Acceptable Ranges for Clinical Trials: Insights from ICH E6(R3)

Understanding the New Guidelines and Their Implications

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Introduction to ICH E6(R3) and Acceptable Ranges

Overview of ICH E6(R3), brief history, principles etc.

- The concept of using a risk-based quality management system to manage quality throughout all stages of the trial was introduced in ICH E6(R2). As part of this risk-based approach, predefined quality tolerance limits (QTLs) were to be established to identify systemic issues that could impact subject safety or reliability of trial results, and to develop a prioritized, risk-based approach.
- In ICH E6(R3), QTLs were reframed to **acceptable ranges** to provide a broader context. Whether these measures are called QTLs or acceptable ranges, the focus should be on assessing the state of control for important risks with the potential to significantly impact the critical to quality factors. The following points remain important from R2 into R3:
  - Evaluation of deviations from acceptable ranges should be done to determine if there are any systemic issues and appropriate actions are taken, if needed.
  - Mitigations are taken to prevent deviations from reoccurring.
  - The remedial actions taken for important deviations from acceptable ranges should be documented in the clinical trial/study report.

Comparison of Language in R2 and R3

ICH E6(R2)	ICH E6(R3)
Section 5.0.4 - Risk Control "The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed."	**Section 3.10.1.3 - Risk Control** "Risk control should be proportionate to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results. Risk mitigation activities may be incorporated, for example, in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, and training. Where relevant, the sponsor should set pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors. These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed."
Section 5.0.7 - Risk Reporting "The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report.(ICH E3, Section 9.6 Data Quality Assurance)."	**Section 3.10.1.6 - Risk Reporting** "The sponsor should summarise and report important quality issues (including instances in which acceptable ranges are exceeded, as detailed in section 3.10.1.3) and the remedial actions taken and document them in the clinical trial report (see ICH E3)."

**Highlighted text shows replaced text from R2 to R3.

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Key Considerations for Acceptable Ranges

- A risk-proportionate (fit-for-purpose) approach informs development of acceptable ranges.
- Acceptable ranges can be set based on statistical design of the trial and prior/emerging knowledge (e.g., investigational product or study population).
- Deviations from these acceptable ranges could help identify systemic issues that could impact participant safety and trial reliability.
- Early detection of important deviations from acceptable ranges can help assure and control the quality of the trial throughout the conduct.
- Remedial actions taken to bring the deviation within the acceptable range should be tracked and monitored.

Defining Acceptable Ranges

Acceptable ranges terminology was recently introduced in ICH E6(R3) expanding the concept of Quality Tolerance Limits (QTLs), which might have been seen as inflexible (as any departure would need to be assessed and could result in a deviation that requires documentation in the clinical trial/study report (CSR). This is aligned with the new approach coming with the ICH E6(R3) version that provides more flexibility and allows for broader ways to manage and oversee clinical trials. This concept is also linked to the idea of risk proportionality, i.e., more controls where it matters the most.

The criteria for the definition of acceptable range needs to be deeply associated with Critical to Quality (CtQ) factors (e.g., critical data and processes) identified for the clinical trial. Additionally, variations to the acceptable ranges that can be accepted should also be set. Both the criteria and acceptable variations should be linked to the trial objectives, design etc.

For example, acceptable ranges could be used to control and monitor risk to:

- Early Treatment Discontinuation
- Inclusion/Exclusion (I/E)
- Lost to Follow-Up (LTFU)
- Serious adverse events
- Efficacy endpoints
- Temperature range
- Visit window

****For illustrative purposes only and is not an exhaustive list of critical to quality factors**

Sample Development and Application of Acceptable Ranges

Use Case Scenario

In a rare disease trial that planned to enroll **X participants** (target **Y participants per site**), the following were deemed critical to trial outcomes and participant safety. Medical and statisticians evaluated prior study data and analysis plan knowledge as rationale and reasoning for selecting the following acceptable ranges:

- **Safety**: Number of AEs or SAEs of allergic reactions or anaphylaxis related to study drug (**A-B%**)
- **Early terminations**: Number of early terminations prior to week 12 (**<C-D%**)
- **Endpoints**: Number of missed endpoint data (**<E-F%**)

It was determined that these acceptable ranges would be assessed twice monthly at the study level:

- **Safety**: **G of H participants (I%)** in a Phase 1 trial had severe anaphylactic AEs. To ensure close supervision of participants in the Phase 2 trial, an acceptable range of Adverse Events (AEs) or Serious Adverse Events (SAEs) related to study drug that are classified as allergic reactions has been set to between **A-B%** at the trial level. Central monitoring will flag when the trial has more than **J%** of participants have had allergic reactions for further evaluation.
- **Early Terminations**: In order to ensure appropriate power of the study, to evaluate safety after dosing and efficacy endpoints, the team has established that **<C-D%** of participants can discontinue prior to Week 12. Central monitoring will flag when the trial has more than **K%** of participants early terminate prior to week 12 for further evaluation.
- **Endpoints**: In order to ensure appropriate power of the study for efficacy, the team has established that missed endpoint data should be between **<E-F%**. Central monitoring will flag when the trial has more than **L%** missed endpoint data for further evaluation.

