in the informed consent document?<br>2. Is the consent form meaningful to the target audience?<br>• Will participants understand the risk?<br>• Will participants understand why following the study procedures is important?<br>• Could the form be shortened to enhance trial participant understanding while still meeting consent requirements in regions in which the study will be conducted?<br>3. What options does the informed consent document provide for trial participants to withdraw from the investigational product but complete follow-up visits, withdraw from the study but permit access to medical records for necessary follow-up data, or withdraw consent entirely?<br>4. Do the informed consent and the investigational plan clearly distinguish between withdrawal of consent for the study vs. withdrawal from the investigational product?<br>5. What is the threshold for amending the consent and the process for ensuring timely provision of new information to trial participants? Who will be responsible for identifying and ensuring appropriate changes to the informed consent document?<br>6. Are there unique features about the study that will affect the consent process (i.e., emergent conditions, need to obtain assent from pediatric trial participants)? |

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| **Withdrawal Criteria and Trial Participant Retention** | Clear criteria for stopping study treatment and/or withdrawing trial participants from the study are necessary to ensure the protection of trial participants; however, consideration should be given to methods that will preserve trial participants' safety and rights, while still minimizing loss of critical outcomes data. | 1. Describe the situations in which trial participants should or may be withdrawn from study treatment.<br>2. For participants who stop the assigned treatment, what data are critical for study analysis and reporting?<br>3. For this study, what steps are required prior to deeming a trial participant "lost to follow-up"? Are there critical data (e.g., survival) that might need to be collected for these trial participants (e.g., survival status)?<br>4. How will trial participants with permanent device implants be followed upon withdrawal?<br>5. In non-randomized trials, how are trial participants who withdraw after treatment assignment but prior to enrollment handled (i.e., will trial participants be replaced, counted as treatment failures, etc.)?<br>6. For disease under study, are there patients/patient advocacy groups/patient support groups active that communicate within the community the importance of full and complete participation in trials? Have these groups been involved with the development of the retention plan? | 1. Do the withdrawal criteria capture all important and likely scenarios in which a trial participant should be removed from treatment?<br>2. Are the withdrawal criteria described consistently throughout the protocol and ancillary documents that compose the investigational plan?<br>3. Do these criteria distinguish between withdrawal from study vs. withdrawal from treatment with the investigational product?<br>4. How will the study team ensure that withdrawal criteria are applied appropriately and consistently, such that trial participants are not withdrawn in error or that trial participants for whom continued participation may be unsafe are withdrawn from the investigational product and/or study procedures?<br>5. What specific activities are planned to ensure data are collected as required for trial participants who stop the assigned treatment but remain on study?<br>6. What measures does the study design include to maximize the number of participants maintained on the protocol-specified intervention through collection of outcome data (while respecting trial participant rights)?<br>7. Does the investigational plan describe efforts to maintain contact with trial participants to prevent "lost-to-follow-up" where feasible, and who is responsible for these efforts?<br>8. Do trial participants have personal issues that can be mitigated to aid retention (i.e., transport, babysitting)? |

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| **Signal Detection and Safety Reporting** | Implementing safety-reporting systems that are designed relative to and appropriate to the nature of the interventions (e.g., what is known about the investigational product and the risk relative to the trial participants) will facilitate timely identification of safety signals and efficient, expedited reporting. | 1. Describe the planned processes for monitoring existing and identifying new or emerging safety signals.<br>2. For known safety concerns:<br>• What specific evaluations does the study include to further characterize the association between the investigational product and event?<br>• How and in what time frame are data from these evaluations to be collected/reported?<br>3. How will emerging safety issues from other sources (e.g., other trials, real-world use) that may have an impact on study design and conduct be identified?<br>4. Consider what events are anticipated to occur in the study population. How and in what time frame will these events be reported in the study?<br>5. For non-randomized studies, how will safety signals be assessed in the absence of comparators?<br>6. What level of risk are different stakeholders willing to assume, including trial participants? | 1. Does the protocol clearly identify what events must be reported in an expedited fashion vs. those that do not required expedited reporting? Is this consistent with other study documentation (e.g., serious adverse event reporting form or electronic CRF instructions)?<br>2. Is there an existing safety governance structure for the investigational product and how will this study fit within the structure? If not, what structure must be in place to manage safety reporting and signal detection efforts?<br>3. How will adverse event information be elicited during the study (e.g., specific inquiry defined in investigational plan, open inquiry, PRO, or a combination)?<br>4. Are there specific failure points in adverse event processes that might result in an inability to detect emergent concerns? Are there handoffs of information with third parties that might have an impact on timeliness of safety reporting?<br>5. Will standard terms/coding (including MedDRA or UDI coding) be applied across studies to facilitate appropriate integrated analyses that are stratified by study and related cross-study analyses (e.g., when greater power is needed to detect important safety signals)?<br>6. How will ongoing communication regarding changes in the risks/benefits occur (e.g., notifying investigators re. safe use)?<br>7. Are standard definitions for adverse events provided in the protocol? |

