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Clinical and non-clinical compliance
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Workshop on risk based quality management in clinical trials 02-03/12/2013

Summaries of the presentations

The workshop was organised by the European Medicines Agency in conjunction with the Clinical Trial Transformation Initiative (CTTI), a public-private partnership founded by the U.S. Food and Drug Administration (FDA) and Duke University on 2 and 3 December 2013.

Reflection paper 'Risk based quality management in clinical trials' and summary of the main changes introduced during the revision

Speaker: Gabriele Schwarz, German Institute for Drugs and Medical Devices (BfArM)

Background: Gabriele Schwarz is head of the GCP Inspectorate of the German Institute for Drugs and Medical Devices (BfArM) and member of the GCP Inspectors Working Group and its Subgroup on Risk-Based Quality Management.

The presentation provided an overview about the creation, public consultation, revision and adoption of the reflection paper and its final content.

As an introduction, the presenter gave an insight into the motivation of the drafting group. The GCP inspectors are of the opinion that sponsors currently too often take a reactive, fire-fighting approach to tackle problems in clinical development projects instead of avoid problems by adequate planning. The risk based quality management subgroup aims to contribute to the improvement of this situation. To this end, the reflection paper provides guidance for an appropriate interpretation of GCP standards in different trial settings and proposes to transfer well-established risk management principles used in the pharmaceutical manufacturing of medicinal products to their clinical development.

The public consultation for the draft paper resulted in an overall positive feedback. However, the drafting group also received some criticisms and suggestions for improvement. Several issues, e.g. monitoring, academic trials and the annex I of the paper were subject to controversy as comments, diverged.

In the follow-up, the paper was thoroughly revised. A glossary was added to clarify the terminology, the two chapters 'introduction' and 'problem statement' were combined and shortened and a chapter 'purpose and content' added. The structuring flow diagram was shifted from chapter 6 to the introduction which led to a rearrangement of subsequent chapters in alignment with the three main sub-processes of the flow diagram. A brief chapter about risk control, risk mitigation and risk acceptance was added. Annex 1 was deleted and instead several practical examples were included in the body text.

The three main processes were briefly explained and the parallels with the ICH Q9 Guideline and related principles and processes were highlighted.

The presenter summarised that risk-based quality management means continuous, systematic and proactive risk assessment on an organisational and project or trial level by a multidisciplinary team with members from the sponsor and if applicable its service provider(s). It was emphasised that more brainstorming and cross-functional cooperation is needed and that this should result in focused resources (training, technical services, data quality checks, monitoring, audits) to mitigate relevant risks. This more careful planning should be complemented by close performance measurement, checking not only timelines and budget, but also quality parameters in relation to pre-specified acceptance criteria or predefined ranges and should lead to a timely escalation of any issues and duly follow-up of agreed corrective and preventive actions.

Finally, the presenter warned against a one-sided misinterpretation of the new concept which could lead to significantly less quality control while no improvements are made in the planning phase. Cost savings are not an acceptable excuse for being out of compliance with standards and established good practice or for less oversight in clinical trials.

A risk-based approach to monitoring and trial quality

Speaker: Jean Mulinde, Food and Drug Administration (FDA)

All stakeholders in the clinical trial enterprise have the shared goal of ensuring that safe and effective products are made available to patients, while the rights, safety, and welfare of clinical trial participants are protected and the data produced by clinical trials are sufficiently reliable and accurate to inform regulatory decisions about the product and to inform appropriate product labelling for use. Drawing on experience in the drug manufacturing sector with Quality by Design-Quality Risk Management approaches, similar quality systems approaches may be adapted to clinical trial conduct to achieve goals of data reliability and patient safety, while at the same time introducing operational efficiencies. Utilising such an approach, one would attempt to prospectively understand and manage potential sources of variation at critical control points in a trial's conduct. For example, risk based monitoring would be one component of an overarching quality management system during clinical trial conduct. FDA regulatory requirements that obligate sponsors to monitor clinical trials are sufficiently flexible to permit risk based monitoring approaches, and the FDA Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, encourages greater reliance on a variety monitoring practices that are designed to address important and likely risks to study data and processes that are identified during risk assessment. In addition, the FDA Guidance emphasises the importance of a well-designed and articulated protocol to ensure clinical trial quality, provides recommendations on monitoring plan development and content, and addresses FDA expectations for documentation of study monitoring activities.

