

Risk Based Approach to Clinical Trial Management – A CRO perspective

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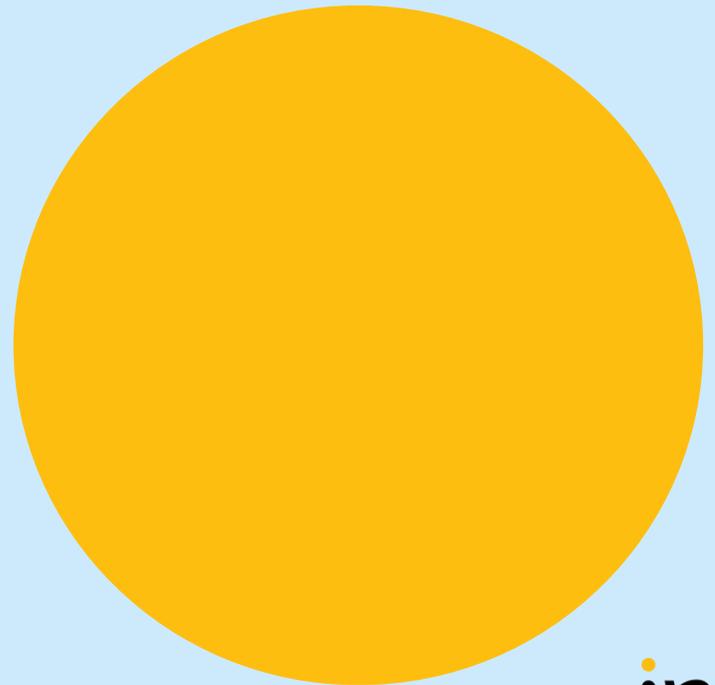
**Background to Risk Based Monitoring & ICH
E6 R2**

Clinical Trial Management post ICH E6 R2

Challenges for CROs

Recommendations for Success

Background to ICH E6 (GCP) R2 Addendum



What is Risk Based Monitoring?

And what is it not?

- Risk Based Monitoring (RBM) is:-
 - A systematic, prioritized approach to monitoring clinical trials, which utilizes real-time data to inform when, where and how to manage clinical trial sites
 - A combination of On-Site and / or Centralized monitoring activities
 - Proportionate to the risks inherent in the trial and the importance of the information collected
 - “...An **adaptive approach** that **directs monitoring focus and activities** to the evolving areas of greatest need which have the most potential to impact **patient safety and data quality**”. – Source: TransCelerate Biopharma Inc.

