BUILDING QUALITY INTO CLINICAL TRIALS TO PROACTIVELY IDENTIFY & MITIGATE RISK

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Agenda

- Understand the definition and purpose of quality by design
- Determine how to apply a quality-by-design approach to clinical risk management
- Examine case studies of fundamental failures that would have been prevented with a quality-by-design approach
- Outline proactive measures to perform in real time to avoid retrospective reactions following audits

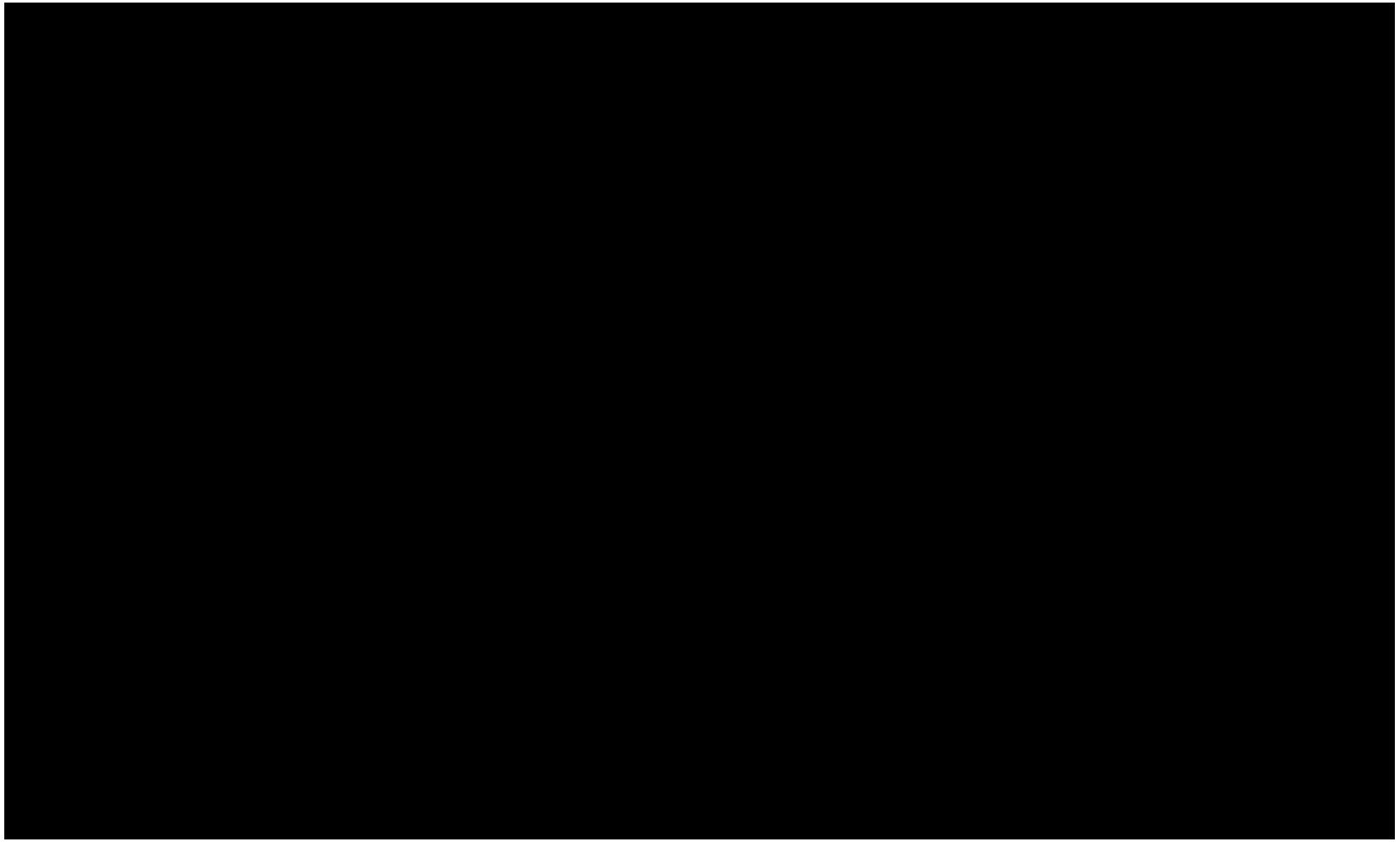
DISCLAIMER

- The views and opinions addressed in this presentation are those of the presenters only; these are not the views of Merck & Co., Inc.

