Risk Management in Clinical Development

Marc Wilenzick, Esq.

Assistant General Counsel
& Chief Compliance Counsel
R&D & Medical, Pfizer

November 2011
Pharma Regulatory & Compliance Congress

Agenda

- The Ecosystem:
  - Sponsors, Investigators, IRBs, Regulators, Patients, Payors
- Quality & Compliance Risk Areas
  - GxP; CAPAs
  - Financial/Payment: FCPA, HCP Payments, MMSEA
  - Outsourcing
  - Out of scope: risks of technical and/or regulatory success
- Enterprise & Process Risk Management
  - Process Owners
  - iqRAMP
- Study Level Risk Management
  - IQMP

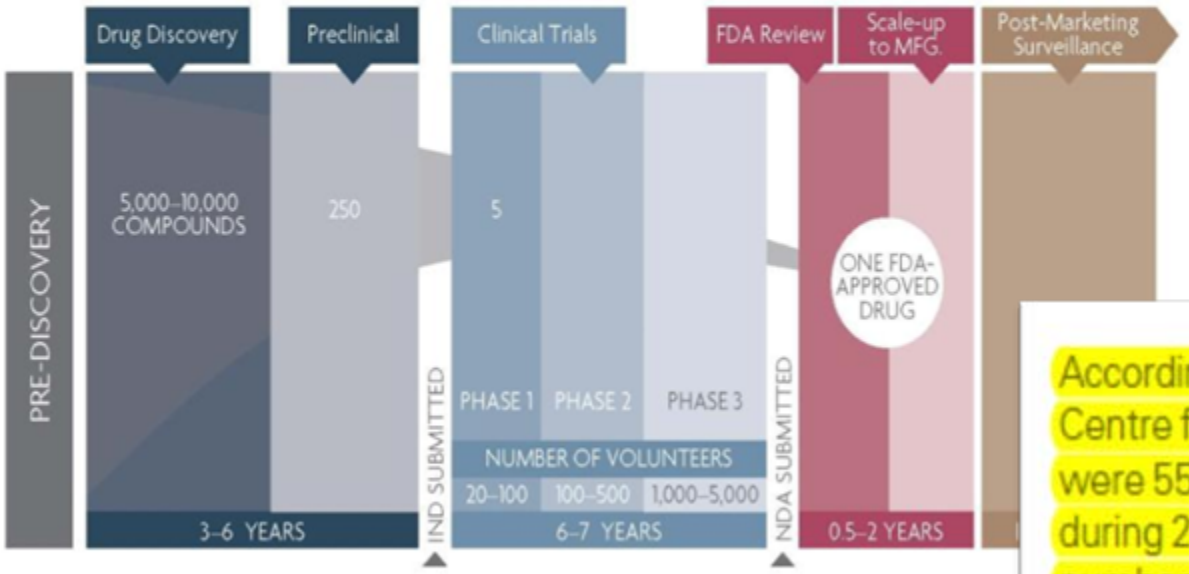
Background/Overview

- Last year, >150 interventional trials initiated; over 400 ongoing
- Almost ½ studies are multi-national; >7,000 sites (>3,000 sites in the U.S.)
- >60,000 monitoring visits/year
- >500 GCP/PV audits/year
- >1,000 IRBs/ECs reviewed studies for us; about ⅓ of studies use an AAHRPP-accredited IRB/EC
- Bringing an alliance partner model on line, in lieu of a functional service model or a traditional CRO model

Ecosystem

The Research and Development Process

Developing a new medicine takes an average of 10–15 years.