- Risk Based Monitoring is NOT just reduced SDV

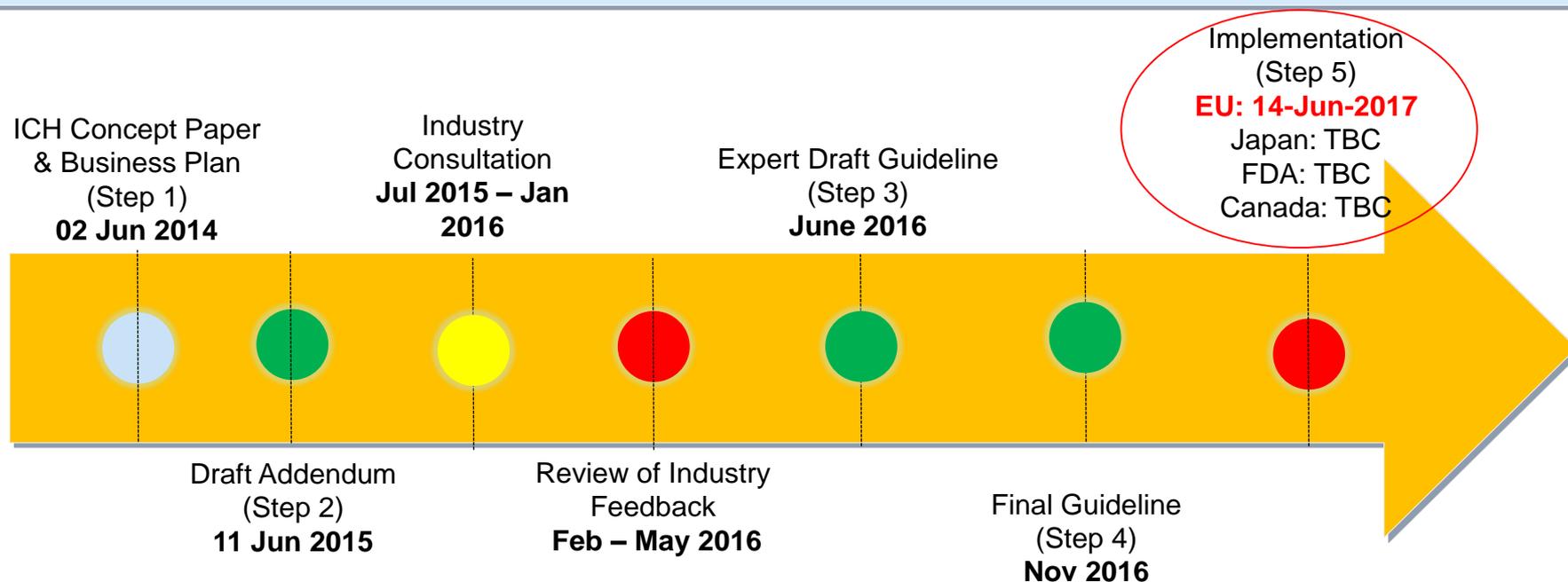
The Changing Regulatory / Industry Landscape



Changing Industry Expectations

Focus on ICH E6 R2 - Key dates and facts

Biggest change to GCP requirements in 20 years!



Focus on “RISK” & “TECHNOLOGY”

REQUIRED: Quality Risk Management, Quality By Design & “Strategic” Monitoring

What has prompted the changes?

- *“To keep pace with the **scale and complexity** of clinical trials and to ensure **appropriate use of technology** we should **modernise our approach to GCP** to enable implementation of **innovative approaches** to clinical trial design, management, oversight, conduct, documentation, and reporting that will **better ensure human subject protection and data quality**.”**



- *“**ICH E6 has been misinterpreted** and implemented in ways that impede innovation, emphasising less important aspects of trials (e.g., **focusing on the completeness and accuracy of every piece of data**) **at the expense of critical aspects** (e.g., carefully managing risks to the integrity of key outcome data).”**

*Source: ICH Concept Paper http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Concept_Paper_July_2014.pdf

What solution(s) is the ICH Addendum Proposing?

- Addendum to ICH E6 (GCP) to promote
 - **Harmonization** - brings together position papers on risk based monitoring by FDA, EMA, MHLW/PMDA, Transcelerate & ICH Q9 (Quality Risk Management)
 - **Quality Risk Management**
 - **Quality By Design** – upfront assessment of risks specific to study design and protocol
 - **Risk Based Monitoring**
 - **Technological Tools** - to ensure robust conduct, oversight and reporting
 - **Compliance** – changes based on inspection finding “hot topics”



High Level Overview of the Changes

26 items of change

Quality Risk Management – New Section 5.0

- Risk management activities & Quality By Design approach required for all trials & includes both system and trial related risks
- 7 stages of risk management
- Trial conduct should be proportionate to the inherent risks and importance of the information collected

Monitoring / Investigator Oversight

- Source Data ALCOA principle amended to ALCOAC (Complete)
- Monitoring Plan mandatory
- Centralized Monitoring Activities & required documentation defined (extends to biostats, medical and data surveillance activities)

TMF

- Must contain all data relevant to reconstruct the trial (not limited to section 8 documents)
- Location of all documents
- Investigator ownership of own data