Quality by design in clinical trials

Speaker: Sabrina Comic-Savic, The Medicines Company (The MedCo)

Clinical trial case study segment included presentation of the Phoenix trial of the Medicines Company.

Some of the key features of trial design and operation which contribute to increased efficiency and quality were identified.

Trial protocol design should be simplified and aligned with health care practice as much as possible. When protocol requirements are simple and relevant, implementation is not a burden to sites, which leads to increased efficiency and quality.

Sponsors should select sites whose practice is consistent with the protocol. Selected sites should have experience and good performance in previous relevant trials. Working with a network of sites from study to study improves site performance and trial efficiency.

Site monitoring should be used to create a culture of learning. By using central monitoring techniques to review data, sponsors can identify issues early, and then use site visits to find solutions through communication, education and innovative thinking. The goal of a learning culture is error prevention, rather than costly error detection and correction through extensive on-site data monitoring.

It is important to restrain data exuberance and collect only data necessary to answer the trial question. Otherwise, the effort is diluted and attention is not focused on what really matters.

How to prepare and plan for evaluation of the risks in a clinical trial

Speaker: Uzma Rayani, Stephen Nabarro, Cancer Research UK

Cancer Research UK (CRUK) Drug Development Office (DDO) sponsored early phase clinical trials historically required on-site monitoring visits every 3 – 4 weeks and 100% source data verification (SDV).

The Risk based monitoring (RBM) pilot aims to reduce the average number of monitoring visits across all studies by 20%, increasing efficiency and quality of monitoring.

A cross-functional working group has developed three work streams for the pilot:

1. Implement a Risk Assessment Tool (RAT) to inform the monitoring strategy for each study.
2. Dynamic Monitoring procedures (targeted SDV, remote monitoring).
3. Pro-active data surveillance of eCRFs by Clinical Data Managers.

During the workshop, Uzma Rayani and Stephen Nabarro presented how the RAT informs the monitoring strategy for individual sites. A risk score is calculated per study and site which determines a low, medium or high risk site. This is then translated into the study monitoring guidelines, in terms of on-site monitoring frequency & percentage of SDV.

The RAT is used to assess project-specific risks of the study by assessing key components related to the IMP and the protocol, for example IMP novelty, safety issues, protocol complexity as well as the patient population being studied. Project specific risk scores are determined prior to the start of the study and remain static.

The RAT also assesses study level evolutionary risks which are subject to change throughout the study. Evolutionary metrics measured include; risks associated with protocol amendments, staff changes, protocol deviations and data quality. Overall study risk scores are used by QA to determine the DDO audit plan.

A second component of the RAT is used to perform the site specific risk-assessment. As well as most of the evolutionary metrics, this includes assessment of the experience and availability of site staff, reporting of safety information and whether SDV is up to date. A separate pharmacy risk score is also measured. The resulting site specific risk score is used to determine the monitoring strategy for the study and site.

The pilot is on-going and an interim review shows significantly faster data cleaning timelines, and more focused monitoring, resulting in a reduction of monitoring visits by 20%. CRUK is willing to share their RAT with other sponsors.

Statistical aspects of quality by design in clinical trials

Speaker: Marc Buyse, International Drug Development Institute (IDDI)/ CluePoints

The recent focus of regulatory agencies on a quality by design offers unprecedented opportunities to re-engineer the clinical trial process. Statisticians, who have traditionally been involved in the design and analysis of clinical trials, will now have to be involved also in checking the data over the course of the trials. In particular, risk-based monitoring will increasingly be driven by indicators of the quality and performance of investigational sites. A common way to evaluate site performance is to monitor predefined metrics, often called "Key Risk Indicators" (KRIs). These typically include variables known to be relevant indicators of quality (e.g. accrual rate, frequency of adverse and serious adverse events, frequency of data queries and time taken to resolve them). One issue with KRIs is to pre-define tolerance limits or thresholds triggering actions, and to account for statistical uncertainty in the observed KRIs. Another approach is to build and validate a multivariate statistical model indicative of overall risk, though it seems doubtful that a single model can be useful in all situations (Pogue et al., *Clinical Trials*, 2013: 10; 225-35). A third approach uses central statistical monitoring to compare the consistency of the data collected at each site with the data contributed by all other sites. This approach uses all the data and as such, it provides a powerful way to uncover detect abnormal data patterns that are indicative of errors, misunderstandings, sloppiness, data fabrication or fraud (Venet et al., *Clinical Trials*, 2012: 9; 705-13). A risk-based monitoring strategy can use statistical evidence to prioritise on-site monitoring for sites identified at higher risk. In multinational clinical trials, a statistical approach can also unveil data patterns that reflect unanticipated differences in patient management or other important aspects of trial conduct. These activities fit in a quality by design approach and help diversify monitoring methods in order to achieve better data quality and lower overall risk (Baigent et al., *Clinical Trials*, 2008: 5; 49-55).

