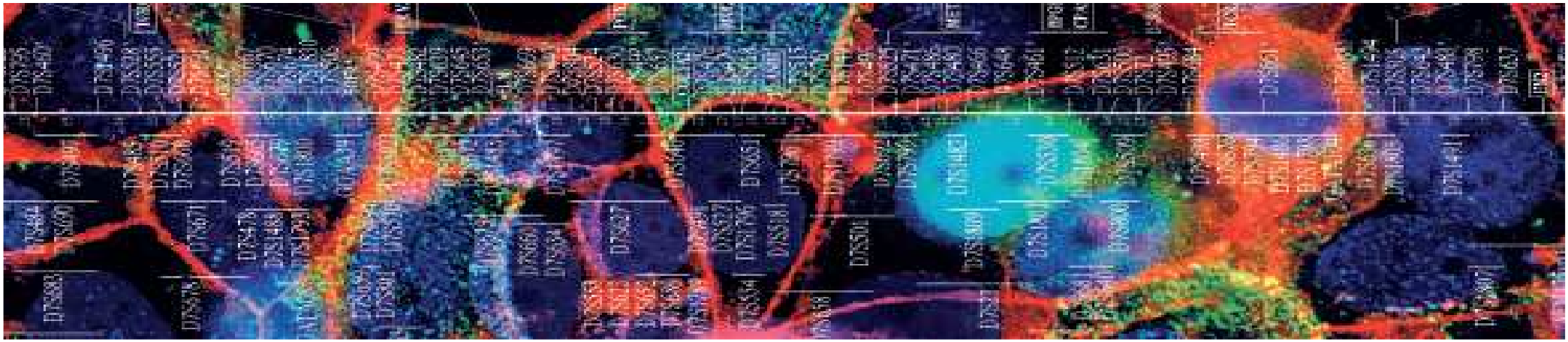
Approaches to Risk-Based Quality Management
Quality by design / Quality Systems

Clinical Trials Transformation Initiative-Sponsored Meeting
Bethesda Marriott Suites
Bethesda, MD

Beat Widler, F. Hoffmann-La Roche
October 13, 2010



The objective of quality management is to ensure safety of patients and integrity of data

Focus

Patient Safety, Rights and Integrity
in all clinical trials and post-marketing activities

Data Integrity
of data created in these clinical trials and post-marketing activities

Diagnostic tools comprise three components: questionnaires, reporting and mitigating action templates

- Diagnostic tools are self surveys which are used for **questionnaire-based risk evaluation of structural elements,** such as processes and organization
- They consist of three components: questionnaires, risk reports and mitigating action templates

- Tailored by Risk Areas and study types
- Structured along different risk assessment categories
- Set-up to ensure quick & convenient report generation

- Data from questionnaires transferred into the respective risk reports
- Allows standardized calculation of risk scores
- Provides signals which allow identification of further optimization potential, e.g. in operations, processes and systems

- Standardized form providing structured guidance throughout the definition process
- Mitigating actions to be defined in case of high risk scores

SQA is intended to allow standardized risk assessments across different study types and guides study teams during risk mitigation

Objectives

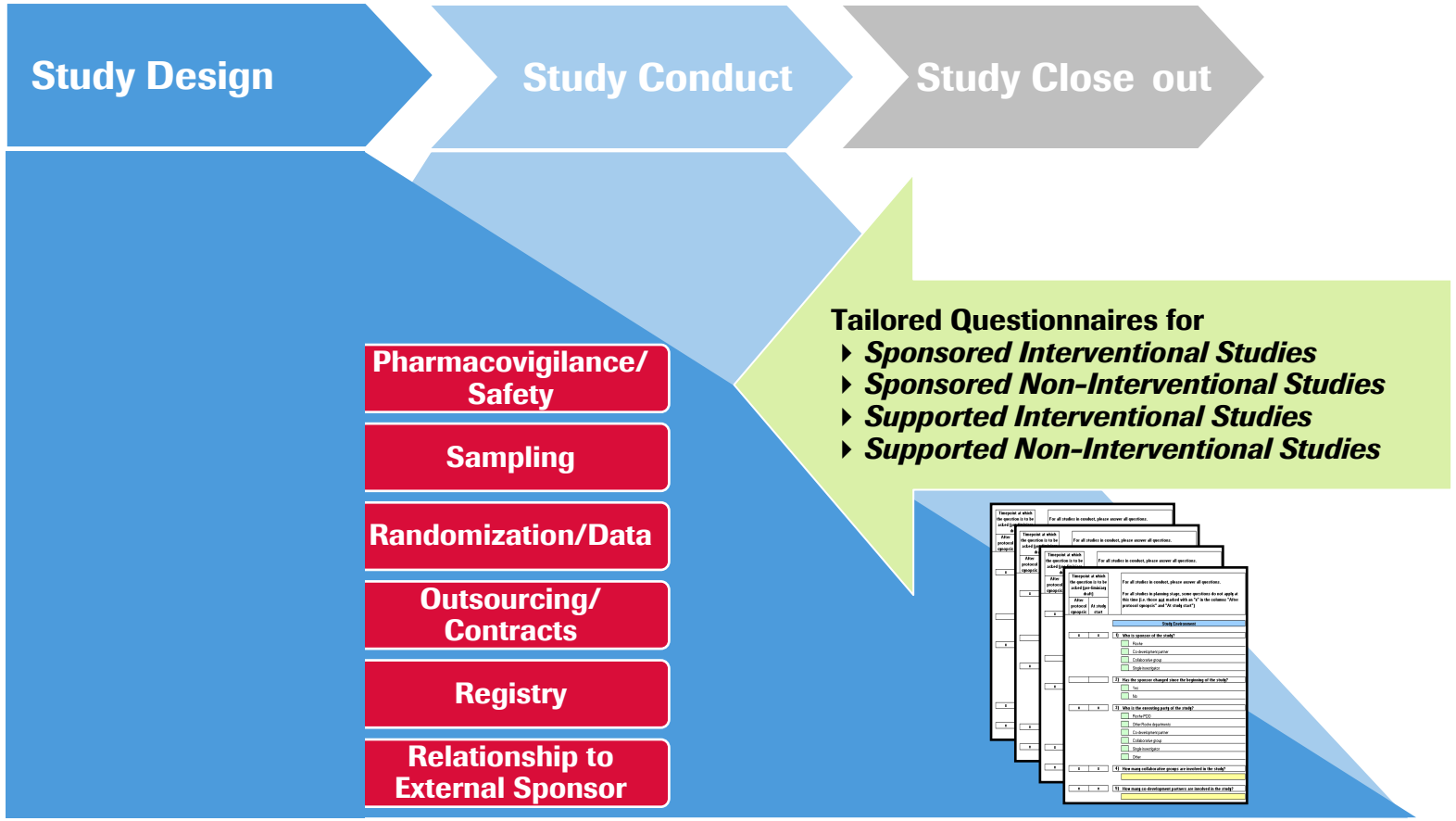
- Support Senior Management and study teams with information on **study set-up based risk levels**
  - Prior to final protocol approval
  - Before FPI and during study conduct
- Provide **standard approach to assess study quality risk** level – allowing comparison across studies
- Offer **guidance to study teams** to mitigate high and medium risk levels

