Risk Based Monitoring Initiative

RISK-BASED QUALITY MANAGMENT:

QUALITY TOLERANCE LIMITS AND RISK REPORTING

TransCelerate BIOPHARMA INC.

ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

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1. Introduction

Historically, sponsors of clinical trials have utilized a conservative approach to try to ensure zero defects, rather than identifying areas of greatest risk and implementing targeted measures and controls to monitor and address the quality of the trial. These traditional methods of ensuring safety and integrity can be time-consuming, expensive, and inefficient in these current times of data technology innovation and globalization of clinical trials. In response to the changing environment of how studies are conducted, several guidance and consultation documents have emerged that encourage the use of risk-based quality management systems that identify, prioritize and control for risks based on probability, detectability, and impact within the conduct of a clinical trial.[1,2,3,4] In this paper, implementation considerations for establishing quality tolerance limits (QTLs) and risk reporting in the clinical study report (CSR) are examined and described. This framework aims to be consistent with ICH E6 (R2)[3] and TransCelerate papers on Risk Based Monitoring (RBM)[5] and Quality Management System (QMS)[6]. The concepts described within this paper are in the early stages of development and practical experience is limited. We acknowledge that the content on risk reporting and QTLs may change, becoming more robust as sponsor knowledge matures.*

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2. Background

Regulatory guidelines, including the FDA Guidance for Industry, "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring", and the EMA "Reflection Paper on Risk Based Quality Management in Clinical Trials", encourage a risk-based approach to the management of clinical trials.[1,2] Most recently, the revision to ICH E6 (R2) includes a new section on quality management that adopts many of the principles noted in the EMA reflection paper.[3]

ICH E6 (R2) recommends a risk-based approach to quality management that comprises 7 key steps: 1-Critical Process and Data Identification, 2-Risk Identification, 3-Risk Evaluation, 4-Risk Control, 5-Risk Communication, 6-Risk Review, and 7-Risk Reporting.[3]

ICH GCP E6 sections pertaining to Quality Tolerance Limits

5.0.4 Risk Control

(...) 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

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).

The updated Good Clinical Practice (GCP) guidance includes requirements for risk control and risk reporting. Encompassed in these requirements are the establishment of predefined QTLs, deviations from which should trigger action. Additionally, the CSR must include a summary of the quality management approach applied in the trial, relevant deviations from the QTLs, and the actions taken.[3]

3. Risk Control

ICH E6 (R2) recommends QTLs to "identify systematic issues that can impact subject safety or reliability of trial results". Thus, QTLs mark the range of tolerated variability. It is important to understand how the terminology applied in ICH E6 (R2) is used in this document. Therefore, the first part of this section will focus on the terms proposed in this paper and how they relate to the terms used in the TransCelerate RBM methodology. Then this section will provide a framework on the establishment and the implementation of QTLs.

Parameters/Quality Tolerance Limits versus Risk Indicators/Thresholds

Risk indicators (RIs, often referred to as Key Risk Indicators [KRIs]) are a major component of the TransCelerate RBM methodology. The TransCelerate RBM position paper defines a RI as "critical data and other study variables to be assessed (in many cases by comparing across program / protocol / country / site)." The paper defines Thresholds as "the level, point, or value associated with a Risk Indicator that will trigger an action." There may be confusion over the terms that will be used in this paper (parameters and QTLs) and the terms defined in the RBM position paper (RIs and Thresholds). This section is intended to differentiate these terms in the context of a clinical trial and reporting requirements.

TransCelerate proposes a separation of these terms based on the context in which they are described, but recognizes the similarities in their meaning. A Parameter, as used in this paper, is a trial variable to be assessed at the trial level. A QTL is a level, point, or value associated with the Parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e. trend has occurred).

Thresholds associated with RIs are designed to be relatively sensitive to detect potential issues that could be mitigated. If a Risk Indicator Threshold is reached, an appropriate action is taken. Risk Indicators are typically defined at the site level but may also defined at the trial level.