How to review the risks and report on quality? A sponsor's view

Speaker: Denis Lacombe, European Organisation for Research and Treatment of Cancer (EORTC)

The speaker presented a concrete case study which was representative of today's norms for oncology clinical trials. His presentation covered multi-modality treatment, such as radiation therapy, surgery, imaging, translational research, and biobanking.

He presented, "An open label randomised multicentre study of accelerated fractionated chemo-radiotherapy with or without an hypoxic cell radiosensitizer, using a 15 gene signature for hypoxia in the treatment of HPV/p16 negative squamous cell carcinoma of the head and neck", a medium-risk study according to the EORTC risk calculator used for the monitoring strategy, but showed evidence that the multidisciplinary approach and the overall complexity of such a clinical trial is now typical, and requires quality assessment at multiple levels and cannot be simply based on a single score.

The levels of quality assurance to be implemented in each trial are determined on a protocol-by-protocol basis for all diagnostic and therapeutic procedures being studied.

In this case study, the risk was assessed for the Radiotherapy delivery and resulted in the decision to implement a certain level of RTQA (Radiotherapy Quality Assurance). Tissue handling adhered to a well-defined chain of custody, and the assay impact class was determined for the hypoxic signature. The associated operational and safety risks required thorough quality management of Biobank and investigator site activities.

Today, study objectives are becoming more complex. This case study includes clinical validation of a new hypoxic signature, and this generates a risk for the sponsor regarding the management of this complex biomarker and a risk for the scientific community, who needs to decide whether this new hypoxic cell signature gene can effectively predict benefit of radiation therapy for the patients.

It is very important during study conduct to ensure a risk control process, and Dr Lacombe showed that committees such as Medical review team and Independent Data Monitoring Committee are indeed needed to monitor the locoregional control rate and be able to propose adaption of the study design, e.g. signature refinement, trial sample size increase, if necessary.

The contemporary challenge in multicentre clinical trial is to reduce complexity, investigator burden and cost of QA without sacrificing the accuracy and integrity of protocol treatment. Today, integration of translational research in cancer clinical trials and the use of multimodal treatment are crucial, but they do raise new risk factors which require a more extended risk assessment and risk control processes.

How to measure and report on quality in clinical trials

Speaker: Dirk Hasenclever, Medical Faculty of the University Leipzig, Institute for Medical Informatics, Statistics and Epidemiology (IMISE),

Background and perspective: Senior biometrician at the Institute for medical Informatics, Statistics & Epidemiology (IMISE) and the centre for clinical trials of the University of Leipzig - Germany, reviewer for government and charity trial funding applications and member in multiple data monitoring and safety committees.

(1) Distinguish between conceptual quality of a trial and its procedural quality. One can generate high procedural quality data within a flawed study design. Measuring quality focuses on procedural quality.

(2) A thorough procedural risk assessment is a prerequisite for ensuring and measuring procedural quality. Procedural quality means minimising the incidence of risk events. The risk assessment must be performed before protocol finalisation.

(3) Procedural risk assessment can be performed by going step-wise through patient-centred procedures and general study processes asking "What can go wrong?" in an interdisciplinary brainstorming session. Be specific - following checklists and guidelines blindly is a major risk in risk analysis.

(4) For each plausible and relevant risk: Are there feasible mitigation measures? Define quality risk indicators measuring the incidence and/or the degree to which the particular risk affects the study. Consider setting targets and tolerance limits – but only if these can be materially justified.

(5) Quality risk indicators have multiple functions: Quality monitoring during trial conduct with the aim of triggering timely corrective interventions, interim quality reports for the data monitoring and safety committee and quality documentation at the end of the study. Those quality risk indicators which are essential for the scientific evaluation of the evidence generated by the trial can be defined as quality endpoints in a respective section of the protocol. This ensures that risk assessment is started early during protocol development. Quality endpoints are later used to compile a study quality report which should be published as a supplement to the main study publication.