Scope

- SQA conducts risk assessments in first step of study value chain: '**Study Set-up**'
- SQA encompasses **all studies with Roche involvement**
  - PD, GPS, PA, pRED and gRED
  - Phase I-IV (global and local)
  - Sponsored and supported
  - Interventional and non-interventional

The SQA tool covers all key activities of the study design and study conduct phase

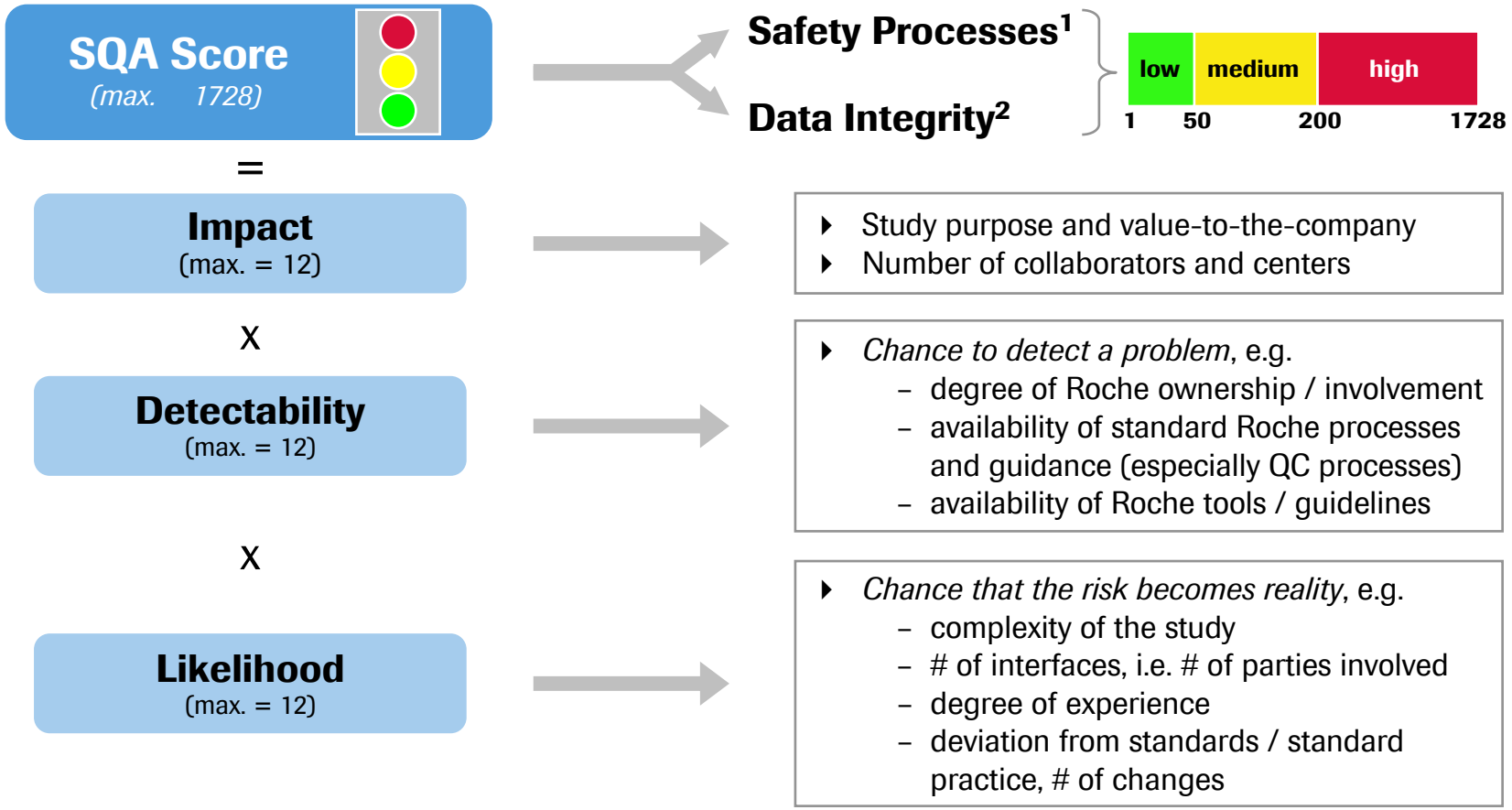
Set-up of SQA Questionnaires



1) Not all of the listed risk assessment categories apply to all different study types

SQA uses a comprehensive and robust calculation logic to evaluate study risks related to *Safety Processes* and *Data Integrity*

