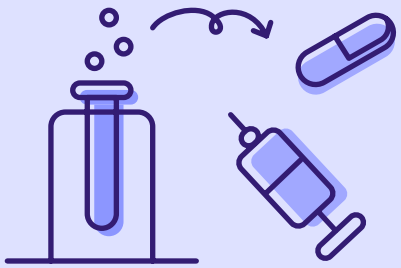
Qualio



# *Phase 1 & 2 clinical trial quality by design walkthrough guide*

Tips & best practice for sponsors & CROs

# *Table of Contents*

*Clinical trials are the ultimate test for your drug. And with only about a third of FDA-regulated drugs making it to Phase 3, the first two phases of the process are the pivotal, defining moments for the future of your product.*

*Both sponsors and CROs have their roles to play at this crucial moment of gestation. Quality by design, manifested in high-quality processes, airtight data integrity and the adoption of continuous improvement and modern technology, is vital.*

*The Qualio quality team has assembled this guide, based on our decades of collective experience working with pharmaceutical start-ups and contract research organizations, to help your business navigate Phase 1 and Phase 2 of your clinical trial journey with maximum quality and control.*

**Kelly Stanton**
Director of Quality, Qualio

# *Quality + compliance*

It's obviously crucial that your clinical trial process is established in a way that's compliant with your relevant regulations and quality guidelines.

**Key guidelines and regulations for clinical trials include:**

- FDA 21 CFR 11: electronic signatures (more on that later!)
- FDA 21 CFR 50: protection of human subjects
- FDA 21 CFR 54: financial disclosure by clinical investigators
- FDA 21 CFR 56: institutional review boards
- HHS 45 CFR 46: protection of human subjects, including Subpart A, 'The Common Rule'
- ICH E6 (R2) Good Clinical Practice

Download GxP toolkit ›

However, recent initiatives like the CDER's Quality Maturity program, and even FDA and ISPE validation guidelines, show a concerted industry push for pharmaceutical businesses to treat quality, not tickbox compliance, as the operational priority.

> ***The FDA has identified that an excessive focus on compliance rather than quality may divert resources and management attention toward meeting regulatory compliance requirements rather than adopting best quality practices...***
>
> **— GAMP 5 Enabling Innovation Good Practice Guide**

Although these initiatives are focused at market-approved pharmaceutical companies that are into the manufacturing stage, there's no harm in taking inspiration from this approach even at the pre-market clinical stage.

This is where quality by design comes in.

# *Quality by design (QbD) for your clinical trial*

A right-first-time, quality-centric approach that maximizes patient safety and data integrity is the key to a successful Phase 1 and Phase 2 experience.

At the core of this approach is:

- Arming yourself with visibility of your quality landscape
- Detecting and fixing potential quality issues early with continuous improvement
- Access to trusted, controlled data
- Clear roles and responsibilities
- Risk-based thinking

Quality isn't just the right thing to do for your patients and product.

A 2013 PwC study found that a proactive, risk-based monitoring approach increases planning and start-up costs by 2%, but in return:

Cuts portfolio costs by **15-20%**

Cuts project & data management costs by **20%**

Cuts monitoring & auditing costs by **25%**

Delivers **5-10%** savings in a range of other adjacent project areas

The last thing you need in your clinical trial is to be forced to pivot unexpectedly. The total median cost to implement a substantial protocol amendment for a Phase II trial is $141,000.

Across the full clinical trial process, both sponsors and CROs can therefore expect 6-7-figure savings with a robust, quality-by-design and right-first-time methodology.

## Top causes of clinical trial quality lapses

Even if the drug being trialed is efficacious and safe, your clinical trial can still break down in Phase 1 and 2 if quality management mistakes are made. Here are some of the leading errors.

### Manual document management

Reliance on paper, time-heavy control and collation of documentation, no verification of data as it's recorded, weak audit trailing

### Poor documentation

The structure of documents themselves may be substandard, providing an insufficient level of guidance or detail and encouraging written procedures to be ignored or worked around

### Poor training

Protocol and GCP training isn't properly planned, executed or recorded. Standardized and competence-based training is performed manually and struggles to keep up as staff are rotated in and out of trials

## Fuzzy protocols

A clear, documented sponsor-CRO relationship is crucial. Unsuccessful trials are often bogged down by unclear roles and responsibilities.