It is important to maintain the separation of these concepts and, in turn, the terms used for the following reasons:

- The ICH E6 (R2) guideline calls for the sponsor to report important deviations from QTLs and actions taken in the CSR.[3] Confusing the two concepts could result in reporting numerous site level RI Threshold breaches in the CSR and potentially missing the intended purpose of the quality report section of the CSR.
- Often, RIs are built using operational data (e.g., data management queries response rate) that highlight site level concerns, but may have limited direct impact on subject safety and data integrity at the trial level.[5]
- Often, RIs are built using Thresholds that can be adjusted for different factors such as enrollment, milestones, and other site performance. This concept can be seen as potentially contradicting the ICH E6 (R2) requirement for predefined QTLs which suggests definition of expectation before the trial in contrast to building the expectation as an average or median which is established during the trial and may evolve over the course of the trial (as more data is collected).[3]

It is possible, and likely, that a risk indicator and a parameter use the same trial variable. For example, rate of premature discontinuation from study treatment can be both measured at the trial level as a parameter with associated QTL and at site level as a RI with associated Threshold. In such cases, a Threshold would be applied to meet the risk-based monitoring design, and a separate QTL would be defined at the trial level. While it is likely that some sites will exceed the Threshold for premature discontinuation from the trial, the QTL at the trial level may not be exceeded and requires assessment and justification if it is.

In summary, both Parameters/QTLs and RIs/Thresholds should be a part of the quality management system, having similar meanings but used in a different context.

Establishing Quality Tolerance Limits

QTLs should be established based on expert (medical and statistical) knowledge of similar trials, historical data of similar trials, and/or statistical methods and modeling. As QTLs are intended to identify systematic issues, it is important to define the expectations and variability that are inherent in executing a clinical trial so to accurately define the limit that may indicate systematic problems.

As QTLs are first established, there will likely be limited historical data, limited knowledge on defining QTLs, and little experience using statistical techniques as predictors of systematic issues. Therefore, it is possible that the defined QTLs may be found to be inadequate during the conduct of the trial. In these cases, the QTL may be modified during the trial with the decision and justification properly reported. It is assumed that over time, the frequency of such cases will decrease with experience.

The principles of QTLs presented in this paper are based on control limit methodology and extrapolations of other industries' practices.[7,8] Sponsors may decide to use other statistical techniques to define and implement QTLs. For example, initial implementations can be based on one-tailed QTLs (always only upper limit) or on statistical tolerance limits. Also, if deemed appropriate by the sponsor, a QTL could be implemented without a defined expectation (see appendix 1).

The Concept of Systematic Error and Random Error

As explained earlier, QTLs are intended to identify systematic issues. Therefore, it is helpful to understand the concept of systematic and random errors.

In statistical process control, a systematic error is a source of variability that can be linked to a certain reason.[7] At the same time, there is no widely accepted definition of systematic issues/errors in clinical trials. In this context, the sponsors are encouraged to consider the following factors:

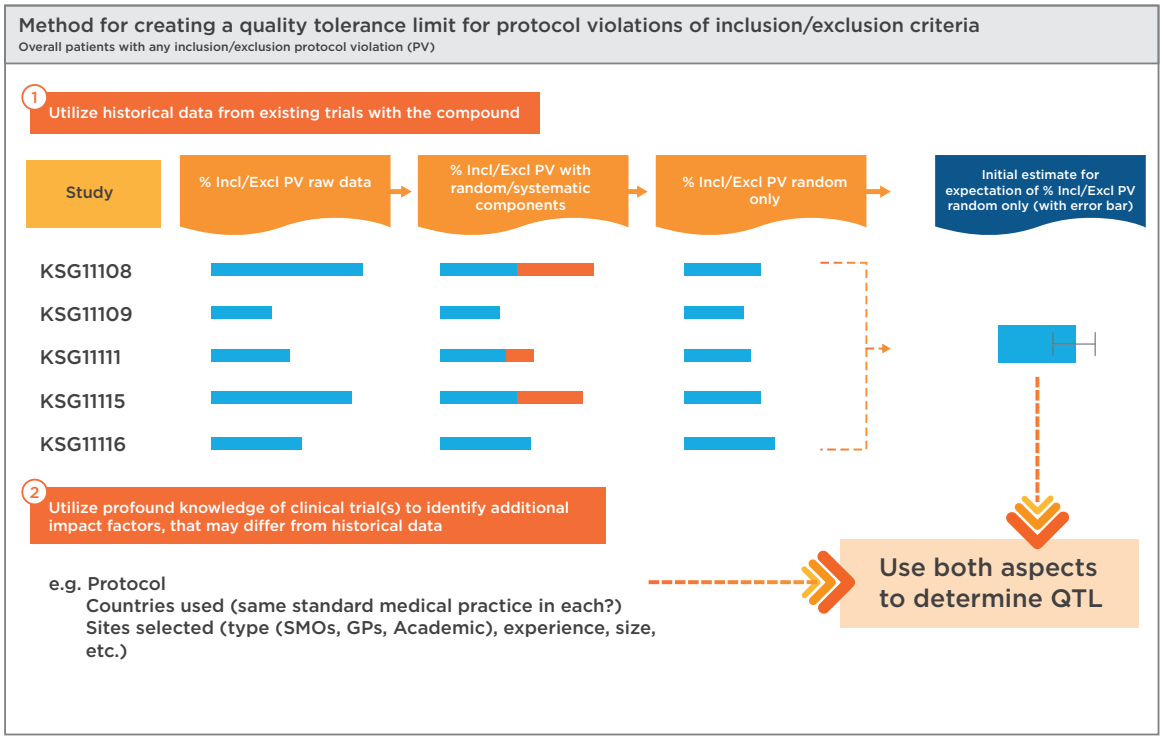
- Common root cause – Multiple events or errors share the same underlying cause (e.g., multiple patients randomized into a wrong stratum due to an imprecise prompt in the Interactive Web Response System [IWRS] system)
- Skewing of results – Imbalance in direction of errors may indicate a systematic component in an apparently random collection of errors (e.g., 26 of 30 incorrectly calculated creatinine clearance [CrCl] results had erroneously higher CrCl values)
- Imbalance in error distribution – Imbalance across geographic regions or treatment arms in open-label studies are examples. This also can be applied to analysis of historical studies (see appendix 3, example 3).

In contrast, random (non-systematic) errors, inherent in running a clinical trial, will not have an identifiable common root cause and their aggregated impact will usually not change the emerging data pattern unidirectionally.

In addition to the points listed above, sponsors are encouraged to further define criteria to delineate systematic errors.

When using historical data to define QTLs, any systematic component of error in that data should be evaluated. In many cases, the data representing the systematic error should be excluded (figure 1). In other cases, the systematic error may be used to help define and/or justify the QTL.

Figure 1: Schematic showing determination of QTL based on historical data and profound knowledge



Implementing Quality Tolerance Limits

The defined QTLs constitute a limit for the parameters that are managed in a trial. As long as the risk under consideration remains within the pre-defined limit, the quality is adequate (figure 2). If limits are crossed, actions need to be undertaken to assess the cause for this deviation (figure 4). It may be advisable to establish secondary limits that justify actions when the identified risk is still in the tolerable range, but shows a tendency to move towards the QTL due to some systematic root cause (figure 3).

Figure 2: Trial parameter within the tolerable range

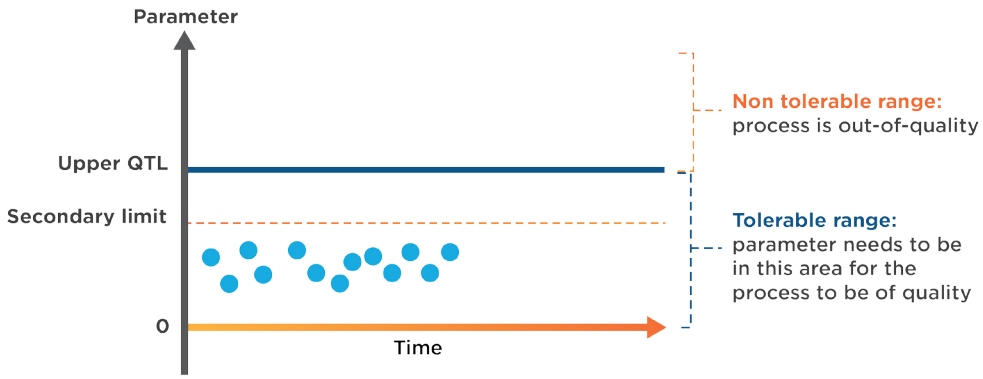


Figure 3: Trial parameter showing a negative trend, but is within the tolerable range