(6) Besides simple rates, cumulative distribution plots are helpful visualisations for critical time lines, problems in long-term follow-up can be detected comparing inverse Kaplan Meier curves of actual and ideal follow-up times (time from study entry to date of analysis) and time to treatment discontinuation can be visualised by cumulative incidence plots.

(7) Serious unanticipated risk incidences may be detected as findings during the conduct of the trial. E.g.: a) Due to terminological ambiguity and bad CRF design treatment discontinuations in a cancer trial were coded “Withdrawal of consent” stopping further follow-up for the primary survival endpoint. b) An international consensus definition of mild infarction proved inadequate after heart surgery and conflicted with clinical routine.

(8) We need an open error culture to learn from blunders in clinical trials. Unanticipated findings should be summarised in an analytic error report, remedies proposed and made public.

Patients’ perspective: Risk-based quality management

Speaker: Debra Madden, National Breast Cancer Coalition and Nancy Roach, Colorectal Cancer Coalition

Two cancer research advocates each gave a presentation discussing patients’ perspectives concerning what “quality” in clinical research truly means to these critical stakeholders in the clinical trial enterprise.

The focus of Part I of this discussion was the importance of determining what patients themselves need from clinical research and the healthcare system. This includes a high-quality, learning healthcare system (LHS) that is patient-centred, efficient, quality-driven, and evidence-based. Improving healthcare requires a LHS that generates knowledge to fill the many current gaps between evidence and practice and rigorous, innovative, and patient-centred research approaches that appropriately account for individual variations in patients’ needs and perspectives. Importantly, success in achieving these goals requires a focus on and understanding of what “quality” means, i.e., what truly matters, to patients themselves. In speaking with patients, patient representatives, and advocates, “quality” and risk-based quality management requires patient-centred clinical trials that are scientifically valid and designed to robustly, efficiently answer questions of true import to patients, rather than questions that are simply of scientific interest but ultimately would have little impact on enhancing patient care. It requires trials that are designed to prevent risks and errors that truly matter to patient safety and the validity of the trial data. In addition, quality means patient-centred trials that appropriately incorporate patient preferences into study design and comprise “rational” design that minimises patient burden and maximises patient benefit. And from the patients’ perspectives, “quality” also is defined by certain “don’ts”: quality trials are those that do not introduce invasive and/or repeated procedures, unnecessarily numerous study visits, and unnecessary costs for patients that are not required for

answering the trial's questions. They do not introduce unnecessarily restrictive inclusion and exclusion criteria that hamper accrual and may generate data that do not accurately reflect safety and efficacy for the larger patient population. And participation in such trials does not require unneeded delays in treatment initiation secondary to screening and trial arm assignment. Coming full circle, quality trials provide uniformity in recruiting patients; are feasible and "practical" for both patients and their providers; include patient-centred, patient-friendly informed consents that truly inform patients; continually keep trial participants informed—whether the results are positive or negative; and move our body of knowledge forward and/or change practice. Achieving such quality requires a change in perspective, where patient engagement is the rule, rather than the exception, from the genesis of the research question through the development of translational tools, and where it is not the trial that drives patient selection, but rather the question of "What is the best trial for the patient?"

What is risk-based monitoring? TransCelerate risk-based monitoring methodology

Speaker: Nicole Sheetz, Transcelerate

The objective of this presentation was to build an understanding of TransCelerate Biopharma, Inc. (TransCelerate), to describe TransCelerate's risk-based monitoring (RBM) methodology, and to provide a practical case study showing the application of RBM. The session began with an overview of TransCelerate's mission statement, active work streams, and member companies. This was followed by a description of the RBM methodology including a step-wise review of the risk assessment, integrated quality risk management plan (IQRMP), and development of the monitoring plan. Finally, a large multi-centre case study was presented to explain the application of RBM including completed examples from the risk assessment, IQRMP, and monitoring plans (on-site and central), as well as real data and findings during the study. This case study demonstrated the complimentary nature of both on-site and central monitoring and showed the benefits of using a risk-based approach to modify monitoring approaches before and during the conduct of the study.

How to efficiently and effectively balance central monitoring with on-site monitoring: Experience from Phase 3 study using risk-based monitoring and eSource methodologies

Speaker: Jules T. Mitchel, Target Health Inc.