## No listening

Inspectors and patients are often an untapped goldmine of feedback and guidance. When inspector reports and patient advocacy groups aren't harnessed, mid-trial corrections and improvements become more difficult to make

## Weak QMS

A disconnected or heavily manual QMS with limited investigational involvement and oversight, and inappropriate SOPs, makes a harmonized, robust quality approach much more difficult to instill. Quality issues remain undetected and can grow into a trial-ending event further down the line.

## Low integration of quality and ops

Clinical trial quality focuses on performance, audits, deviation control, and of course control/assurance of product quality through QC and QA activity. Clinical trial operations focus on the nuts and bolts of the trial experience: staffing, data, protocol execution and scientific review. Where these two streams run in parallel without touching, quality by design is not in place.

# *4 ingredients for clinical trial QbD*

Your quality management system should touch all layers of your clinical operation as follows:


Download NIDCR's clinical quality management plan template ›

Next, let's examine the 4 key ingredients that should form your quality by design approach.

## 1. Good Clinical Practice

Good Clinical Practice (GCP) sets the quality benchmark for the completion of your Phase 1 and 2 trials. It's mutually accountable, offering a shared quality framework for sponsors, IRBs, investigators (CROs) and regulators to follow.

And it protects the safety of your patients and the integrity of your clinical data. Quality by design rests on careful embedding of GCP at all levels of your clinical experience.

**GCP requires:**

- A fully trained and qualified inspector with deep understanding of GCP, willingness to follow it, and responsibility for maintenance of the Delegation of Responsibilities log

- Adequate resources: enough time and trained staff to complete Phase 1 and 2, within a properly maintained facility supported by technology (more on that later!)
- Proper medical care as required by patients
- Clear communication and documentation exchanged with the IRB/IEC
- Complete compliance with the protocol, deviating only for admin/ logistical changes or where there is an immediate danger posed to subjects. The IRB, sponsor and (if necessary) the regulatory authorities should be notified
- Control of investigational product usage and storage
- Randomization and unblinding
- Informed consent
- Clear records and reports (more on that below!)
- Safety reporting

Read ICH E6 (R2) GCP guidelines ›

## 2. Data integrity

The number '11' is an important one to remember for your data integrity, whether you're going through trials in the US or the EU.

In the US, FDA 21 CFR Part 11 compliance is key.

Part 11, as it is commonly known, applies to all electronic records and signatures created, modified, maintained, archived, retrieved, or transmitted by FDA-regulated entities. Every document and record generated to meet requirements for 21 CFR Part 312 (Investigational New Drug Application) or other regulations must also be in compliance with those specified in 21 CFR Part 11.

21 CFR Part 11 applies once the design and/or development of the medical product is underway. All drug manufacturers need to comply with Part 11 requirements right out of the gate, and these requirements continue to apply through the clinical trial process and the commercial phase as well.

If you're going through European clinical trials, EU Annex 11 compliance is crucial, even if not expressly mandatory like the FDA regulations.

Annex 11 has a similar intent to FDA CFR 21 Part 11, but its scope is even wider - going beyond just electronic records and signatures to include the full gamut of activity for computerized systems. This also includes data storage, audit trails, business continuity and data validation, among other key areas.

Getting a grip of data integrity fundamentals like e-signatures doesn't only get your drug a step closer to regulatory approval. It helps to provide a clear, traceable flow of information throughout the clinical trial process, making decision-making and data access snappier and simpler. There are a number of key clinical documents which will require signatures, including:

- 21 CFR 312.62 (b) signed and dated consent forms
- 21 CFR 312.53 (c)(1) signed investigator statement (Form FDA-1572)
- 21 CFR 312.23 (a)(1)(ix) signature of the sponsor or the sponsor's authorized rep

On top of that, any digital platform you use for your clinical trial (and we highly recommend you *do* go paperless) such as an electronic Clinical Trial Management System (eCTMS), Electronic Data Capture (EDC) system or electronic quality management system (eQMS), will create key electronic documents such as site and trial master files, which all require airtight control and integrity.

