

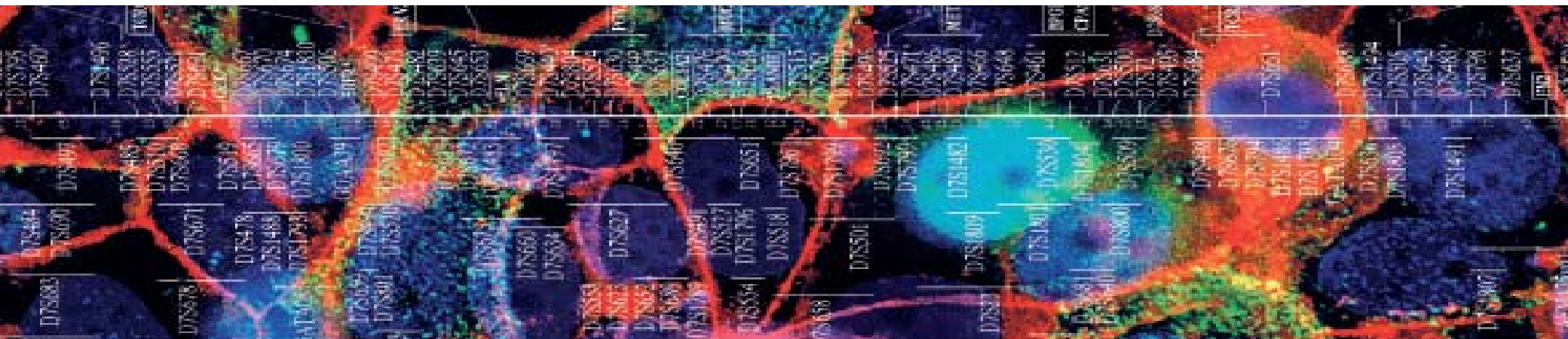
## **FERCAP Conference**

# ***Empowering Stakeholders in Health Research: Towards Developing an Ethics of Accountability and Responsibility***

*Beat Widler, F. Hoffmann-La Roche*

*Bangkok , Thailand*

*November 24 -25, 2008*



# Promoting Human Subjects through the Risk Management Approach

From this image  
or perception



# Promoting Human Subjects through the Risk Management Approach

To this  
assurance



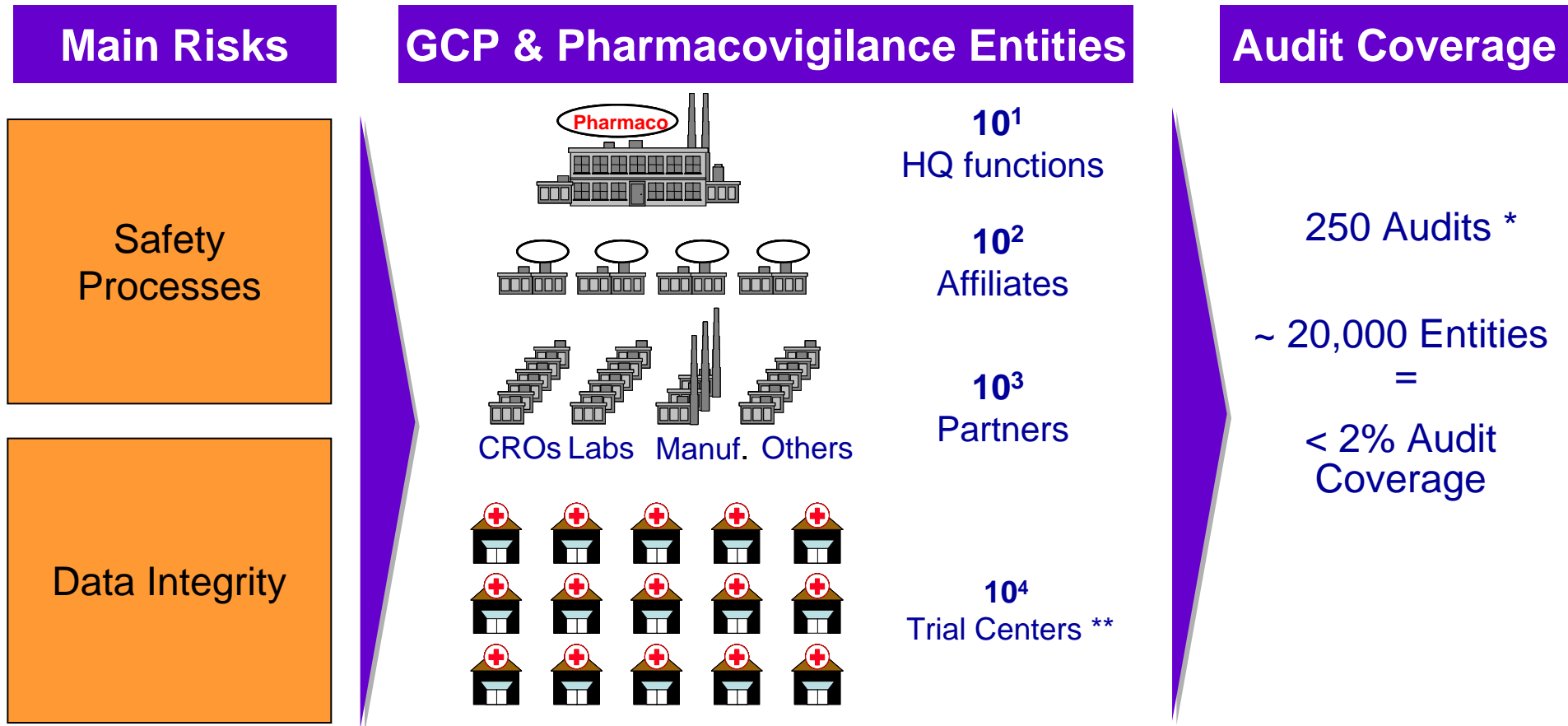
# Promoting Human Subjects through the Risk Management Approach