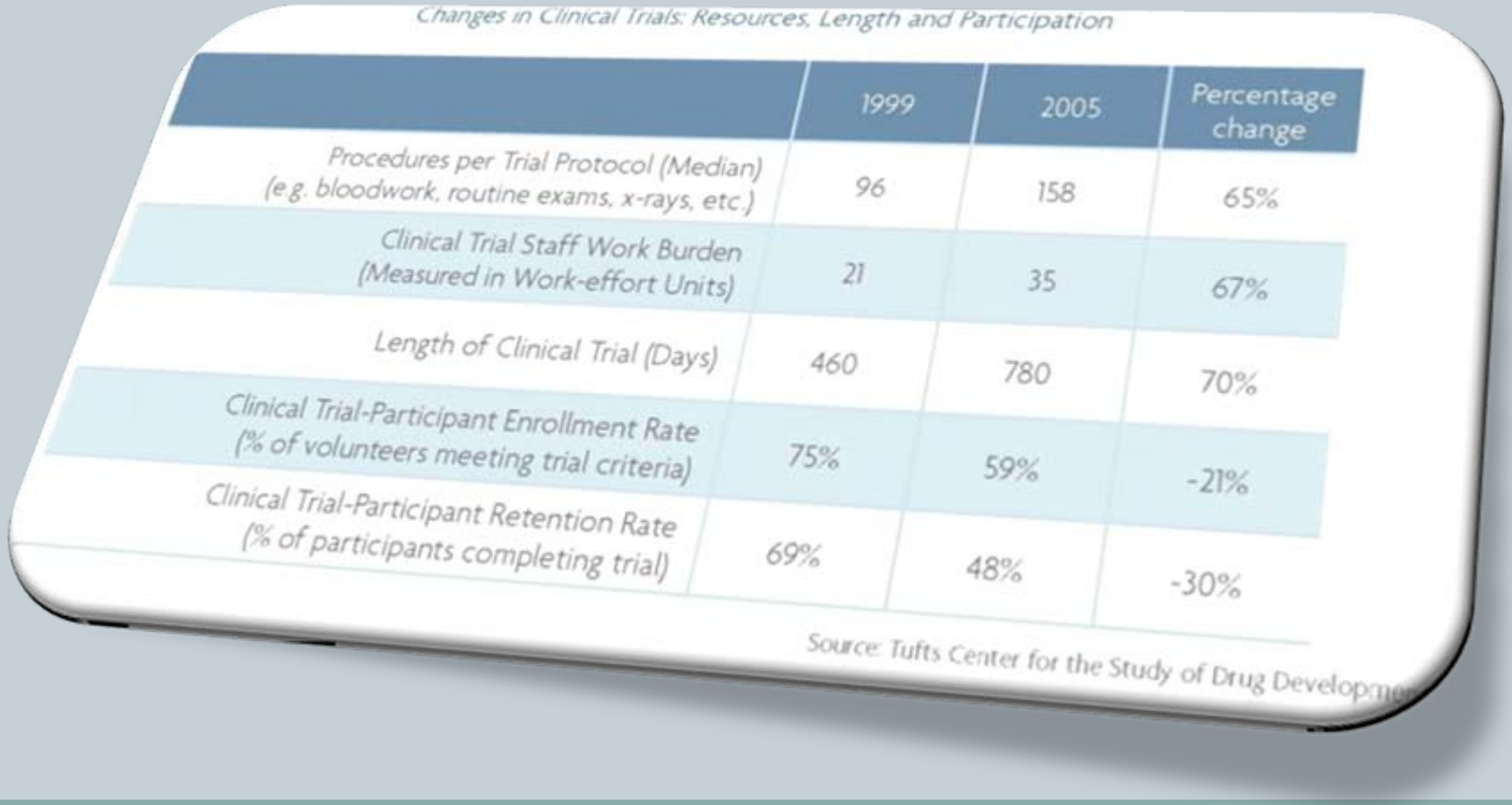


According to a recent report from the Centre for Medicines Research there were 55 phase III drug terminations during 2008-2010, more than double the number of terminations during 2005 – 2007; and in addition the number of drugs entering phase III clinical trials fell by 55 per cent in 2010[8]. We see a growing trend

KPMG *Future Pharma* Report (Oct. 2011)

Ecosystem

5



Changes in Clinical Trials: Resources, Length and Participation

	1999	2005	Percentage change
Procedures per Trial Protocol (Median) (e.g. bloodwork, routine exams, x-rays, etc.)	96	158	65%
Clinical Trial Staff Work Burden (Measured in Work-effort Units)	21	35	67%
Length of Clinical Trial (Days)	460	780	70%
Clinical Trial-Participant Enrollment Rate (% of volunteers meeting trial criteria)	75%	59%	-21%
Clinical Trial-Participant Retention Rate (% of participants completing trial)	69%	48%	-30%

