Risk-Based Monitoring: A Regulatory Perspective

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Overview of Today's Presentation

- Background on the importance of quality in clinical research
- Quality by design (QbD) and risk-based monitoring (RBM) projects that have informed FDA policy
- FDA's requirements for clinical trial quality
- FDA expectations, including update on ICH guidelines and FDA guidance on:
  - QbD, including identifying clinical trial's critical to quality factors
  - Sponsor's quality management (QM) of the clinical trial, including the risks to those critical to quality factors
  - RBM

Quality in Clinical Research

Clinical trial results are relied on for decision-making by

- Industry
- Regulators
- Physicians/Medical Personnel
- Patients and Caretakers

There is a need to produce high-quality evidence to inform decision-making on use of a preventive, diagnostic, or therapeutic intervention

The purpose of a clinical trial is to generate reliable information to answer research questions and support decision-making while adequately protecting the rights, safety, and welfare of trial participants

Scientific question is important, and the trial design should be adequate to answer this scientific question; and if well-conducted the results will be credible

High Quality Evidence?

- Major guideline recommendations for patient care rely on less than high quality/optimal evidence[1,2]
  - 41 Infectious Disease Society of America Guidelines[1] recommendations based on:
    - 14% Level 1 evidence (≥1 properly randomized clinical trial)
    - 31% Level 2 evidence (≥1 well-designed clinical trial without randomization, cohort or case-controlled analytical study, or dramatic result from uncontrolled study)
    - 55% Level 3 evidence (opinion respected authority, descriptive study, report of expert committee)

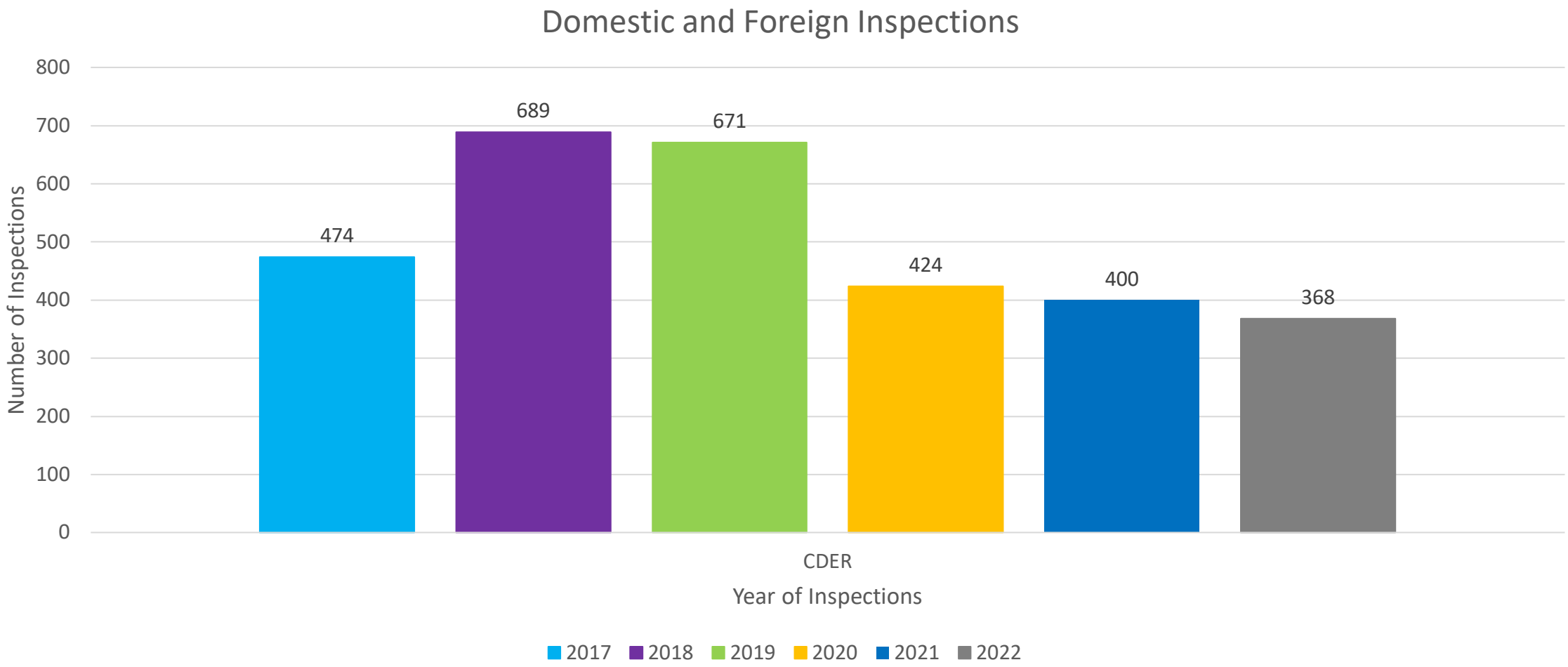
[1]Lee DH, Vielemeyer O. Analysis of overall level of evidence behind Infectious Diseases Society of America practice guidelines. Arch Intern Med. 2011;171(1):18-22
[2]Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA. 2009;301(8):831-84