**Essential clinical trial documents include:**

- Investigator of Record (IoR) or 1572
- CVs for PI and Sub-Investigators
- Licenses (as appropriate)
- Training records for all study personnel
- Protocol/amendment signature page
- IRB membership list or roster
- IRB approvals of protocol, consents, ads, handouts
- Communications with IRB, sponsor, CRO as required

**Other connected data integrity ingredients to think about are:**

- Disaster recovery and business continuity
- Backups
- Indexing and searchability of documents and trial data
- Training of relevant personnel on systems and key processes

## 5 requirements for top clinical data integrity

1. Ensure data in your CRFs matches the source documents and updates are fully audit-trailed with date and signature
2. Ensure UP/SAEs are thoroughly recorded, with causality and follow-up information
3. Follow record retention rules, following the longest requirement applicable to you (ICH GCP dictates 2 years after final approval)
4. Ensure documents are available at central and satellite sites, with no variance between
5. Submit a written report to sponsor/IRB/IEC annually, or when significant trial changes occur

**Trial sponsors should:**

- Be aware of their territory-specific data integrity requirements, since responsibility for regulatory adherence ultimately falls to them
- Take steps to strengthen their clinical trial approach where possible with a digital approach, underpinned by automated functionality for key areas like e-signatures
- Scope the data processes of potential CROs (if outsourcing) and consider them when qualifying candidates
- Integrate data management principles like ALCOA+ into their trial activities as early as possible

CROs should:

Download 21 CFR Part 11 checklist ›

- Consider explicitly designating Part 11 compliance as part of the transfer of sponsor responsibility to remove any ambiguity
- Optimize data management processes and embed ALCOA+ to become as attractive and trusted as possible to new business
- Factor Part 11 and/or Annex 11 compliance into scoping decisions when looking for a new eCTMS, EDC or eQMS

> *Showing that we have an eQMS, and that quality is high on the list, is a big checkmark for our potential customers.*
>
> **— John Stapleton, MIS Manager, AGADA Biosciences (Canadian CRO)**

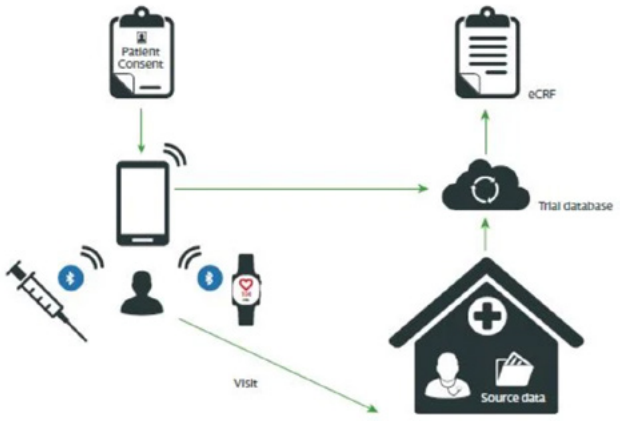
# 3. Leveraging technology

## DHT devices

Successful quality by design in a modern clinical environment is almost invariably embedded with digital tools and technology. Digital health technology (DHT) is one such example.

DHT usage has exploded in recent years, as increasingly decentralized, digitized clinical trials take shape and organizations enjoy unprecedented access to real-time e-data.

DHTs are unlocking deeper and more continuous collection of feedback from clinical trial patients; biometrics can be monitored for trial participants across countries and continents, while electronic patient-reported outcome (ePRO) devices allow experience data like reactions and




*The modern, digital, decentralized clinical trial*

pain levels to be submitted by the patient through user interface 'wearable' actigraphic technology like digital watches.

This evolution is creating regulatory response and structure too. In December 2021, in reaction to this digital shift, the FDA revealed its draft guidance on "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations".

Before the draft, DHT quality professionals were relying on overly cautious, conservative development approaches which slowed innovation and marketization. This clear and modern regulatory guidance, in line with the broader shift to computerized system assurance, should make it simpler and faster for DHT providers to launch their products, and for their clinical customers to begin using them.

Any business progressing through Phase 1 and 2 trials should consider the potential of DHT.

## AI

AI, too, has a potentially revolutionary role to play for clinical trials.

Qualio welcomed François-Henri Boissel, CEO of Novadiscovery, onto the From Lab To Launch podcast in 2022 to discuss his company's vision. Novadiscovery is developing a health-tech innovation it calls *in silico*, leveraging virtual patients and AI-powered mechanistic modeling to simulate and predict drug effects.

The usual 150 flesh-and-blood patients of a Phase 2 trial could, therefore, be augmented by tens of thousands of virtual patients, offering a deeper and richer data set for a faster and less risky route to market.

Forward-looking clinical organizations should explore how cutting-edge technology can empower them with unprecedented data possibilities.

## eQMS

An electronic quality management system (eQMS) is an increasingly popular and powerful tool for centralizing, automating and optimizing your quality by design approach.