Other

- Serious Breach per local regulations
- Increased PI / Sponsor Oversight requirements
- Subcontracting by CRO requires Sponsor approval
- Computer Validation & Electronic Record Requirements

7 stages of Quality Risk Management

**Critical Process
& Data
Identification**

**Risk
Identification**

Risk Evaluation

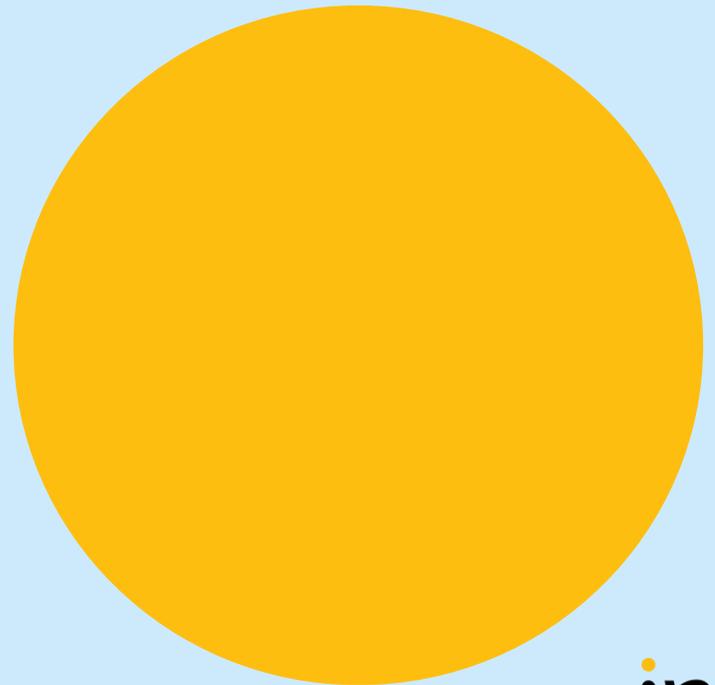
Risk Control

**Risk
Communication**

Risk Review

Risk Reporting

Clinical Trial Management post ICH E6 R2 – what is changing for us?



Early Risk Discussions with Sponsor

- ICH 5.0 – *“The Methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected.”*
- ICH 5.18.3 – *“The sponsor should document the rationale for the chosen monitoring strategy”*
- In order for a CRO to propose the most appropriate monitoring strategy we need to understand
 - The processes & data the Sponsor considers to be critical (ICH 5.0.1)
 - Any known risks identified by the Sponsor during protocol development (ICH 5.0.2)
 - Related to IMP
 - Related to Study Design
 - Related to Geography
 - Relate to Study Population
- Risk Assessment activities need to start during bid defense period to identify key risks for discussion with the Sponsor and to help inform the proposed monitoring strategy

Integrated Quality Risk Management (IQRM)

- Integrated Quality Risk Management (IQRM) activities will become central to the clinical trial management approach
 - Development of an Integrated Quality Risk Management Plan (IQRMP) is recommended
 - Identification of Critical Processes & Data with Sponsor, which drive the monitoring strategy & determine On-Site and Centralized Monitoring activities is essential
 - Risk Identification, Assessment and Management should be conducted utilizing a formal assessment tool, for discussion with Sponsor
 - Definition of Tolerance Limits for Systemic, study wide Key Risk Indicators to be established
 - Alignment of all functional plans & monitoring activities with the overarching IQRMP
 - Re-evaluation of risks and assumptions at defined points throughout the study
 - Sponsor input to those services not contracted to the CRO is critical
 - Where Sponsor only outsources a single service it is important to consider how CRO's activities fit into Sponsor's overarching monitoring strategy
- At INC these controls will become part of our established Trusted Process[®] methodology

Risk Management Methodology – what's new?

- **Critical Process and Data Identification**

- Starts at the protocol development stage
- Often CRO is not contracted to be part of protocol development
- Critical for Sponsor to share their assessment with the CRO

- **Risk Identification**

- System vs. Clinical Trial Level Risks
- Sponsor to share identified risks from previous / parallel studies

- **Risk Evaluation**

- Addition of Detectability



Risk Management Methodology – what's new?