HOPE

Is NOT a STRATEGY

Hope is NOT a Strategy



Let's Consider Other Industries

What We Do is Complex

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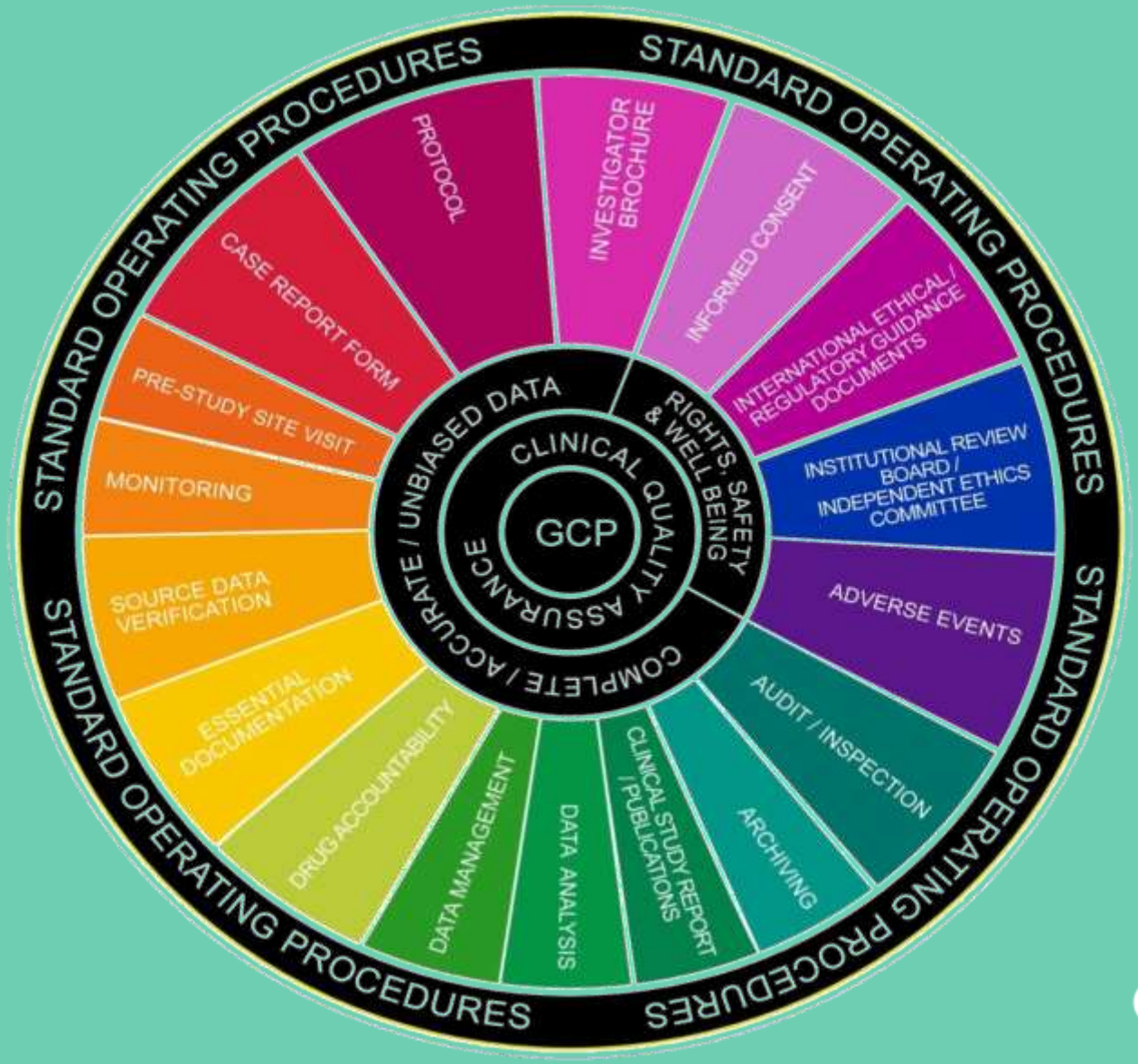
There are So Many Tasks in Clinical Trials



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How Do We Detect Problems?

Reactive Quality

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Key Concept

You can’t “AUDIT” quality into a product

Quality by Design (QbD) builds quality into a process rather than ensuring quality of a product or service through audits or inspections