A reputable eQMS, such as Qualio, doesn't only make managing and accessing clinical documents and data easier, or standardize how your clinical staff are trained. A single source of digital quality truth enables a collaborative culture of quality to take root, in turn helping your business meet the requirements of ICH E6 (R2) Good Clinical Practice and making quality by design natural and automatic.

| ICH E6 (R2) Good Clinical Practice (GCP) requirement | How Qualio helps |
|---|---|
| **ICH E6 (R2) §2: GCP principles** | • Plan and execute a quality management system which embeds the ethical principles of GCP and the Declaration of Helsinki<br>• Build eQMS procedures, processes and monitoring systems that ensure subject rights, safety and wellbeing are maximized and scientifically sound, risk-benefit principles are actioned at all stages of your contract manufacturing activity |
| **Clinical Investigation Planning/ICH E6 (R2) §4: Investigator** | • Fulfill your regulatory requirements as a contracted investigator by documenting, actioning and demonstrating controlled, risk-based, IEC/IRB-compliant processes, policies and procedures<br>• Build a scalable and centralized source of quality truth housing trial subject data, the qualifications and training of involved personnel, risk assessments, protocols, progress/safety reports and more |
| **ICH E6 (R2) §5: Sponsor** | • Drive a concerted, controlled relationship with your sponsors, demonstrate competence and win new business with a fully documented and visible eQMS<br>• Plan and control procedures for QA, QC and QI, from trial management to labeling, monitoring and auditing - then share them quickly and easily with sponsors and add fresh sponsor requirements with speed and agility |
| **ICH E6 (R2) §6: Clinical trial protocol and amendment(s)** | • Build a complete electronic trial protocol with safety/efficacy data, design, objectives, and so on. Manage quality issues like deviations and CAPAs with ease in real time<br>• Guarantee data integrity and control in a secure eQMS underpinned by ALCOA+ principles and change/amendment control |

| | |
|---|---|
| **ICH E6 (R2) §7: Investigator's brochure** | • Securely store your sponsor's IB and provide a controlled, up-to-date and fully audit-trailed version to your IRB/IEC<br>• Underpin your IB and trial activities with incorruptible quality data, from trial documentation to personnel training records, quality event histories and more |
| **ICH E6 (R2) §8: Essential documents for clinical trials** | • House all QMS data in a single source of truth to demonstrate your GCP competence and compliance as an investigator<br>• Store, categorize, control and share IBs, protocols, financial records, sponsor agreements, normal values/ranges, test results, screening logs, clinical study reports and so on |

## 4. Continuous improvement thinking

As we've seen, this emphasis on line-by-line compliance is important in the fledgling stages of your clinical journey, but shouldn't be allowed to obscure a proactive, continuously improving best practice focus.

Traditional quality improvement tools like Plan Do Check Act (PDCA) have their role to play in your Phase 1 and 2 trials as much as basic quality control and assurance tasks.

The lines of dialogue between sponsor and CRO should include careful evaluation of flaws, defects and areas for improvement, and the practical steps that could be taken to realize improvement. KPIs are crucial for driving this approach.

Let's see an example from a 2015 Pfizer case study:

| CATEGORY | OUTCOME COMPONENTS |
|---|---|
| **Scientifically valid and ethically sound investigational plan** | • Answers intended scientific question parsimoniously<br>• Feasible=compliance is achievable and not too burdensome<br>• Clear and unambiguous<br>• Qualified and appropriate Investigators/sites |
| **Execution per protocol** | • Sufficient subjects for valid analysis<br>  ○ Meet eligibility criteria<br>  ○ Compliance with protocol procedures/evaluations<br>  ○ Compliance with conmed restrictions<br>  ○ Integrity of randomization and of the blind<br>  ○ Integrity of investigational product and administration<br>  ○ Completed study |
| **Integrity of data** | • Total data errors/missing<br>• Critical data errors/missing<br>• Underreporting of AEs |
| **Integrity of analysis and interpretation** | • Valid analysis plan to answer protocol questions<br>• Analysis free of "errors that matter"<br>• Correctly interpreted (by qualified personnel)<br>• Clearly expressed in report |
| **Protection of subjects' rights** | • Ethics approval<br>• All subjects consented appropriately throughout study<br>• Notification of new safety information to patient, Investigator, IRB<br>• Privacy |
| **Protection of subjects' safety/welfare** | • Capture of safety information<br>• Qualified and timely review of safety information<br>• Notification to Investigators performed promptly<br>• Subjects removed from study when appropriate<br>• Appropriate emergency un-blinding |
| **Compliance: Documentation and Submissions** | • TMF complete, accurate, and in compliance with regulations<br>• Safety reporting complete, accurate, and in compliance<br>• Regulatory submissions complete, accurate, and in compliance with regulations<br>• Regulatory responses complete, accurate, and in compliance |