We need



# Major challenge #1: The numbers are against us

## *Audits cover only about 2% of clinical-related activities*

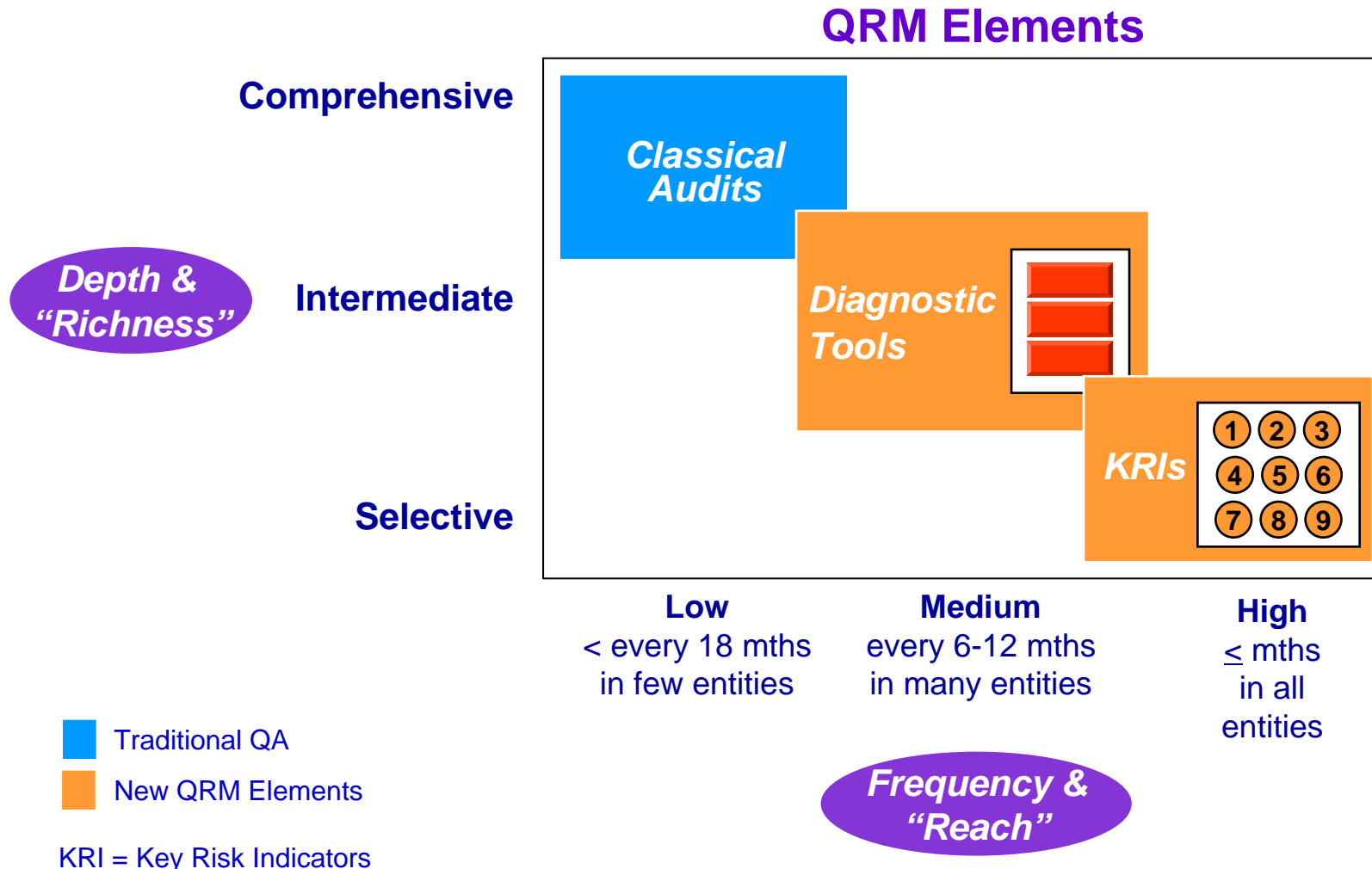


\* PDQ is able to conduct about 250 Audits annually with the help of contract auditors who perform 50% of the activities

\*\* For clinical trials centers, more than 15´000 entities in 2005; in October 2007 more than 18´000 entities were registered