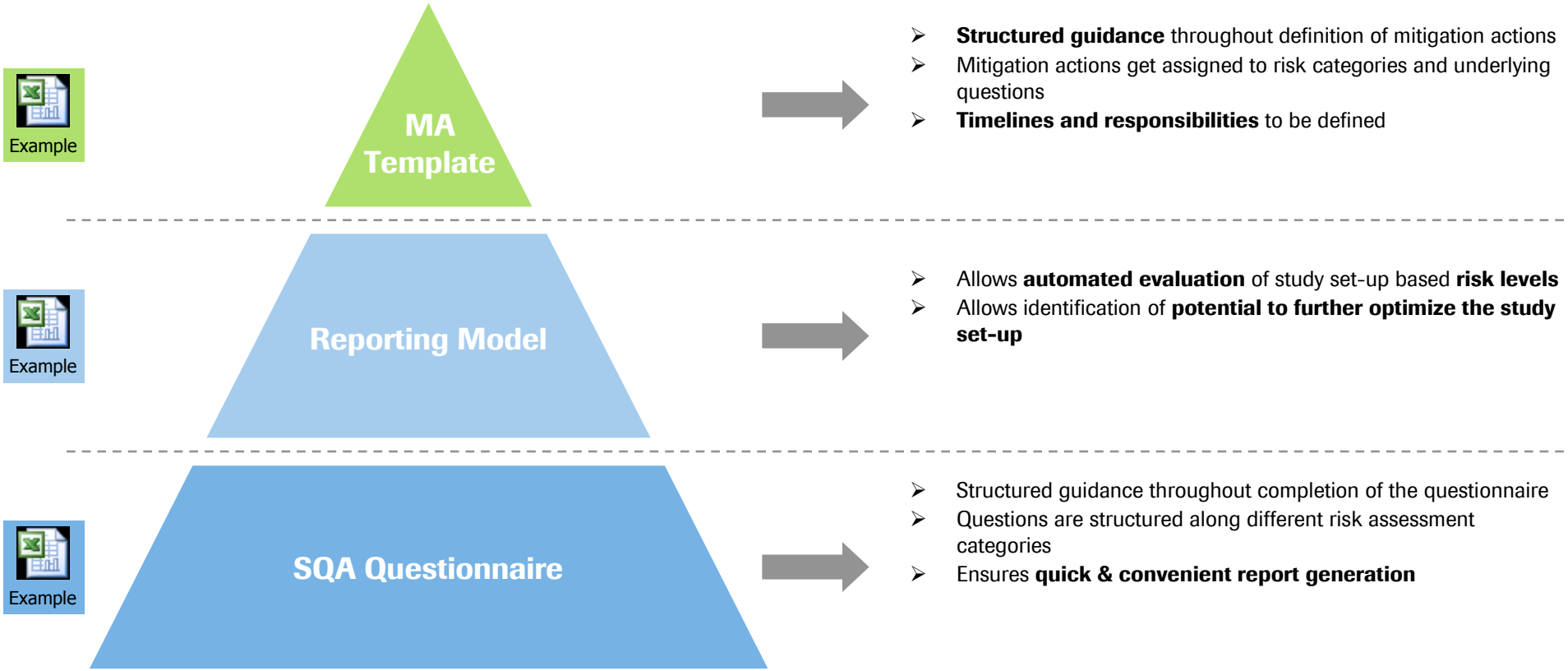
SQA Score Calculation Logic



1) Safety Processes aim to ensure the timely and complete forwarding of Adverse Event notifications stemming from individuals enrolled in clinical trials or exposed to Roche drugs in the market
2) Data Integrity is considered as one of the main risks that is covered by QRM. It is a description for the consistency and utility of efficacy and safety data. Low quality conduct of clinical trials in development or post market surveillance potentially generates a low level of Data Integrity representing a significant source of quality risk

The SQA Tool comprises three components and facilitates reporting and mitigation of study design-based risks

SQA Tool - Overview



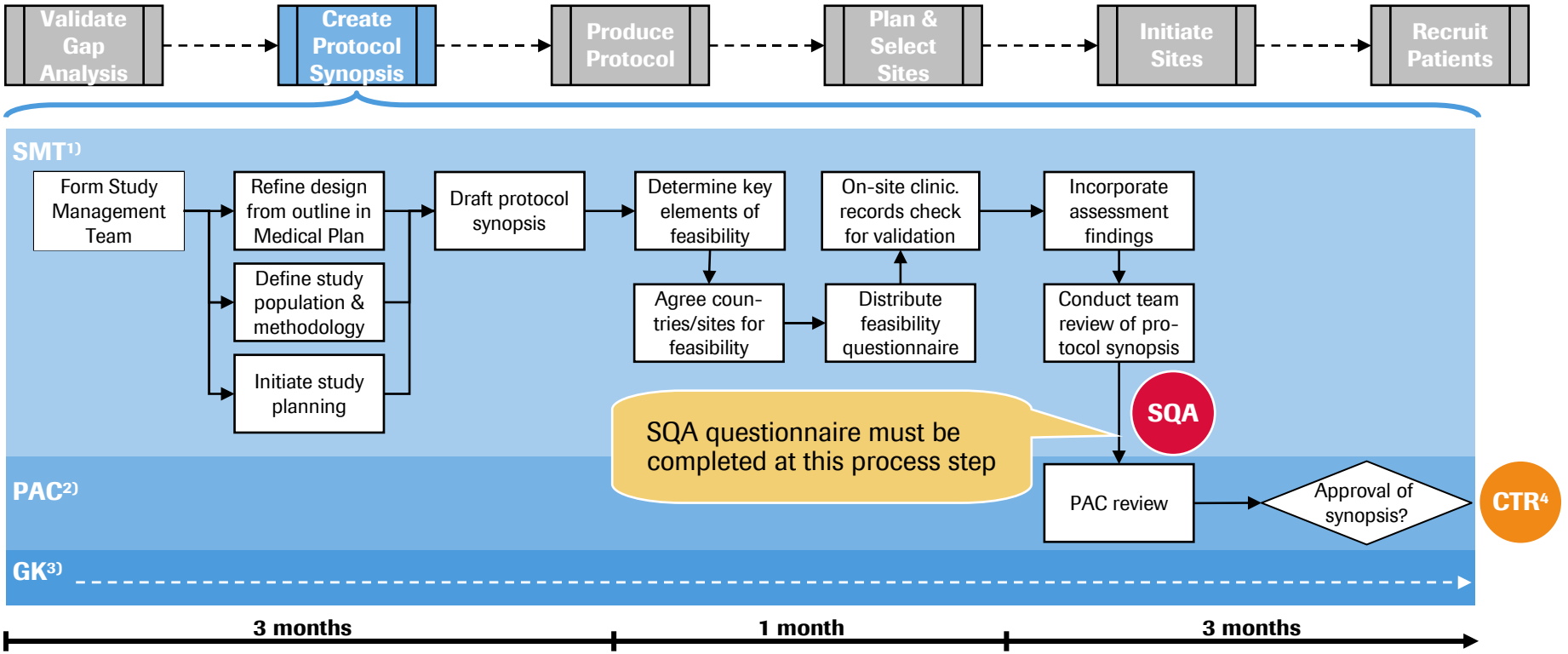
- **Structured guidance** throughout definition of mitigation actions
- Mitigation actions get assigned to risk categories and underlying questions
- **Timelines and responsibilities** to be defined

- Allows **automated evaluation** of study set-up based **risk levels**
- Allows identification of **potential to further optimize the study set-up**

- Structured guidance throughout completion of the questionnaire
- Questions are structured along different risk assessment categories
- Ensures **quick & convenient report generation**

