

Integrating Risk-Based Quality Monitoring (RBQM) into each phase of the trial to ensure maximum efficiency and robust data validation processes

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Disclaimer

- The contents of this presentation represents the Presenter's personal interpretation of 21CFR and FDA/ ICH Guidance Documents, and the Presenter's [personal opinions](#)
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Objectives

- Designing and executing a successful RBQM framework to meet your specialized trial goals
- Sharing best practice on implementing new modern EDC systems to provide built-in validation checks and automated information checks when some CROs are lacking corporate memory
- Focusing on critical data and processes by documenting risks, roles, and mitigation strategies
- Meaningful key performance indicators for RBQM

Documents referenced

- 21CFR312.52 Transfer of obligations to a contract research organization
- Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (August 2013)
- A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry (April 2023)
- ICH Harmonised Guideline Good Clinical Practice (GCP) E6(R3) (May 2023)

[Code of Federal Regulations]
[Title 21, Volume 5]
[CITE: 21CFR312.52]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D - DRUGS FOR HUMAN USE

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION
Subpart D - Responsibilities of Sponsors and Investigators

Sec. 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any this part to a contract research organization. Any writing. If not all obligations are transferred, the obligations being assumed by the contract research organization, a general statement that all obligations transferred. Any obligation not covered by the written description transferred.

(b) A contract research organization that assumes with the specific regulations in this chapter apply subject to the same regulatory action as a sponsor assumed under these regulations. Thus, all referred



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

ICH HARMONISED GUIDELINE
GOOD CLINICAL PRACTICE (GCP)
E6(R3)

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)

August 2013
Procedural

OMB Control No. 0910-0014
Current expiration date available at <https://www.reginfo.gov>
(Search CFE and enter OMB control number 0910-0014)
See additional PRA statement in section VII of this guidance.

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A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Clinical Policy (OCLIP)
Office of Regulatory Affairs (ORA)

April 2023
Procedural

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Designing and executing a successful RBQM framework to meet your specialized trial goals

- Identify your critical variables and processes
- Ensure proper training and qualified personnel
 - Design CRFs to record compliance metrics
 - Timing of procedures
- Review incoming data (remotely and on site)
 - # of expected assessments
 - By site
 - # of missing assessments
 - # of out of window assessments
- Mitigation and early intervention

Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (August 2013)

Guidance for Industry

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Contains Nonbinding Recommendations

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What is a risk?

- ...it focuses sponsor oversight activities on preventing or mitigating important and likely **risks to data quality and to processes critical** to human subject protection and trial integrity (FDA RBM p2)

Identify critical data and processes

- Standard
 - Informed Consent,
 - Eligibility,
 - Exposure/Accountability,
 - Study Endpoints,
 - Safety/ AEs,
 - Maintain blinding
- Procedures that are different from standard of care
 - e.g., Study drug administration/ Investigational device application

