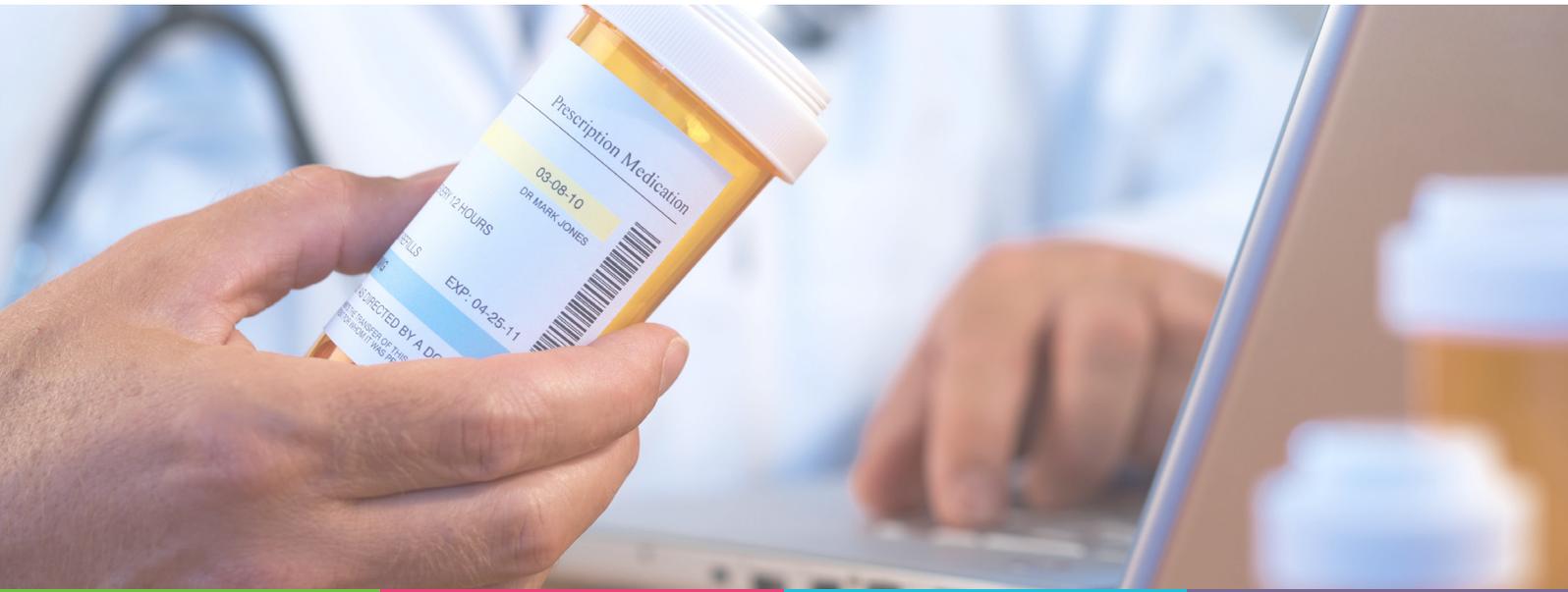


# The Case for ICH E6(R2) Compliance Assessment

The Clinical landscape has become increasingly challenging due to growing demand from regulators and the public for more and better clinical research results. With an estimated R&D cost of \$2.5 billion for a drug to reach the market, sponsor companies face increasing pressure to complete clinical trials within time and budget. This places a particular burden on trials in personalised medicine and orphan diseases, where the patient populations are typically small and not yet located around the globe. One of the responses to this rising cost and inefficiency has been an update to the International Council of Harmonization (ICH) Good Clinical Practices (GCP), which now require a risk-based approach (predictive and proactive models) to quality management of clinical trials. Essentially, updated regulation accelerates adoption of technology and process / role changes to enhance **operational efficiency, quality, and patient safety**.

TAKE Solutions has a proven ICH E6(R2) compliance assessment framework that has been developed by an experienced team of SMEs, operations leaders and supporting technology professionals. Our framework can be easily customized to your organization's structure, culture and objectives, and covers the key areas that are being addressed by this regulation. Some of the key areas covered by this framework include quality management and risk-based approach, data integrity and analysis, operating model and governance model redesign, risk based monitoring, redefined roles and responsibilities (RACI) translating to a robust set of SOP updates. Additionally, our framework is centred around the fundamental organizational principles - people, process, and technology; ensuring technology and processes are working together to provide people with the support they need to become compliant with ICH E6(R2) and manage transformed clinical operations.