# Traditional approach of Quality Management

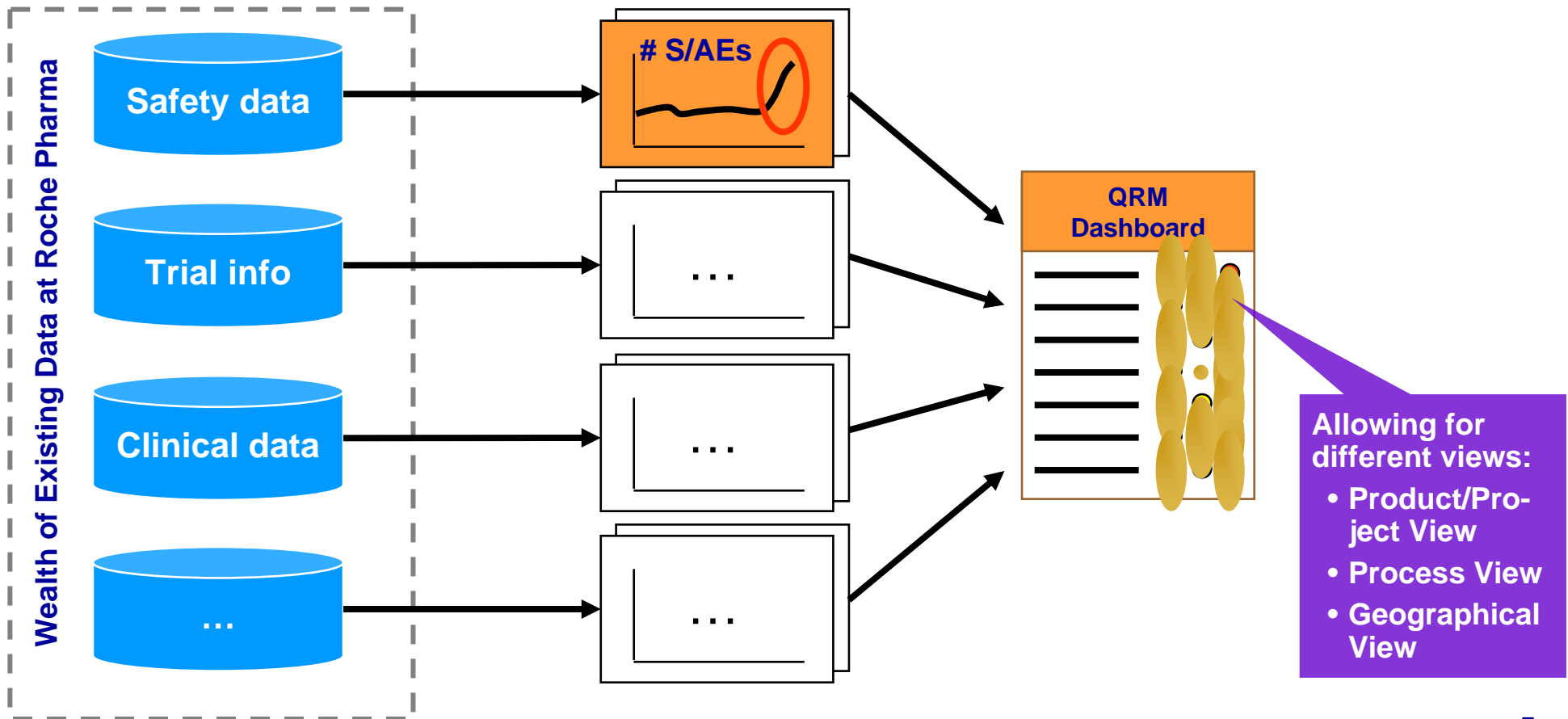
*Focus on in-depth, comprehensive but infrequent audits*



# “Continuous Risk Evaluation”

## *Critical is automatic analyses of existing data*

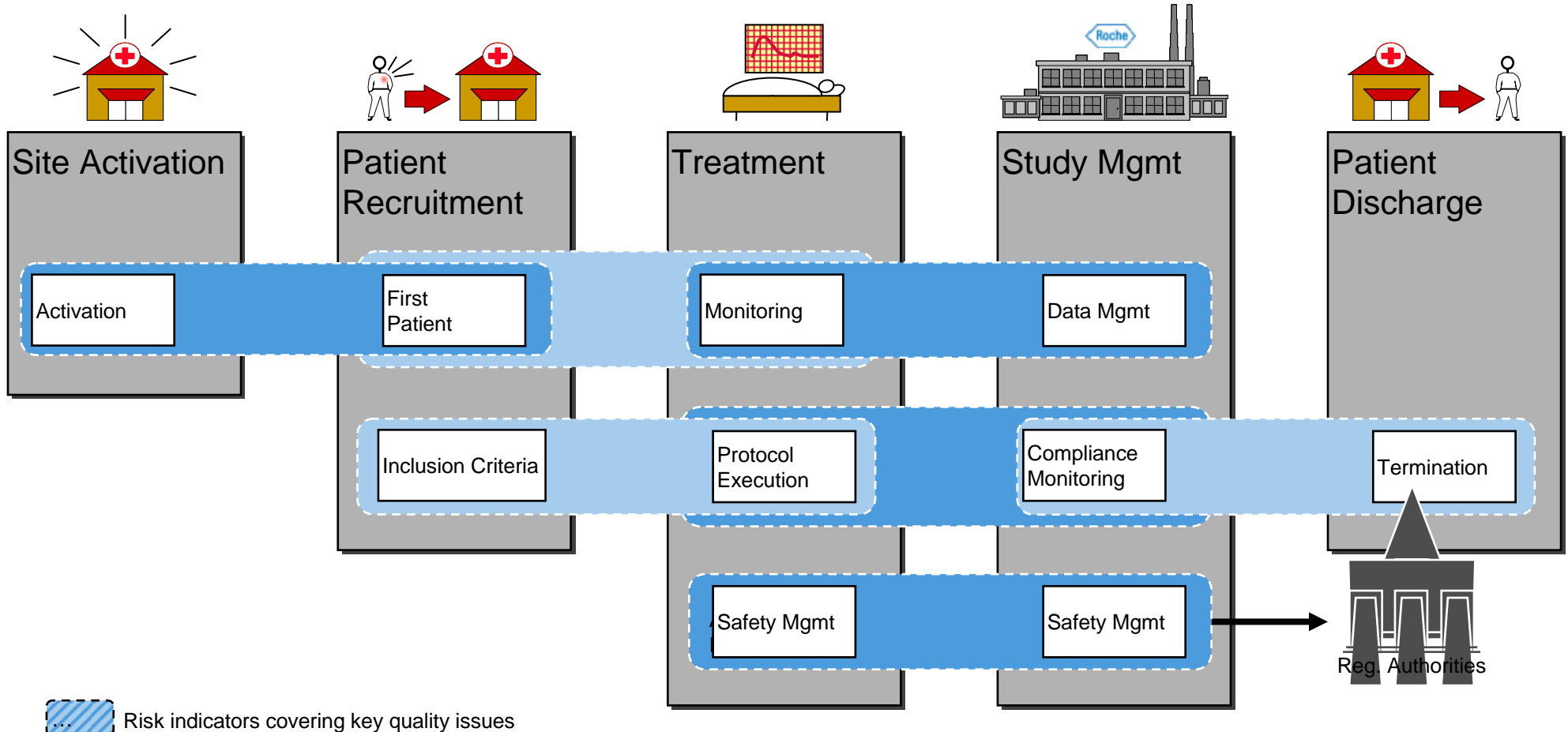
Use existing data... ... to identify areas with increased quality risks