| PATIENT SAFETY | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| **Data Monitoring Committee (DMC)/ Stopping Rules (if applicable)** | When interim monitoring of accumulating efficacy and/or safety data is considered necessary to make determinations on whether to continue, modify, or terminate a trial, this process may be best accomplished by use of a DMC. Use of an appropriately convened DMC should protect the integrity of the trial from adverse impacts that might otherwise arise from access of unmasked interim trial data by individuals involved with the design, conduct, and monitoring of the trial. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking, and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it to prevent the introduction of bias. | 1. Describe the circumstances in which the study should be terminated early. At what point, if any, would the study be stopped early for efficacy?<br>2. Evaluate whether the study should include a DMC. DMCs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity (FDA DMC guidance).<br>3. Will the DMC be responsible only for this study, or will they monitor trials across a development program?<br>4. If there is not a DMC, how will analyses be performed on accumulating safety data and how will decisions be made about necessary actions?<br>5. How might new information from outside the trial (such as results from a competitor) be incorporated into ongoing assessments of the benefit/risk ratio for participants in the study?<br>6. If the trial has multiple adaptive procedures (adaptive randomization, early stopping, sample size re-estimation), how will these rules interact with others to be used by the DMC?<br>7. Consider, a priori, the data reporting order (e.g., DMC → steering committee → sponsor) for stopping rules or preplanned adaptations. | 1. Is the study governance structure clear—i.e., who is ultimately accountable for the decision to stop the study?<br>2. If a DMC is to be used:<br>• What mechanisms will ensure that stopping rules and/or guidelines are clear and applied appropriately?<br>• What measures are in place to ensure the independence of DMC members from those responsible for study conduct?<br>• What controls are defined to ensure the quality and timeliness of data provided to DMC members?<br>• How clean will the data be to support DMC analyses?<br>• How will the sponsor clean data and remain masked?<br>• Is it defined how and when DMC recommendations will be implemented and communicated?<br>• How will data be handled that are collected between the decision to end the study and the actual end of the study?<br>3. Are there specific rules for reporting if the DMC chooses to ignore a protocol-defined adaptation or stopping rule (e.g., report rationale to head of steering committee)?<br>4. Are interim analyses defined by trial participants enrolled? Trial participants at their primary outcome? Trial participants with primary outcomes adjudicated?<br>5. If a trial meets early stopping bounds, how should trial participants enrolled but not yet at their final endpoints be included in the final analyses? |

| STUDY CONDUCT | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| **Training** | Study-specific training may involve all stakeholders, including but not limited to sponsors, third-party service providers, DMCs, adjudicators, investigators, coordinators, other local site staff, and/or trial participants. Ongoing focused training of study staff during the study can reinforce protocol requirements as well as provide needed updates when some portion of the investigational plan has been amended (e.g., protocol, CRF, EDC, monitoring plan). Study-specific training minimizes site-to-site variability in conduct of critical study procedures and ensures that all stakeholders understand and appropriately implement the protocol. | 1. Consider the critical elements of the investigational plan, including whether these activities are carried out and/or critical data generated by:<br>a. Sponsor staff.<br>b. CRO/ARO staff.<br>c. Other third parties (e.g., adjudication committee).<br>2. For what critical activities are focused and/or targeted training necessary to ensure appropriate and consistent conduct?<br>3. Consider any study-specific assessments for which staff must be certified vs. trained (i.e., use of the investigational product).<br>4. How applicable will the training employed during the study be in more general settings?<br>5. Will roll-in trial participants be used at sites? How many? How will these trial participants contribute to the overall findings of the study?<br>6. How might human factors (HF) play a role in the intended use of the investigational product? How can training be used to mitigate HFs? | 1. Is training focused on critical elements of the investigational plan that if not followed would add risk to the study outcome and trial participant safety (i.e., they generate “errors that matter”)?<br>2. Who will be trained and how will training be provided and documented? Do trial participants need specific training?<br>3. Could delivery of training be tailored dependent on the topic and audience?<br>4. Are the steps required to achieve any required certification clearly described in the protocol/investigational plan, as well as any requirements for maintaining certification?<br>5. What measures are in place to ensure that sponsor, CRO/ARO, and investigators/site staff receive required training in a timely manner (e.g., before carrying out the activities described in the training/protocol)?<br>6. Is it feasible to test the effectiveness of training? Does the investigational plan describe early checks/feedback on performance?<br>7. If changes to the protocol are made during a study, what measures will ensure that new information is provided in a timely manner to affected stakeholders?<br>8. How will the need for additional training, whether for on-site staff, sponsor personnel, or CRO/ARO employees, be determined? |