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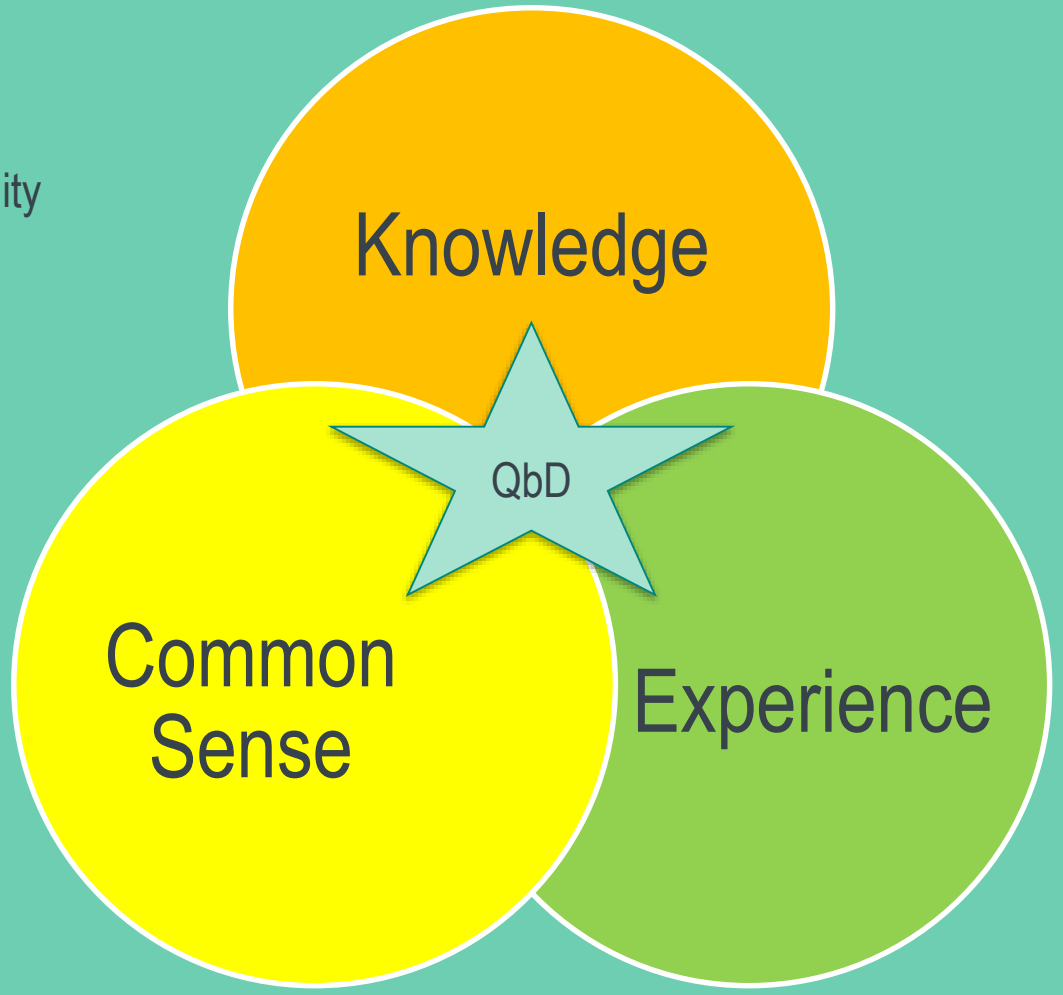
What is Quality by Design (QbD)?

Proactive Quality



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We Can Get Things Right by Knowing Where Things Can go Wrong

People - unqualified, inexperienced, incompetent, or poorly trained

Process – flawed, unclear/ambiguous, or sub-optimal

Systems / Tools – unvalidated, poor design, not fit-for-purpose, non-intuitive

You can have a perfect process but unqualified people performing it = potential failure

You can have stellar employees but a poor process = potential failure

You can have a highly qualified team and an efficient process but flawed technology = potential failure

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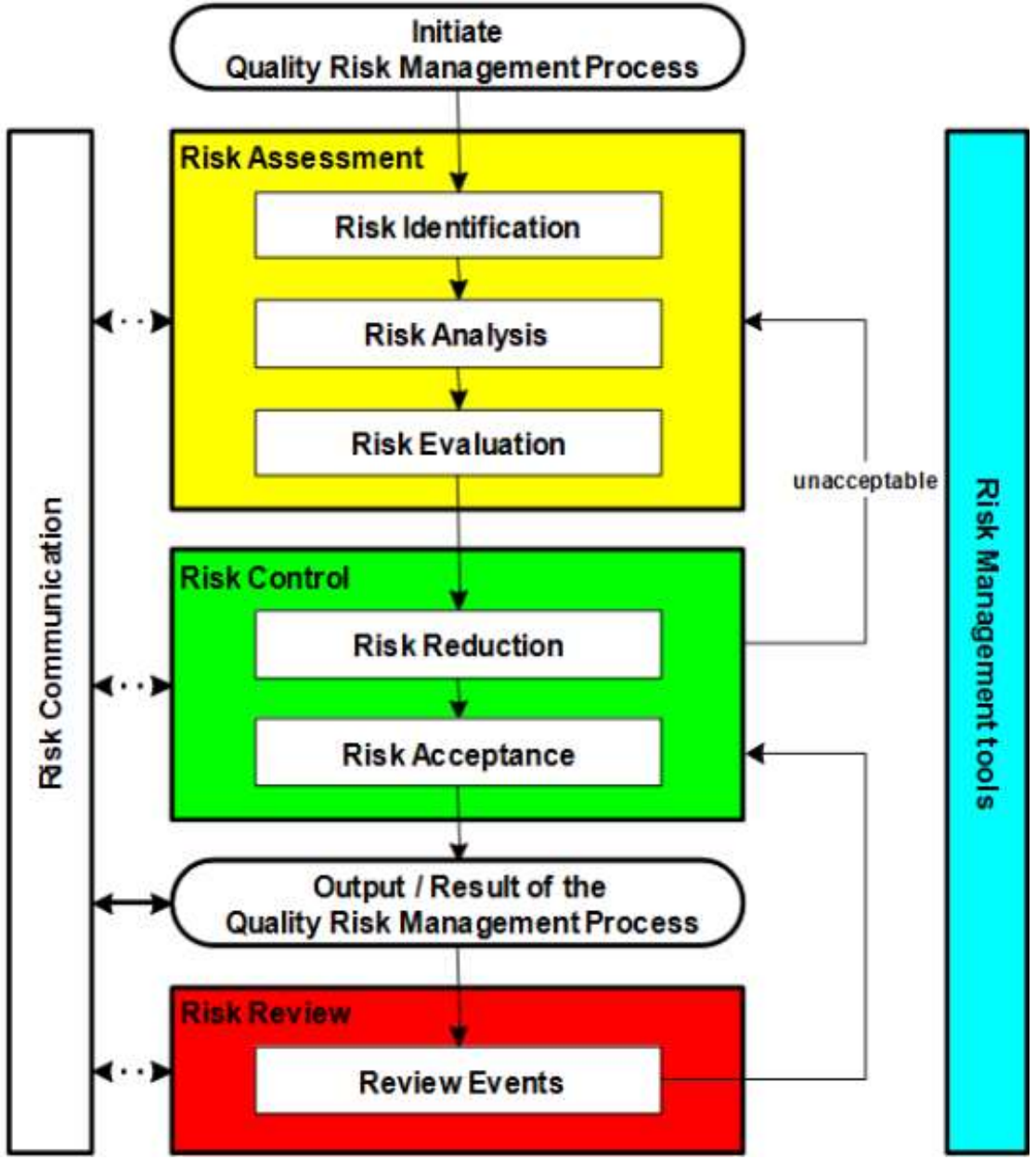
ICH Q9 Quality Risk Management Process Diagram