Source: Tufts Center for the Study of Drug Development

Agenda

- The Ecosystem:
- Quality & Compliance Risk Areas
- Enterprise & Process Risk Management
- Study Level Risk Management

Agenda

- The Ecosystem:
- Quality & Compliance Risk Areas
- Enterprise & Process Risk Management
- Study Level Risk Management

- *GxP; Regulatory;*
- *CAPAs*
- *Outsourcing*
- *Other such as* FCPA, MMSEA, and payment controls

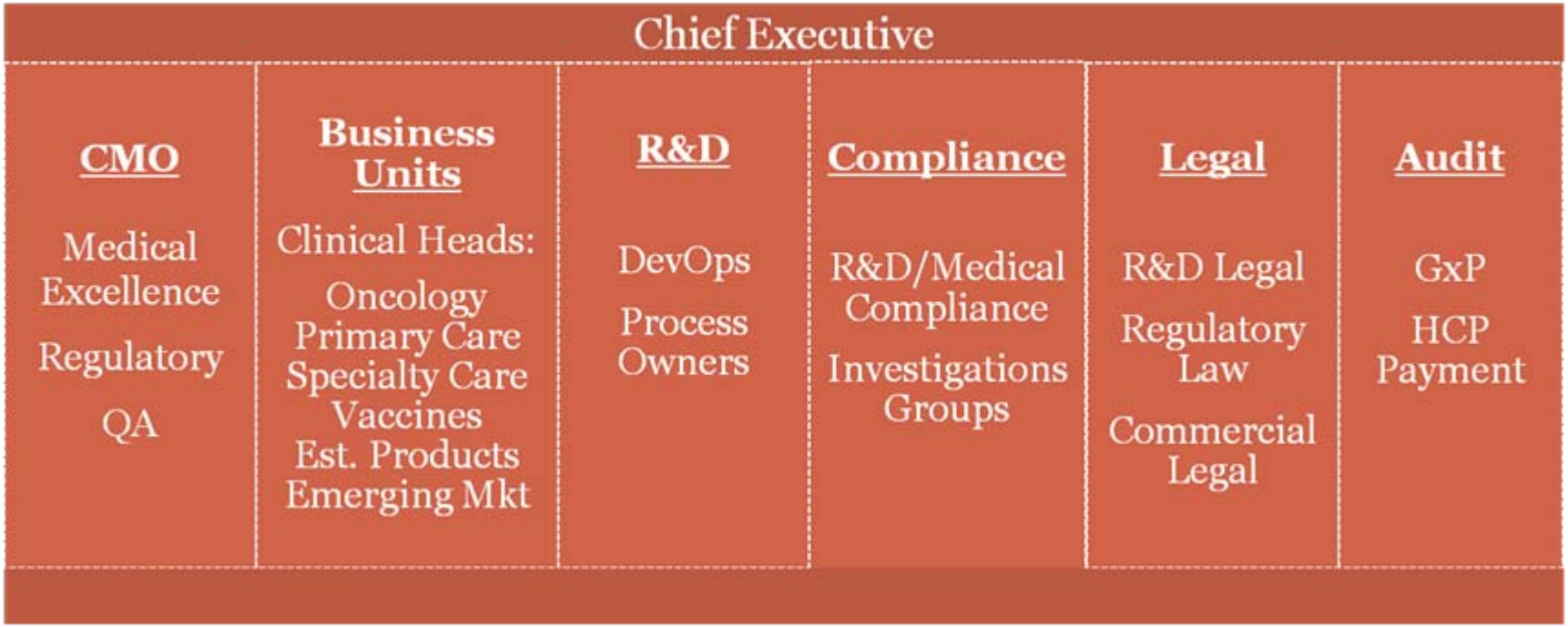
Agenda

- The Ecosystem
- Quality & Compliance Risks
- Enterprise & Process Risk Management
- Study Level Risk Management

Enterprise Compliance Assessment

- What Components make up the Compliance Program
  - Is this likely to be effective?
  - Anything missing?
  - Can and how do we measure that?
- Can and have we assessed the existing and emerging risks and risk mitigation efforts
- Do we have clear accountabilities and governance established
- Do we have clear standards for issue escalation