**TAKE Solutions Clinical Consulting ICH E6(R2) Readiness Assessment framework enables risk-based quality management of clinical trials by enhancing operational efficiency, quality and patient safety**

**ICH E6 (R2) Compliance Readiness Assessment Focus Areas across the Clinical Trial Value Chain**

 <b>Strategy</b>	<b>Quality Management &amp; Risk Based Approach</b>	Quality by Design - Protocol / Trial Design	Quality by Design -Protocol / Trial Feasibility	Quality Factors Limits-QTL / CTQ / CQA	Monitoring Strategy	Document Management Strategy
	<b>Data Integrity &amp; Analysis</b>	Data Surveillance Plans	Statistics Driven Data Analysis	Trial Analytics, KPIs & KRIs for Risk Management	Endpoint Adjudication	Signal integration/ detection - Monitoring Decisions
 <b>Organization</b>	<b>Operating Model Design / Re-Design</b>	Clinical Operations inclusive of Data Quality Lead, Clinical Data Scientist, Site Lead, and Central Monitor etc.		Centralized / Decentralized or Both Monitoring	Next-Gen CRO Oversight / Vendor Quality Management Model (Risk-Based Model)	
	<b>Governance Model Design</b>	IRB / IEC Governance Model	IDMC (Independent Data Monitoring Committee)	eTMF &/or non-eTMF Governance Model	Enterprise / Trial Data Governance Model	eTMF &/or non-eTMF Governance Model
 <b>Process</b>	<b>Risk-Based Monitoring</b>	On-Site and/or Centralized Monitoring	Remote Monitoring through Statistical Analysis	Adaptive Monitoring	Monitoring Plans with RBA	Integrated Quality Risk Management Plan (IQRMP)
	<b>Quality, Compliance &amp; Regulatory SOPs</b>	Records & Reports - Source Data Verification	Site Management / Inspection Readiness	Computer System Validation	eTMF &/or non-eTMF Management	Site, Monitor & PI Communication
 <b>Technology</b>	<b>Electronic Sources</b>	EDC System	ePRO	Sensors, Smart Pills and Smart Bottles	Source Doc Implementation Tools	eAdjudication Tool
	<b>Advanced Automation Tools</b>	Modeling & Simulation Tool for Protocol / Trial Feasibility	Workflow-Based Tool - TMF/non-TMF Documents	Quality Management Tool	Patient Registry Tool	Security System without unauthorized access

**CLINICAL TRIAL VALUE CHAIN**



## Quality Management & Risk Based Approach

*Quality Management and Risk Based Approach incorporates Quality by Design (QbD) to address inefficiencies and variabilities along the Clinical Trial Value Chain*

ICH E6(R2) mandates the use of Quality by Design principles right from planning and protocol design, which can be achieved through the use of workflow-based modeling and simulation of processes and tools. According to section 5.0.7 of

ICH E6(R2) “Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making” and “Predefined quality tolerance limits (QTLs) 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.” These guidelines essentially require sponsors to define the challenges and opportunities, identify data sets, risks to subject safety and data quality, testing assumptions, debate pros and cons, create multiple protocol strategies, and finalize trial design through cross-functional collaboration; and integrate historical clinical trial data from various sources (i.e. ClinicalTrials.gov, eHR, and site data etc.). If possible, sponsors could simulate and model clinical trial design prior to finalizing the protocol. This can be done by selecting systems and processes that are aligned to the organization’s strategy, goals and requirements, to methodically conduct “what-if” scenario analysis using various dimensions such as patient, site, country, cost, and time etc., thus improving the success rate of clinical trial and reduce cost and risk to patient. Essentially, this aligns study data points, procedures, and variables to the objectives of the clinical study, forecasts trial challenges with enrolment curves, timelines and cost estimates, supports scientific and operational trade-off decisions, and defines optimal country/site profiles based on actual geographic footprint. During the protocol design exercise, and (as needed) throughout the course of the clinical trials, critical to quality (CTQs), critical quality attributes (CQAs) and quality tolerance limits (QTLs) can be established to develop a predictive and proactive quality management system including risk management process (risk identification, evaluation, control, communication, review and reporting).

