Understanding Quality by Design (QbD) and applying it

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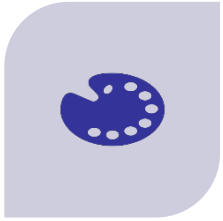
Topics

COMMON QUALITY ISSUES (FROM INSPECTIONS AND AUDITS) AND ITS REPERCUSSIONS



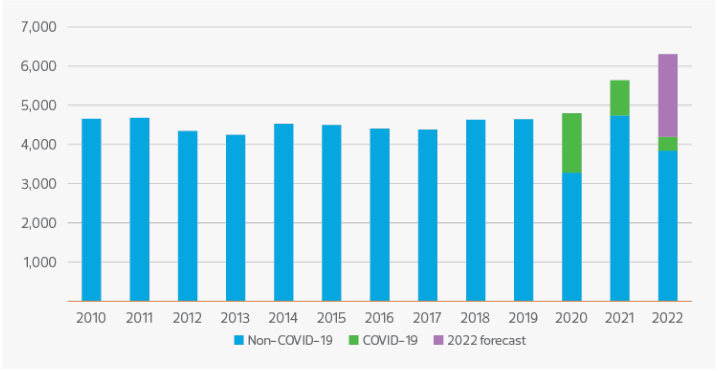
WHAT IS QUALITY BY DESIGN?

QBD AND ITS PRINCIPLES

APPLICATION OF QBD BY CRCS IN YOUR DAILY WORK

Introduction

- Accelerated adoption of agile, decentralized or hybrid clinical trials
  - Adoption of innovative methodologies in trial designs
  - Integration of enabling digital tools
  - Collaborations between regulators, industry and sites



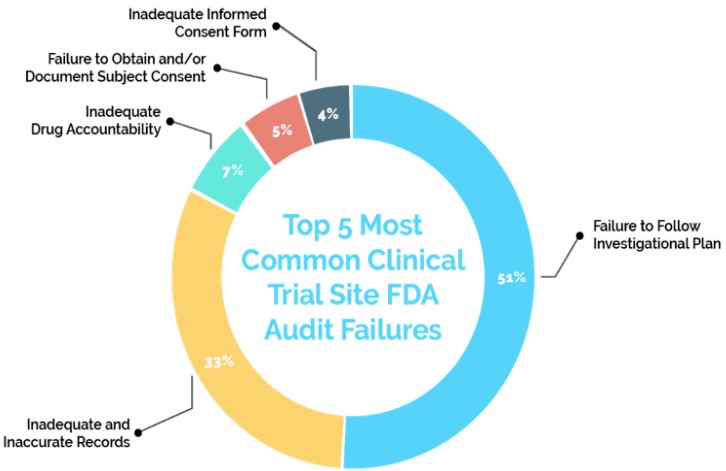
Source: ClinicalTrials.gov; RSM US LLP

*count; industry-funded; interventional

- Quality and integrity should not be compromised
  - To safeguard against non-compliance, which impacts patient safety and data integrity

Common Inspections Findings

Over the past five years, the FDA has reported a failure rate of 36% in clinical trial site inspections. Below are the top five reported failures the FDA has found in these inspections and solutions to reduce your risk.



