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The Importance of Being Ernest – Risk Based Approach (RBA)

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ABSTRACT

I will allow myself the use / misuse the title of Oscar Wilde' play, but with the risk based approach it is most appropriate. The play on words on Ernest can be seen with Risk, the view of the pharmaceutical industry is that risk is bad. It has been suggested by multiple companies that we should not use the term risk and yet the Regulatory bodies are driving us in that direction, and it is the correct path.

This presentation will cover the changes in the ICH E.6 (GCP) addendum and impact on programming, either direct or via requirements, for both RBM (Risk Based Monitoring) and the overall RBA (Risk Based Approach).

INTRODUCTION

ICH GCP (E6) was implemented in 1996 and the first major revision came 20 years later in November 2016. The focus of the revision is dominantly on the responsibilities of the sponsor and introduces concepts that have been used and accepted in other industries for over 70 years for quality management, such as Quality Tolerance Limits (QTLs).

New quality areas that are specific to clinical trials, include the concepts used for RBM, with a more metrics based focused on centralized monitoring

Within this presentation we will concentrate on three areas that impact programming:

1. Computer System Validation (CSV)
2. QTLs
3. RBM / Central Monitoring

ICH E6 R2

The fundamental concept that have driven the changes ICH E6 R2 have been discussed and presented for 20 years by regulatory bodies (EMA and FDA), that is the need for quality by design. Changes in the clinical trial environment in terms of the data collection, with the transition to dominantly electronic methods have resulted in a greater emphasis on Computer System Validation, to ensure the quality of the data from the concept stage.

COMPUTER SYSTEM VALIDATION

ICH E6 R2[5]

1.65 Validation of computerized systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

Since the introduction of ICH E6 in 1996 the landscape of data collection has changed significantly with a greater reliance on electronic data capture, and thus the requirement for RBA in the area of CSV. The focus should be on patient safety and reliability of data (results).

All processing of electronic data is included and so the risk assessment applies to SAS (or other) programming for Analysis Datasets (ADS) and Tables, Figures and Listings (TFL). Whilst all companies address CSV in one form or another for SAS programming, such as duplicate programming. Few undertake a risk assessment and differentiate the level of validation to the associated risks.

QUALITY TOLERANCE LIMITS

ICH E6 R2[5]

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.

It is worthwhile going through the ICH E6 R2 text, and I have taken the liberty of highlighting some critical parts.

Predefined quality tolerance limits should be established

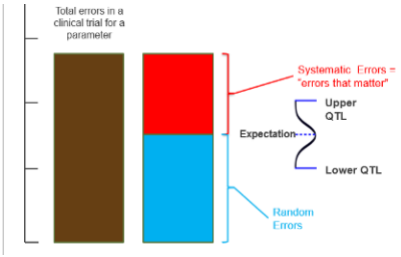
This means that we have to predefine the quality before the trial starts. Many will feel that this is impossible to predefine quality, it is not, we just have to understand the area we are in and use the tools available to us, big data methods and vast knowledge in publications and internally.
The paragraph also tells us what we need to consider, and that is
medical and statistical characteristics
And also the
statistical design
All have to be used in defining the quality tolerance limits, and the design of the study also takes into account the countries, type of sites, size

Now the purpose is to identify
systematic issues
And they also tell us what areas to focus on, areas that can impact subject
safety or reliability
of trial results, and of course reliability also includes integrity.
And now we come to a big change from the traditional use of quality tolerance limits in industry, where in industry a breach of a tolerance limit would lead to the reject of a batch. In ICH the
Detection of deviations
from the predefined quality tolerance limits should **trigger an evaluation** to determine **if action is needed**.
ICH is not calling for the rejection of a trial for a deviation from a Quality Tolerance Limit, but an evaluation to see if there is a systematic component, this will involve root cause analysis, most likely on a metrics basis.

QTLs[6] are a critical part of the QbD process and have been used in at all the quality initiatives, from the 1930's onto Six Sigma, all have as a vital component - the concept of Quality Tolerance limits.

The initial concept of Quality Tolerance limits came from the statistician Walter Shewhart who worked for the Bell Laboratories (US telephone system). His initial use was to justify the quality and hence the prices, that Bell as a monopoly, charged. Shewhart also came up with the Plan-Do-Check-Act cycle for continual quality improvement, Although I have to say that I prefer Deming's adaption of Plan-Do-Study-Act, as Study more correctly reflects the third stage.

W Edwards Deming, enhanced Shewhart's methods and applied them to the whole manufacturing organisation, rather than just the production line process, and we can see from the references in ICH E6 R2 to "system level" risks that ICH are taking us in the direction of the whole organisation.
I should also mention that Joseph Juran the father of Quality by Design, worked with Shewhart at Western Electric.