| | | Downstream metrics | | Upstream metrics |
|---|---|---|---|---|
| | | **Outcome Metrics** | **Predictor Metrics** | **Contributors** |
| **Scientifically valid and ethically sound investigational plan (Protocol Quality=PQ)** | PQ Outcome 1 | | | |
| | PQ Outcome 2 | | | |
| | PQ Outcome 3 | | | |
| **Execution per protocol (Protocol Execution=PE)** | PE Outcome 1 | | | |
| | PE Outcome 2 | | | |
| | PE Outcome 3 | | | |
| **Integrity of data (Data Integrity=DI)** | DI Outcome 1 | | | |
| | DI Outcome 2 | | | |
| | DI Outcome 3 | | | |
| **Integrity of analysis and interpretation (IAI)** | IAI Outcome 1 | | | |
| | etc. | | | |
| | etc. | | | |
| **Protection of subjects' rights** | | | | |
| | | | | |
| | | | | |
| **Protection of subjects' safety/welfare** | | | | |
| | | | | |
| | | | | |
| **Compliance: Documentation and Submissions** | | | | |
| | | | | |
| | | | | |

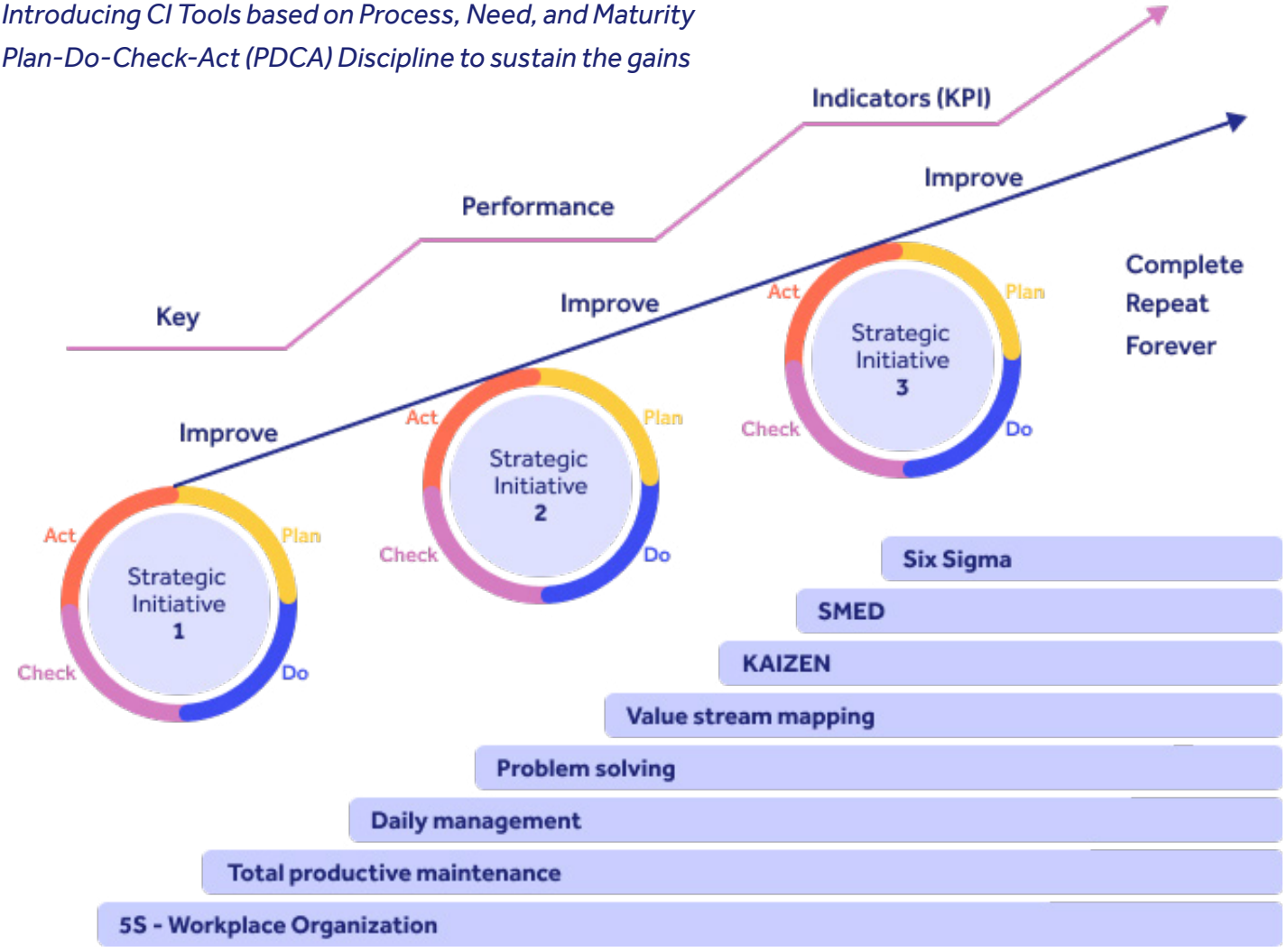
By breaking their clinical trial quality framework into 7 categories, then assigning a desired outcome for each, Pfizer gave themselves a clear, measurable structure around which to fix issues and continuously improve. 'Contributor' and more direct 'predictor' metrics feed into the overarching 'did we achieve?' metrics of the desired outcome.