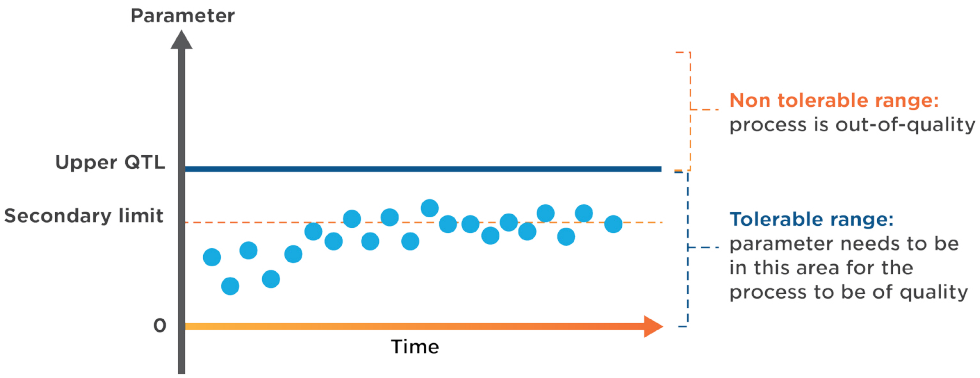
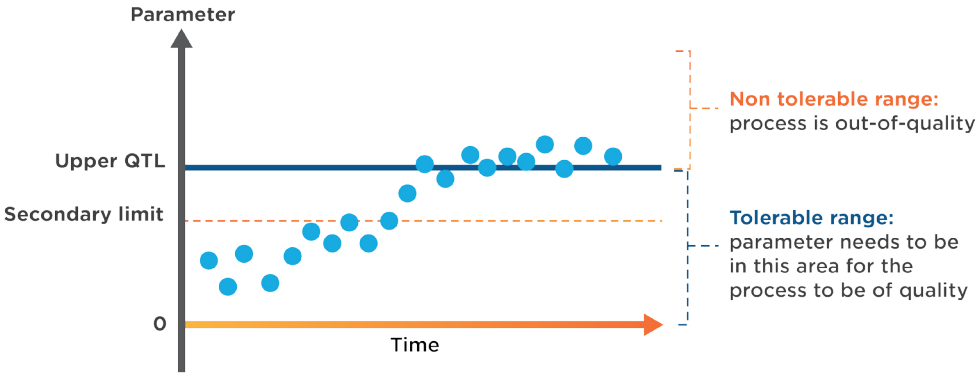


Figure 4: Trial parameter showing a potential systematic effect causing the process to be out-of-quality



General Do's for QTLs

- QTLs should be established at the trial level during the planning stage of a clinical trial, possibly in coordination with risk assessment activities (e.g., using the Risk Assessment and Categorization Tool [RACT])[5] and determination of critical data and processes required to achieve study objectives.
- QTLs should be established for a limited number of parameters (for example, 3 to 5) that can impact subject safety and reliability of trial results.
- Before initiation of the trial, sponsors should develop written, prospectively defined plans for monitoring parameters and addressing deviations from the QTLs.
- The following elements should be considered when defining QTLs: parameter, definition, unit, expectation, tolerance limit (upper, lower, or both), and justifications (see appendices 1 and 3).