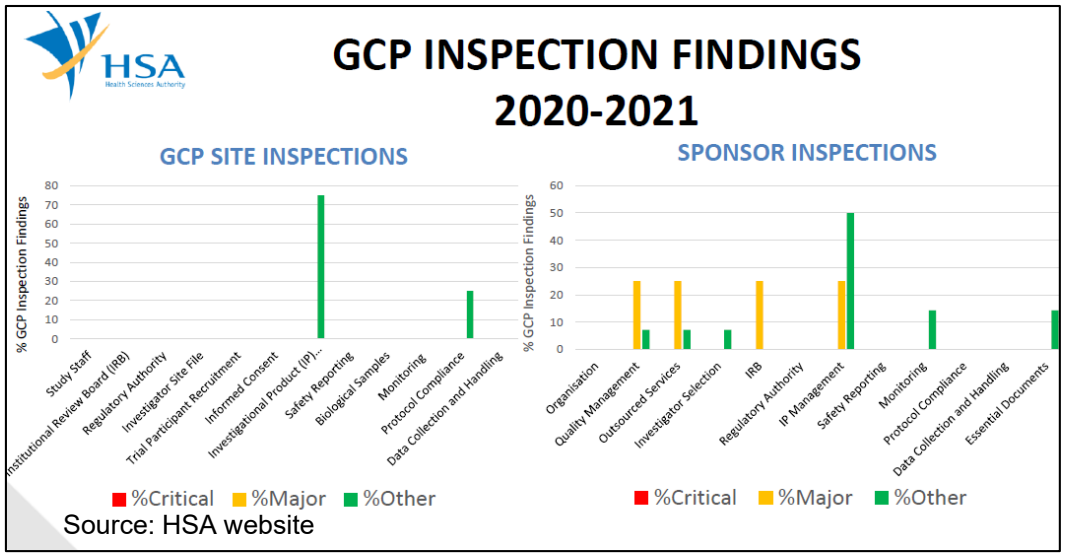
Source: https://florencehc.com/blog-post/how-to-avoid-the-top-5-clinical-trial-fda-inspection-failures/

FDA and EMA mostly align on GCP inspection deficiencies, study finds

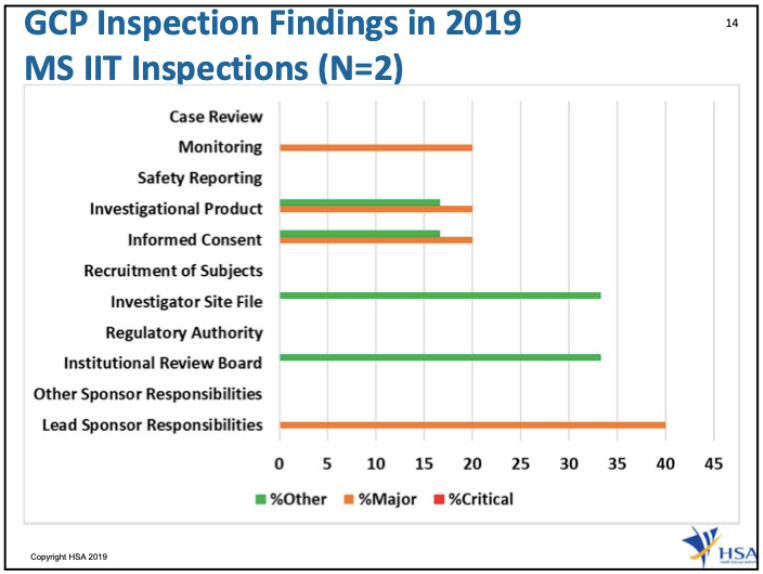
Regulatory News | 31 May 2022 | By Joanne S. Eglovitch

A study conducted by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) found that the agencies are identifying the same types of deficiencies in joint good clinical practice (GCP) inspections with respect to protocol compliance, documentation deviations, and human subject protections.

FDA and EMA Inspectors Found Similar Issues at GCP Inspections
(Thursday, June 2, 2022)
A report on inspectional findings during GCP audits by FDA and EMA inspectors found that both regulators found similar issues 9 out of 10 times. The findings of



Source: HSA website



Common Site Audit Findings

Informed Consent

- Use of unapproved ICF version
- Incomplete completion of ICFs
- Inappropriate use of witness

Study Team

- Missing delegation log, training records, CVs
- Failure to update IRB of STM changes