Data Integrity is the foundation for a successful clinical trial and provides insights into the key stakeholder groups such as sites, investigators, patients and sponsors. Solid data integration and analysis starts with data

## Data Integrity & Analysis

*Data integrity and analysis principles emphasize data quality and successful risk assessments*

strategy, processes and technology that ensure data integrity starting from data collection to data archival to data destruction. Data integrity is defined as the extent to which all data (whether electronic or paper-based) are complete (i.e., include metadata) consistent, accurate, trustworthy, and reliable throughout the data lifecycle—from creation through archival status and their eventual destruction. With an increase in trial complexity, starting from overall larger trial size to collection of additional data points such as genetic information, it becomes crucial to use technology to generate an aggregated view of the data before it is analyzed versus relying on inefficient manual methods like spreadsheets. Furthermore, the use of next-gen technology such as workflow-based tools, electronic data capture solutions, ePRO, and sensors etc. should help in structuring, linking and integrating data for key activities such as defining KPIs and KRIs that are needed for statistics-driven data analysis; endpoint adjudication; and signal integration and detection. Essentially, if the data is collected with the next-generation technology solution (EDC,

ePRO, and mobile devices etc.) then it helps in seamlessly analyzing and acting on data from multiple sources and arriving at a 360-degree view of the patient's needs real-time or near real-time.

## Operating Model and Governance Model Design or Re-Design

*Operating Model and Governance Model Design or Re-Design is necessary to address site quality control, and predictive and proactive risk assessment*

The ability to respond to the changes in ICH E6(R2) will be the key to future success of clinical trials and it implies that Life Science companies need to change the way they operate by developing new strategies and operating

models while taking into consideration people, process and technology. At its core, each life sciences company needs to be "quality and risk obsessed" with relentless focus on adoption of capabilities (technology, standards, processes, governance and best practices) to enhance operational efficiency, quality, and patient safety. The operating model will need to be transformed to consist of roles such as Data Quality Lead, Clinical Data Scientist, Site Lead and Central Monitor. Additionally, companies will need to determine on-Site and/or centralized Monitoring and ultimately determine next-gen and risk-based CRO oversight model. For example, "Off-site Monitoring activities are performed by Monitors and can be distinguished from Central Monitoring which could also be performed by Monitors or other roles within clinical operations or by other functions (e.g. Statistics, Data Management, Safety). Off-site and Central Monitoring include various types of data review activities." First the Life Science companies need to understand the business, technology and organization implications that the regulation is bringing (perhaps by a ICH E6(R2) compliance assessment by an external party) and then determine the prioritized roadmap to become compliant with the addendum to the original regulation. Life Sciences companies will need to design or re-design governance models to comply to the changes to IRB/IEC and/or take into consideration recommendations around forming IDMC (Independent Data Monitoring Committee). Additionally, to address changes to the management and storage of "essential documents for the conduct of clinical trial," it is highly recommended that governance model should be developed to track lifecycle of essential documents; and provide oversight and set business direction for all essential documents. ICH E6(R2) states "The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval."

One of the most pivotal areas that ICH E6(R2) addresses is RBM which can be driven through investing in on-site and/or centralized monitoring and specifically via statistical data analysis, and development of a

## Risk Based Monitoring

*Risk Based Monitoring (RBM) requires sponsors to develop a systematic, prioritized, risk based approach to monitoring clinical trials*

detailed monitoring plan and an integrated quality risk management plan (IQRMP - risks identified during the risk assessment process can be documented within the IQRMP) that take into consideration quality management and risk based strategies highlighted in multiple sections of the updated regulation (ICH E6(R2)). The regulation states "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)." If done methodically, with the right processes, the statistical analysis of linked and integrated data thru centralized monitoring can be used to identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol

deviations; examine trends, such as the range, consistency, and variability of data within and across sites; 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; analyze site characteristics and performance metrics; and select sites and /or processes for targeted on-site monitoring. The onus of ensuring RBM is weaved into the design and conduct of clinical trial is on the Sponsor and the regulation states *“Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.”* For successful RBM, it is important to define key metrics. and according to TransCelerate’s model, key metrics measure changes in quality, timeliness of data collection and query resolution, and efficiency of trial operations affected by RBM, on an ongoing basis and after the closure of a study. The ICH E6(R2) does not allude to SDV / SDR, however, requires that risk assessment and mitigation process is put in place. TAKE Solutions ICH E6(R2) assessment framework leverages TransCelerate’s RBM methodology which *“uses quality risk management as a foundation in ensuring subject safety and data quality through the implementation of the following: (1) building QbD into trials, (2) early and ongoing risk assessment, (3) a focus on Critical Processes and Critical Data, (4) use of Risk Indicators and Thresholds, and (5) adjustment of monitoring activities based on the issues and risks identified throughout the study. By monitoring available data Off-site or Centrally, On-site Monitoring can be targeted to activities that cannot be assessed remotely. Additionally, TransCelerate has adopted the term Source Data Review (SDR)*