System Inertia

- Despite increasing costs of clinical development programs, in particular costs attributed to clinical trials, problems with trial conduct persist impairing our ability to attain high-quality evidence
  - Patterns of critical audit findings have shown little change over years
  - CDER's BIMO Inspection Program shows little change in patterns of regulatory violations over the years[3]

[3] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438250.pdf

CDER Inspections of Clinical Investigators, Sponsors, CROs, and Sponsor-Investigators Conducted FY 2017 -2022



Due to the COVID-19 pandemic, RRAs (not reflected in the above table) were conducted in 2020, 2021, and 2022

For more information, see https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/bimo-inspection-metrics

Common Clinical Investigator Inspectional Observations*

- Failure to comply with Form FDA 1572 requirements, protocol compliance
- Failure to follow the investigational plan; protocol deviations
- Inadequate and/or inaccurate case history records; inadequate study records
- Inadequate accountability and/or control of the investigational product
- Safety reporting; failure to report and/or record adverse events
- Inadequate subject protection; informed consent issues

*Most common observations collected from issued FDA Form 483s

Common Sponsor/CRO Inspectional Observations*

- **Failure to ensure proper monitoring of the study** and ensure the study is conducted in accordance with the protocol and/or investigational plan
- Failure to meet the abbreviated requirements for investigational device exemptions (IDEs)
- Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product; Investigator Statement (Form FDA 1572); Financial disclosures
- Failure to submit an Investigational New Drug (IND) application; IND safety report
- Failure to submit current list of all participating investigators to FDA at six-month interval after FDA approval of the study

*Most common observations collected from issued FDA Form 483s

Common Sponsor-Investigator Inspectional Observations*

- Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product; Investigator Statement (FDA 1572); Financial disclosures
- Failure to select qualified investigators and/or monitors, **ensure proper monitoring of the study** and ensure the study is conducted in accordance with the protocol and/or investigational plan
- Failure to submit an Investigational New Drug (IND) application
- Inadequate subject protection; informed consent issues
- Failure to notify FDA of termination of investigator