# QRM “risk indicators” are designed to detect potential compliance issues during clinical development before they become problems



Clinical Trial Centers – Key Risk Indicator Landscape



Note: Recruitment, treatment and follow-up are phases that vary per patient, i.e. one patient could be in the recruitment phase while at the same time the second patient is already in the treatment phase



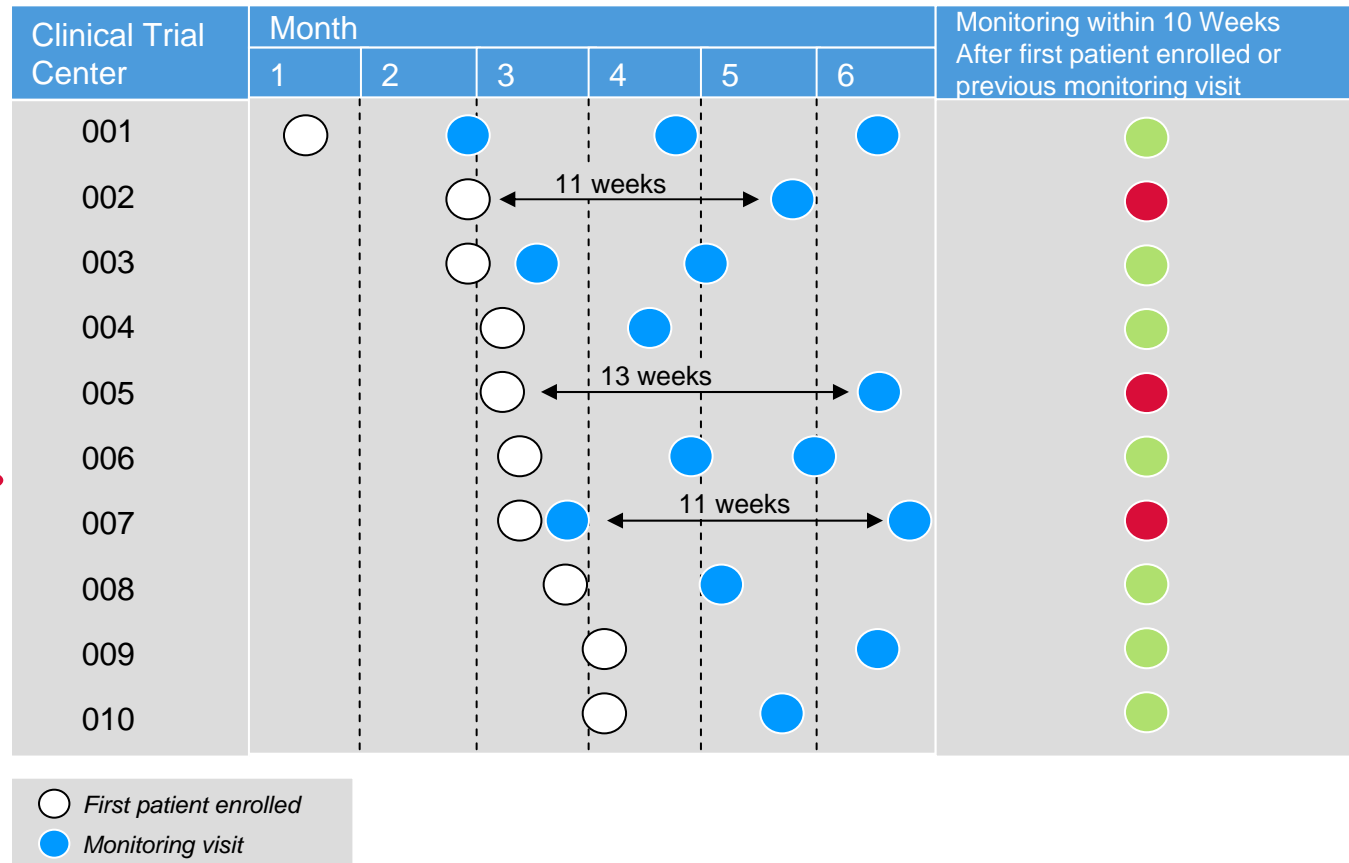
# A set of 12 Key Risk Indicators (KRIs) helps to ensure patient safety, in particular, during clinical development