*that describes review of source data for protocol compliance, quality of documentation, as well as site processes in contrast to transcription checking, referred to as Source Data Verification (SDV).”*

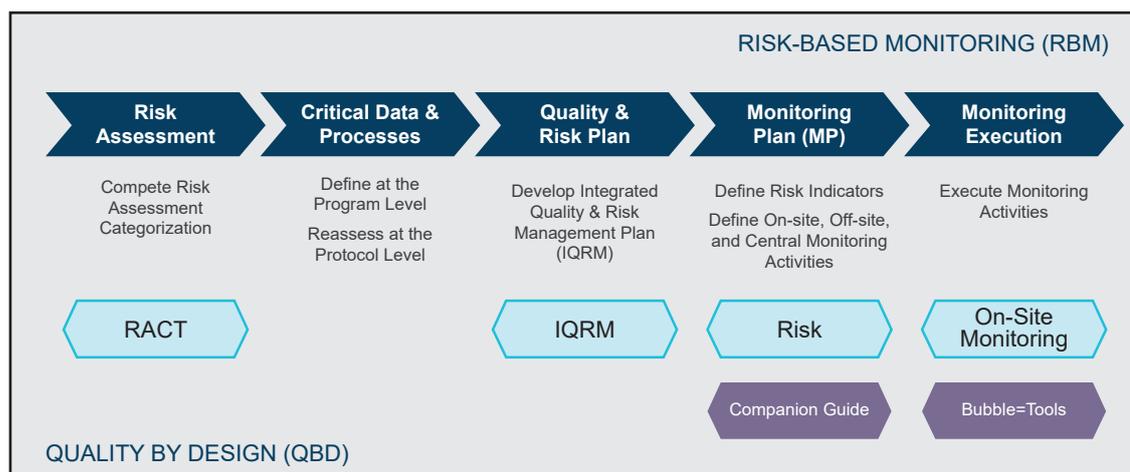


Figure 1: TransCelerate Methodology for Risk-Based Monitoring – High Level Process and Associated Tools

Clinical trial SOPs manage the compliance obligation by incorporating regulations, GCPs and institutional

policies, and guidelines to create operational efficiency by ensuring people, process and technology are all aligned and optimized. A detailed review of all Clinical trial SOPs across the clinical trial value chain needs to be completed to

### Quality, Compliance & Regulatory SOPs

*Updates to quality, compliance and regulatory SOPs is the most critical step in driving compliance*

determine gaps and prioritize updates. Based on the updates to ICH E6, SOPs on risk-based monitoring, audits and inspection readiness, quality assurance, quality control of computerized systems, and management of essential documents (TMF or non-TMF) are most critical SOPs and require immediate updates.

One of the essential factors for quality risk management approach requires the use of next-gen

technology solutions such as EDC, CTMS, ePRO, sensors, and smart pills etc. that allow aggregation of disparate data sources seamlessly. Subsequently, data can be linked and integrated by applying

## Electronic Sources & Advanced Automation Tools

*Electronic sources and advanced automation tools are essential for quality risk management*

algorithms developed by a team of resources with therapeutic area expertise and data scientists etc. to generate predictive and proactive data models and analytics. Once the data (could be past trial data or other external data for site and investigator targeting) is integrated real-time or near real-time, it can be used to design new trials or manage existing trials. Overall, the use of next-gen technology can help in dramatically accelerating trial start-up and result in a higher percentage of activated sites, faster patient recruitment and operational savings.

## Our Approach - ICH E6

TAKE Solutions' comprehensive and customizable ICH E6(R2) compliance assessment leverages a structured framework that includes questionnaires and required accelerators that have been designed to assess current maturity of an organization and gaps to become compliant to ICH E6(R2). The output of this assessment results in key recommendations and a high-level roadmap that identifies strengths and weaknesses and ties back to the relevant ICH E6(R2) sections and updates to produce a clear picture of areas of greatest risk. Based on the assessments that we have conducted in the past, below are examples of some high-priority recommendations that surface (irrespective of the organization) to drive compliance to ICH E6(R2):