● Risk Control

- Control mechanisms should be proportionate to significant of risks
- CRO needs to understand the risk appetite of sponsor
- New concept of Tolerance Limits
 - Who defines?
 - How are deviations detected?
 - To consider consistency across studies

● Risk Communication / Review

- Important for Sponsor and CRO to share information regarding emerging risks
- Particularly important where only selected services are contracted to CRO e.g. signals identified by Sponsor medical director may be important to clinical monitoring team

● Risk Reporting

- How will deviations to pre-defined tolerance limits be tracked and shared with Medical Writing team for inclusion in the Clinical Study Report?

Changes in Monitoring Strategy

- Monitoring is defined as On-Site Monitoring + Centralized Monitoring
 - Less focus on SDV; more focus on SDR
- Centralized Monitoring is a remote evaluation of aggregated data by:-
 - Off-Site Clinical Operations Staff
 - Data Management
 - Statistics
 - Medical Review
 - Other Data Surveillance activities
- Centralized Monitoring considers
 - Missing & inconsistent data, data outliers, lack of data variability , protocol deviations
 - Trends in data across sites
 - Systematic / Significant errors in data, data manipulation, data integrity issues at single or multiple sites
 - Site characteristics and performance measures
- Output from Centralized Monitoring activities drives decisions on when and where to target on-site monitoring visits

Centralized Monitoring in Practice

Impact between Sponsors and CROs

- Important to work as a holistic team, sharing signals across functional areas
- Where Sponsor is responsible for some of the centralized monitoring activities, consider how output will be shared between CRO and Sponsor, in order to inform on-site monitoring decisions
- Technology facilitates centralized data review
 - EDC system
 - Safety Management Systems
 - Key Risk Indicator Dashboards
- Choice of Sponsor vs. CRO technology may reduce Centralized Monitoring effectiveness if data integrations are interrupted
- Change in monitoring activities may result in changes to CRO costing models as on-site visits and SDV are no longer the key drivers of work activities



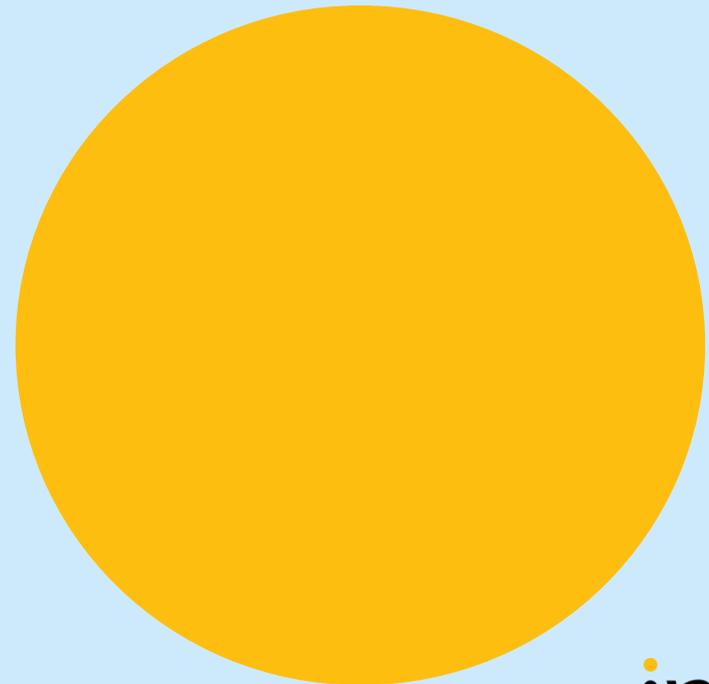
Centralized Monitoring in Practice

Impact on Sites

- Move away from “one-size fits all” approach to monitoring
- On-site visits driven by enrolment rates, quality of data and levels of compliance
- Increased requests for remote resolution of issues
- CRA focus at on-site visits on those activities that can only be resolved at the site
 - Source Data Review / Verification
 - IP Management
 - Site File Management
 - Relationship Building & Face-to-Face support