- Justification for QTLs should be based on historical data (previous trials conducted by the sponsor for similar indications and published data), medical and statistical assumptions made during the planning of the trial, and profound knowledge (see figure 1 for an example of the usage of historical data and profound knowledge to establish a QTL).
  - In the initial stages of QTL implementation, sponsors will most likely face the problem of limited availability of historical data regarding the systematic or random nature of observed issues. In these cases, the use of published data to define QTLs is encouraged (see appendix 3 for example). In the case of new indications or compound classes, extrapolation of experiences from similar indications or trials may be appropriate.
  - The profound knowledge needed to establish QTLs for new trials should be subject to knowledge management principles, such as what has been described in the TransCelerate QMS knowledge management publication.[9]
- For data integrity-related parameters, sponsors should consider the scientific rigor used during enrollment of the trial population; exposure to interventions; and efficacy and safety measurements, including completeness of those measurements, when defining QTLs (see appendix 3 for an example of a set of parameters and corresponding QTLs pertaining to data integrity for a hypothetical trial).
- Sponsors are encouraged to set non-zero QTLs, although size and type of trial may require exceptions.
  - In small trials, issues occurring at a single site or with a single patient can constitute a deviation from a QTL if those issues impact trial-level data integrity or subject safety.
  - In non-inferiority trials, where accumulation of errors can promote positive trial outcome, data integrity QTLs should be adjusted correspondingly.
- The trial quality should be monitored against the QTLs throughout the trial; QTLs that are exceeded will in most cases be considered an "issue that matters" and should be handled using principles described in the QMS issue management publication.[10] In many cases, this may trigger an impact assessment across multiple trials.
  - Many sponsors and contract research organizations (CROs) perform trial level data reviews during the conduct phase of a trial. It is proposed that review of QTLs be included in the agenda of these meetings.
- A summary of the QTLs should be reported in the CSR. The intention of including risk reporting within the CSR at the end of a trial is to transparently demonstrate how subject safety was assured and how data quality was maintained throughout the trial. This should be done by examining the pre-defined QTLs and summarizing the deviations from them.
- Knowledge management at the program, indication, and therapeutic area should be used to ensure appropriate application of QTLs, accounting for trial phase, type and size.

4. Risk Reporting

At the end of a trial, the CSR should include a summary that meets the requirements described in ICH E6, section 5.0.7.[3] In general, reporting QTLs should be considered for inclusion in the CSR, either as a summary within the body of the CSR, as an appendix of the CSR, or as a combination of both (see appendices 2 and 4).

Reporting should focus on the QTLs that were set for a trial with a summary of mitigations that were implemented if the QTLs were exceeded during the trial and should be complementary to other sections of the CSR that discuss compliance issues, such as protocol deviations and serious breaches.

Each sponsor company may adapt various approaches to how they address risk reporting in the CSR, depending on the conventions of each sponsor company and the templates used.

General Framework for the Investigational Plan (CSR Section 9.6):

- Describe the considerations leading to the selection of QTLs and how these correspond to the design of the trial and the patient population in order to measure the issues that matter.[6]
- Reference the overall Quality Management System (QMS) and how it was taken into account in the risk assessment for the trial. Briefly describe the quality management approach applied.
- Reference the QTLs that define the quality parameters prior to study start. If any QTLs were adapted during the course of trial conduct, give a brief explanation of the justification for this revision.

General Do's for Risk Reporting:

- Describe the parameter values and QTLs at the end of the trial. Explain which parameter values exceeded the QTLs and which parameter values were within the QTLs. It is recommended to utilize brief tabular summaries to display results.
- If there were deviations from the pre-defined QTLs, describe the impact on and potential consequences to the interpretation of the trial results and the overall integrity of the trial. There may be various reasons for the deviations to the QTLs; these explanations should be brief and to the point. Considerations to include:
  - Which critical data and processes were concerned;
  - Whether a systematic error occurred;
  - Whether an assessment was performed;
  - If measures were taken to limit the impact on patient safety, data validity, and/or regulatory compliance;

  - What were the medical and/or statistical justification(s) for the interpretation of the events;
  - Whether the trial results were still regarded as acceptable (e.g., for submission for marketing authorization, for analyzing the safety profile of a marketed compound) and if so, why

» Avoid subjective interpretations without supporting data. Parameters should be managed similar to protocol deviations, where impact to data integrity, patient safety, and trial results are based on root-cause analysis or assessments.