*Most common observations collected from issued FDA Form 483s

Quality by Design, Quality Management, and Risk-Based Monitoring

Quality by Design

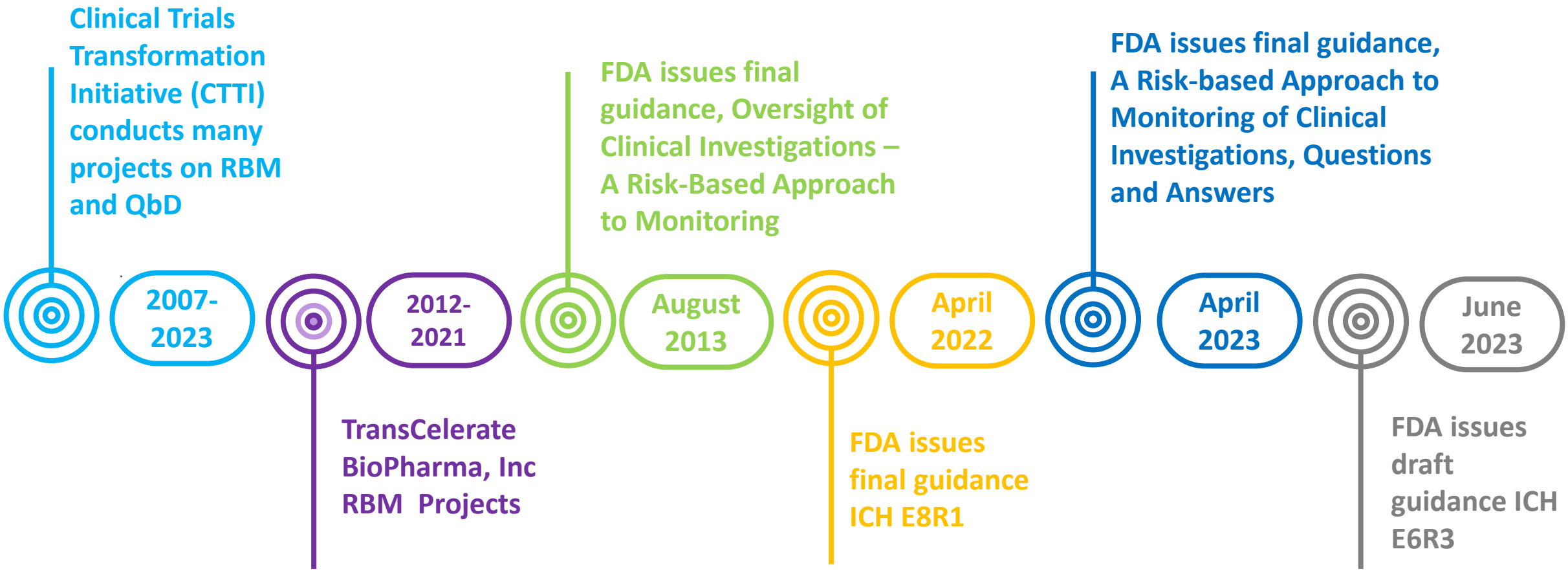
Quality Management

Risk-Based Monitoring

The Risk of Not Building Quality Into the Study Foundation

- We don't want to see a fire-fighting mentality applied to clinical trials where the sponsor/CRO is frantically rushing, making impulsive decisions; applying "Band-Aids" to problems without in-depth investigation, and suppressed problems with short-term solutions
  - This could result in
    - Loss of data integrity and in the rejection of study to support regulatory and therapeutic decisions
    - Discontinued development of potentially beneficial therapy

QbD, QM, and RBM



Major Lesson Learned

Focus on What Matters

"You start out with a beautiful green tree that should be admired, and then everybody in the family wants to put an ornament on it... and no one will take grandma's ornament off the tree. So, you end up with a protocol that is impossible to do and is very distracted from answering the question you originally had."

- Dr. Robert Califf, Mind the Gap seminar, "Innovative Approaches to Clinical Trials"

Major Lessons Learned

Monitoring is a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected

Monitoring, or oversight, alone cannot ensure quality

Rather, quality is an overarching objective that must be built into the clinical trial enterprise

FDA Requirements: Clinical Trial Quality

- 21 CFR 314.126 broadly describes what constitutes an adequate and well-controlled study*
  - Study design permits a valid comparison with a control to provide a quantitative assessment of drug effect
  - Method of selection of subjects provides adequate assurance that they have the disease or condition being studied
  - Method of assigning patients to treatment and control groups minimizes bias and assures comparability of the groups
  - Adequate measures are taken to minimize bias
  - Methods of assessment of subjects' response are well-defined and reliable

* The primary basis for determination of whether “substantial evidence” has been provided to support the claims of effectiveness for new drugs.

FDA Requirements: Sponsor Oversight/ Sponsor Responsibilities

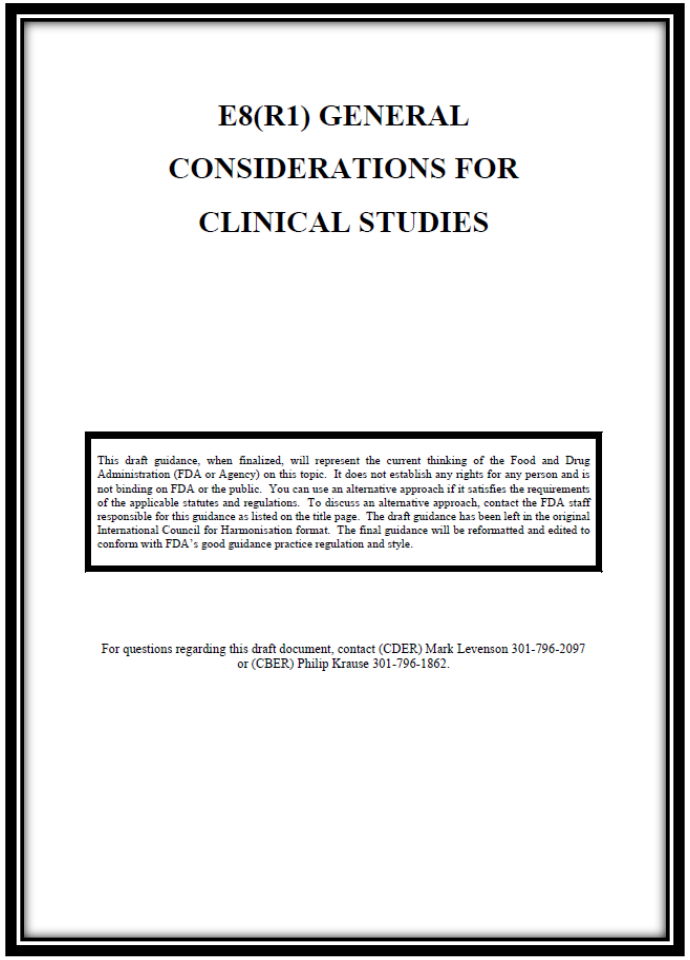
21 CFR 312 broadly describes sponsor oversight and sponsor responsibilities for clinical trials