Learning From Failures

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Randomization Schedule Disaster #1

- Full Service CRO hired to create the Randomization Schedule
  - Midway into Pivotal Trial, a Data Manager emailed the full randomization schedule to the entire study team

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What Went Wrong

- Data Manager attached the wrong file; he intended to attach a data transfer agreement that needed review & approval
- CROs' SOP on Randomization Schedule did **NOT** require the file to be password protected
- CROs' SOP did **NOT** require the file to be stored in a firewalled / limited access area

QbD

- Identify Randomization Schedule as "high risk" document, SOP should mandate
  - Password protection of the file & file stored in a firewalled / controlled access area
- Process could require 2 person sign off to ensure compliance with these requirements OR
- QA strategy should include random checks to verify adherence
- Dual approval when intending to release the randomization schedule; avoids misunderstandings

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Randomization Schedule Disaster #2

- Full Service CRO hired to create randomization schedule & manage IxRS
  - After IxRS UAT was complete, no one replaced the DUMMY codes with the ACTUAL codes; patients were not randomized correctly

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What Went Wrong

- The usual time pressure to “go-live”
- The CROs’ SOPs allowed use of prior study randomization codes to serve as DUMMY codes (i.e., looked like valid randomization codes)
- The CROs’ SOPs did not have a “standards” checklist and did not require multiple sign-offs to review and approve release of system

QbD

- Identify IVRS as a “high risk” system
- Process could require 2 person sign off to ensure correct randomization schedule and/or stratification programming are in place prior to go-live
- Ensure “dummy” codes **look different** than actual randomization codes; for example, use different leading digits
- QA strategy should include random checks to verify adherence

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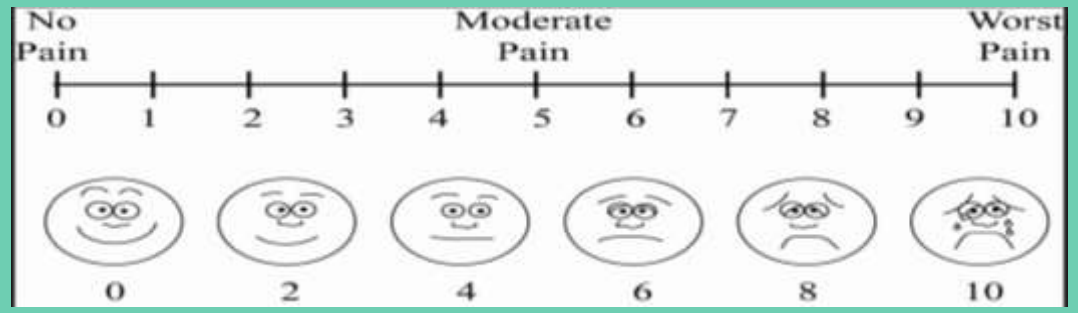
The Case of the “Missing” Primary Endpoints



- Top ePRO provider contracted to collect the primary endpoint (pain rating scale)
- 200 evaluable patients were needed for analysis
- Pain scale completed post surgical procedure (times 0, 5 min, 30 min, 2 hours and 6 hours)
- Study charts contained notations by site personnel that the ePRO devices appeared to “malfunction” during use

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What Went Wrong?