Name	Rationale and Parameters that Could Compromise Patient Safety
<b>Late first monitoring visit</b>	Indicator for lack of oversight by sponsor, inadequate budget and/or lack of site cooperation
<b>Low monitoring frequency</b>	Indicator for lack of oversight by sponsor, inadequate budget and/or lack of site cooperation
<b>No first monitoring visit</b>	Indicator for lack of oversight by sponsor, inadequate budget and/or lack of site cooperation
<b>Fast enrolment</b>	Indicator for inadequate monitoring and/or site capacity
<b>Over-Enrolment</b>	Indicator for inadequate monitoring and/or site capacity
<b>Delayed enrolment</b>	Indicator for inadequate site management and/or insufficient resources
<b>Protocol violations</b>	Indicator for inadequate site-staff training and/or insufficient resources
<b>Premature terminations</b>	Indicator for not-well defined inclusion/exclusion criteria, lack of oversight by monitors and medical oversight at the sponsor
<b>Unusable samples/ wrong labeling</b>	Indicator for inadequate handling of samples for storage or laboratory analysis
<b>Long time to resolve data mgmt discrepancies</b>	Indicator for site staffing training status and resource availability at site
<b>Incomplete adverse event reporting</b>	Indicator for inadequate site-staff training and/or insufficient resources
<b>Late adverse event reporting</b>	Indicator for inadequate site-staff training and/or insufficient resources

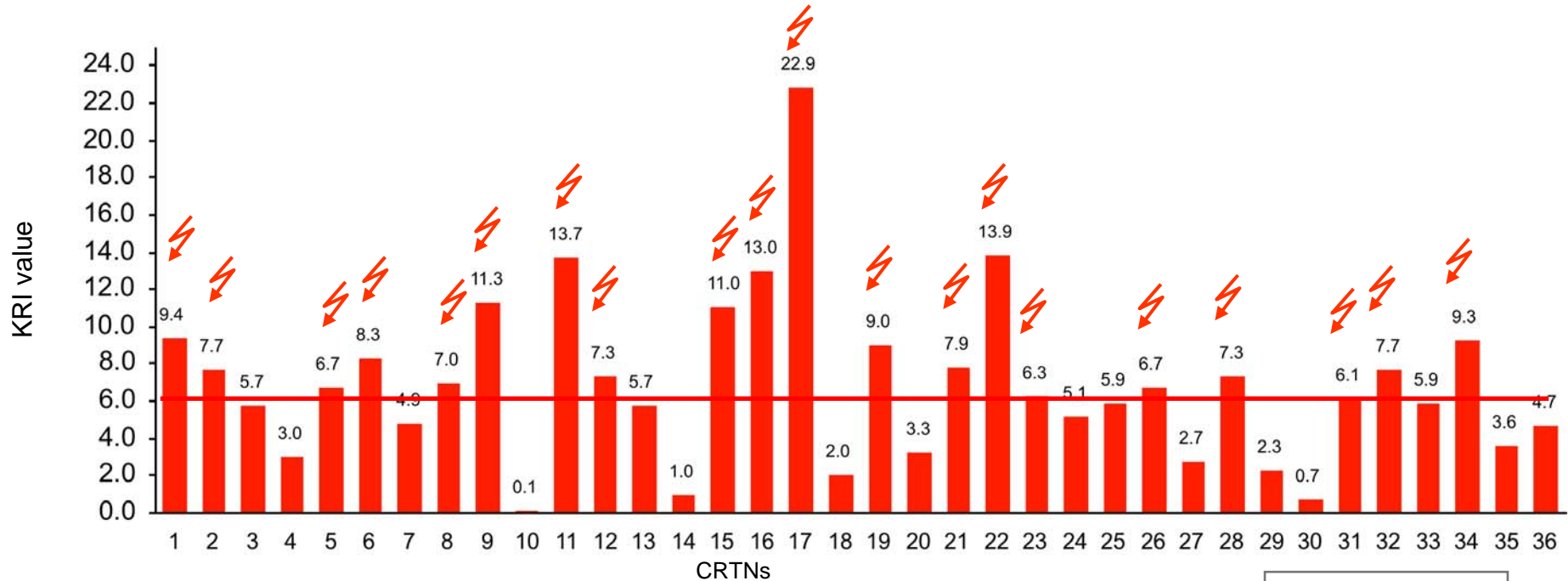
# The KRI 'late first monitoring visit' helps to ensure adherence to the protocol and GCP compliance in study centers

Analysis of Several Study Centers in One Study with Key Risk Indicator: Late First Monitoring Visit



# It is in particular powerful in large multi-center trials

KRI 'Late First Monitoring Visit' for a Large Oncology Study in a Western European Country



- Weeks between first patient enrolment date and first monitoring visit date
- Threshold (>6 weeks)
- Critical area