A "quality clinical trial" is one where 1) there is "absence of errors that matter" and 2) "are the data fit for use/purpose." Errors "that matter" are those that have a 1) meaningful impact on patient safety and/or 2) Interpretation of trial results

In May 2011, a clinical trial program in the area of urology was initiated under a US and Canadian Investigation New Drug Application (IND). The program was operationally designed for the clinical sites to perform direct data entry (DDE) of subject data at the time of the office visit, and for the clinical research associates (CRAs) to execute risk-based (adaptive) monitoring (RBM). After meeting with the US FDA and Health Canada to review both the protocol and the use of this eSource methodology, a Phase 3 clinical trial was initiated in the US and Canada in August 2012 which utilised 18 clinical sites to screen 656 subjects to treat 180. All of the clinical sites were required to use DDE to enter the trial results at the time of office visit and the CRAs were instructed to conduct both on-site monitoring and central monitoring from the home office using a RBM approach based on the clinical data monitoring plan (CDMoP). Results from the study indicated that data quality and protocol compliance were best impacted by 1) initial intensive training of the sites on protocol compliance and additional training at

critical stages of the study; 2) performance of initial monitoring of the clinical site after 2-3 subjects were treated to assure protocol compliance; 3) identification of Critical to Quality (CTQ) parameters, risks to protocol compliance and subject safety; 4) the implementation of mitigation strategies; 5) daily review of entered data by the monitors to identify issues associated with protocol compliance and completion of the eCRF; and 6) weekly Quality by Design (QbD) meetings to review critical events and risk factors such as adverse events, time to data entry, time to data review by CRAs, edit check notices, query generation and resolution etc. As a result of the monitoring activities described above, 1) there was close to 100% compliance with all protocol requirements; 2) necessary protocol amendments were identified and implemented rapidly when just a few subjects were enrolled; 3) modifications to EDC edit and logic checks were done early in the program which minimised issuing the same query multiple times; and 4) the CRAs and site personnel could be retrained based on findings made during the weekly review meetings. It is concluded that once RBM and DDE are adopted, there will be improved quality, a major reduction in monitoring resources and costs needed to manage a clinical trial, and reduced time to database lock.

Scientific advice & risk-based approach to clinical trial management

Speaker: Thorsten Vetter, European Medicines Agency (EMA)

Only few Scientific Advice (SA) requests have yet asked for feedback on proposals to implement risk-based streamlined monitoring approaches. The focus of these requests was on phase 3 pivotal trial design in the field cardiovascular and metabolic diseases. Requests were received during early protocol development which is encouraged as the initial CHMP feedback maybe high level, but will help to develop a high quality draft protocol. CHMP recommends follow-up SA on mature protocols before finalisation. The recently published EMA Reflection paper on risk based quality management in clinical trials (EMA/269011/2013) provides a valuable framework.

During previous discussions, CHMP mentioned that: directed on site monitoring in conjunction with/driven by centralised data examination is recognised; a thorough risk assessment to the overall trial design and its related procedures is to be applied; streamlined approaches can be acceptable: the determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial; the key risks have to be identified in advance and a plan to mitigate these risks, the acceptability of certain risks and corresponding tolerance limits will have to be established; CHMP considered important to clearly describe how the central data review will influence site activities, including monitoring; the triggers for enhanced monitoring or other actions at the different investigator sites should be specified; a trial quality report should be planned. Quality assurance and quality control measures should be sensitive to detect the relative/comparative extent of non-compliance at a particular site, and respond accordingly to threats to patient safety and data quality; there should be mechanisms in place to verify that issues rose by monitoring and audit procedures have been acted upon in both a corrective and preventative way.

Scientific Advice is the ideal forum to discuss approaches to risk-based quality management in clinical trials at any stage of the development programme. Risk assessments can be discussed and commented by the CHMP via Scientific Advice including the expertise of the Compliance & Inspections Department. Follow-up Scientific Advice procedures provide a means to receive CHMP input along the way during protocol development.

What should be provided in the SA Briefing Package? Concise standalone briefing document, protocols, analysis plans etc. Explain the motivation for the risk-based approach and describe the pros and cons

in a balanced way; present the major points and data summaries, and use references for the supporting data; how was the proposed strategy derived and why does it promote and provide data quality that is adequate for MA? How will the strategy be assessed / appraised / amended in real time? How will success or otherwise be reported? Overall a balanced presentation is recommended; present as comprehensive data as available at the time of submission and remain scientific throughout.