Risk Management Groups

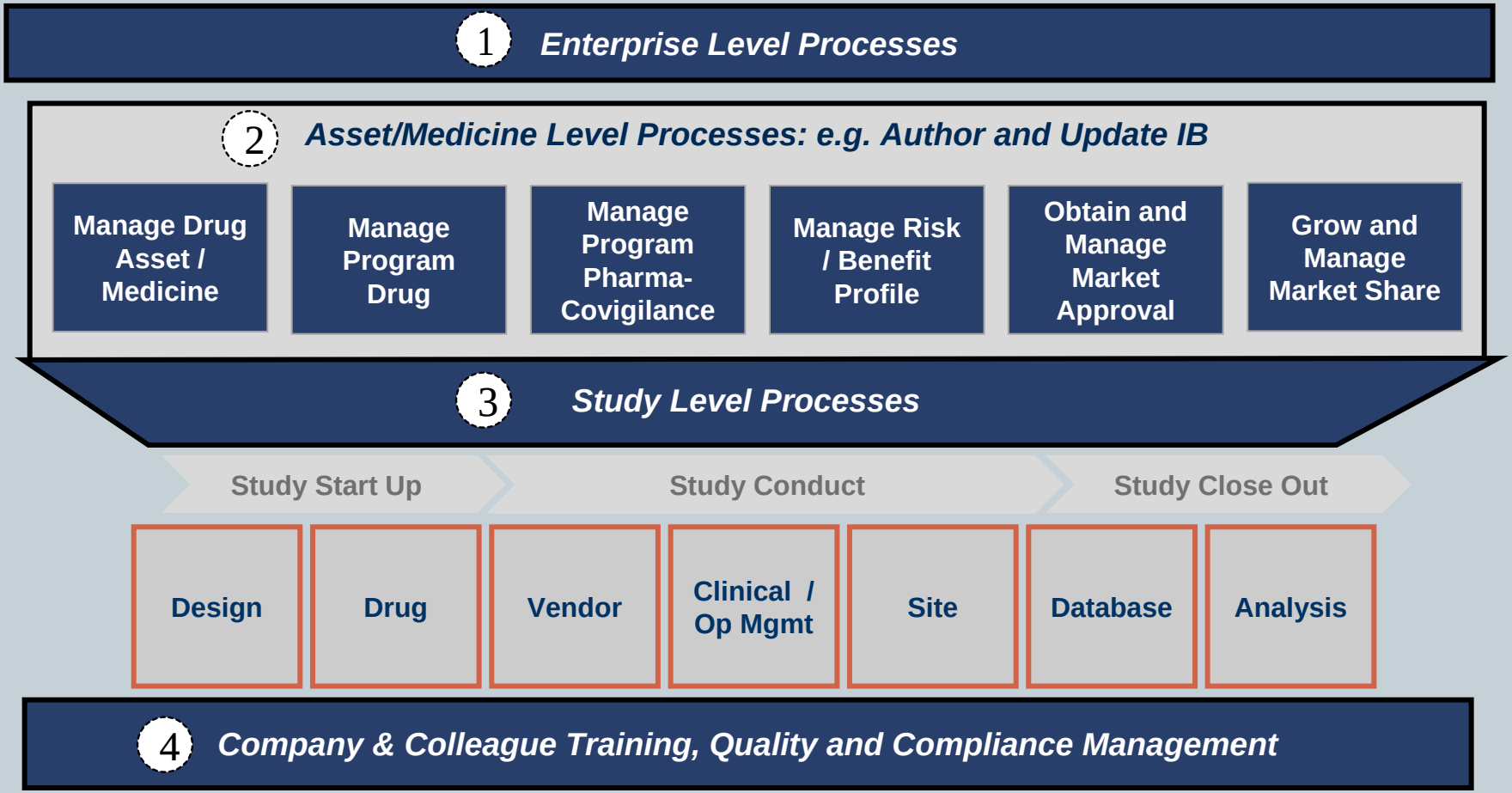


Quality & Compliance Points of Accountability

Process Owner Network

- An approach to ensuring/establishing/maintaining single points of accountability, transcending organizational boundaries, who can manage the core quality and compliance processes
  - The Accountable Owners are supported by and connected to the critical SMEs from Legal, Compliance, Clinical and others.
  - The Accountable Owners are fully responsible for overseeing process control (enabled by robust metrics, reporting and monitoring)
  - The Accountable Owners use/follow structured mechanisms to identify process issues that can affect quality and compliance
  - The Accountable Owners drive outcomes for performance and improvement of processes