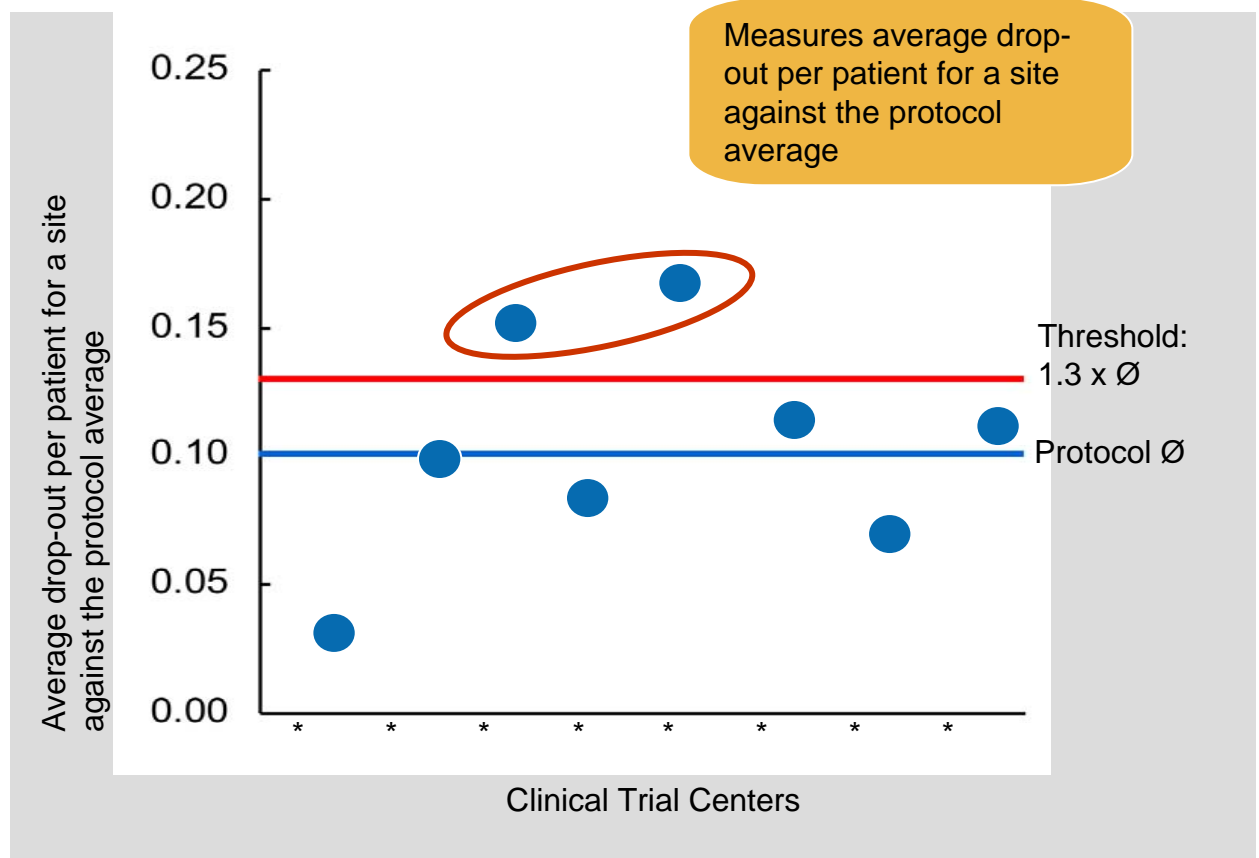
⚡  
 QRM signal: Time period between first monitoring visit date and first patient enrolment date exceeds six weeks

Note: Results for February 2007  
 Source: Roche QRM Project Team

# The KRI 'premature termination' helps to identify study centers that face an unexpected number of patient drop-outs

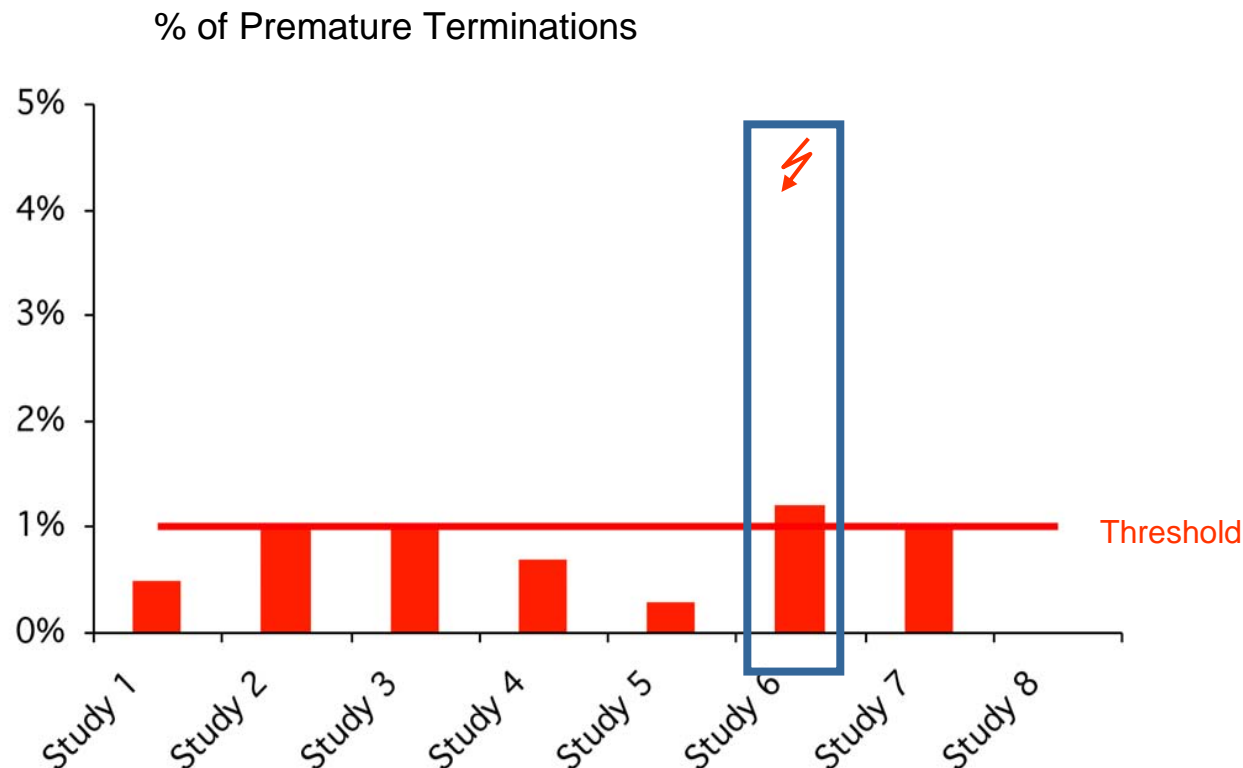
Analysis of Several Study Centers in One Study with Key Risk Indicator: Premature Terminations