- Selection of qualified investigators
- Ensuring the trial is conducted according to the investigational plan
- Review and analysis of accumulating evidence relating to product's safety and effectiveness
- Monitoring the conduct and progress of clinical trials being conducted under its IND (see 21 CFR 312.50, 312.53(d), 312.56(a))

The regulations are not specific about how sponsors are to conduct such monitoring and are therefore compatible with a range of approaches to monitoring (e.g., onsite, remote, and central monitoring)

Quality by Design (QbD)

- The quality and amount of the information generated in a clinical trial should be sufficient to support good decision-making
- Quality of a clinical trial is considered fitness for purpose
  - Avoidance of errors that matter to decision making—that is, avoidance of errors which have a meaningful impact on the safety of trial participants or credibility of the results
- QbD entails proactively designing quality into the study protocol to ensure
  - The protection of the rights, safety, and well-being of trial participants
  - The generation of reliable and meaningful results
  - The management of risks to critical to quality factors using a risk proportionate approach



E8(R1) GENERAL

CONSIDERATIONS FOR

CLINICAL STUDIES

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page. The draft guidance has been left in the original International Council for Harmonisation format. The final guidance will be reformatted and edited to conform with FDA's good guidance practice regulation and style.

For questions regarding this draft document, contact (CDER) Mark Levenson 301-796-2097 or (CBER) Philip Krause 301-796-1862.

Critical-to-Quality (CTQs) Factors

CTQ factors are attributes of a study whose integrity is fundamental to the protection of trial participants, the reliability and interpretability of the study results, and the decisions made based on the study results

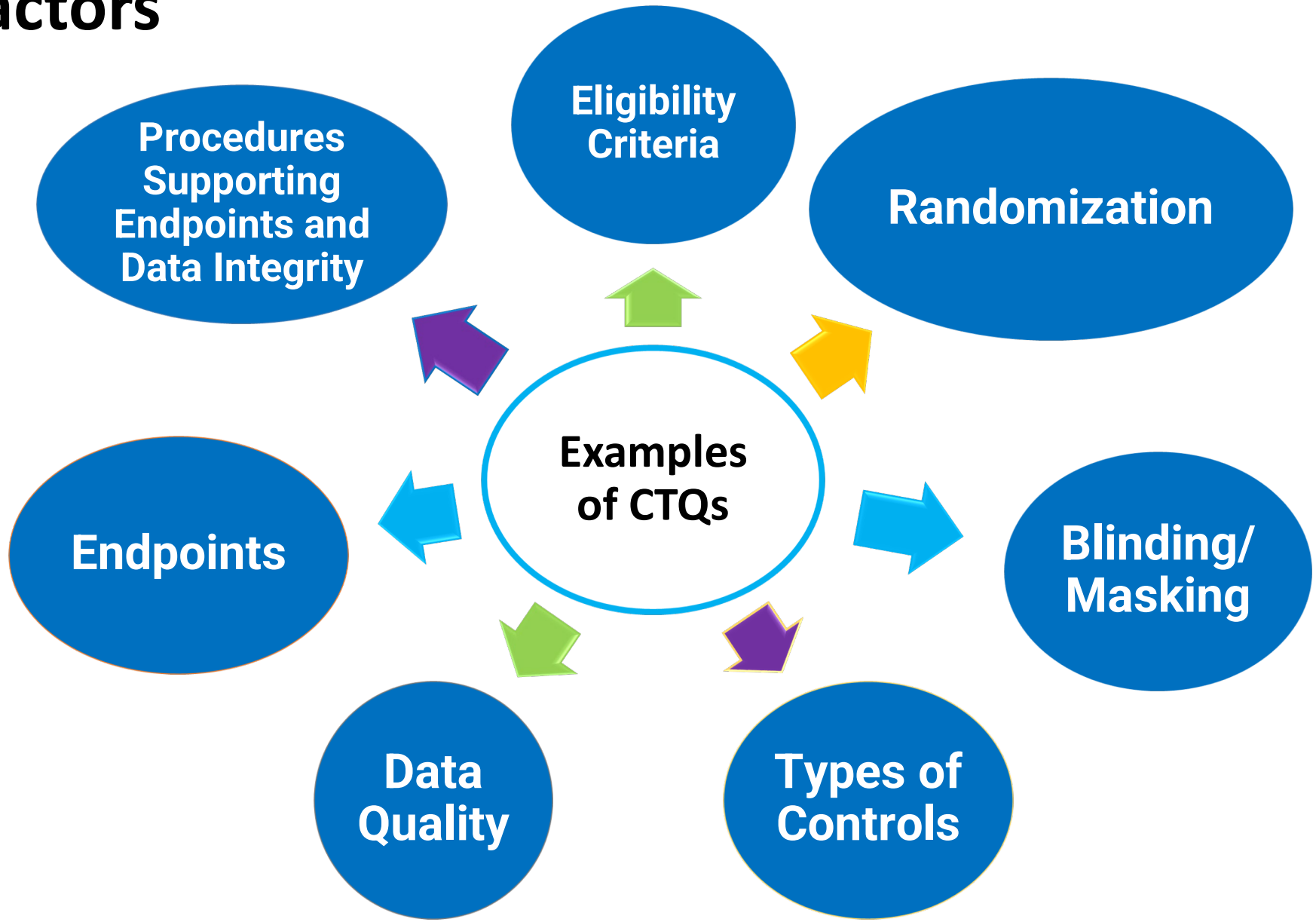
CTQ factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making based on the results of the trial would also be undermined