| STUDY CONDUCT | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| **Data Recording and Reporting** | The manner and timeliness in which study data are collected and submitted to the clinical trial database are critical contributors to overall trial quality. | 1. Consider how and by whom critical data will be collected and reported (e.g., CRF, EDC, PRO).<br>2. Can IT systems (e.g., EDC) also be used to encourage and enforce compliance with the protocol requirements for data capture and reporting?<br>3. Will standardized data definitions be used when available?<br>4. Will there be eSource records, and how and by whom will they be managed?<br>5. Can study data be captured in parallel with routine clinical assessments and documentation?<br>6. Does the investigator need to review and/or take action on data generated directly by the trial participant or a third party.<br>7. Will multiple data systems be utilized, requiring transfer and integration (e.g., central lab, interactive voice response system, imaging reader)? | 1. What controls are in place to minimize data entry errors if site staff interacting with the trial participant are different from those completing the CRF?<br>2. How will the CRF and database design reflect current data standards for reporting? Are data capture systems user-friendly? What opportunities are there to pilot the electronic CRF and to test the usability of EDC systems?<br>3. Will timely entry and transfer of data using EDC be feasible in all the regions in which the study will be conducted?<br>4. Are any responsibilities for reviewing and, as necessary, acting on data recorded/reported by others (at the site or at a third party) clearly defined in the investigational plan?<br>5. If collecting PROs, what measures/controls will support timely entry and integrity of these data? What role does the PRO data serve (endpoint or supportive?)<br>6. Are the time frames for data submission from sites and/or transfers from third-party vendors appropriate to facilitate timely review whether by the investigator or an internal team at the sponsor?<br>7. Have investigator sites been trained on the importance of timely and accurate data entry to support centralized/remote monitoring and/or in preparation for on-site sponsor monitoring?<br>8. If using eSource, will the access to the source data have sufficient controls such that any changes remain under the authorization of the clinical investigator and are adequately documented? |

| STUDY CONDUCT | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| **Data Monitoring and Management** | Sponsors have an obligation to monitor the progress of their trial. Ongoing data monitoring provides assurance that trial participants' safety will be protected (e.g., a trial will be terminated if it presents an unreasonable and significant risk) and that the data gathered during a trial will be fit for purpose. Operational checks (e.g., on-site, remote, and centralized monitoring) and statistical surveillance can identify important data quality issues at a point at which corrective action is feasible. | 1. Identify departures from study conduct that may generate "errors that matter."<br>2. Which data are not critical to study analysis?<br>3. By what methods will data be monitored while the study is ongoing? At what frequency?<br>4. Will centralized statistical monitoring approaches be used in combination with on-site monitoring activities? (Find additional resources through CTTI and the FDA here)<br>5. What functional lines will be involved in ongoing data monitoring?<br>6. Identify which function/individual is ultimately responsible for the decision to lock and unlock the database.<br>7. What types of issues is the monitoring plan designed to detect? Is it sufficiently comprehensive?<br>8. Define critical data elements for data management during protocol development. | 1. Does the investigational plan clearly define which departures from study conduct are "errors that matter" and which are not?<br>2. Are planned data edit checks focused on critical data and processes?<br>3. Have realistic tolerance limits for "errors" been defined?<br>4. Who generates queries and how will the sponsor ensure that queries are focused on ensuring the integrity of critical data?<br>5. Will self-evident corrections be permitted, and are the criteria and processes for self-evident corrections clearly defined?<br>6. Is there a defined process for escalating issues identified during routine data monitoring (e.g., implausible data at a site, failure to report data to the sponsor in a timely way, trends suggesting inconsistent implementation of the protocol across sites)?<br>7. Is there a defined process for identifying when corrective and preventive actions should be created, including verifying that these actions are implemented and effective?<br>8. Are database lock procedures clearly defined, including roles, responsibilities, and processes for correction of errors identified after database lock?<br>9. What types of discrepancies are permitted to remain through study closure? |