- ePRO provider denied there were device malfunctions without further investigation
- ePRO provider was not tracking number of actual vs anticipated entries
- After issue was escalated through numerous layers of management, it was revealed that 30% of the scores were missing, resulting in the need to increase enrollment
  - ultimately resulting in loss of time & significant budget increase

QbD

- Identify primary endpoint as a “high risk” element of the trial
- Collect and review “real time” metrics on actual vs anticipated scores captured
- Perform periodic review of “help desk” inquiries from patients / site personnel; any concerning signals?
- Proactively ask sites/patients about their experience using the technology in the trial

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The Global Document “Version” Catastrophe

- Full Service CRO was hired to run a global trial in 30 countries
- Five countries had not received the 3rd protocol amendment nor the latest 2 versions of the Informed Consent Form which contained significant new safety information

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What Went Wrong?

- A trial manager responsible for 5 Eastern European countries went out on an unanticipated medical leave
- The under-resourced CRO did not find a replacement for 2 months
- There was no centralized monitoring of protocol signature pages or IRB approvals to detect the breakdown in communication

QbD

- Identify the breakdown in distribution of documents, such as protocol amendments / revised informed consent forms (ICFs), in a global trial as a potential risk; this is a “hand-off” where distribution can break down
- Collect and review real time metrics on actual vs anticipated ethics committee approvals to track risk at country level
- Collect informed consent data in eCRF to track implementation of multiple ICFs at subject level

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Case of the Delayed Interim Analysis

- A planned interim analysis was delayed 2 months due to the following issues:
  - Database reconciliation with the ECG, ePRO, IxRS and Lab vendors had not occurred
    - Numerous queries had to be issued and reconciled
  - PIs had not been trained on the EDC and thus could not sign off on the CRF
  - PIs had not been trained on the IxRS

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What Went Wrong?

- Data Management personnel had not adhered to the data management plan due to being "under-resourced"
- Site Activation checklist did not identify training requirements for EDC or IxRS
- Pressure to "go-live" and to hit "First Patient In (FPI)" deadlines resulted in corners being cut
- 8 out of 20 PIs had not been trained on IxRS and EDC
  - Representing a Safety Risk to Patients
  - Delay to resolving data inconsistencies

QbD

- Identify lack of data reconciliation and training of sites as a potential risks
- Request weekly / monthly status reports on reconciliation of data between all sources
- Collect and review metrics on actual vs anticipated # of PIs trained

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The Case of the Rogue Reg Docs

- Full Service CRO hired to handle all aspects of the trial, including Regulatory
- 1572s, CVs, IRB approvals and all other documents were collected according to the Reg Doc checklist & filed in eTMF
- 1572s and PI CVs were **NEVER** submitted to the FDA
  - 30 sites received drug in violation of 21CFRpart 312

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What Went Wrong

- An inexperienced employee assigned responsibility for regulatory doc processing
- The regulatory document checklist did not contain instructions to submit the 1572s & PI CVs to Regulatory Affairs within 30 days of collection / site activation
- No supervision of the process / employee by CRO management

QbD

- Identify inexperienced team members as a risk; ensure there is routine supervision
- Ensure SOPs have clear instructions for hand-offs / fail-safes built in
- Request weekly / monthly status reports on regulatory filings
- Random sampling as part of QA auditing strategy

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Drug Accountability Disaster

- Full service CRO was hired to handle all aspects of the trial including designing the process and documentation for study drug accountability (gel in a tube)
  - The drug accountability forms did not prompt / require calculation of compliance
  - Scales provided to sites could not measure to a decimal appropriate for performing accurate drug accountability

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What Went Wrong

- The CRO did not familiarize themselves with the investigational product
- Budget pressures prompted the ordering of inadequate scales
- Inexperienced personnel were left responsible for designing the drug accountability process and forms
  - Starting weight of gel tubes was not collected
  - Retrospective calculations revealed 20% of patients had used an incorrect dose
    - Risk to safety and efficacy

QbD

- Consider adding operational feasibility to drug packaging SOPs to ensure awareness; have necessary stability data to provide study drug in the most convenient form for patients
- Discuss packaging options with sites and patients; accommodate their needs
- Minimize the amount of “overage” given to patients to reduce potential for overdoses
- Simulate the drug accountability experience to ensure it is feasible / accurate
- Perform a “study audit” prior to go-live or perform site audits early