Other “risks” addressed elsewhere...Risk Management Plan

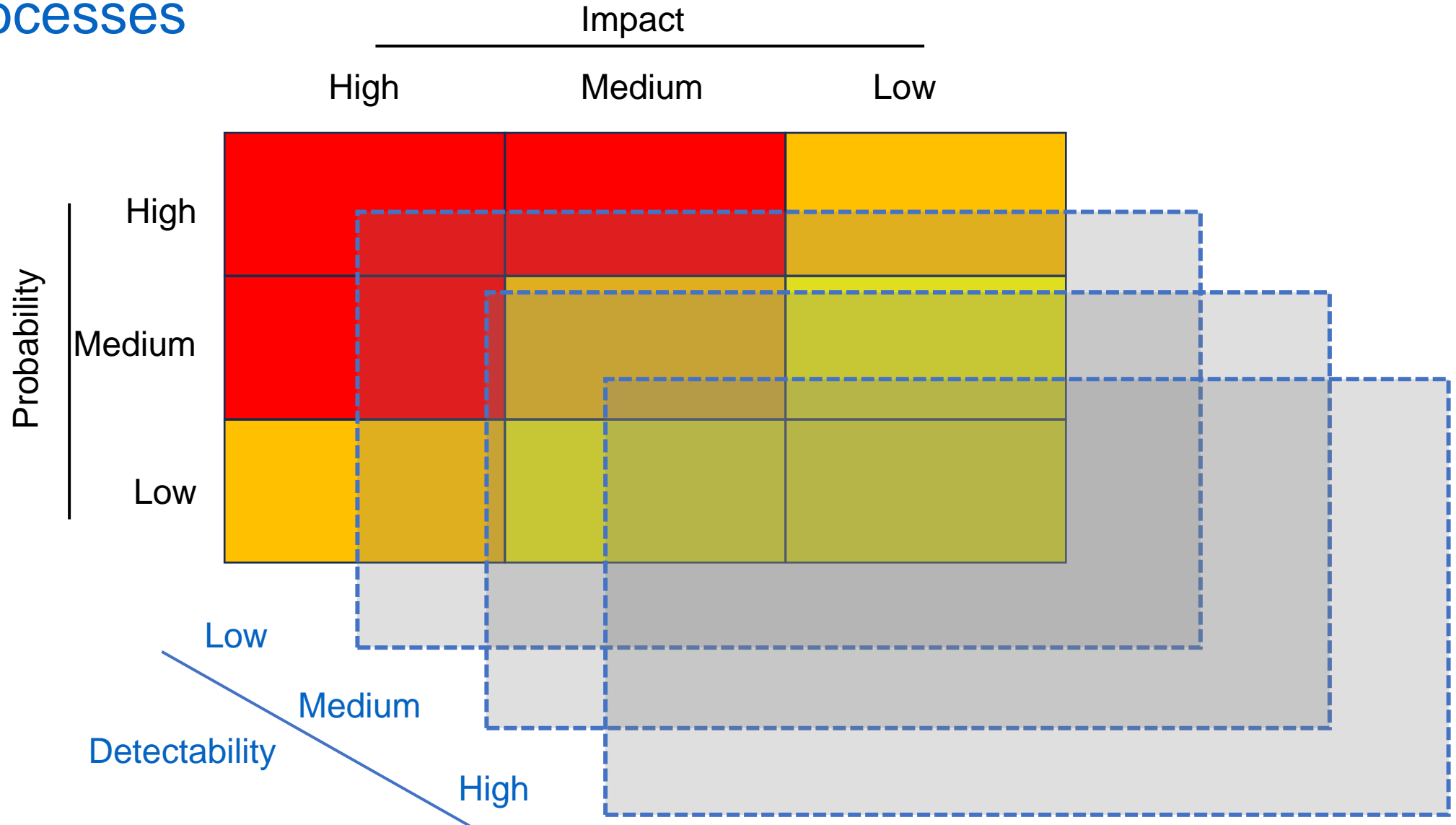
- Enrollment slower than expected
 - # of planned sites
 - Back-up sites
 - etc.
- Site activation issues
 - Feasibility assessments
 - Site selection
 - etc.
- *“Sponsor slow to respond to CRO requests, resulting in timeline delays...”*

Risk Assessment of Critical Variables and Processes

		Impact		
		High	Medium	Low
Probability	High			
	Medium			
	Low			

likely risks to data quality and processes critical to human subject protection and trial integrity

Risk Assessment of Critical Variables and Processes



Quantify Risk

- Use Impact, Probability, and Detectability
- What is Risk Score cut-off?
 - “5”...“6”
- Amount of risk tolerance is Sponsor-dependent

Impact	Probability	Detectability	Risk Score/ Category	
1 - Low 2- Moderate 3- High	1 - Low 2- Moderate 3- High	1- High 2- Moderate 3- Low	Score	Category
3	3	3	9	Critical
		2	8	
		1	7	
	2	3	8	
		2	7	
		1	6	
	1	3	7	
		2	6	
		1	5	Noncritical
2	3	3	8	Critical
		2	7	
		1	6	
	2	3	7	
		2	6	
		1	5	Noncritical
	1	3	6	Critical
		2	5	Noncritical
		1	4	
1	3	3	7	Critical
		2	6	
		1	5	Noncritical
	2	3	6	Critical
		2	5	Noncritical
		1	4	
	1	3	5	
		2	4	
		1	3	

Sponsor is in the best position to assign risk score

Problem in prior studies?

	Impact	Probability	Detectability	Risk	
				Score	Category
Informed consent	3	1	3	7	critical
Eligibility	3	1	3	7	critical
Demographics					
General medical history					
Randomization	3	2	1	6	critical
Primary efficacy endpoint	3				
Secondary efficacy endpoint	2				
Exploratory endpoints	1				
Study Intervention	3	1	3	7	critical
Safety endpoints (other than AEs)	3	1	3	7	critical
Recording of adverse events	3	1	3	7	critical
Recording of concomitant medications					

Even if
Low probability = 1
High detectability = 1
Overall score = 5

Electronically captured?

Is this performed routinely as normal standard of care or “novel”?

Sharing best practice on implementing new modern EDC systems to provide built-in validation checks and automated information checks...