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| **Statistical Analysis** | Details of the study design and conduct, as well as the principal features of its proposed statistical analysis, should be clearly specified in a protocol written before the study begins. The extent to which procedures in the protocol are well defined and the primary analysis is planned, a priori, will contribute to the degree of confidence in the final results and conclusions of the trial. | 1. What data are critical to the statistical analysis plan (SAP)?<br>2. Does the study include multiple endpoints? If so, how will the results be tested and interpreted?<br>3. Consider how:<br>• Data that are differentially obtained will be handled (e.g., lost-to-follow-up or early withdrawal).<br>• Missing data will be dealt with in the analysis.<br>4. Clearly identify which trial participants are to be included in intention-to-treat (ITT) analysis vs. per protocol or as treated analyses.<br>5. How will evaluation and/or implementation of stopping rules affect the statistical analysis? [See PATIENT SAFETY – Independent Data Monitoring Committee (DMC)/Stopping Rules above for additional information] | 1. Are there measures to ensure that study statisticians are aware of the clinical implications of study objectives and endpoints at the design phase and during the protocol, and are apprised of clinical site quality issues?<br>2. What controls will ensure that the SAP is finalized prior to unmasking (key is prior to knowledge of treatment assignment)?<br>3. Are there clearly defined plans for handling missing data in the study protocol?<br>4. What triggers might lead to re-evaluation of the SAP? What controls are necessary to ensure that SAP modification is appropriate?<br>5. Are there specific controls/measures defined to ensure that the analysis will be validated and performed appropriately? |

| STUDY REPORTING | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| **Dissemination of Study Results** | To assess a trial accurately, readers of a published report need complete and clear information. Study reporting may include submission of clinical study reports (CSRs) to regulators, reporting to public clinical trial registries (e.g., ClinicalTrials.gov), and other means of disclosing study results to stakeholders. Transparency of both the data and the processes for analyzing the data allows both regulators and the public to understand the scientific and ethical conduct of the trial.<br><br>The protocol (including statistical methods) should be clearly articulated sot that the nature of the planned analyses is transparent. | 1. Identify who will have rights to publish or otherwise disseminate study results. Consider a writing committee to oversee all papers resulting from a study database. The committee should include all stakeholders involved with the trial development.<br>2. To whom will trial results be submitted and for what purposes?<br>3. Does the trial sponsor have obligations to publish or disclose study data (e.g., corporate policy, national clinical trial registry)?<br>4. Will the CSR include a quality by design section describing all relevant quality findings during the study and actions taken?<br>5. When/how should study data be shared with trial participants? How will important information be communicated to trial participants?<br>6. Clearly identify primary vs. secondary vs. post hoc analyses in study reports.<br>7. Clearly identify which subset analyses were preplanned vs. which were post hoc.<br>8. Can ITT, per protocol, and as treated definitions, as defined in the protocol, be appropriately translated in the study report? | 1. Is it clear who has the right to prepare publications and reports using the study data? Is this consistently described in contracts, the protocol, and other related documentation?<br>2. What mechanisms are in place to ensure consistent disclosure of study information — both voluntary and mandatory — and to ensure timely correction of errors in reported data?<br>3. Are there specific considerations for report content or format that should be considered when designing data collection tools (e.g., ClinicalTrials.gov adverse event tables may differ from standard CSR tables and listings)?<br>4. If a quality by design section of the CSR is planned:<br>a. Is the definition of what is “relevant” clear to all who may identify such a quality finding or review the CSR?<br>b. What systems are necessary to ensure consistent identification and tracking of quality findings and actions throughout a study by sponsor and CRO/ARO staff members, so that an accurate reporting may be compiled?<br>c. Which of these quality findings may require urgent reporting during study conduct, to whom will the reporting be done, and how will this process be managed? |