Data collection, Source Documentation

- Failure to comply to ALCOA principles

Essential Documents

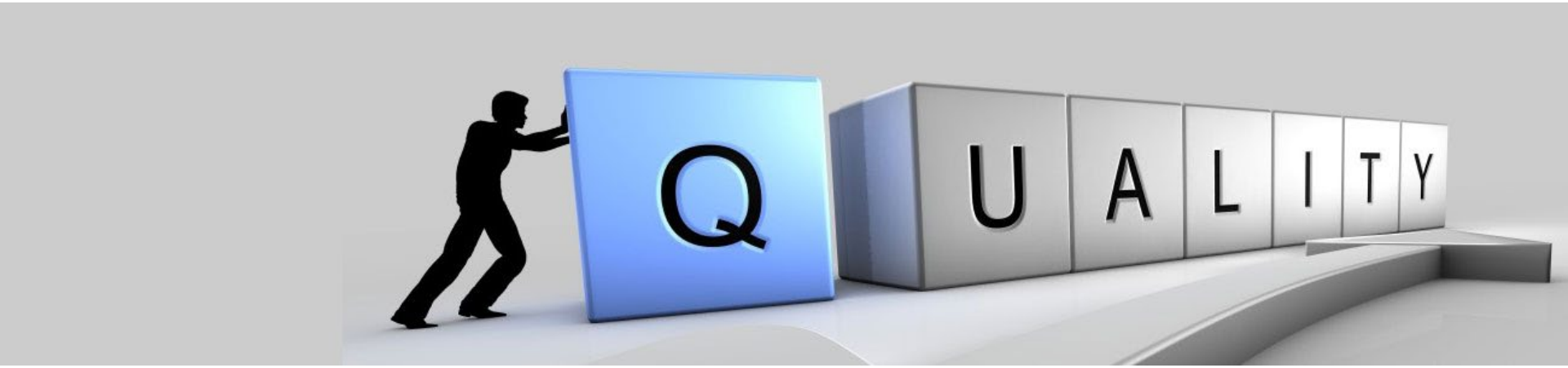
- Missing IP management plan and log
- Missing IRB application forms, study documents

Site Procedures including Recruitment Procedures

- Use of unapproved recruitment strategy
- Missing subject screening, enrolment log
- Screening without consent taking

Requires proactive approach to Quality and not retrospective reaction

Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing, or inspection



Have you heard of

QUALITY BY DESIGN (QbD)?

ICH E8(R1) address importance of Quality

Quality of Clinical Research relies on

Good design

- Clear objectives and endpoints that address the primary scientific questions
- Selection of appropriate subjects and sites
- Approaches that minimise bias (randomisation, blinding/masking, control of confounding factors)

Good design execution

- Ensures feasibility quality of facilities, procedures and processes

ICH E8 3.1 What is Quality by Design (QbD)?

Preventing important errors by paying attention to the design of the protocol, procedures, operation plans and training

A primary consideration in the **design, planning, conduct, analysis, and reporting** of clinical studies and a necessary component of clinical development programmes.

The likelihood that a clinical study will answer the research questions while **preventing important errors** can be dramatically improved through prospective attention to the **design of all components of the study protocol, procedures, associated operational plans and training**.

Activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study.

How Risk Drives Quality

Identify critical to quality factors when designing a study

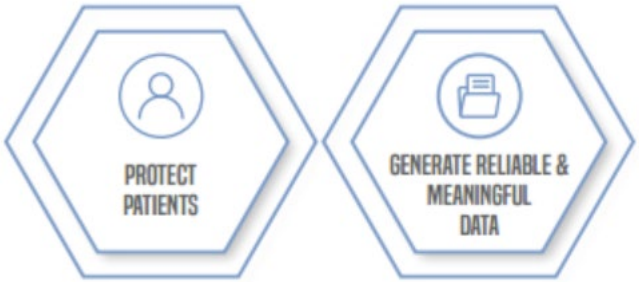
Implement control process to manage risks

ICH E8 3.2 What is Critical Quality Factors?

To design quality into a clinical study, its important to identify **Critical Quality Factors** which ar**e** attributes of a study whose integrity is fundamental to:

- the protection of study participants
- the reliability and interpretability of the study results
- and the decisions made based on the study results

And determine the risks that threaten the integrity of each of the factors



ICH E8 3.3 How to identify Critical Quality Factors?