General Don'ts for Risk Reporting:

» Do not provide the risk report as a separate document. It should be integrated within the body of the report (sections 1-14) of the CSR and/or included as an appendix (section 16).[11] Consider including on the cover page of appendix 16.1.9, Documentation of Statistical Methods, if the information can be accommodated on a single page or as a separate lower level 16.1.9 appendix, where the Statistical Analysis Plan and Risk Report would be labelled as Appendix 16.1.9.1 and Appendix 16.1.9.2.[11] Summary statements can be made within the body of the report, where appropriate, referencing the location of the risk report.

» Do not include a general description of the Integrated Quality Risk Management Plan (IQMP) and functional plans that go into the risk management activities. Functional plans may be made available to the regulators by other means.

» Keep in mind that QTLs are set at the trial level; therefore, don't include insignificant detail (e.g. do not describe every site that may have contributed to the exceeded QTL) and do not provide details of minor issues.

» Do not include a lengthy description of the QMS.

» Do not include data line listings or other detailed listings on every instance where a QTL was exceeded. Limit to appropriate data to support the conclusions in the CSR.

» Do not duplicate content in the CSR that is already described in other sections of the CSR or other functional plans. They may be referenced or hyperlinked.

Appendix 1. Items to be defined and documented for QTLs

1	Parameter	The subject of the QTL
2	Definition	Full definition including how the QTL will be measured
3	Justification for parameter	Rationale and any limitations to the use of the parameter
4	Unit	e.g., number, proportion
5	Expectation (*)	The expected (mean/median) value of errors that are of a random nature (i.e., excluding errors that are due to systematic issues)
6	Justification for expectation (*)	Historical data from previous trials within the organization or published data. When referencing historical data, it is important to state whether systematic issues have been excluded.
7	Tolerance limit	Statistical limit and whether it is one-sided or two sided (*)
8	Justification for tolerance limit	How the tolerance limit was set. Include a statistical method if used.
9	The mitigations/ actions taken and the outcome/impact to the trial	If a QTL is exceeded, explain the deviations. Provide the rationale if the trial results are still regarded to be acceptable (e.g., for submission for marketing authorization, for analyzing the safety profile of a marketed compound). Clearly state if the results are not valid.

(*) These are additional fields/considerations that may be helpful in establishing the QTL.

Appendix 2. Example - CSR narratives

The following is an example of a general narrative section that may be included in the CSR Section 9.6 (Data Quality Assurance) :

> *The QTL <give name of QTL, eg. 'maximum number of protocol deviations per treatment year (normalizing value e.g. how long has the patient been exposed to the treatment)'> was implemented to measure the <give parameter that should be covered by QTL, e.g. 'occurrence of protocol deviations throughout the trial conduct phase'>. The limit is based upon <give rationale why the limit was deemed appropriate to cover the risk e.g. 'historic experience with successful studies in the same indication, conducted by <Pharma company>, see also Appendix <xx'>.*

The following is an example of a general narrative section that may be included in the CSR to describe when values were within limits:

> *During the trial, the QTLs were routinely assessed and it was confirmed that values remained within the given QTLs upon completion of data review.*

The following is an example of a general narrative section that may be included to describe when there have been deviations to the pre-defined QTLs describing the actions/mitigations taken (including any root cause analysis or assessments conducted) and the impact and/or outcome to the trial

> *During the trial, <insert number of times the QTLs were exceeded>, deviations from the pre-defined QTLs [refer to Section 9.6] were detected. These deviations are described in the following: <describe summary of deviations, when these occurred, how high the deviations were compared to the set QTL>. Upon occurrence of these deviations, the following <root cause analyses/assessments> were done: <describe root cause analysis/assessment activities>. The results of the <root cause analysis/assessments> were that the deviation was caused by <describe root cause> resulting in an increased level of <QTL exceeded>. These deviations are expected to impact the patient safety and trial objectives as follows: <give a brief description and discussion of the potential impact on patient safety and / or trial objectives; ensure that a clear rationale is given as to why the impact is assessed as given in the analysis; ensure input from the relevant trial team members, such as biostatistician, project manager, drug safety representative, etc. Give information whether the QTL was adjusted after a thorough root cause analysis/assessment, as e.g., the QTL was set too low at the beginning of a trial (as using QTLs will be a learning journey, we expect this to happen occasionally). >.*

Appendix 3. Example – defining QTLs (within a functional plan)

Hypothetical trial design: A phase III randomized, open-label trial comparing a novel oral anticoagulant to warfarin in patients with atrial fibrillation (AF) with a primary efficacy endpoint of stroke. Key safety risk is bleeding. Visit frequency is every 90 days. Trial monitored by data and safety monitoring committee. The trial will randomize 20,000 subjects.