Looking at the application of the concepts and the principles of Shewhart and Deming, if we consider the bar of the left, in brown, represents the frequency of the errors noted in a trial or process.
Now we can the errors into two parts, looking at the blue and red column then the Blue part represents the Random component, also called common errors, and the Red part is the Systematic component, also called special errors. I have also noted that these "systematic errors" are what often talked about in regulatory circles as "errors that matter".

The objective is to predefine the expected number of random errors (Expectation) and then draw the Quality Tolerance Limits around them.

Random errors are the normal failings of human beings and processes, however extreme it may be, errors such as for failing to obtain Informed Consent, albeit a critical error, may sometimes just be random.
Systematic errors cover a whole range from fraud and gross misconduct at its most extreme down through to "surprising sloppiness" as the FDA term it. Why are these systematic issues important

- They can impact and bias the trial results, leading to integrity and reproducibility issues
- They can be detected. Both the FDA and PMDA have SAS JMP software which can tell them of multiple issues at the press of a menu button.

It is not the Regulatory bodies role to investigate and resolve such issues if they find them, but knowing there is an issue which has not been identified or acted on by the sponsor is a problem.

Areas that Quality Tolerance Limits can be used in:-

- The expected number of Inclusion / Exclusion Protocol deviations, or a particular type of protocol deviation. We never achieve perfection and this is recognition
- The number of adverse events expected per patient year of exposure
- Based on the TransCelerate paper on using SDV as a Quality measure[1], Data changes can be quantified and SDV changes identified allowing us to use the level in the paper as an expectation and draw QTLs

around it, this is a simple one to implement as all the background data is available.

- Lost to follow-up at the end of the study has become an issue of increasing concern, and so has to be minimised. It is highly dependent on the indication area, complexity of study and duration, as well as a number of systemic issues. Literature references can be useful such as the Rodriguez[2] paper from Stanford for Cardio-Vascular trials.

Defining both the expectation and the variation, when publications are not available, becomes a task for programmers, to extract from internal trial or project databases, and to model.

The final part of the programmers involvement with QTLs, is their preparation for inclusion into the Quality Management System to enable the use of the data as quality control charts for the whole company process From these charts the sponsors can

- Monitor quality on a continuous basis, and demonstrate that the sponsor is achieving Continuous Quality improvement
- We can Address trends in our processes, not just at study level, and we can become more proactive, than the current reactive state that sponsors are in.

RISK BASED MONITORING / CENTRAL MONITORING

ICH E6 R2[5]

5.18.3 Extent and Nature of Monitoring

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data. Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

b) examine data trends such as the range, consistency, and variability of data within and across sites.

c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.

d) analyze site characteristics and performance metrics.

e) select sites and/or processes for targeted on-site monitoring.

Section 5.18.3 above details the variety of topics that are expected to be covered by central monitoring. Whilst the first three points under 5.18.3 a) are covered by existing Data Management tools, the rest are not. Programming is required to address these areas, in drawing data from not just the clinical data database, but also the audit trail for clinical data, the CTMS, Site Management System, IVRS, Laboratory data, etc.

The methods described in 5.18.3 are often noted as Central Statistical Monitoring[3] (CSM). The statistical referenced here is more to the methodology, then the practice. The development for use of these tools will be with programming and the monitoring most likely with Central Monitors or Data Management.

REFERENCES

Year - Reference
1 2014- Sheetz et al, Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials, TIRS
2 2015- LTFU and Withdrawal of Consent in Contemporary Global Cardiovascular Randomised Clinical Trials. Rodriguez et al, Critical Pathways in Cardiology
3 2015- Knepper et al, Detecting Data Quality Issues in Clinical Trials: Current Practices and Recommendations, TIRS
4 2016- WHO : GUIDANCE ON GOOD DATA AND RECORD MANAGEMENT PRACTICES, Annex 5
5 2016- ICH : ICH E6 (GCP) Revision
6 2017- TransCelerate Risk Based Quality Management: QUALITY TOLERANCE LIMITS AND RISK REPORTING

RECOMMENDED READING

1982- W.E. Deming's Quality, Productivity, and Competitive Position with 14 Key Principles
#3- Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place
1986- Motorola develops Six Sigma
1987- FDA's first Guideline on Process Validation
1988- US DoD implements Total Quality Management
1991- J. Juran's Juran on Quality by Design: the new steps for planning quality into goods and services
1999- Early,J.F. and O.Coletti. Section 3: "The Quality Planning Process."Juran's Quality Handbook. 5th Ed.
2003- The Philosophy of Shewhart's Theory of Prediction, Mark Wilcox, Proceedings of the 9th Research Seminar: Deming Scholar's Program
2005- ICH QbD related drafts appear- ICH Q8-11
2008- FDA's Guidance for Industry Process Validation: General Principles and Practices (Rev. 1, 2011)

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