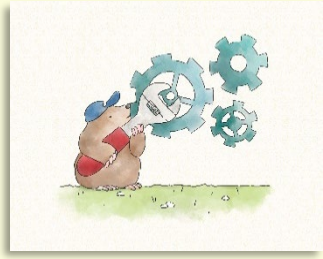
1) Establishing a Culture that Supports Open Dialogue
   e.g. customise tools and checklists specifically to each study
2) Focusing on Activities Essential to the Study
   Simplify conduct, improve study efficiency, and target resources to critical areas and prevent or control errors that matter
3) Engaging Stakeholders in Study Design
   Stakeholders such as clinical investigators, study coordinators and other site staff, and patients/patient organisations
4) Reviewing Critical to Quality Factors
   Periodic review to adjust the risk control mechanisms as new or unanticipated issues may arise once the study has begun.
5) Critical to Quality Factors in Operational Practice
   Feasibility assessment is important to determine successful completion of the trial from an operational perspective.

How can I apply QbD in my work?

CRC

SOPs, Work Instructions

Risk assessments and mitigation plan



Workflow and site processes

PIs, Study team members training

Images by rawpixel.com

1. Embrace the Quality Culture

- QbD should become an intrinsic corporate attitude and be integrated into organizational structures, daily rituals, stories, and symbols

Organisation level

- Quality Management System

(focus on documentation, roles & responsibilities, quality metrics, policies & procedures, risk management)

Study and site level

Implementation of QbQ

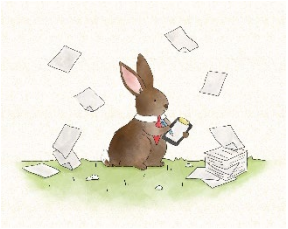
(plan > do > check metrics > act >0

Study and site level

Risk based monitoring implementation

(quality monitoring, centralised monitoring)

"Culture eats strategy for breakfast", said Peter Drucker, the legendary strategist.