The QbD approach involves identifying and reviewing CTQ factors at the time of design and planning of the trial, and throughout the trial conduct, analysis, and reporting

What do we really need to get right to ensure the reliability of results and patient protection?

Inflexible, *one size fits all* approaches are discouraged

CTQs Factors



Adapted from CTTI, Quality-by-Design Projects- Critical-to-Quality Factors Principles Document, available at https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_QbD_CTQ_Priniciples_Document.pdf

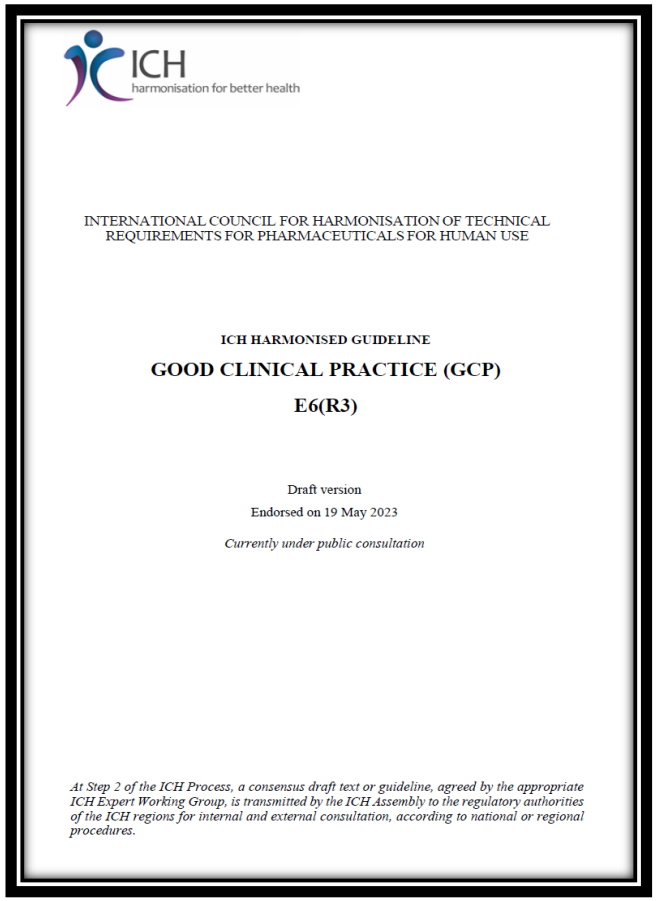
Approaches to Enhance Identification of the CTQ Factors

- Create a culture that values and rewards critical thinking and open, proactive dialogue
- Focus on activities essential to the study
- Engage stakeholders in study design
- Periodic review of critical-to-quality factors
- Critical-to-quality factors in operational practice