SQA is now in global Phase IV mandatory for protocol approval – ensuring improvement of quality prior to study start

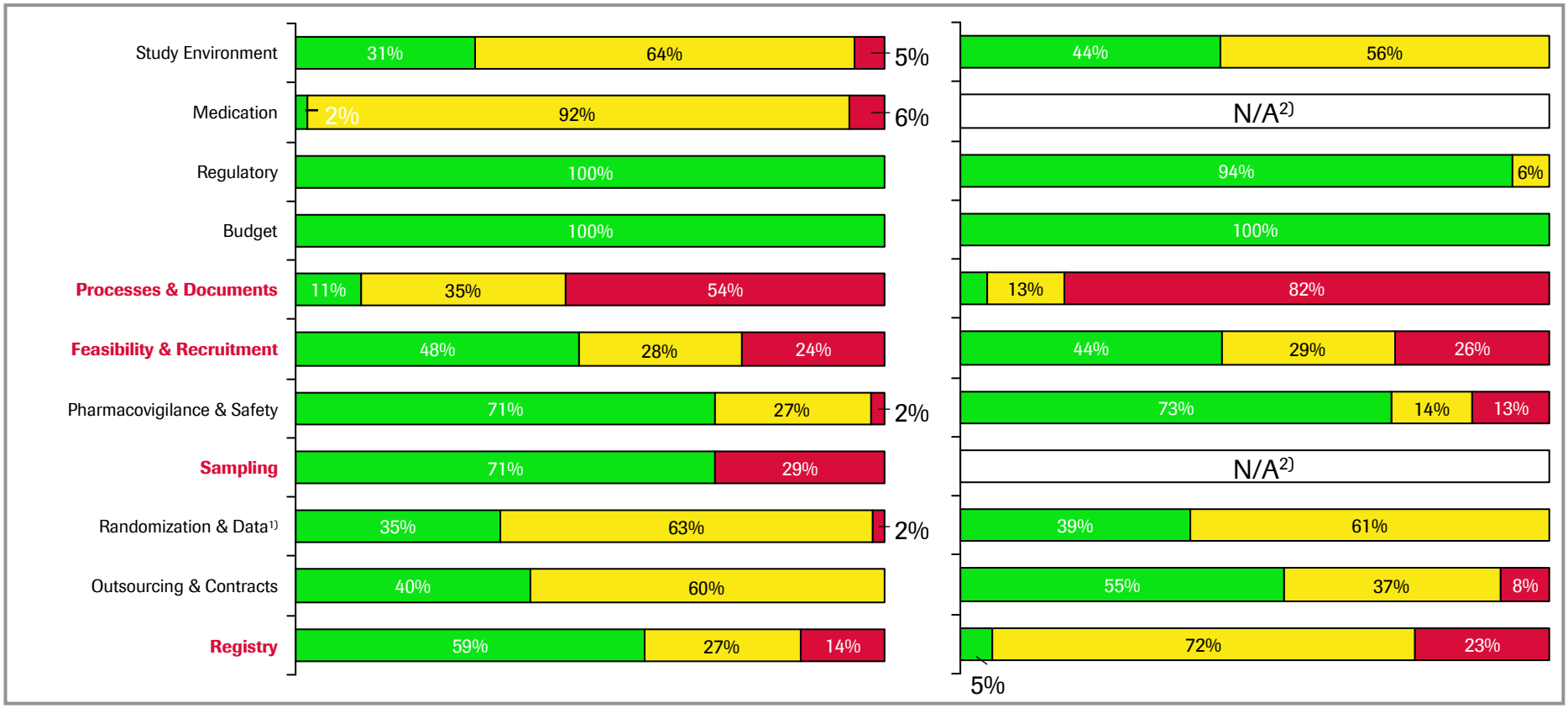
SQA Integration with Protocol Approval Process



Category breakdowns show similar risk distribution in both Interventional and Non-Interventional, with exceptions

Analysis
as of 31st July 2010

SQA Category Risk Level Distribution for Locally Sponsored PA Studies



1) For Non-Interventional studies, this category does not include questions on "Randomization"
2) Not applicable for this study type
Source Initial SQA Roll-out, 2010; Booz & Company analysis

GCP DT assesses infrastructure and clinical trial related capabilities of affiliates across all regions

GCP DT Objectives & Scope

Objectives

- Support local and global Senior Mgmt. to facilitate decisions (e.g. countries' participation in clinical trials) triggered by affiliate:
  - **Infrastructure set-up**
  - **Clinical trial capabilities**
- Provide **standard approach to assess affiliates' GCP compliance** level – allowing comparison across affiliates and regions
- Offer **guidance to local clinical operations** functions to mitigate high and medium risk levels related to GCP compliance

Scope

- GCP DT encompasses **all affiliates** across all regions **with clinical trial activities** conducted by Roche
  - North America
  - Latin America
  - Western Europe
  - CEMAI
  - Asia Pacific
- GCP DT covers **clinical trial activities** within an Affiliate
  - Pharma Development (PD)
  - Global Product Strategy (GPS)
  - Pharma Affiliate (PA)

The GCP DT is set up as a self assessment questionnaire with various risk assessment categories

Set-up of GCP DT Self Assessment Questionnaire

Affiliate Demographics
(Questionnaire Section 1)

Information on number and type of:

- Clinical Trials
- Study Sites
- Patients
- Clinical Trial Staff
- Vendors

Number of questions: 9

Affiliate Infrastructure
(Questionnaire Section 2)

Information on:

- Communication & Support
- IT Systems
- Archiving
- Resource Management
- Training
- Issue Management
- Medical & Safety

Number of questions: 30

Study Management
(Questionnaire Section 3)

Information on:

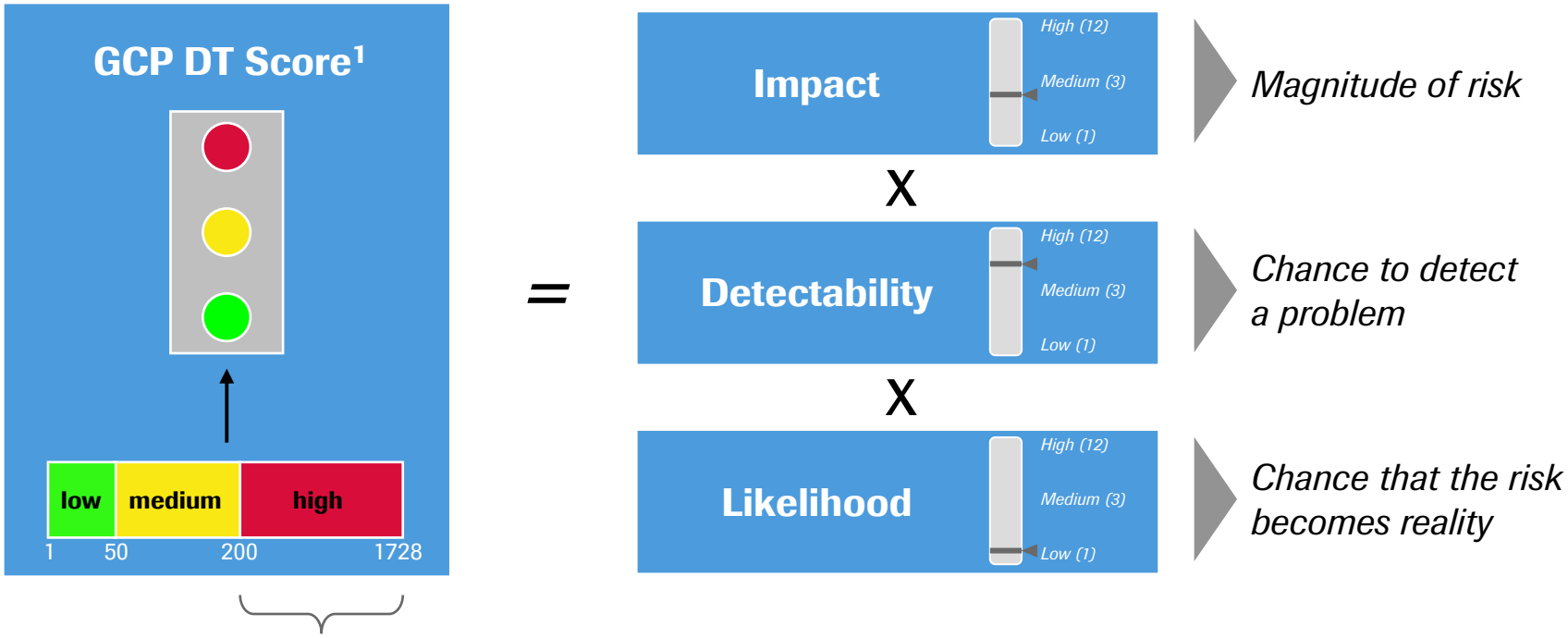
- Study Planning & Conduct
- Outsourcing
- IMP Management
- Monitoring

Number of questions: 22

- The GCP DT Questionnaire needs to be completed on an annual basis by the local 'GCP DT Coordinator'
- In case both local PD and GPS/PA activities are ongoing, the questionnaire needs to be completed individually
- After having completed the questionnaire, reports are generated by PDQ and discussed with the business partners

This data is used to calculate risk scores based on *Impact*, *Detectability* and *Likelihood*; red scores require mitigation

GCP DT Scoring and Mitigation Logic

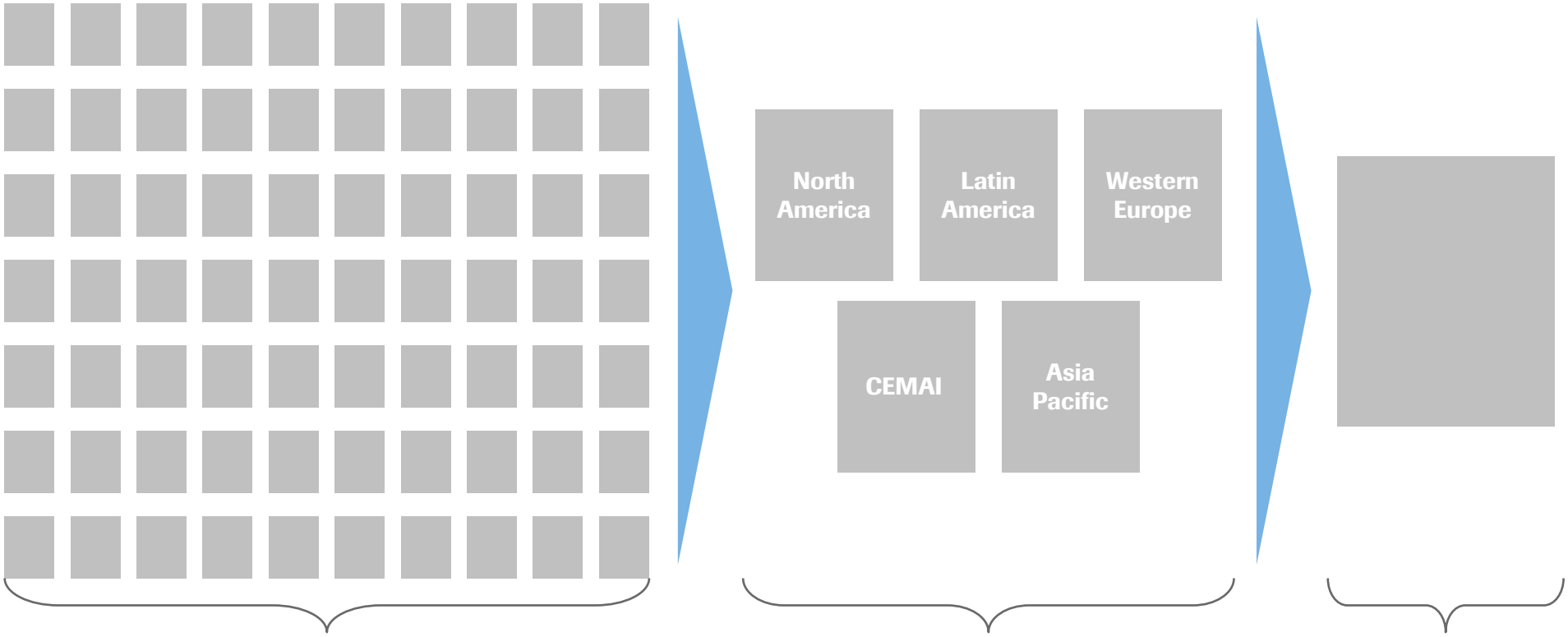


Definition and implementation of Mitigating Actions mandatory

1) Separate GCP DT scores are calculated for Safety Processes and Data Integrity

As a result >70 affiliate-specific GCP DT reports can be generated, which can then be aggregated to create regional and global reports