Parameter	Definition	Justification for Parameter	Unit	Expectation	Justification for Expectation	Tolerance Limit	Justification for Tolerance Limit
% of randomized subjects not meeting per-protocol population criteria	Proportion (%) of randomized subjects with pre-defined important inclusion/ exclusion criteria violation(s) that lead to exclusion from the per protocol population.	A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results.	%	1.5	Overall number (%) of patients not meeting per-protocol population criteria and excluded from the primary analysis in the reference trial [12]	One-sided upper limit 1.7	Based on maximum reported rate in one of the randomized groups in the reference trial.[12]
% of subjects with premature drug discontinuation (both arms)	Proportion (%) of randomized subjects who discontinued the trial treatment prematurely (before protocol defined time point)	Premature drug discontinuation rate is the key factor limiting exposure to studied treatments in the setting. Decreased exposure decreases the power of the trial.	%	Not Defined	In similar studies, the rate ranged from 27% to 37%[12-14]	One-sided upper limit 35	Benchmarked near maximum, based on scientific understanding of the compound/ indication and from previous trial data.
% of subjects classified as lost to follow-up in the close-out period of the trial	Proportion (%) of subjects who have no status documented by the site in the close-out period	A high number of sub-jects lost to follow-up can have a negative impact on interpretation of primary endpoint.	%	0.23	The median from studies reviewed in Rodriguez et al, excluding data from the NAVIGATOR trial, considered to be at high risk of systematic errors.[15]	One-sided upper limit 1.01	The 95th percentile from studies reviewed in Rodriguez et al, excluding NAVIGATOR.[15]

Appendix 4. Example – reporting on QTLs

The following is an example table that may be included as an appendix in the CSR. The scenarios are based on the QTL pertaining to the parameter: % of randomized patients not meeting per-protocol population criteria, as presented in appendix 3. Varying scenarios are included, as follows: parameter below QTL; parameter exceeded QTL with no impact; parameter exceeded QTL during the trial, but was below QTL by end of the trial.

Parameter	Justification for Parameter	Unit	Tolerance Limit	Actual Occurrence – End of Trial	Mitigation/Remedial Actions Taken	Impact to Data Integrity/Quality
% of randomized subjects not meeting per-protocol population criteria	A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results.	%	1.7	1.2	N/A – Parameter remained below limit throughout the trial	N/A
% of randomized subjects not meeting per-protocol population criteria	A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results.	%	1.7	1.8	During trial conduct, when 15000 of planned 20000 subjects were randomized, 300 subjects (2%) did not meet eligibility criteria Trial-wide review and analyses of individual cases were performed in order to determine if any systematic error component was present. This activity revealed no systematic component and no trends in violating certain criteria. The QTL was still exceeded at the end of enrollment period (360 of 20000 subjects randomized [1.8%]).	Analysis reveals no potential impact on patient safety and trial objectives.
% of randomized subjects not meeting per-protocol population criteria	A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results.	%	1.7	1.0	During trial conduct, when 9000 of planned 20000 subjects were randomized, 162 subjects (1.8%) did not meet eligibility criteria. An assessment of individual cases revealed consistent misinterpretation of inclusion criterion #24. As a result, the protocol was revised to clarify inclusion criterion #24. In addition, refresher sessions were held with all sites to address compliance with inclusion/exclusion criteria. Result of actions brought parameter value below QTL by the end of the enrollment period (201 of 20000 subjects randomized [1.0%]).	Analysis reveals no potential impact on patient safety and trial objectives.

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