ICH E8(R1) Step 4: https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

QM of the Clinical Trial

- The sponsor should implement an appropriate system to manage quality throughout all stages of the trial process
- ICH E6(R3), draft version currently under consultation, integrates quality management of the trial with QbD principles described in ICH E8 (R1)
- Quality management should be proportionate to the risks inherent in the trial and importance of the information collected
  - Focus on those processes and data that may have an impact on the trial participants' rights, safety and well-being and the reliability of the trial results



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

QM in Clinical Trials

FDA encourages implementation of a systematic, prioritized, risk-based approach to QM of the clinical trial and this approach should be described in the clinical study report (see ICH E3)

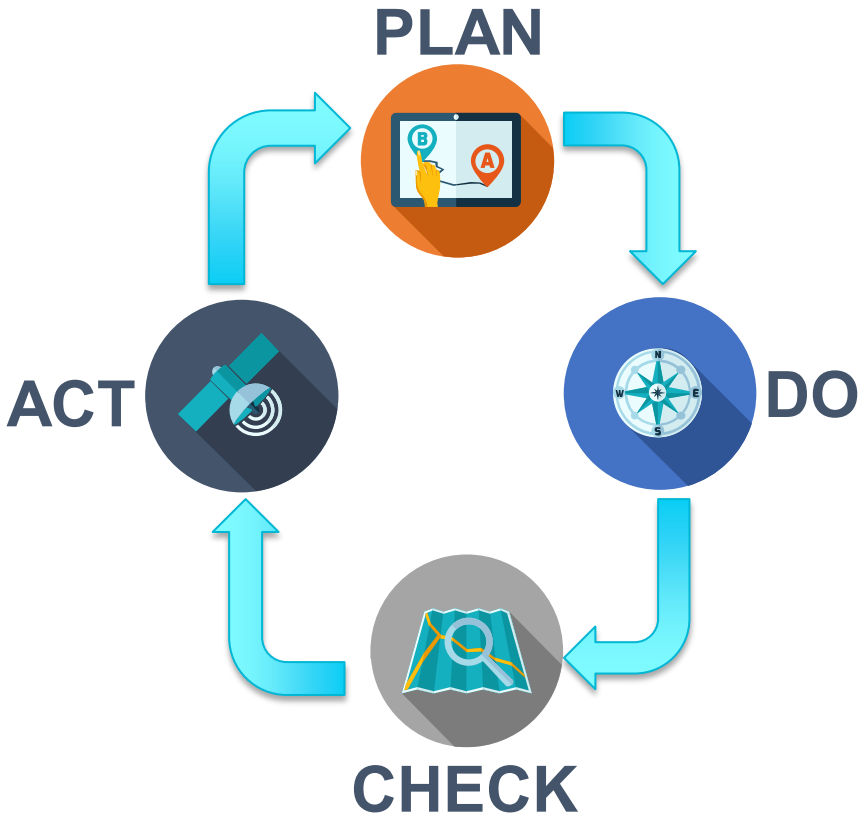
Includes the design and implementation of efficient clinical trial protocols including tools and procedures for trial conduct and data collection and management

Includes incorporating strategies for risk evaluation, risk control, risk communication, risk review, and risk reporting at the level of the sponsor, investigator, and service provider

Implementation: Plan, Do, Check, Act

- Prospectively identify the aspects of a trial/likely risks that are “CTQ” (e.g., identify which data and processes underpin data integrity and clinical trial quality)

- Systematically drive remediation and learning (e.g., ensure that effective corrective/preventive actions are designed and implemented; retraining)