Overview of GCP DT Reports



Affiliate specific GCP DT reports
Key addressee: Local GCP DT Responsible

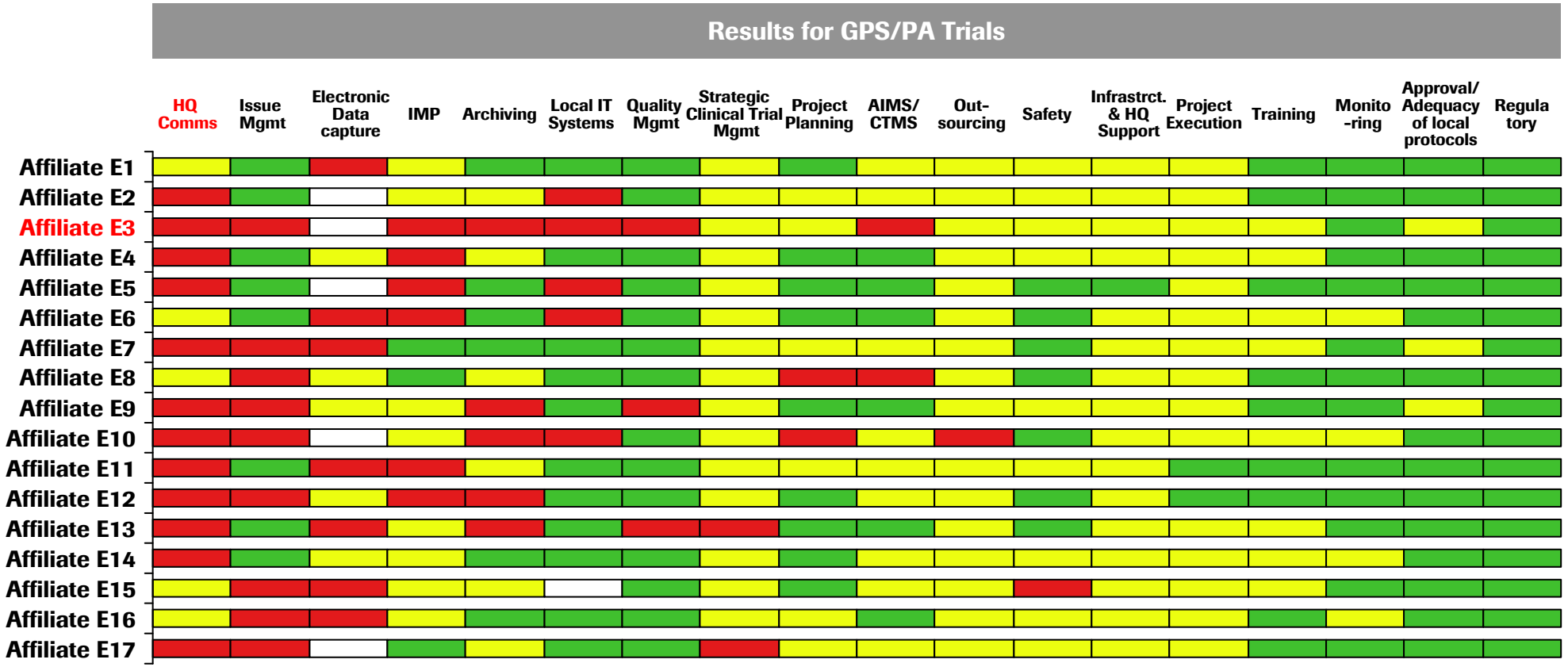
Regional GCP DT reports
Key addressee: Regional Business Heads