Is there an unusually high rate of unexpected drop-outs at any site?



# It can also be applied to compare drop-out rate across different studies

Analysis of Several Studies with Key Risk Indicator: Premature Terminations

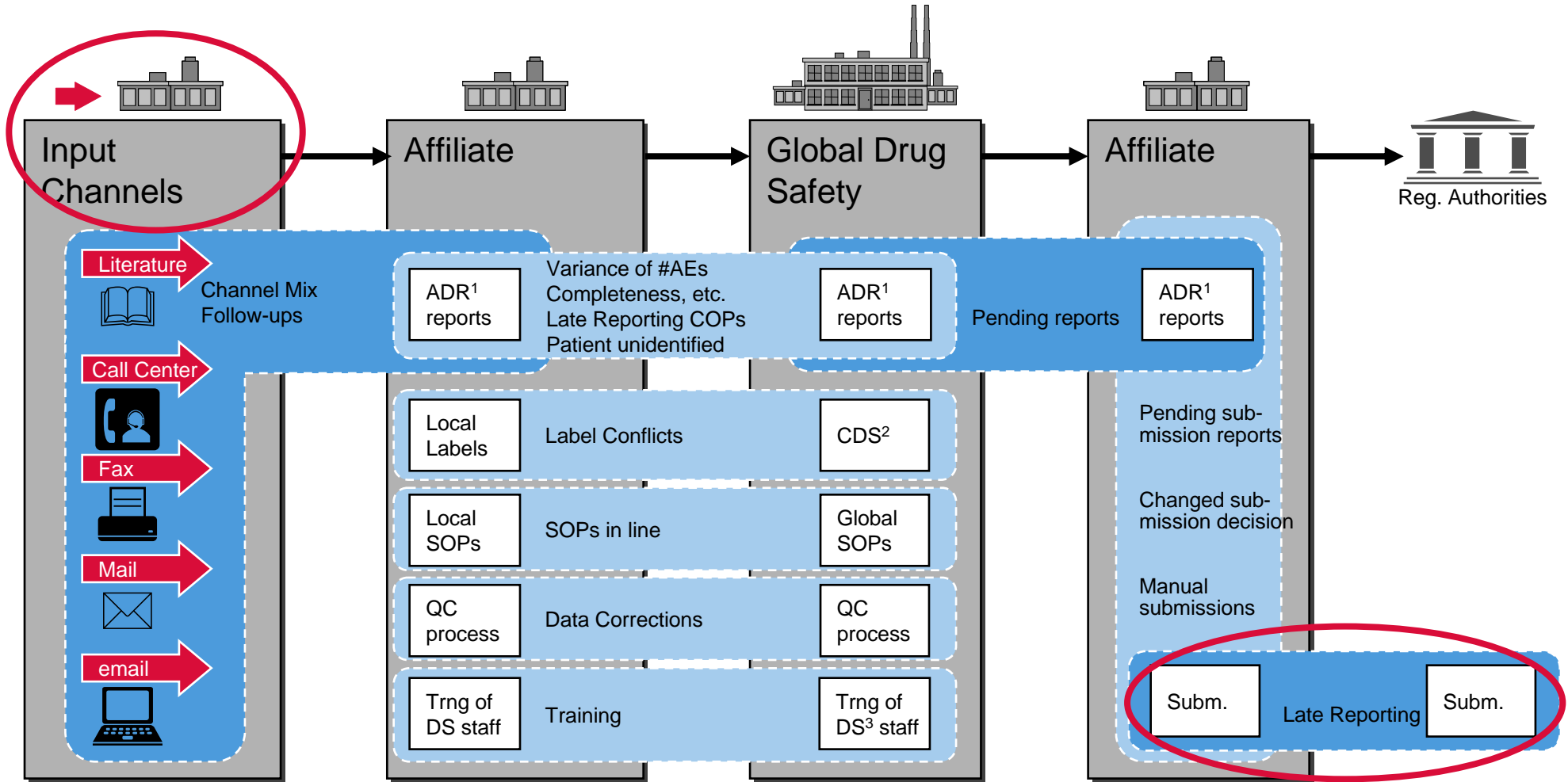


- ▶ Key Risk Indicator Signal for Study 6 is above the threshold of 1% for premature terminations of patients
- ▶ All other studies are below the threshold
- ▶ Study 8 does not have any terminations