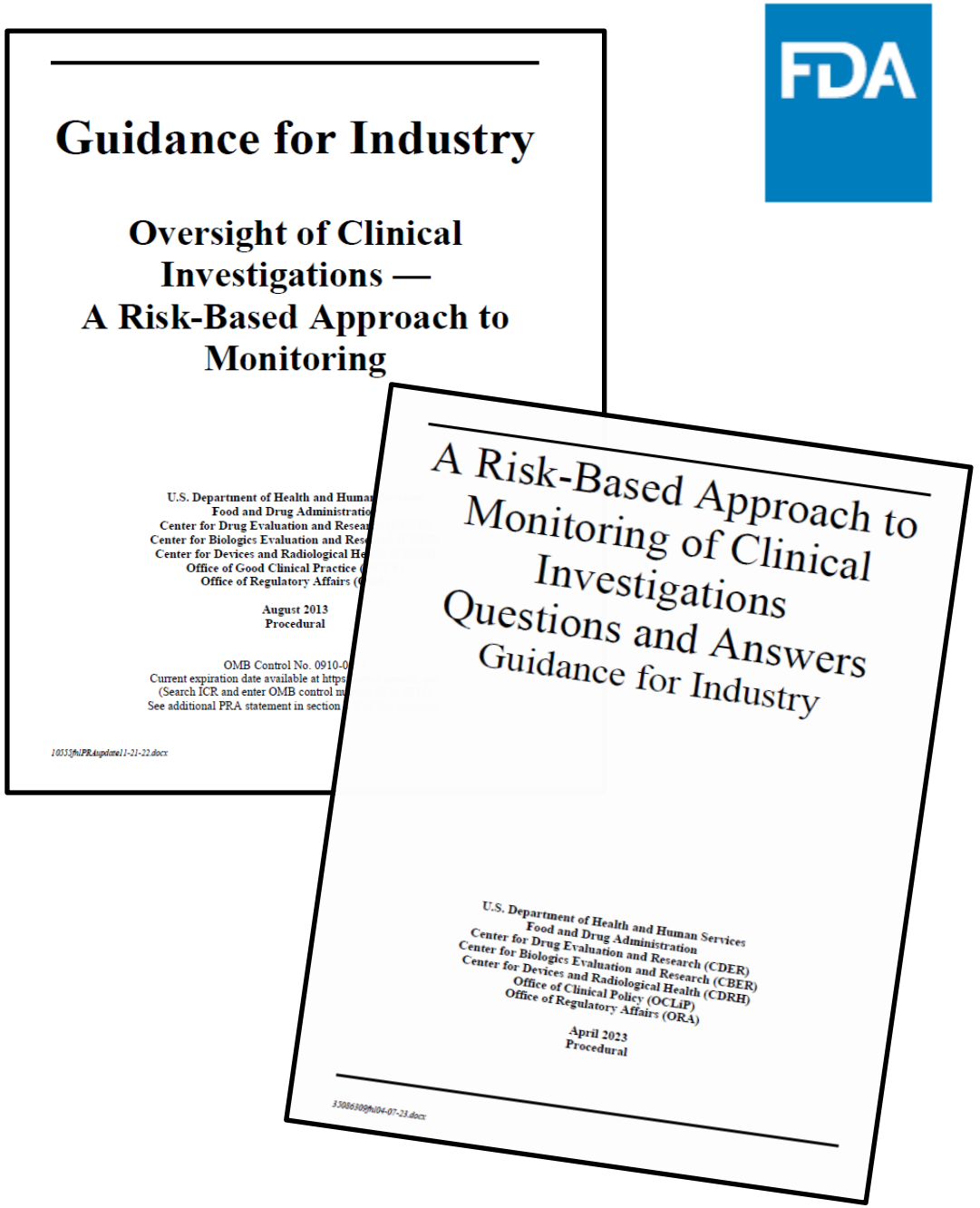
- Implement trial risk management strategies (e.g., ensure that procedures and roles/responsibilities for generating, collecting, and reporting data are prospectively defined and communicated)

- Establish a mechanism to proactively identify compliance signals
- Monitoring methods used should be proportionate to the risks inherent in the trial and the importance of the information collected

Adapted from CTTI
FDA/ICH E6(R2): https://www.fda.gov/media/93884/download
ICH E6(R2): https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

RBM

- The 2013 RBM guidance outlines factors that sponsors should consider when developing and tailoring a monitoring plan to the needs of the trial and provides examples of monitoring methods and technique
- The 2023 guidance provides additional recommendations for planning a monitoring approach, developing the content of monitoring plans, and addressing and communicating monitoring results
  - Encourages QbD/risk-based QM approaches