| THIRD-PARTY ENGAGEMENT | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| **Delegation of Sponsor Responsibilities** | Sponsors are increasingly reliant on third-party service providers (e.g., CROs, AROs, and other study-specific vendors) to assist with activities, from designing a study through reporting its results. As a result, multiple parties have or share responsibility for study conduct and/or oversight at different points of the study. To ensure oversight of third parties, sponsors should have appropriate levels of internal governance and oversight when engaging third parties in the design, conduct, and reporting of clinical trials. The sponsor should ensure that CROs/AROs and other study vendors are (and remain) qualified to carry out contracted activities. Sponsors must also consider appropriate controls to ensure, in an ongoing manner, that CROs/AROs and vendors are carrying out these activities appropriately and in accordance with contractual requirements or other defined quality expectations. | 1. What activities will be delegated to a CRO/ARO or conducted by another third party?<br>2. Which of these are CTQ activities?<br>3. Will the entire activity be delegated, or will the sponsor retain responsibility for some aspects?<br>4. Are there unique risks that matter to the trial inherent in this partnership?<br>5. What infrastructure and capabilities are required to manage the relationship and provide appropriate oversight of the deliverables from the third party?<br>6. Is there clarity of what needs to be escalated and when? Is there a clear escalation pathway for all parties? Do all parties understand escalation pathways? | 1. Are there available data on prior performance by the third party that might inform decision making about whether to use a particular vendor?<br>2. By what mechanisms will the sponsor and third party ensure there is agreement on what elements of the vendor's performance are critical?<br>3. How will potential conflicts between standard operating procedures of the sponsor and the third party be resolved prior to study initiation?<br>4. How will system access be handled to ensure timely and appropriate access to information for all parties?<br>5. What is the nature of the contractual relationship between the sponsor and third parties responsible for CTQ activities — is there shared risk, or is it a strictly fee-for-service relationship?<br>6. Is there the need to establish quality parameters to measure performance? Is there a defined function or individual(s) at the sponsor with responsibility for monitoring performance of third parties?<br>7. How will roles be clearly defined, such that clinical investigators and site staff know with whom they need to interact and when?<br>8. Is performance by one third party dependent upon inputs from another? Are there mechanisms planned to ensure appropriate communication between third parties?<br>9. Are there defined plans to manage mergers and acquisitions that may occur during study conduct?<br>10. Can the DMC access a third party for data while maintaining masking of sponsor?<br>11. Are all relevant decisions and agreements regarding the relationship between the parties |

| THIRD-PARTY ENGAGEMENT | | | |
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| **Factor** | **Description/Rationale** | **Potential Considerations in Evaluating Relative Importance of CTQ Factor** | **Examples of Issues to Consider in Evaluating Risks to CTQ Factor** |
| | | | accurately reflected in the contract? |
| **Collaborations** | Sponsors are increasingly using alternative models to develop medicines, such as co-sponsorships (where permitted), co-development programs, licensing agreements, collaborations, and acquisitions. These result in the need to ensure mutual understanding of the roles and responsibilities at different stages of the development life cycle. The type of collaboration will drive the nature and degree of oversight and control necessary and/or feasible. | 1. What is the intended use of the data?<br>2. Is there a clear understanding of who the sponsor is, and who holds the investigational new drug/clinical trials application?<br>3. Is there a mutual understanding on what is CTQ to ensure that collaborative partners give proper attention to CTQ areas?<br>4. Are there unique risks that matter to the trial inherent in this partnership? | 1. Where and how will data from trials be used, including data from completed trials transferred as part of an acquisition?<br>2. Will data be used in a submission or registration to a health authority?<br>3. Who will have ownership of safety data and responsibility for safety reporting?<br>4. Is relevant information available and will appropriate access be granted to assess and confirm that CTQ aspects of the trial were carried out correctly and to provide confidence in data reliability of completed trials?<br>5. What mechanisms are in place to ensure timely and appropriate access to information for all parties? |

## Glossary & Acronyms

**ARO:** Academic research organization

**Clinical equipoise:** A state of genuine uncertainty as to the advantages or disadvantages of each therapeutic arm in a clinical trial (thefreedictionary.com)

**Competitive Enrollment:** Indicates that the local site may enroll more trial participants than originally planned by the study sponsor, while the total number of trial participants enrolled study-wide does not change

**CRF:** Case report form

**Critical to Quality (CTQ) Factors:** Factors relevant to the integrity and reliability of conclusions based on study data and to the safety of trial participants

**CRO:** Contract research organization

**CSR:** Clinical study report

**EDC:** Electronic Data Capture

**Data Monitoring Committee (DMC):** An independent group of experts who monitor trial participant safety and treatment efficacy data for a clinical trial; also known as Data Safety & Monitoring Board (DSMB) or Data Safety Committee (DSC)

**Foreign Corrupt Practices Act (FCPA):** Enacted in 1977 for the purpose of making it unlawful for certain classes of persons and entities to make payments to foreign government officials to assist in obtaining or retaining business (www.justice.gov/criminal/fraud/fcpa/)

**Handoffs:** Specific points in the clinical investigation when data are transferred between groups (i.e., sponsor, third-party service provider, investigative site)

**Human Factors (or Ergonomics):** The scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human wellbeing and overall system performance (The International Ergonomics Association)

**Investigational Product (IP):** The device, drug, biologic or diagnostic product under investigation

**ITT:** Intent to treat

**MedDRA**: "Medical dictionary for regulatory activities"; standardized international medical terminology

**PPAO:** Patients and patient advocacy organizations

**PROs/ePROs:** Patient-reported outcomes/Electronic patient-reported outcomes

**SAP:** Statistical analysis plan

**UDI:** Unique device identification