Disclaimer: This use case scenario is illustrative only. Variables have been used instead of actual numbers for demonstration purposes.

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Tips for Implementing Acceptable Ranges in Clinical Trials

Planning/Design of Acceptable Ranges

- Consider CtQ factors (e.g., eligibility, safety, toxicology etc.), review statistical section of protocol, consider impacts to endpoint interpretation/analyses
- Engage key stakeholders (e.g., Medics, Statisticians, Operations) from Sponsor and CROs. Use knowledge of participant population, historical data of similar trials, and/or statistical methods and modeling
- Assess available data sources (frequency and format)
- Define parameters that are specific, measurable, and actionable

Monitoring of Acceptable Ranges

- Frequency should be documented in a plan that specifies responsibilities (e.g., QTL Monitoring Plan or Clinical Monitoring Plan (CMP))
- Document review and key stakeholder assessment of deviations (data that falls outside of the defined acceptable ranges)
- Determine an action plan – Root cause, corrective actions, mitigations taken. If a deviation is determined due to inappropriate ranges, these can be amended with substantiated rationale and adjustments documented
- Assess if deviations meet important/relevant deviation criteria (take action and report)

Reporting of Relevant Deviations from Acceptable Ranges

- Important deviations should be assessed by the impact to participant safety and data integrity, by the extent to which the deviation exceeds the acceptable range, and by the outcome of the systematic issue investigation for potential discussion in the CSR

NOTE: The list of tips set out above is non-exhaustive and not intended for use as a checklist. There may be other points that a company may want or need to consider.

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Potential Benefits of Implementing Acceptable Ranges

- **Flexibility:**
  - Acceptable ranges provide greater flexibility by acknowledging that variability is inherent in clinical trials, especially in complex or multi-regional studies. It allows for a more realistic approach where minor deviations from the protocol that do not affect trial outcomes can be tolerated.
  - Modern trials are increasingly using innovative designs that involve continuous modifications based on interim results and/or may be complex, such as those involving multiple treatment arms or variable dosing. Acceptable ranges offer the flexibility needed to manage such trials, where rigid predefined limits might not be appropriate.
- **Dynamic Monitoring:** Acceptable ranges enable sponsors (and study teams) to adjust monitoring thresholds based on evolving trial data. This means that corrective actions can be better aligned with the real-time needs of the trial rather than being triggered by rigid, predefined limits.
- **Real-Time Risk Management:** This approach fosters a more holistic assessment of trial risks by promoting continuous risk evaluation and decision-making, leading to more proactive and prioritized trial oversight. Noncritical deviations can be managed within appropriate parameters without triggering unnecessary alarms.
- **Trial Quality:** As noted in Appendix B, "Building adaptability into the protocol, for example, by including acceptable ranges for specific protocol provisions, can reduce the number of deviations or in some instances the requirement for a protocol amendment."

Potential Challenges of Implementing Acceptable Ranges

- **Requires Study-specific Customization:** Unlike QTLs, which were perceived to be too narrow and ridged, acceptable ranges are intended to be more flexible and can differ across trials and even within different phases of the same trial. Establishing standardized criteria for these ranges may be challenging due to various factors, which may include therapeutic area, trial phase, or multi-national trials where variations in practice may exist.
- **Requires Real-time Data Analysis:** The acceptable ranges approach requires real-time monitoring and the ability to quickly adapt as new data emerges. This may require enhanced integration of data from different types of systems and dedicated teams capable of monitoring multiple parameters continuously and adjusting acceptable ranges accordingly.
- **Training and Expertise:** Trial staff, including monitors (e.g., statisticians, central/on-site monitors, medical monitors, CRAs etc.), investigators, sponsors, and service providers, will need to develop new competencies to manage acceptable ranges with a clear understanding of how this new method is working to assure and control the quality of clinical trials.
- **Regulatory Alignment:** Regulators may find it challenging to assess whether sponsors are effectively managing acceptable ranges, as the flexible nature of these ranges means fewer clear-cut thresholds for compliance. Regulatory bodies will need to evolve their review and inspection processes to account for this shift.
- **Change Management:** Organizations that are used to working with predefined QTLs may find it difficult to shift to a more flexible and adaptive model. This change may require additional resources and adjustments in mindset, processes, and systems.

Summary and Closing Remarks

The implementation of acceptable ranges in ICH E6(R3) introduces a more flexible, adaptive approach to risk-based quality management in clinical trials.

- This approach emphasizes meaningful responses to deviations, prioritizing participant safety and trial integrity.
- Resources can be focused on significant risks, reducing unnecessary interventions and administrative burdens associated with minor deviations.
- Acceptable ranges may work well for complex and adaptive trials, enabling more tailored and context-specific quality management.

However, with this increased flexibility may come some challenges.

- Study teams will need to be able to define acceptable ranges, ensure consistent monitoring and manage data and trial risks on an ongoing basis.
- Regulatory agencies will need to align on expectations and documentation requirements.
- Sponsors and trial teams will need to invest in new competencies, technology, and processes to address these challenges effectively while maintaining participant safety and trial integrity.

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