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General QbD Recommendations

- Perform risk analyses of processes AND protocols; where are the weak and/or complicated points
  - Are there inclusion/exclusion criteria that require a specific degree of evidence?
  - Are you taking sites out of routine “standard of care”?; if so, ensure you provide clear guidance
  - Are you working in an “in-patient” environment where personnel not associated with study team will be evaluating patients?
- Identify processes where there are “hand offs” and ensure there are “fail safes” built in to prevent breakdowns
- Build performing “simulations” into your routine business practices; this takes the written word into practice
  - visualize where things are unclear or where hand-offs / breakdowns may occur so you can improve processes and instructions

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General QbD Recommendations

- Ensure metrics are designed to pick up breakdowns in critical tasks, early
  - Examples:
    - # of actual primary endpoints vs expected/anticipated
    - # of lab samples received vs processed/analyzed
    - # of actual IRB approvals of revised consents vs expected/anticipated
- Add the “study audit” to your routine set of audit types
  - Large return on investment – early detection and may reduce # of site audits
  - Evaluates both procedures and performance
- Bid-defense meetings and/or study kick-off meetings should not be a “dog and pony” show
  - Jump into how you will “operationalize” the specific trial at hand

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Consequences of Poor Design & Operations

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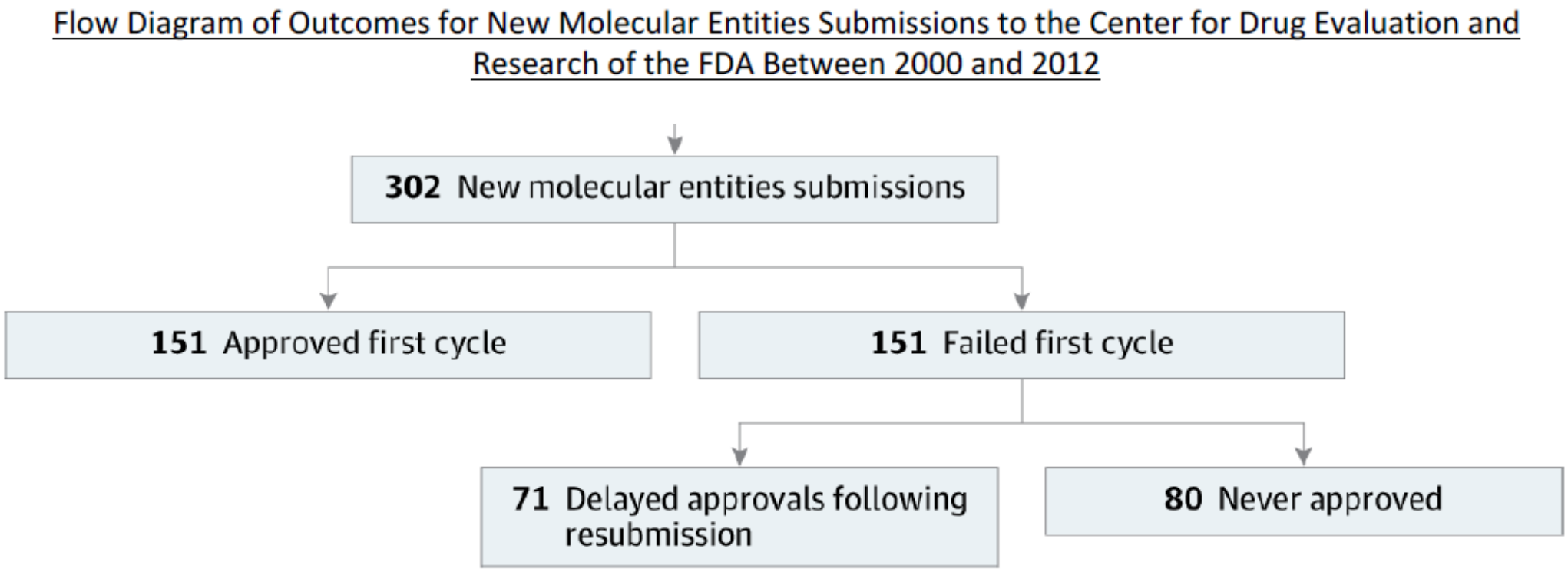
Regulatory Filings – Approved / Failed



Source: http://jama.jamanetwork.com/article.aspx?articleid=1817795

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Regulatory Filings – Impact of Poor Quality

	First-Cycle Review Failures (n = 151)
Population	
Population not appropriate to reflect intended use	11 (7.3)
Size of population too small to demonstrate efficacy	4 (2.6)
Intervention	
Uncertainty/disagreement about appropriate dose	24 (15.9)
Inability to define noninferiority margin[b]	9 (6)
Confounding by concomitant medication	8 (5.3)
End point	
Unsatisfactory	20 (13.2)
Study conduct	
Missing data	3 (2.0)
Data integrity	8 (5.3)
Study outcome	
Inconsistent results for multiple end points	20 (13.2)
Inconsistent results in different trials or at different study sites	17 (11.3)
Inadequate efficacy compared with standard of care	20 (13.2)

- 32% of first-cycle submission failures due to quality-related issues
  - 53% of first-cycle failures **never** approved
  - 47% eventually approved – median delay of **14 months**