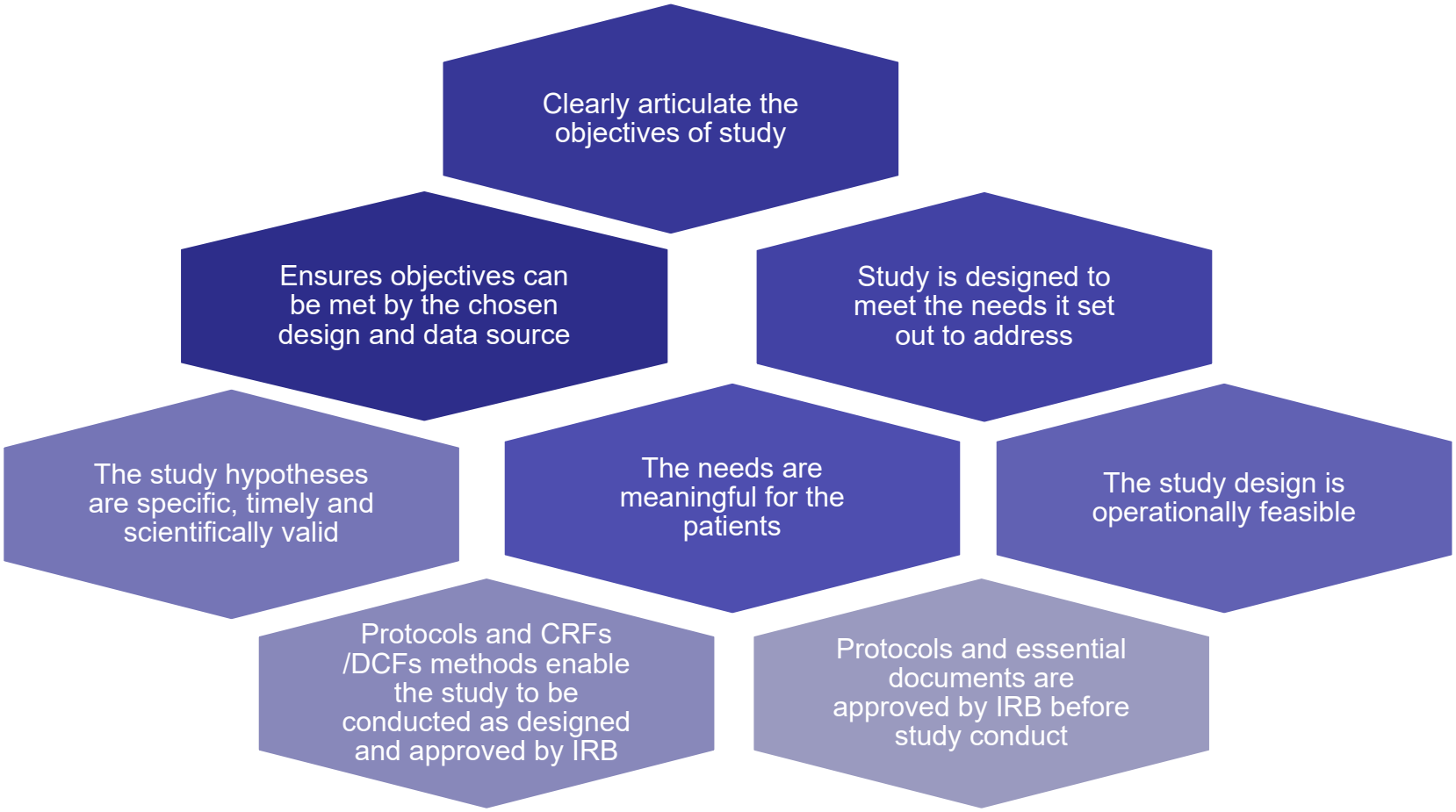


SOPs, Work Instructions

- Institution based SOPs and Work Instructions (e.g. Informed Consent, IP management, Biological specimen management, collaborators management, etc.)
- Generic study manuals such as IP, biological specimen management manuals for customization to study manuals.
- Documents should be clear, concise and consistent

Always customize to the study, cannot be "one size fits all"

2. Study Design – quality approach



PIs, Study team members training

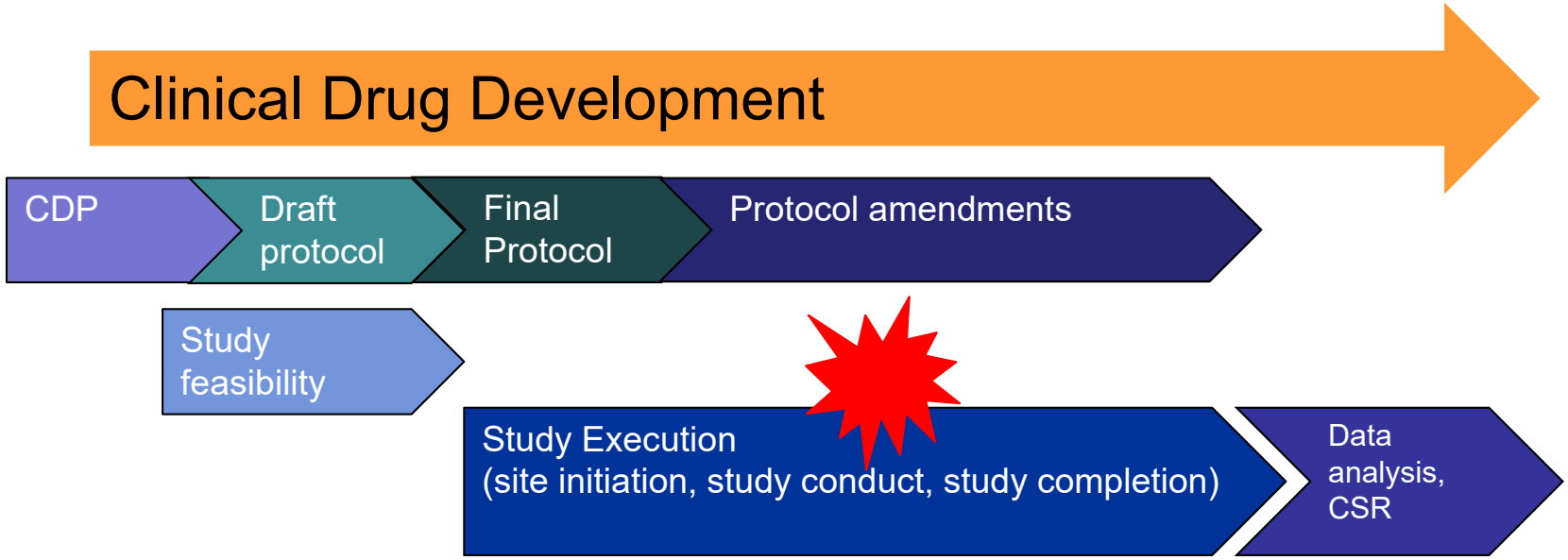
- Ensure adequate/up-to date training in GCP, CITI and/or HBRA prior to involvement in study
- Ensure adequate and effective training in study procedures
  - study team members vs non-study team members, e.g. ward nurse
  - study team members must be protocol trained while non-study team members to be trained specifically on certain study procedures only