Process Owner Network



Enterprise-level risks: iqRAMP

- "XXX… should consider expanding the IQMP model to address enterprise-level risks inherent to clinical trial conduct in a regulated environment. XXX's Risk Assessment and Mitigation Plan program developed for its sales and marketing operations might inform development of a standard risk assessment tool applicable across clinical development programs. This standard tool could be supplemented by study-specific assessments such as the one presented in the IQMP."

- What information would/should an enterprise-level risk assessment tool collect?

iqRAMP

- Process to capture and assess both:
  - Inherent Risks – those which may exist regardless of execution effectiveness (e.g., protocol/design issues, trial location, etc.)
  - Execution Risks – risks related to Pfizer's compliance control environment (e.g., policy, training, oversight, etc.)

iqRAMP

Examples of Key Risks:

- Number of exclusion criteria?
- Are subjects required to be taken off their background medications prior to or during the study?
- Does the study involve a significant departure from the established standard of care?
- Is investigator discretion permitted in decisions related to: inclusion/exclusion, dosing, or measurement?
- Are subjects allowed to take multiple concomitant medications during the study?
- Novel or unprecedented study design involved?

Agenda

- The Ecosystem
- Quality & Compliance Risk Areas
  - GxP; CAPAs
  - Financial/Payment: FCPA, HCP Payments, MMSEA
  - Outsourcing
  - Out of scope: risks of technical and/or regulatory success
- Enterprise & Process Risk Management
- Study Level Risk Management

Integrated Quality Management Plan

- A recommendation from the CTTI initiative (October 2010) that an "Integrated Quality Management Plan" could be developed in parallel with protocol to help drive quality and compliance
- Emphasis to be on prospective identification and mitigation of risks rather than in-depth monitoring (so-called "quality by design")
- Use prospectively defined metrics to monitor effectiveness of mitigation plans
- We are running a pilot program with FDA/CDER/DSI for an IQMP involving a phase III program.