=> **16%** of total FDA submissions severely impacted by quality issues

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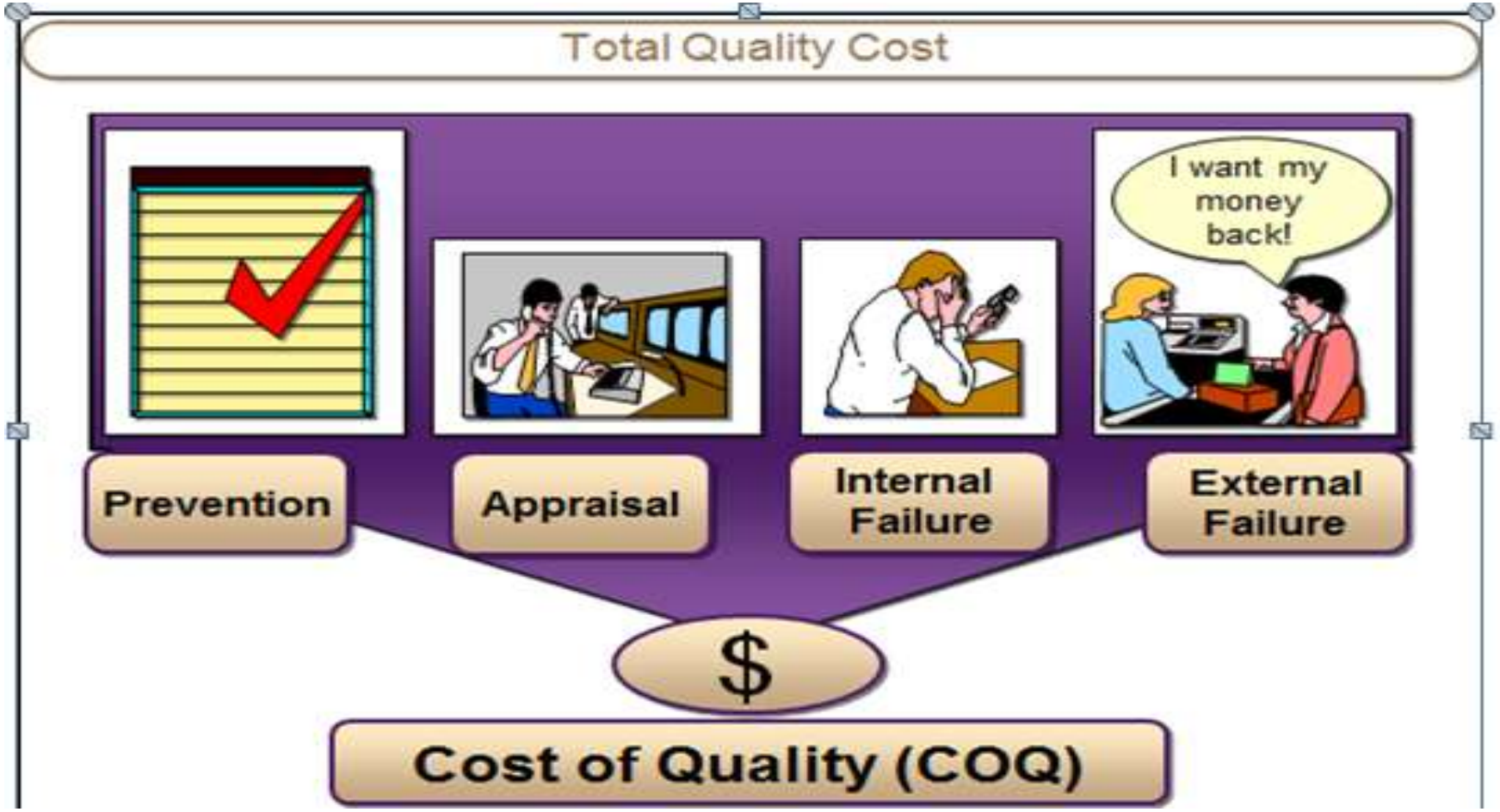
Cost of Quality