Global GCP DT report
Key addressee: P. Soriot

Example: Selected results from regional GCP DT report

EXAMPLE FROM PREVIOUS VERSION

GCP DT Regional Report – Previous GCP DT Version

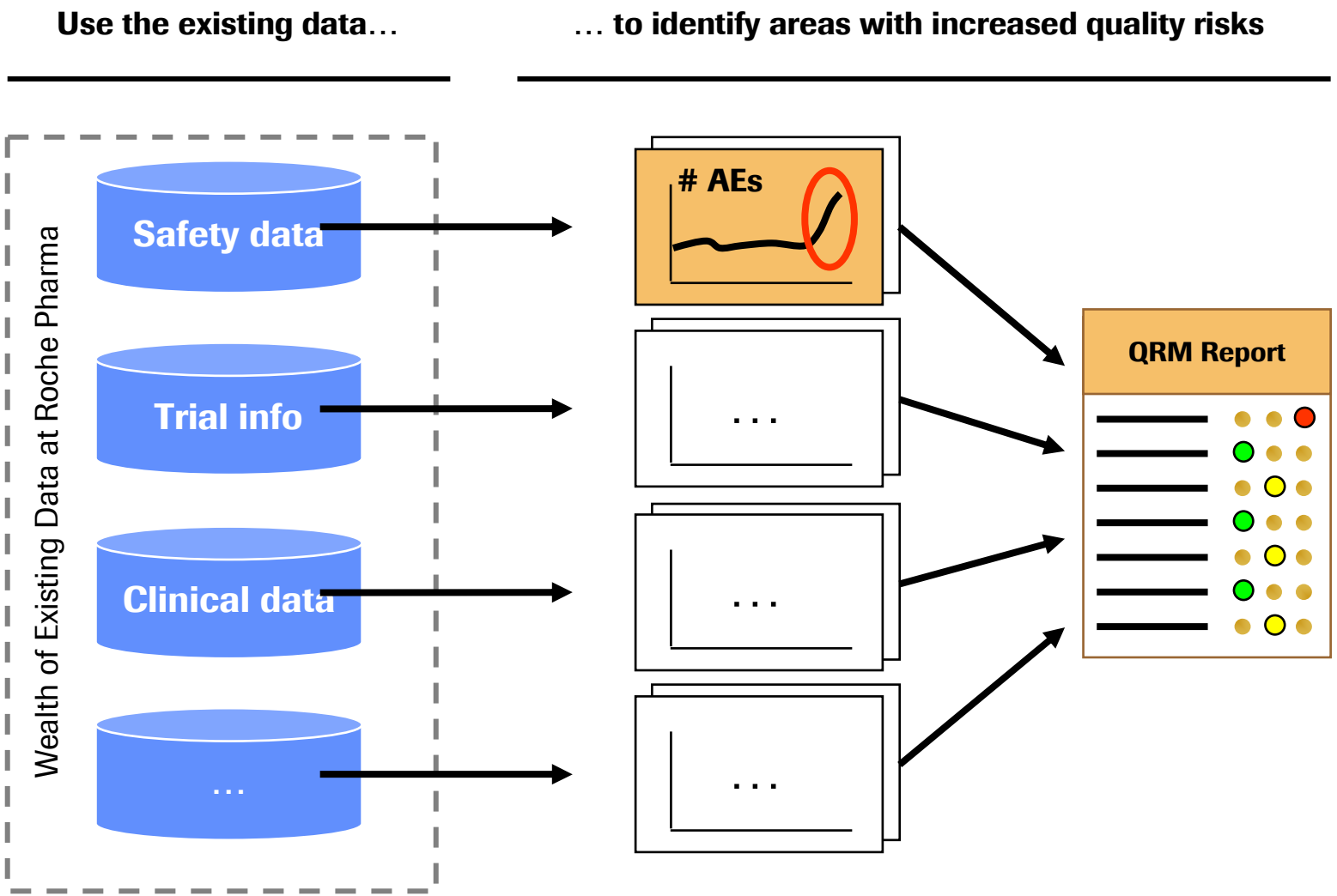


Affiliates/ risk areas highlighted in red to indicate highest risk

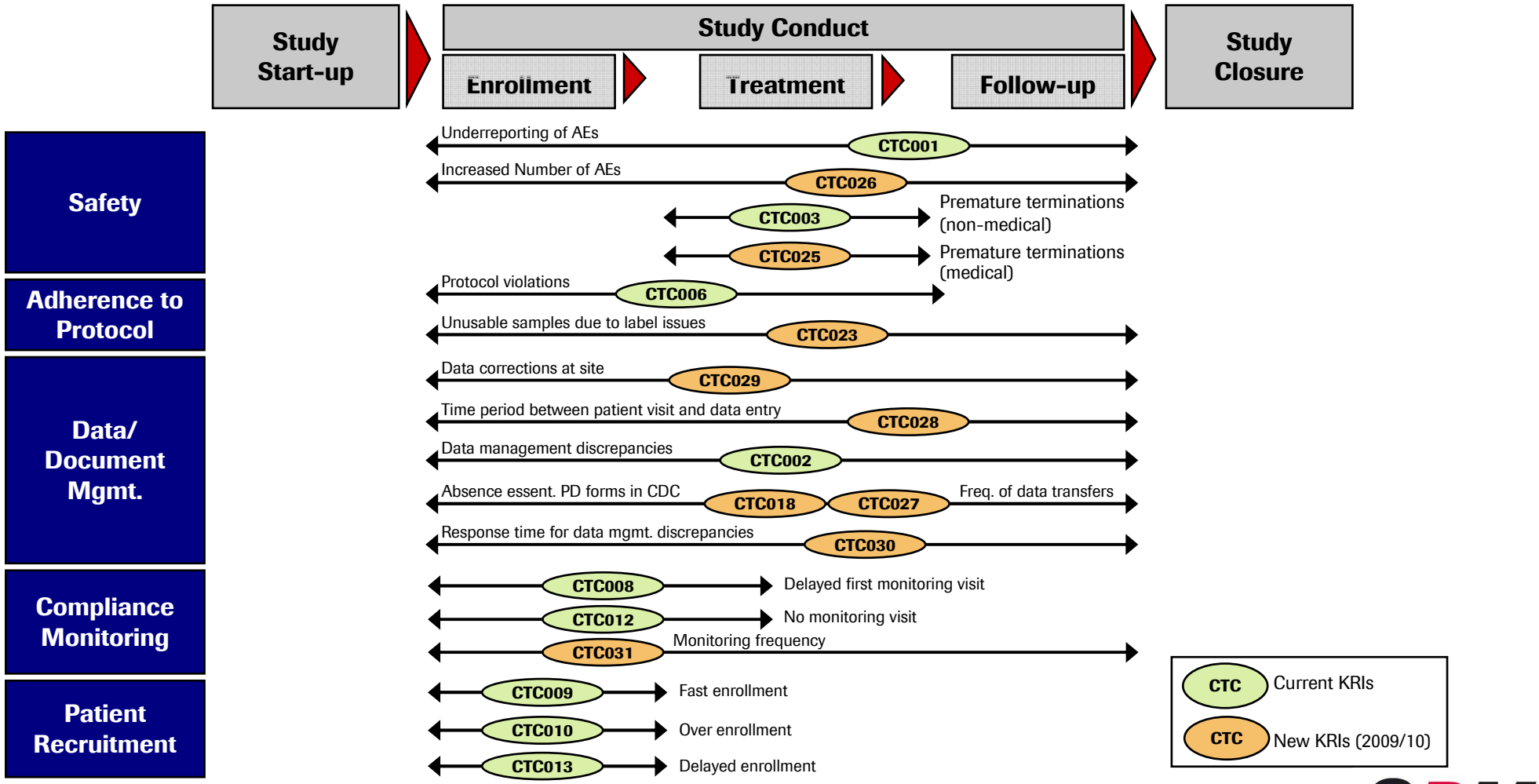
N/A | High risk | Medium risk | Low risk

QRM Quality Risk Management

Continuous Risk Evaluation by Analyses of Existing Data



Clinical Trial Centers (CTC) – Key Risk Indicator Landscape



First set of CTC KRIs

Different influence and predictive value

KRI #	KRI Name	Influence on Detectability (D) or Likelihood (L)	Link to Risks and Predictive Value (H High, M Medium, L Low)	
			Data Integrity	Safety Processes
1	Underreporting of AEs	L	M	M
2	Data management discrepancies	L	M	
3	Premature terminations (non-medical)	L	L	
6	Protocol violations	L	H	H
8	Delayed first monitoring visit	D	M	M
9	Fast enrollment	L	L	L
10	Over enrollment	L	L	L
12	No monitoring visit	D	H	H
13	Delayed enrollment	L	L	L

Predictive Value -> Matrix

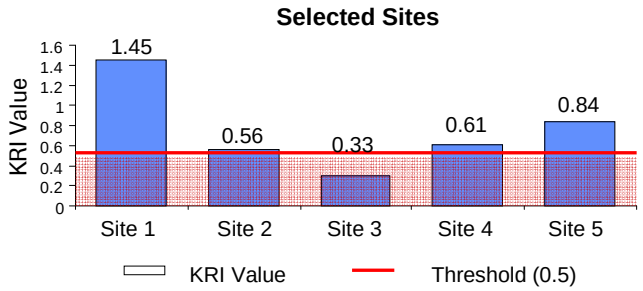
Underreporting of AEs

Description	Lower than average number of AEs reported per patient visit per site compared to the average number of AEs reported per patient visit per country
Rationale	Possible indicator for inadequate monitoring, lack of source data verification, site-staff training and/or insufficient resources