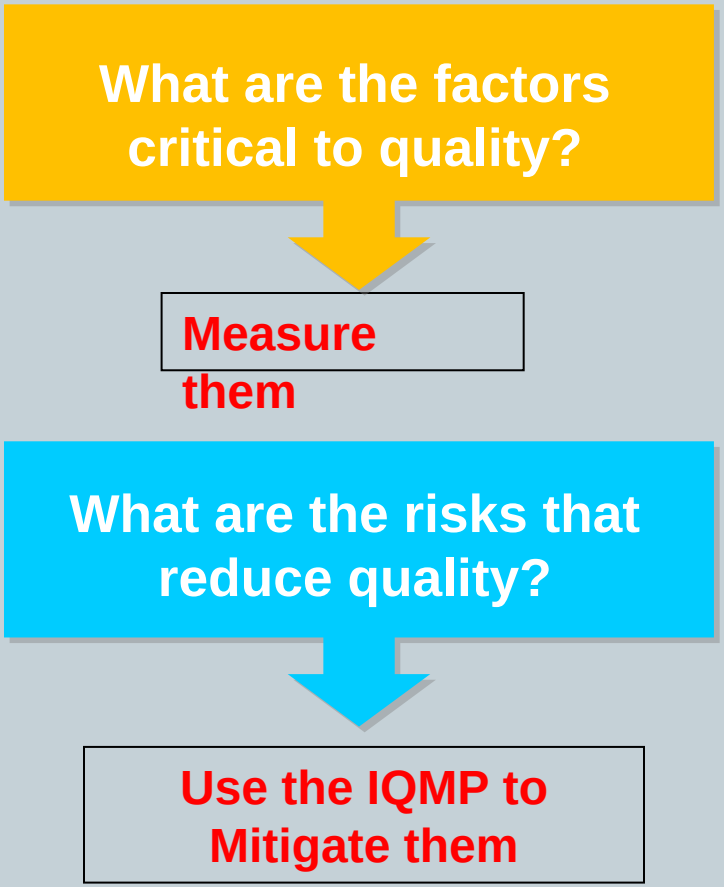
IQMP

- Determine the factors that are critical to quality ("CTQ"s)
- Use a risk-based approach to determine where quality should be improved (i.e., where does quality matter?)
- *Build in, rather than trying to ensure quality post-hoc, through audit*
- Develop a "closed loop system" to manage quality/compliance, including a feedback mechanism to check that the mitigation plans are working, and to modify the risk factors and plans if necessary
- Example: SAE Reporting
  - **CTQ Requirement:** SAEs are reported from Site to Sponsor in a timely manner
  - **Metric:** Number of SAEs not reported from Site to Sponsor within 24 hours
  - **Target Value**: 0
  - **Threshold** at which action is taken: >0

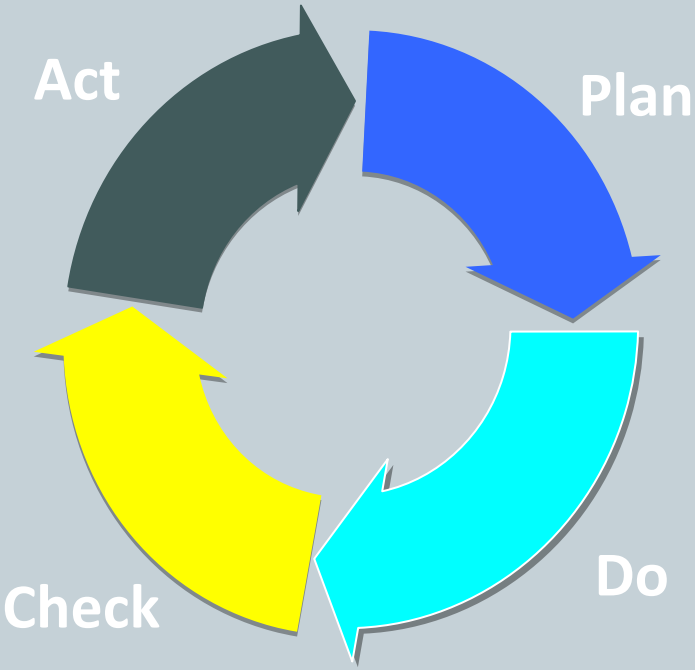
IQMP - Process Overview

- A semi-quantitative/qualitative snapshot assessment of risk areas (relating to patient safety, data quality/integrity, and protocol compliance) in ongoing clinical trials based on core IQMP CTQs and associated metrics
- Process: We ask "*For each CTQ metric, which of the following responses best fits your study*?".
  - 0 = CTQ/metric is not applicable
  - 1 = No issues observed or expected
  - 2 = No issues observed but recognize that cannot measure
  - **3 = Issues observed but mitigation plan in place**
  - **4 = Issues observed but no mitigation plan in place at this time**
- For areas where issues have been experienced (e.g. responses of 3 or 4), teams will capture a summary of the mitigation plans that have been or will be put in place to improve quality