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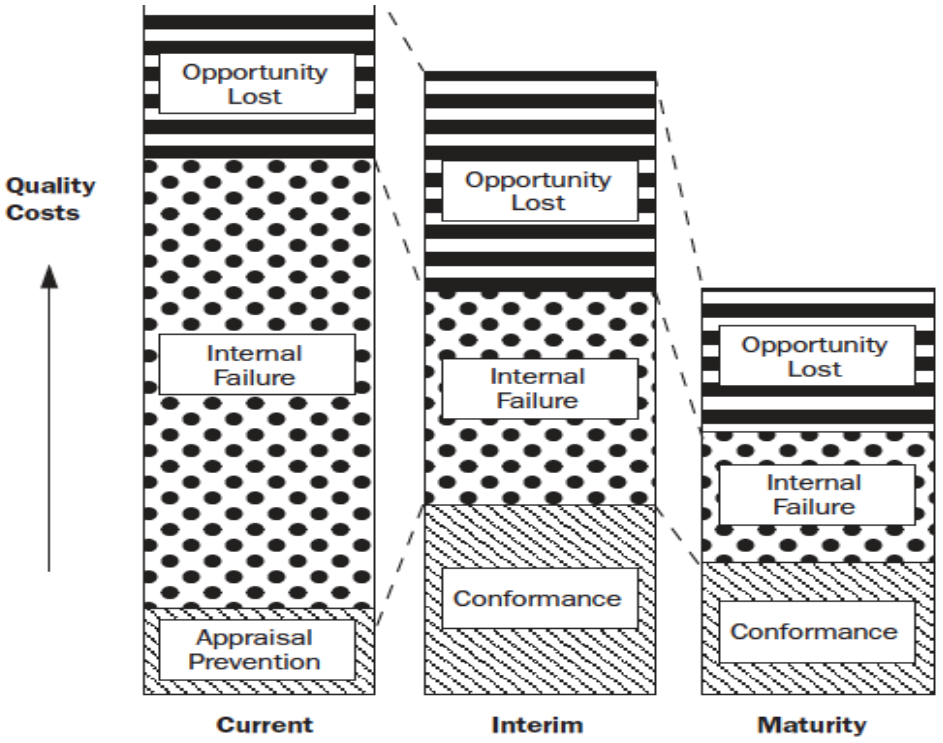
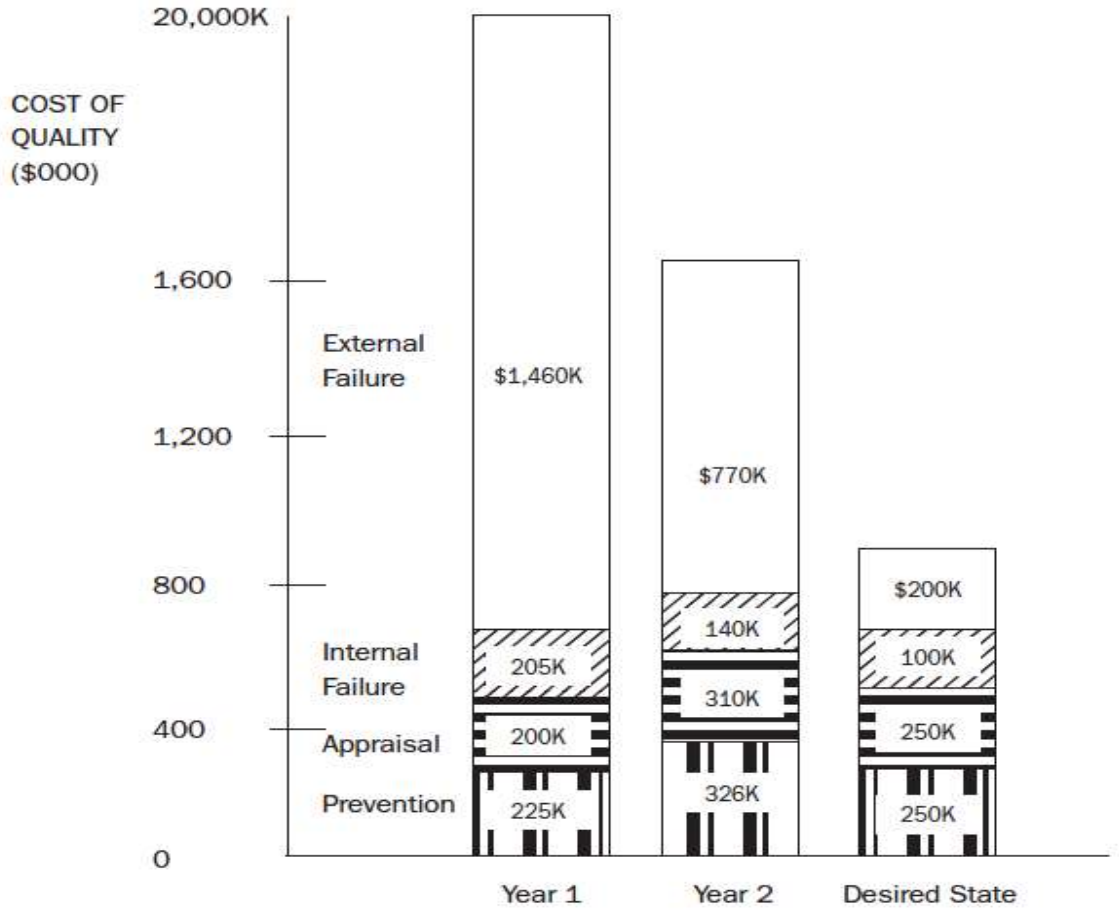
Cost of Quality – Implementing Change After Failure





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Hope Can’t Be a Strategy

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Thank You!!!

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