This can then be taken a step further with role-specific responsibilities:

| Role | Definition | Questions to be answered by quality metrics |
|---|---|---|
| **Study Directors** | those primarily responsible for quality outcomes in a particular study | • Is my study on track to achieve the required level of quality? *(predictor metrics)*<br>• If not, where does the problem lie? Do I need to involve another level of management in remediation activities? *(cuts of predictor metrics, and drill-downs from predictor to associated contributor metrics)*<br>• Are there any signals to suggest that my study is at risk of going off track? *(predictor metrics, selected contributor metrics based on risk profile)*<br>• In the end, did my project achieve the desired/required quality outcomes? *(outcome metrics)* |
| **Higher-Level Leads, i.e., Program/Asset/ Therapeutic Area, etc. (also to include the Enterprise itself)** | those primarily responsible for quality outcomes over a defined, logically related set of studies | • Is there evidence of a problem that's rooted in, or that broadly affects, my level of responsibility/my resource?<br>  ○ What fraction of completed studies in my domain have achieved the required level of quality? *(domain-specific "cuts" of outcome metrics)*<br>  ○ What fraction of ongoing studies in my domain are on track to achieve the required level of quality? *(domain-specific "cuts" of predictor metrics)*<br>• If there is evidence of a problem in my domain, where does it lie? Is there a pattern by resource/process step/business unit? *(domain-specific drill-downs from outcome to predictor to contributor metrics)*<br>• Are there any signals to suggest that things are at risk of going off track? *(predictor metrics, selected contributor metrics based on risk profile)* |

Adopting this framework and setting a handful of KPIs in your sights is important if you are to move beyond the 'bare minimum' of GCP compliance. Couple your KPIs with targeted quality initiatives like 5S and Kaizen, and you have a mechanism for continuously refining and sharpening your clinical trial execution as Phases 1 and 2 unfold:

*Introducing CI Tools based on Process, Need, and Maturity*
*Plan-Do-Check-Act (PDCA) Discipline to sustain the gains*



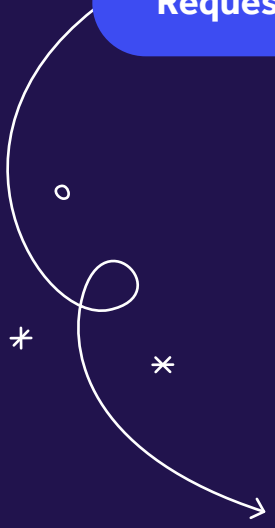
# *Conclusion*

Taking a proactive, risk-based, quality-first approach before your Phase 1 trial even begins is the key to clinical success.

Quality by design rests on good clinical practice, airtight data integrity, the leveraging of new and exciting technology to make a quality culture gel, and a willingness to go *beyond* your baseline compliance requirements with a continuous improvement focus.

## *Learn about our award-winning quality management software*

**Request a demo today**



**Call us today**

1.855.203.2010 • +353 1 697 1522