Applying CTQ Factors



Close (Quality Management) Loop



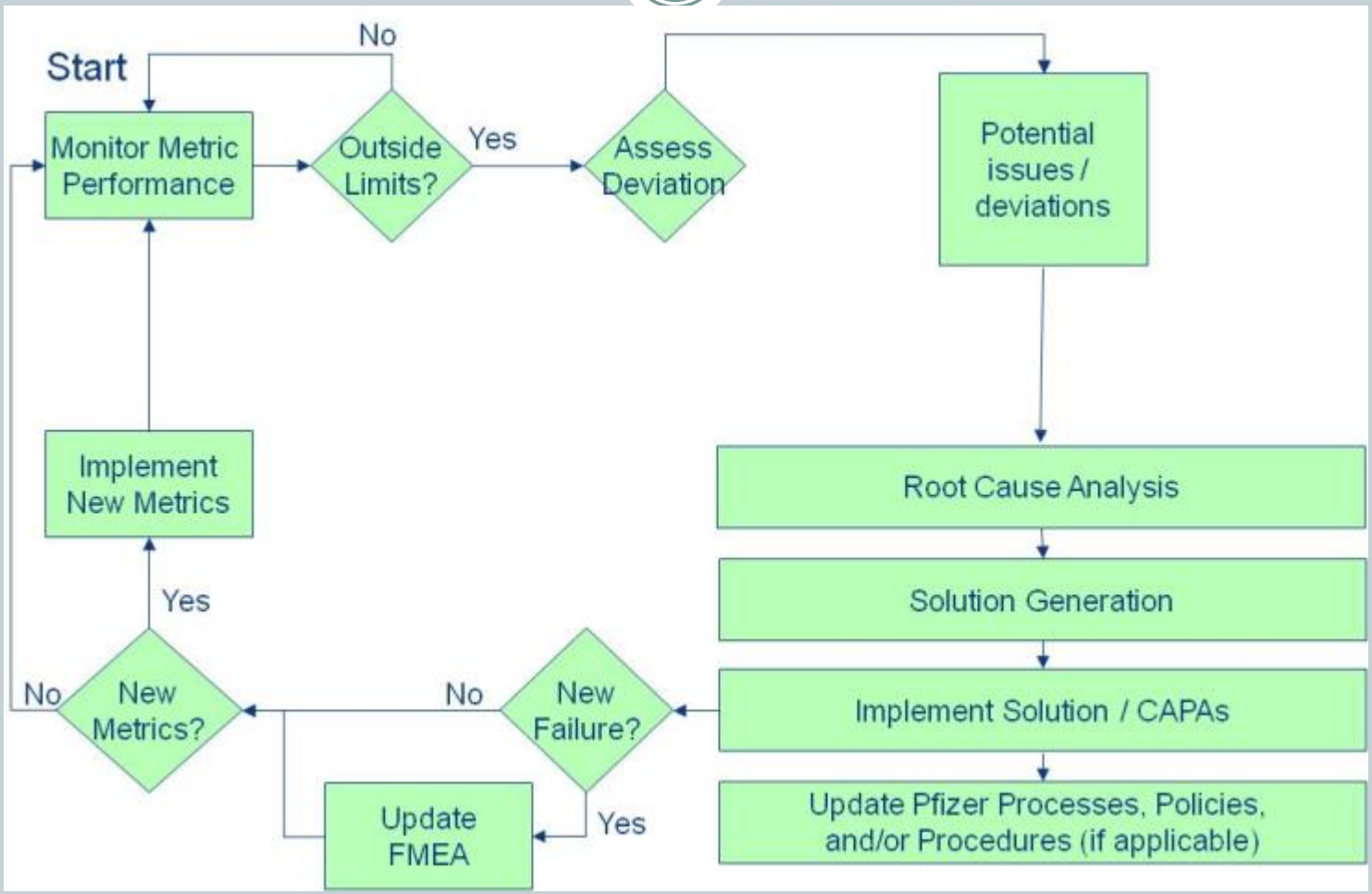
1 **Plan.** Identify factors critical to quality (CTQ). Perform risk assessments and mitigate these

2 **Do …** start the Clinical Trial

3 **Check.** Use CTQs and risk metrics to monitor performance

4 **Act.** Perform root cause analysis, take corrective and preventitive actions

Closed-Loop Quality Control Process



Quality System: The CHECK-ACT Phase

- During the conduct of the clinical trial, the IQMP sets forth a framework for monitoring the metrics on a regular basis to ensure quality and compliance
  - If quality and compliance is found to have crossed specification limits, then appropriate actions will be taken to remediate the issue
  - The quality system needs to also ensure that actions are built back into the standard processes (“continuous improvement”)
  - The quality system also needs to maintain vigilance to ensure that the actions have had the desired effect on quality and compliance

