Proposed Framework of Characteristics that Define the Quality Conduct of a Clinical Trial

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Defining Quality Conduct of Clinical Trials

Rationale: If you don’t know where you’re going, anywhere will get you there

We are defining quality as the absence of errors that matter
- Errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients).
Proposed Draft Framework

Intended to describe the characteristics that are synonymous with the quality conduct of clinical trials.

In scope are characteristics and indicators that are within the control of investigators and their delegates and that could be modified through training.

Out of scope are characteristics that are beyond the control of sites, investigators and their delegates, including those characteristics that relate to protocol design and study reporting.

- For more information on improving the quality of clinical trials through improved design, see CTTI’s Quality by Design recommendations.
Organization of the Draft Framework

- The relevant categories of critical to quality factors as defined in [CTTI’s Principles Document](#)
- The Donabedian model used to classify different types of quality measure. This model has also been adopted by [AHRQ](#).
# Feasibility

<table>
<thead>
<tr>
<th>Structural Measures</th>
<th>Process Measures</th>
<th>Site Level Outcome Measures</th>
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**Expertise**
- Investigators and their delegates have sufficient experience in the specialty area of the study.
- Investigators and their delegates have relevant research understanding and experience.

**Capacity**
- Sufficient and appropriate site staffing for the protocol.
  - Are there sufficient team members with enough time to meet the responsibilities of the trial?
  - Identify and resolve possible conflicts.
## Study Conduct

### Structural Measures

**Culture**
- Presence of a participant centered culture
  - A culture that values and promotes partnership between investigators & their delegates and patients and their families in order to align decisions with patients' wants, needs, and preferences.
- Cooperative institutional environment
- Environment that emphasizes ethical conduct
  - Culture of learning

**Processes**
- Clear division of roles and responsibilities
- Clear and effective lines of communication with
  - Other site staff
  - The sponsor/CRO

**Systems**
- Ability to assess whether it is possible to recruit/conduct protocol
  - Example: a thorough review of the protocol against patient charts to determine if site can really enroll the patients
- Ability to develop / existence of a clear recruitment plan likely to be successful in the environment of the site
- Ability to identify and address issues through process improvement

### Process Measures

**Pre-Trial Planning**
- Appropriate planning
  - Investment in time needed to understand thoroughly the study design, study procedures and protocol
  - Development of an accurate and useable study process map, to lay-out clearly the steps needed for all trial processes, start to finish. Ex: who receives study documents, who files them with the IRB, who will handle drugs/devices, who will administer informed Consent, etc, etc

**Recruitment**
- Optimized enrollment
  - Time to enrollment (knowing subject pool, defining recruitment methods in advance, contingency plans if enrollment not progressing)
  - Eligible patients
  - Evaluable patients
  - Absence of selection bias

**Protocol Compliance**
- Minimal preventable protocol deviations
- Correct assessment of outcomes

**Retention**
- Subject follow-up
  - Adequate
  - Appropriate
  - Minimal loss to follow-up

**Data Quality**
- Quality and completeness of data
  - No missing data
- Data integrity
  - Data in EDC system consistent with source documents; entries and corrections are timely
  - Critical data completely in the EDC, esp safety and primary efficacy within X timeframe
  - Allied data (labs, images, etc) not directly controlled by the PI is accurate, complete, timely
- Time to crf completion
- Resolution of monitoring visit action items by the next visit

**Quality Control**
- Establishment of key performance and quality indicators appropriate for and aligned with the trial objectives. These could include, for example:
  - Absence of critical findings and less than three major findings
  - Absence of IRB reprimand letters
  - Absence of suspension or termination of investigators or sites
  - Absence of ineligible subjects enrolled
  - Informed consent available for subject prior to intervention
  - x% of subject visits scheduled in visit window
  - Data queries resolved within x weeks of issue
- Review of those KPIs and KQIs periodically, as appropriate for the trial
- Rapid corrective and preventive action/continuous improvement cycle