- Edit checks
 - Required data
 - Conforming formats
 - Some logic checks
 - e.g., Laboratory ranges
- Queries
 - Automated and Manual
 - Review of these can provide ongoing risk assessment

Review Queries to Identify Patterns

	N	All Queries (n= 2348)	Manual Queries (n=1410)
Edits Checks	938	39.9%	-
Manual Queries	1410	60.1%	-
Remote DM	436	18.6%	30.9%
Remote Sponsor Review	348	14.8%	24.7%
Onsite	626	26.7%	44.4%

Manual queries originally summarized by Site/ Reviewer did not result in meaningful data

Manual Queries (All) by page/type (not data variable)

Adverse Events	381 (27.0%)	PK/ADA Assessment	11 (0.8%)
Concomitant Medications	257 (18.2%)	Cytokines	9 (0.6%)
Prior Systemic Therapy	82 (5.8%)	Fresh Tumor Biopsy	9 (0.6%)
Treatment	71 (5.0%)	Eligibility	8 (0.6%)
Chemistry	66 (4.7%)	PD Assessment	8 (0.6%)
Concomitant Procedures	47 (3.3%)	Discharge Information - Cycle 1	7 (0.5%)
End Of Study	46 (3.3%)	New Lesions - RECIST V1.1	7 (0.5%)
Medical History	46 (3.3%)	Screening	4 (0.3%)
End Of Treatment	43 (3.0%)	Demographics	4 (0.3%)
Response Assessment	42 (3.0%)	ECOG Performance Status	4 (0.3%)
Target Lesions - RECIST V1.1	41 (2.9%)	Physical Examination	3 (0.2%)
Disease History - General	34 (2.4%)	Subsequent Systemic Therapy	3 (0.2%)
Non-Target Lesions - RECIST V1.1	32 (2.3%)	Death Page	2 (0.1%)
Vital Signs	28 (2.0%)	Disease Progression Summary	2 (0.1%)
Visit	20 (1.4%)	Electrocardiogram (ECG)	2 (0.1%)
Prior Surgery	17 (1.2%)	Patient Information	2 (0.1%)
Hematology	15 (1.1%)	Serologies	2 (0.1%)
Prior Radiation	14 (1.0%)	Death	2 (0.1%)
Coagulation	13 (0.9%)	Subsequent Radiation	1 (0.1%)
Disease History - Metastatic Sites	12 (0.9%)	Subsequent Surgery	1 (0.1%)
Follow Up	12 (0.9%)		

626 CRA Queries (All) by data type (not data variable)

CRF	N	%	CRF	N	%
Concomitant Medications	149	(23.8%)	Prior Radiation	6	(1.0%)
Adverse Events	112	(17.9%)	Discharge Information - Cycle 1	5	(0.8%)
Prior Systemic Therapy	52	(8.3%)	New Lesions - RECIST V1.1	5	(0.8%)
Chemistry	31	(5.0%)	PK/ADA Assessment	5	(0.8%)
Disease History - General	27	(4.3%)	Coagulation	4	(0.6%)
Concomitant Procedures	26	(4.2%)	ECOG Performance Status	3	(0.5%)
Medical History	25	(4.0%)	Hematology	3	(0.5%)
Target Lesions - RECIST V1.1	25	(4.0%)	Subsequent Systemic Therapy	3	(0.5%)
Visit	23	(3.7%)	Cytokines	2	(0.3%)
Non-Target Lesions - RECIST V1.1	21	(3.4%)	Death Page	2	(0.3%)
Vital Signs	16	(2.6%)	Screening	2	(0.3%)
Prior Surgery	15	(2.4%)	Demographics	1	(0.2%)
Treatment	15	(2.4%)	Electrocardiogram (ECG)	1	(0.2%)
End Of Study	11	(1.8%)	End Of Treatment	1	(0.2%)
Disease History - Metastatic Sites	10	(1.6%)	Patient Information	1	(0.2%)
Response Assessment	8	(1.3%)	PD Assessment	1	(0.2%)
Eligibility	7	(1.1%)	Physical Examination - 2016/08/17	1	(0.2%)
Fresh Tumor Biopsy	6	(1.0%)	Serologies	1	(0.2%)



626

112 CRA “AE” Queries coded by type

Query Type	N	AEs	Query Type	N	AEs
Progress Note- unreported AE	28	28	Action Taken	2	
Discharge Summary- unreported AE	7	7	Please complete AE log	2	
Please add to AE Log	7		Please save page	2	
Follow-up query	6		Dose adjustment	1	
Grade	6		Duplicate	1	
Outcome	6		EMR- unreported AE	1	
SAE reconciliation	6		IV Feedback Form- unreported AE	1	1
Stop date	5		Medical History duplicate	1	
Please complete	4		Nursing questionnaire- unreported AE	1	1
SAE?	4		Please update	1	
Unreported AE	4		Relationship	1	
"Intermittent"	3		Remote Progress Note- unreported AE	1	1
Add to AE Log	3		Site Call - unreported AE	1	1
<u>AE Log- unreported AE</u>	3		Verbatim Term	1	
Start Date	3				
				112	39