Challenges

– 1 model doesn't fit all for a CRO



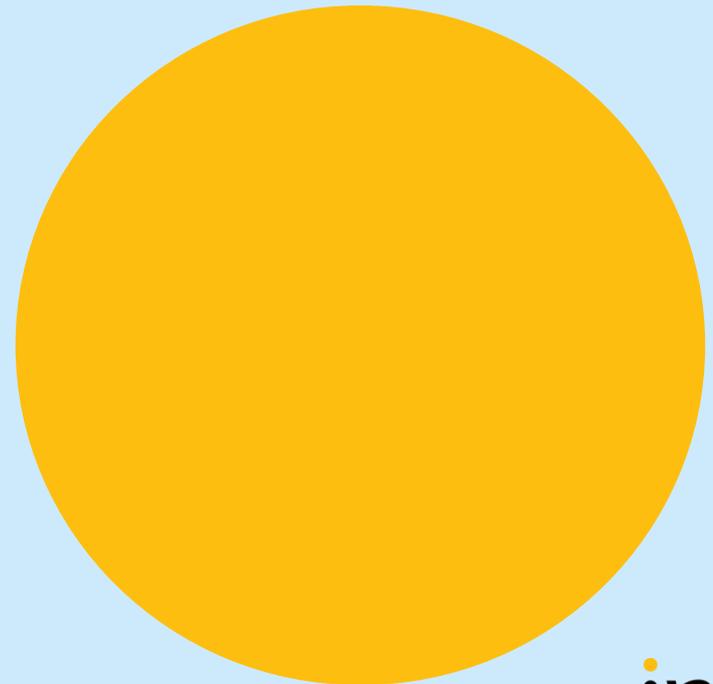
RBM Challenges for CROs

- A CRO's ability to conduct RBM studies efficiently relies on use of their core technologies
 - Data Integrations feed KRI Dashboards
 - Use of Sponsor systems requires additional programming or manual workarounds
- RBM requires a holistic approach to monitoring – contracting a CRO for limited services requires careful management
 - Sponsor / Vendor input required into Critical Data & Process evaluation and Risk Management activities
 - May not be clear who drives IQRM related activities where multiple parties involved
 - Centralized monitoring signals inform on-site monitoring – Sponsor / 3rd party and CRO need to collaborate
- Risk is a subjective phenomenon – different sponsors will have a different risk appetite for the same core risks & so risk response / acceptance mechanisms may differ from Sponsor to Sponsor

RBM Challenges for CROs

- Sponsors partner with multiple CROs across a development program
 - Standard Tolerance Limits and KRIs may differ between vendors
- Timing of CRO involvement will determine the influence CRO has on the monitoring strategy
 - Protocol often not finalized until after study award
 - Critical Data and Process evaluation and Risk Management activities may result in a change in proposed monitoring strategy
- Risk Management is not an exact science – there may be a need to adjust the monitoring strategy based on study conduct in order to effectively manage emerging risks
- Transparency of data in dashboards may result in Sponsor micro-management

Recommendations for Success



Recommendations for Success

- Involve your partner CRO as early as possible
- Share critical data / process and risk assessment information in the pre-award phase
- Be open to adapting the monitoring strategy in response to risk signals
- Carefully consider technology options – dashboards and automated signalling tools may depend on using the CRO's core technology
- Where you or a 3rd party are conducting some services, provide input to the post award critical data, process and risk evaluation activities
- Encourage transparency in sharing risk signals to inform centralized monitoring and when and where to conduct on-site visits
- Be open to changes in CRO costing models to reflect the change in monitoring approach



: am connected

**Helping develop the medicines
people need is something
we take personally**

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