# Roche needs to ensure compliance with regulatory reporting timelines for products on the market to support patient safety



Key Risk Indicator Landscape for Products in the Market



- (1) Adverse Drug Reaction
- (2) Core Data Sheet
- (3) Drug Safety

Risk indicators covering key quality issues

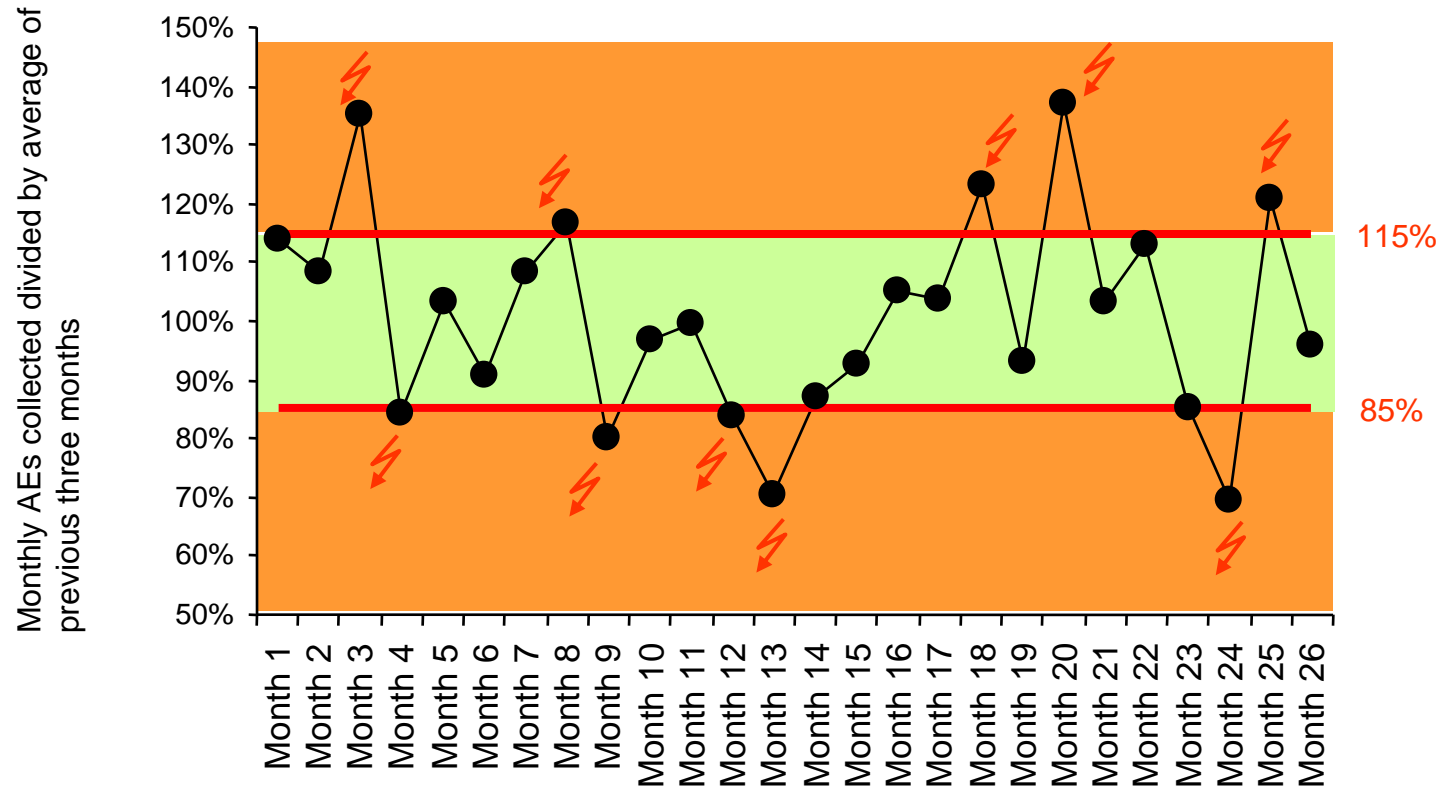
# Five of these Key Risk Indicators have particular focus on signaling risks for compromising patient safety

Name	Rationale and Parameters that Could Compromise Patient Safety
<b>Variance in ADR<sup>1)</sup> collection</b>	Indicator for insufficient resources and/ or backlogs
<b>Different Case Types</b>	Indicator to assure that case report are collected from all available sources (process of collection)
<b>Label conflicts</b>	Indicator for inadequate assessment of spontaneous cases due to insufficient resources or training
<b>No follow-up of spontaneous cases</b>	Indicator to inadequate follow-up/ handling due to insufficient resources and/or training
<b>Delay of serious ADRs<sup>1)</sup></b>	Indicator for potential non-compliance due to collection process and/or insufficient resources




# Continuous high variance in adverse drug reaction reporting by a country represents a high risk of non-compliance

Relative Number of Adverse Drug Reactions Collected from a Country



► At various time points the variance in the ADR collection rate at the country shows a higher than expected variance indicating erratic collection patterns

● Collected ADRs three month average — Upper Threshold ( 115%) — Lower Threshold (85%)

  
 QRM Signal:  
 higher or lower than expected variance in ADR collection





*We Innovate Healthcare*