39/112 AE queries related to unreported AEs

Edit checks bypassed without a change

Validation Message	
252 Magnesium value is not within expected range. Please verify.	 Programmed ULN was incorrect
162 Red Blood Cells value is not within expected range. Please verify.	
143 This item is required.	
53 Date must be prior to next Visit Date. Please verify.	
40 Lactate Dehydrogenase value is not within expected range. Please verify.	
26 Date must be on or after Date of Informed Consent. Please correct.	
23 Monocytes value is not within expected range. Please verify.	
22 SGPT/ALT value is not within expected range. Please verify.	 > ULN... 1X, 2X, 3X, etc.
21 Glucose value is not within expected range. Please verify.	
19 Bicarbonate value is not within expected range. Please verify.	
33 19 This item is required. Please provide complete date or enter partial date.	
14 This item is required. Please provide complete date.	
12 Total Bilirubin value is not within expected range. Please verify.	
11 Start Date must be after previous End Date. Please verify dates for continuous AE.	
10 SGOT/AST value is not within expected range. Please verify.	
8 Alkaline Phosphatase value is not within expected range. Please verify.	
8 Eosinophils value is not within expected range. Please verify.	

Better to focus sites on critical variables (e.g., AE data)?

Focusing on critical data and processes by documenting risks, roles, and mitigation strategies

- Repetition is good, Redundancy not so much
- Repetition is good, Redundancy not so much
- An organized **Data Review Plan** will identify risks/roles/mitigations
 - Ensures all data is monitored (on site or remotely)
 - **Repeat when needed**

“CRAs don’t do that, they know there is an edit check”

“Shall I change that to ‘probable’ ?”

Meaningful KPIs for RBQM

- Most KPIs measure CRO performance
 - CRA and staff bonuses and annual reviews
 - Of value to CRO, less so to Sponsor
- KPIs can identify GCP issues in close to real time
 - If properly designed and implemented
 - Can quantify risk-associated metrics
 - Can be used to monitor GCP compliance

Actual KPIs:

Many “KPIs” are related to CRO functional group performance

Metric	Functional Group
% of sites activated vs # projected (cumulative to date)	Study Start Up
# days from site qualification to executed contract	Contracts Group
# of monitoring visits completed outside minimum visit plan window defined in monitoring plan	PM and CRA
% of monitoring reports completed outside defined window in monitoring plan	CRA
% of open queries unresolved for more than 30 days	DM and CRA

More “Actual” KPIs

Basic	Issues
% of enrolled patients vs. projected (cumulative to date)	<ul style="list-style-type: none">• Unable to see trends
% of actively enrolling sites (of all activated sites)	<ul style="list-style-type: none">• How is “actively” defined?• How many sites should be activated?• 1 out of 1 is 100%
% of actively screening sites (of all activated sites)	<ul style="list-style-type: none">• How is “actively” defined?• 1 out of 1 is 100%

Are these KPIs or metrics?

More “Meaningful” KPIs

% of evaluable participants enrolled compared to projected	<ul style="list-style-type: none"> • If on target <ul style="list-style-type: none"> • Activation activity was adequate • Regardless of target qualification, etc.
# of IMVs where GCP issues were noted	<ul style="list-style-type: none"> • It does not matter how quickly the reports were filed • What matters is “were there any issues and were they addressed”
Number of protocol deviations by type	<ul style="list-style-type: none"> • If a large amount <ul style="list-style-type: none"> • Protocol may be unclear, • SIVs may have been ineffective • Site performance could be an issue

Absence of data
is not
data of absence

Other performance metrics to consider

- Number of
 - Queries, by site by type
 - Protocol deviations, by site by type
 - Missed and late assessments
 - Safety
 - efficacy
 - ICF issues
 - SOP deviations
 - ...

Example of Deviations Tracker, by study or by site

	2024				2025		
PD Code	Q1	Q2	Q3	Q4	Q1	Q2	Total
Number of Subjects	x	x	x	x	x	x	
ICF0	-	-	-				0
ICF1	-	-	-				0
INC# (Criteria #)	-	-	-				0
EXC# (Criteria #)	-	-	-				0
SV0	1	-	-				1
SV1	-	-	-				0
SDA0	-	-	-				0
SDA1	1	2	1				4
SDA2	-	-	-				0
VS0	2	3	2				7
VS1	1	1	1				3
PCM	-	2	-				2

Note: the number of subjects is provided to help put the frequency of deviations into context

Questions