### Site Level Outcome Measures

**Trial Conduct & Administrative**
- Complete Investigator Site File (ISF)
- Minimal subjects lost to follow-up
- Protocol compliance rate greater than xx (may vary with therapeutic area). Examples:
  - Study visits
  - Procedures
  - Dosing
- Complete IP reconciliation / accountability for all IP

**Data**
- Rapid data entry and query resolution
- Query free data at the end of the trial
- Site data reliable (can be included in the study without concern)
Study Conduct – Structural Measures

Culture
- Participant centered
- Partnerships - Investigators; their delegates, patients, families
- Values scientific inquiry, research integrity and methods
- Supportive and cooperative institutional
- Integrity and Ethical conduct
- Inquiry and learning

Processes
- Clear division of roles and responsibilities
- Clear and effective lines of communication with:	• Other site staff
  • The sponsor/CRO
- Established study conduct systems (record mgmt., IP mgmt., etc)
Study Conduct – Structural Measures

Systems

- Ability to critically assess protocol accrual requirements to determine and demonstrate existence of required patient population AND participation

- Ability to establish of a clear recruitment, retention and adherence plan based on understanding of clinical realities, patient behaviors and Institutional requirements

- Ability to identify and address issues through process improvement
Study Conduct – Process Measures

Pre-Trial Planning
- Investment in training for understanding the study design as it prescribes study procedures
- Protocol specific training of outcome definitions, major protocol definitions, patient safety, etc.
- Quality plan / map for study conduct

Recruitment
- Time to enrollment Eligible patients
- Evaluable patients
- Absence of selection bias
Study Conduct – Process Measures

Follow-up and Protocol Compliance
- Procedures to prevent and/or identify protocol deviations
- Procedures to support correct assessment of outcomes

Retention and Adherence
- Subject follow-up for data integrity and patient safety
- Teaching for participant compliance, adherence
- Practices to establish open discussions with participants to maintain participant engagement
Data Recording and Reporting

- Procedures to achieve data quality, integrity and completeness:
  - Attributable
  - Legible
  - Contemporaneous
  - Original
  - Attributable

- Timely and comprehensive resolution of monitoring visit action items
Quality Control

- Establishment of key performance and quality indicators:
  - aligned with the trial objectives
  - Eg:
    - Informed consent available for subject prior to intervention
    - x% of subject visits scheduled in visit window
    - Data queries resolved within x weeks of issue
    - Absence of ineligible subjects enrolled

- Systematic monitoring and review of those KPIs and KQIs
- Integrated corrective and preventive action/continuous improvement cycle
Study Conduct – Outcome Measures (Site Level)

Trial Conduct & Administrative
- Complete Investigator Site File (ISF)
- Minimal subjects lost to follow-up
- High protocol compliance for:
  - study visit schedules
  - Accuracy and completeness of procedures
- Complete IP reconciliation / accountability

Data
- Rapid data entry and query resolution
- Query free data at the end of the trial
- Site data reliable
## Third Party Engagement

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<td>Clear understanding, definition, and acceptance of the roles and responsibilities of allied personnel and departments (IRB, contracts, labs, etc)</td>
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<td>SOP’s for site specific procedures exist including:</td>
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<td>- how to identify and resolve problems</td>
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<td>- how to elevate the awareness of problems to the investigator and project leadership at the sponsor</td>
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# Patient Safety

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<tr>
<td>Patient centered culture</td>
<td>Informed Consent</td>
<td><strong>Safety</strong></td>
</tr>
<tr>
<td>Knowledgeable staff</td>
<td>➢ Effective communication during informed consent</td>
<td>➢ Complete SAE / AE reconciliation</td>
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<tr>
<td></td>
<td>➢ Informed consent available for subject prior to intervention</td>
<td>➢ Timely review/signatures/assessments of adverse events, procedure/lab results and other diagnostic testing</td>
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<td></td>
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<td>➢ Compliance with protocol safety algorithms, where applicable</td>
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