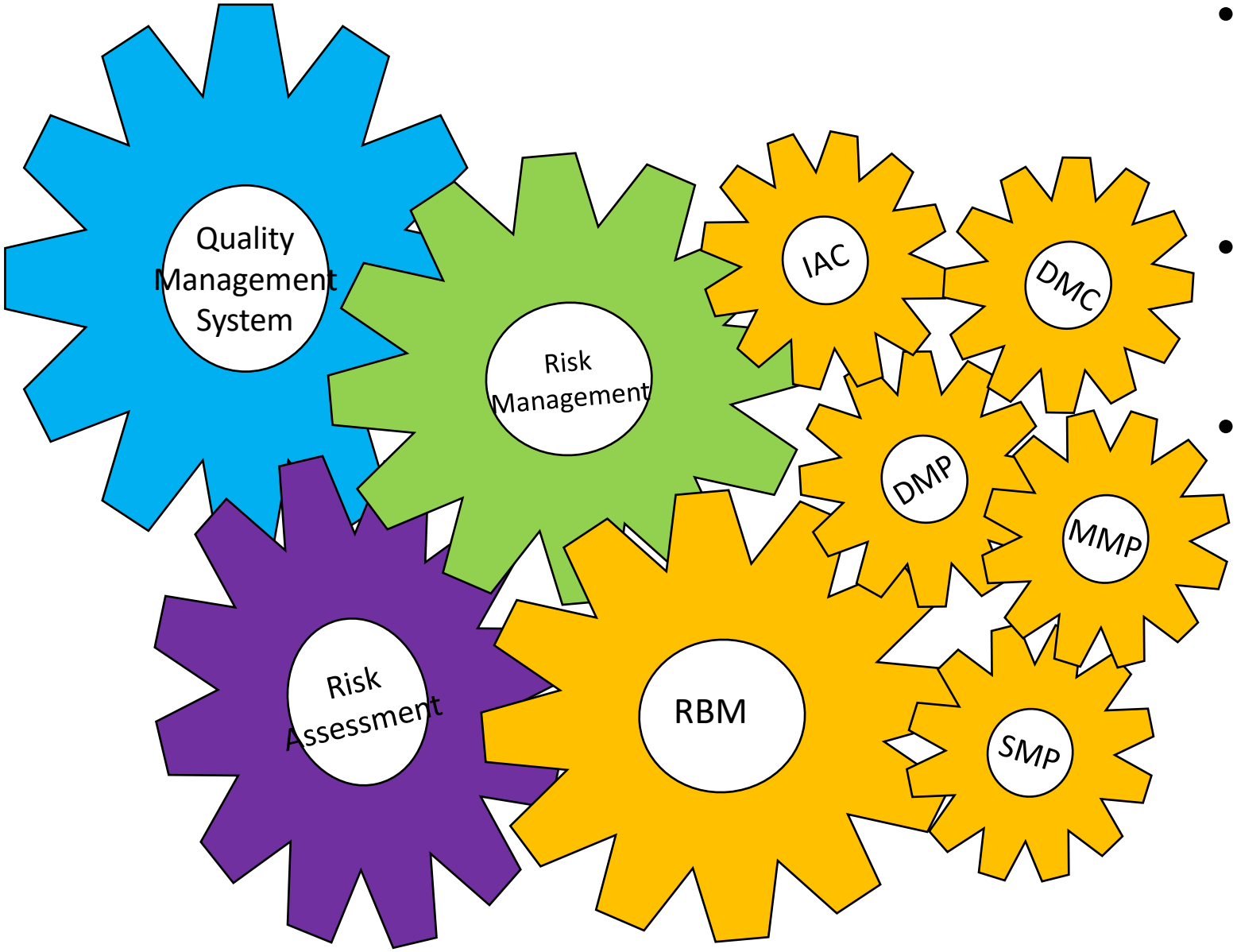
RBM

- High-level FDA recommendations for sponsors
  - Use a risk-based approach to monitoring
  - Conduct a risk assessment to identify and evaluate risks to critical study data and processes
  - Tailor their monitoring plan to the needs of the trial; monitoring plan should be designed to address important and likely risks identified during risk assessment (discourages “One Size Fits All” approach to monitoring)
  - Focus their oversight on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity
- FDA encourages use of a variety of monitoring techniques:
  - Centralized
  - Remote
  - On-site

RBM

Onsite, remote, and/or central monitoring	The sponsor's monitoring approach will vary depending on multiple factors, such as	Protocol should be considered blueprint for quality
• The appropriate extent and nature of monitoring (e.g., use of onsite, remote, and/or central monitoring and the amount of SDV that should performed) should be based on identified risks of the specific trial	• Trial's objective • Design • Complexity • Blinding • Number of trial participants • Investigational product • Current knowledge of the medical product's safety profile • Endpoints	• FDA emphasizes need for a well-designed and articulated protocol • A poorly designed or ambiguous protocol may introduce systemic errors that can render a clinical trial unreliable despite rigorous monitoring

Main Take Home Messages



- Study plans all feed from your QbD approach, risk assessment, and management processes
- And of course, assessment and management processes are iterative
- Errors that involve critical trial data or participant safety should be identified and corrected as early as possible (RBM) or avoided all together (QbD/protocol quality-risk assessment)