1. Establish a cross-functional governance model and formalize a funding model
2. Develop or update operational strategies and operating models with quality management and risk-based approach, centralized monitoring guidelines and CRO oversight principles
3. Develop new or update existing processes, policies, SOPs and/or work instructions based on risk-based principles including the establishment of critical to quality (CTQs), critical quality attributes (CQAs) and quality tolerance limits (QTLs)
4. Refine roles and responsibilities and implement change management and training programs to ensure **quality by design** is incorporated as part of the culture and day to day reviews

**Is your organization compliant with ICH E6(R2)?**  
**Contact TAKE Solutions to conduct an assessment and proactively address risks and ensure compliance**

**TAKE Solutions ICH E6 GCP Health Check delivers a crystal clear view of what it takes to be compliant**

### Approach

- Compilation and review of all SOPs, templates, work instructions and associated documents
- Stakeholder interviews to understand internal processes
- Cost effective – 3-6 weeks work, majority off site

### Results

- Detailed description of gaps between operational procedures and current legislation
- Heatmap of functions in which the gaps reside
- Provision of a clear roadmap for change to become compliant; with prioritization of risks and mitigation strategies
- Vendor assessment if required
- Feedback to senior management on strategy for success

### Benefits

- Reduces inspection risk
- Enables effective and efficient compliance with improved visibility and control of risks
- Provides clear and credible roadmap for internal and external communication
- Efficient use of scarce resource to focus prioritised and systemic risks
- Facilitates continuous improvement

ICH GCP regulations, effective June 2017, require **risk based, quality management of clinical trials; quality by design; effective oversight; increased transparency and quality driven, targeted source data verification.**

**1 in 10 FDA inspections require official action**, 1 in 4 require voluntary action

**1 in 10 EMA inspection findings are critical**, 4 in 10 are major

**3 in 10 MHRA inspections have critical findings**, half have major findings

**Our experience shows that:**

- Many companies have not yet started on the journey to implement risk based monitoring
- Legacy technology systems are not designed to manage risk or quality tolerance limits
- Central monitoring requires different staff skill sets from on-site monitoring, and can usually be off-shored

### HOW MANY ITEMS HAVE YOU CHECKED OFF THE LIST?

-  Risk based, off-site monitoring
-  Quality management, with Quality by design
-  Quality tolerance limits
-  Risk evaluation, control, review and reporting
-  CRO oversight
-  Data handling and record keeping
-  Computer system verification
-  Control of essential electronic documents

**“ I oversee a lot of consulting partners and no one has the performance levels that match TAKE Solutions ”**

*- VP Global Head of Safety and Regulatory, Top 5 Pharma Company*

## Authors



### **Dawne Nanda** - Senior Managing Consultant

With 15+ years of experience in life sciences, Dawne has worked across the clinical trial value chain. Her focus is on Clinical Operations Strategy, Trial Design, Execution & Feasibility, Trial Analytics and Clinical Data Management. She also has expertise in strategy & roadmap development, business process optimization, operating model design and vendor partnership model design.

### **Dr Krishnan Rajagopalan** - Chief Growth Officer

Over two decades of experience in Life Sciences – functional domain and technology consulting, advisory services and P&L management. Instrumental in building Tier 1 LS consulting and functional BPO services for Infosys and Cognizant Life Sciences, USA. PhD in Bio-organic Chemistry from University of Kentucky and Harvard Cancer Research Fellow with over 20 publications and 1 patent.



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### **About TAKE Solutions**

TAKE Solutions delivers domain-intensive services in Life Sciences. In the fast-growing Life Sciences space, TAKE offers clients a unique combination of full-service Clinical, Regulatory and Safety services backed by unique technology expertise. Our range of services span from clinical trials to regulatory submissions to post-marketing safety, all backed by insights derived through proprietary industry networks forums. With a team of leading Life Sciences experts, best-in-class systems and processes, and bespoke, industry-specific technology and analytics, TAKE delivers successful outcomes for clients. Our global roster of clients includes large and small innovator biopharmaceutical companies as well as generics manufacturers. With operations spread across North America, Europe, Asia, and South America, TAKE is a Public Company, listed in India on the Bombay Stock Exchange and the National Stock Exchange. Led by a team of industry stalwarts and domain experts, TAKE has been growing steadily with FY18 revenues touching INR 15,872 Mn, (USD 246 Mn).



### **For more information**

Americas **+1 609 720 1002**

Europe **+49 69 668 0300**

APAC **+91 44 4590 9000**

[✉ contact@takesolutions.com](mailto:contact@takesolutions.com) [🌐 www.takesolutions.com](http://www.takesolutions.com) [in /company/take-solutions](https://www.linkedin.com/company/take-solutions)