Input Parameter	Source
Number of patients per site, per country	Oracle Clinical, AIMS/CTMS
Number of patient visits per site, per country	Oracle Clinical
Number of AEs per site, per country	Oracle Clinical

Results

5 Sites in Spain



Allocation		
Risks	D/L	Predictive Value
SP, DI	Likelihood	Medium

Formula: Signal is Red if

A) KRI Value Above Threshold:

At least 3 patients enrolled at site (OC) *and*

$$\text{KRI Value} = \frac{\text{Acc. } \Sigma \text{ of AEs per patient visit per site}}{\text{Acc. } \Sigma \text{ of AEs per patient visit per country}} < 0.5$$

(1) If there are less than 4 sites in a country, the average number of AEs per patient visit per site is divided by the average number of AEs per patient visit per study

B) Significant Data Missing:

At least 3 patients enrolled at site (AIMS/CTMS) *and*

significant data missing
(no AEs reported in entire country)

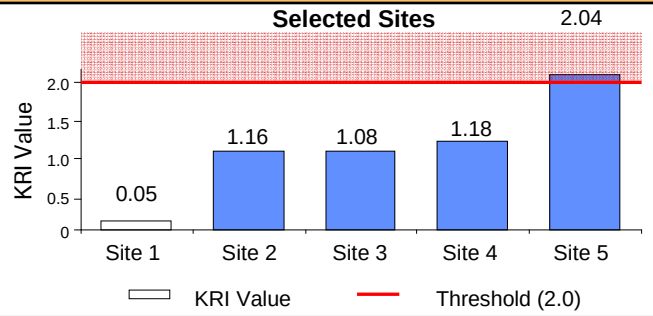
Increased number of AEs

Description	Increased average number of AEs per patient visit at site compared to the average number of AEs per patient visit in country (or per study)
Rationale	KRI serves as an indicator for potential issues with medical care and/or disease severity and/or patient selection at site.

Input Parameter	Source
Number of patients per site, per country	Oracle Clinical, AIMS/CTMS
Number of patient visits per site, per country	Oracle Clinical
Number of AEs per site, per country	Oracle Clinical

Results

5 Sites in France



Allocation		
Risks	D/L	Predictive Value
SP	Likelihood	Low

Formula: Signal is Red if

A) KRI Value Above Threshold:

At least 3 patients enrolled at site (OC) *and*

$$\text{KRI Value} = \frac{\text{Average number of AEs per patient visit per site}}{\text{Average number of AEs per patient visit in country (or per study)}^{(1)}} > 2$$

(1) If there are less than 4 sites in a country, the average number of AEs per patient visit per site is divided by the average number of AEs per patient visit per study

B) Significant Data Missing:

At least 3 patients enrolled at site (AIMS/CTMS) *and*

significant data missing
(no AEs reported in entire country)

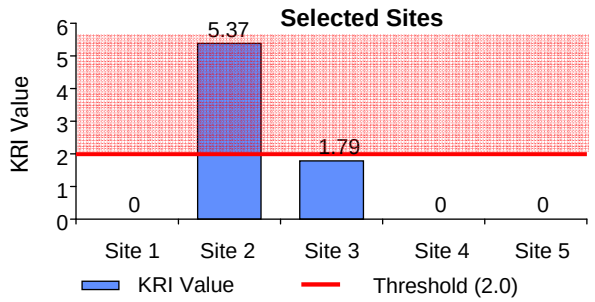
Premature terminations (non-medical reasons)

Description	
Rationale	Possible indicator for inadequate site management, including lack of protocol adherence

Input Parameter	Source

Results

5 Sites in USA



Allocation

Risks	D/L	Predictive Value
DI	Likelihood	Low

Formula: Signal is Red if

A) KRI Value Above Threshold:

At least 3 patients enrolled at site (AIMS/CTMS[1]) *and*

$$\text{KRI Value} = \frac{\text{Acc. } \Sigma \text{ of premature terminations per patient enrolled per site}}{\text{Acc. } \Sigma \text{ of premature terminations per patient enrolled per study}} \quad \textbf{> 2.0}$$

[1] data source will be changed to OC in 2010

Premature terminations (medical reasons)

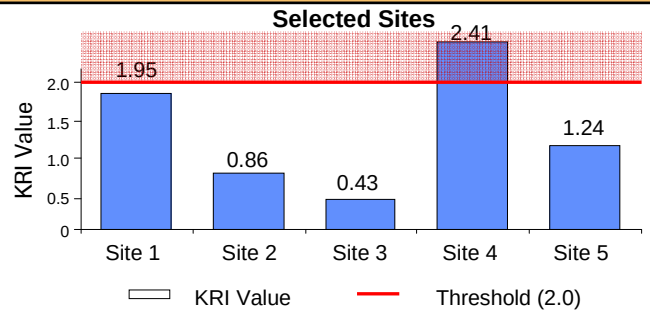
from AE, intercurrent illness, insufficient therapeutic response, death

Description	KRI measures the number of premature terminations (due to AE, intercurrent illness, insufficient therapeutic response and death) per patient enrolled per site compared to the average number of premature terminations (same reasons) per patient enrolled per study
Rationale	KRI serves as an indicator for potential issues with safety management at site and investigator oversight

Input Parameter	Source
Site, protocol	Oracle Clinical
Number of premature terminations per site	Oracle Clinical
Number of premature terminations per protocol	Oracle Clinical
Number of patients enrolled at site	Oracle Clinical
Number of patients enrolled at protocol	Oracle Clinical

Results

5 Sites in Spain



Allocation

Risks	D/L	Predictive Value
SP, DI	Likelihood	Low

Formula: Signal is Red if

A) KRI Value Above Threshold:

At least 3 patients enrolled at site (OC) *and*

$$\text{KRI Value} = \frac{\text{\# of premature terminations (due to AEs, death, insuff. therap. response, intercurr. Illness) per patient enrolled per site}}{\text{\# of premature terminations (due to AEs, death, insuff. therap. response, intercurr. Illness) per patient enrolled per protocol}} > 2$$

Managing Mega-Trials: a New Frontier

Further enhance compliance oversight “universe” by a controlled sharing amongst sponsors of, e.g.

- Monitoring outcome data
- Auditing outcomes
- KRI data
- CAPA & mitigating action data

Enhances credibility of own QRM data and leads to continuous benchmarking and quality improvement

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