Going through study processes step-by-step

FDA guidance on ICH E8(R1)

Individuals involved in study conduct should receive training commensurate with their role in the study, and this training should occur prior to their becoming involved in the study. Updated training or retraining may be needed to address issues related to critical-to-quality factors observed during the course of the study, and/or to implement protocol modifications.

3. Quality Execution



Sites Workflow, Processes

Start up

- Site feasibility has been assessed for the study to be conducted
- All regulatory and IRB documents (including protocol, CRFs) are ready
- Adequate supplies of IP, equipment
- Set up of TMFs
- Site initiation readiness, training

Consent

- Check appropriate version of ICF used
- Ensure ICF template used contain the essential and additional elements
- Adequate time to consent research subjects, date and sign

Documentation

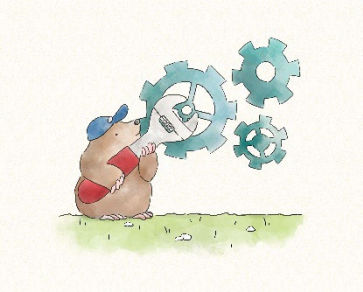
- Data collected must meet ALCOA principles
- Data must match with the source
- All amendments must be signed and date
- All essential documents must be archived in accordance with IRB retention period/institutional requirements

Safety management

- Timely reporting of SAEs, SUSARs
- Report AEs and lab abnormalities critical for evaluation
- Identify if DMC is needed

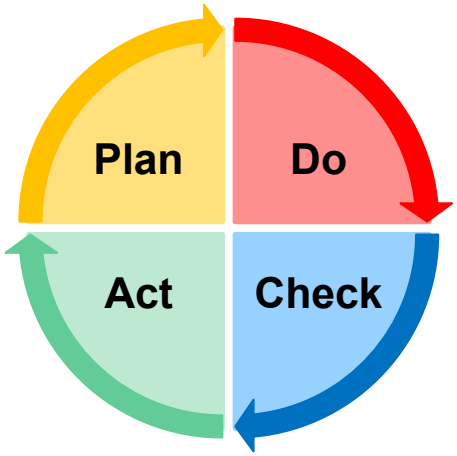
IP management

- Appropriate coding and labelling, to protect blinding
- Acceptable storage temperatures, storage conditions, storage times, reconstitution fluids and procedures, and devices for product infusion
- IP accountability management (shipment, administration, return, destruction)



Risk assessments and mitigation plan

- A risk management plan should be created, according to QbD principles
  - Sets out how risks will be managed in risk mitigation plan
  - Risk identification, assessment, mitigation and monitoring
- Access the study risks
  - Risk associated with study design
  - Operational trial risks
  - Quality risks (noncompliance)
  - Systemic risks (cross functional/process risks)
- Periodic review of risk management plan
  - Adding in new risks with mitigation plan
  - Retiring invalid risks



Summary

Quality-by-design (study design and planning)

Optimal study and monitoring strategy based on critical data, critical processes, and risks.

Risk-based study execution

Quality execution of centralized/remote/onsite monitoring; continual risk evaluation, adaptation and reporting

THANK YOU!