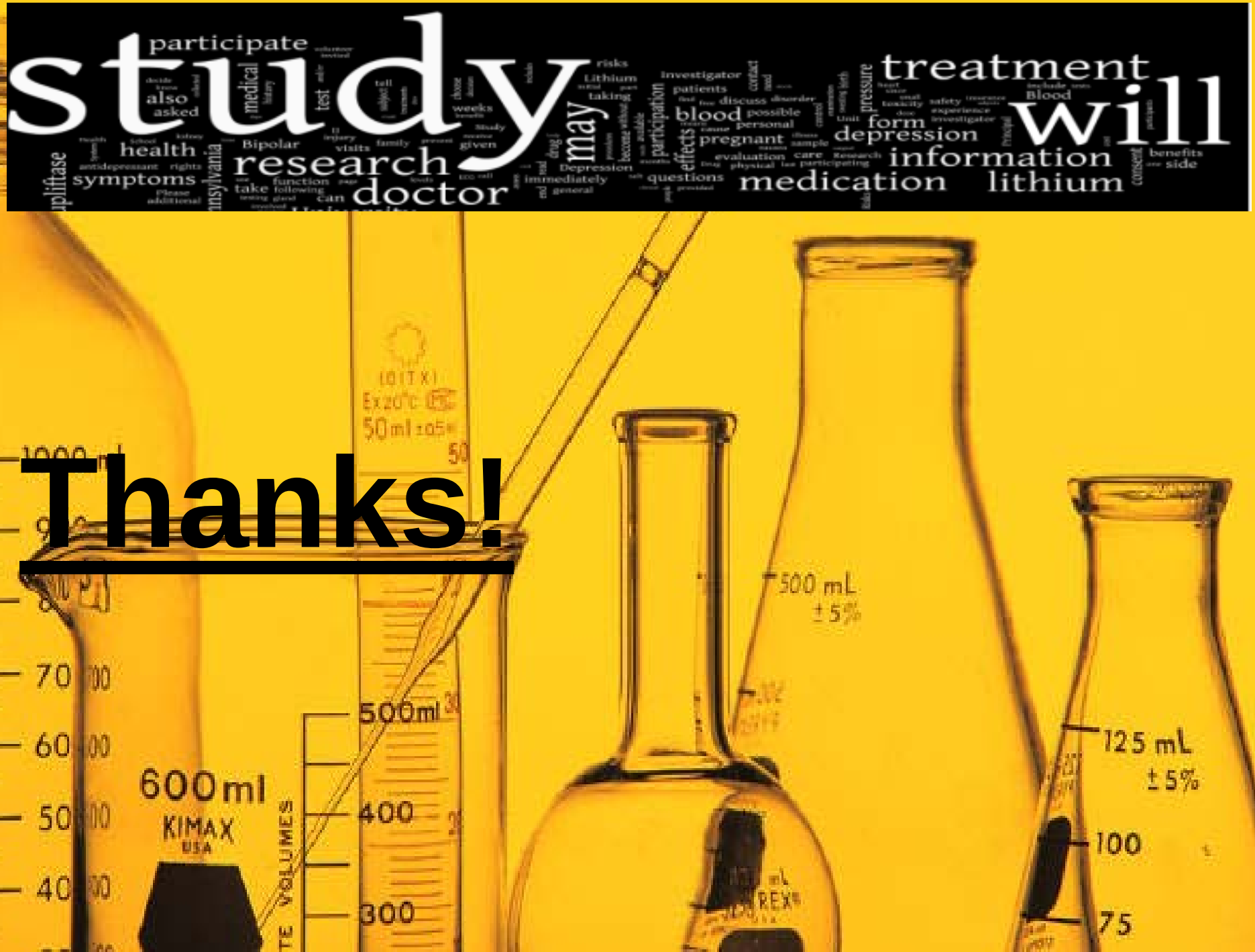
The Future is Here…

Guidance for Industry
Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

FDA (August 2011)

No single approach to monitoring is appropriate or necessary for every clinical trial. FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would include a mix of centralized and on-site monitoring practices. The monitoring plan should identify the various methods intended to be used and the rationale for their use (see section IV.D for recommendations on the components of a monitoring plan).[30]

sponsor to a CRO and require the CRO to comply with the regulations.[37] Although sponsors can transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the work completed by the CRO(s) who assume this responsibility.


study
participate
treatment
will
research
doctor
medication
information
lithium
depression
blood
pregnant
health
symptoms
may
Thanks!
600ml
KIMAX
USA
500ml
400
300
500 mL
±5%
125 mL
±5%
100
75