RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

RISK
RISK STATEMENT
KRI & THRESHOLDS

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** meal is below 60°C **due to** food staying out on the buffet table longer than 4 hours, **then** food poisoning **may result**.	
event	*meal is below 60°C*	
cause	*food staying out on the buffet table longer than 4 hours*	
negative impact	*food poisoning*	
KRI	**(Too) low Buffet Serving Temperature**	
Metric (underlying)	°C	Temperature
KRI thresholds	Green	> 63°C
	Yellow	60°C - 63°C
	Red	< 60°C
Associated metrics (percentage or number)	%	of meals that left the kitchen in the temperature danger zone
	%	of served meals that passed the 4 hour danger zone limit
	%	of reported food poisoning cases within 48 hours

Conduct protocol assessment

RISK HISTORY

- Metric results
- Lessons learned

RISK ASSESSMENT

- Gather data for risk identification
- Assess study to identify risks
- Quantify risks

RISK MITIGATION & CONTROL

- Take actions to reduce risks
- Define KRIs & set tolerance limits
- Develop issue mitigation plans

ISSUE MANAGEMENT

- Monitor KRIs for issues
- Manage events / conditions

Archive risk management results

Risk communication

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CLINICAL EXAMPLES

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** only a few endpoint data can be acquired **due to** under recruitment, **then** a low study power, a delay in study completion, or a protocol amendment **may result.**	
event	*Only few endpoint data can be acquired*	
cause	*Under recruitment*	
negative impact	*A low study power, a delay in study completion, or a protocol amendment*	
KRI	**Under Recruitment**	
Metric (underlying)	No.	Number of patients recruited
KRI thresholds	Green	≥ 90% of planned patients
	Yellow	80 - 90% of planned patients
	Red	< 80% of planned patients
Associated metrics (percentage or number)	No.	Number of screened patients
	%	Percentage of screened patients

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** a site recruits more patients than statistically permitted (20%) **due to** a lack of control over the IXRS and the screening, **then** an unusual statistical analysis and difficulties in the result interpretation **may result.**	
event	*A site recruits more patients than statistically permitted (20%)*	
cause	*A lack of control over the IXRS and the screening*	
negative impact	*An unusual statistical analysis and difficulties in the result interpretation*	
KRI	**Over Recruitment**	
Metric (underlying)	No.	Number of patients per site
KRI thresholds	Green	≤ 85% of the max planned patients
	Yellow	85 - 95% of the max planned patients
	Red	> 95% of the max planned patients
Associated metrics (percentage or number)	No.	Number of enrolled patients in study
	No.	Number of screened patients

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** informed consent violations occur **due to** for example the recruitment of an elderly population with severe pathology, **then** GCP non-compliance **may result.**	
event	*Informed consent violations*	
cause	*The recruitment of elderly population with severe pathology*	
negative impact	*GCP non-compliance*	
KRI	**High Rate of PD (Protocol Deviation) in Informed Consent Form/Process**	
Metric (underlying)	No.	PDs related to informed consent
KRI thresholds	Green	0
	Yellow	N/A
	Red	> 0
Associated metrics (percentage or number)	No.	Number of PDs for in- and exclusion criteria
	No.	Number of enrolled patients
	No.	Number of PDs overall

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** a high number of patients withdraws their informed consent **due to** unknown reasons, **then** an insufficient patient participation and/or poor statistical significance **may result.**	
event	*A high number of patients withdraw their informed consent*	
cause	*Unknown/various reasons*	
negative impact	*Insufficient patient participation or poor statistical significance*	
KRI	**High Percentage of Dropouts due to Informed Consent Withdrawal**	
Metric (underlying)	%	Percentage of drop out due to IC withdrawn
KRI thresholds	Green	0 - 5
	Yellow	5 - 10
	Red	> 10
Associated metrics (percentage or number)	No.	Number of enrolled patients
	No.	Number of patients with premature termination
	No.	Number of patients lost to follow-up

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** a high number of patients are lost to follow-up **due to** various reasons, **then** non-acceptance of the investigational product as the treatment of choice by the health authorities **may result.**	
event	*A high number of patients lost to follow-up*	
cause	*Various reason*	
negative impact	*Non-acceptance of the investigational product as the treatment of choice by the health authorities*	
KRI	**High Percentage of Lost to Follow-Up**	
Metric (underlying)	%	Percentage of lost to follow-up
KRI thresholds	Green	0 - 1
	Yellow	1 - 2
	Red	> 2
Associated metrics (percentage or number)	No.	Number of enrolled patients
	No.	Number of dropouts in total

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** a high number of datapoints have not been entered into the eCRF **due to** sloppiness or workload at the sites **then** a delayed reporting of serious adverse events and eventually a delayed database closure **may result.**	
event	*A high number of datapoints have not been entered into the eCRF*	
cause	*Sloppiness or workload at the sites*	
negative impact	*A delayed reporting of serious adverse events and a delayed database closure*	
KRI	**High Percentage of Missing CRF Entries/Pages**	
Metric (underlying)	%	Percentage of missing CRF pages
KRI thresholds	Green	0 - 10
	Yellow	10 - 20
	Red	> 20
Associated metrics (percentage or number)	No.	Number of enrolled patients
	No.	Weeks after enrollment

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** a delayed data entry happens **due to** frequent study visits, **then** poor data integrity, and a negative impact on study timelines **may result.**	
event	*Delayed data entry*	
cause	*Frequent study visits*	
negative impact	*Poor data integrity, negative impact on study timelines*	
KRI	**Long Mean Time for Data Entry**	
Metric (underlying)	Days	Time for data entry
KRI thresholds	Green	0 - 7 days
	Yellow	8 - 15 days
	Red	> 15 days
Associated metrics (percentage or number)	No.	Number of days to respond to queries
	No.	Number of enrolled patients
	No.	Visits taken place
	%	Visits taken place vs planned visits

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** patients could not come to the healthcare unit **due to** their health condition or mobility, **then** missing of important endpoints **may result.**	
event	*Patients could not come to the healthcare unit*	
cause	*Health condition or mobility*	
negative impact	*Missing of important endpoints*	
KRI	**High Rate of Missing Visits**	
Metric (underlying)	%	Missing percentage of visits
KRI thresholds	Green	0 -10%
	Yellow	10 - 15%
	Red	> 15%
Associated metrics (percentage or number)	No.	Number of enrolled patients
	%	Percent of dropouts
	No.	Number of planned visits

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** long term data or outcome data is missing **due to** patients dropping out of the study, being lost to follow-up, or being untraceable, **then** the non-acceptance of the study by health authorities **may result.**	
event	*Missing long term or outcome data*	
cause	*Patients dropping out of the study, being lost to follow-up, or being untraceable*	
negative impact	*Non-acceptance of the study by health authorities*	
KRI	**High Percentage of Missing Outcomes**	
Metric (underlying)	%	Percent missing outcomes
KRI thresholds	Green	0 - 2%
	Yellow	2 - 5%
	Red	> 5%
Associated metrics (percentage or number)	%	Percent of dropouts
	%	Percent of dropouts due to lost to follow-up
	%	Percent of dropouts due to withdrawal by subject

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** a site does not timely respond to queries **due to** sloppiness, **then** a delay for the database lock **may result.**	
event	*A site does not timely respond to queries*	
cause	*Sloppiness*	
negative impact	*A delay for the database lock*	
KRI	**High Rate of Delayed Query Responses**	
Metric (underlying)	%	Percent queries per patient responded to after more than 7 days of query being posted
KRI thresholds	Green	0
	Yellow	> 1
	Red	> 2
Associated metrics (percentage or number)	No.	Total number of queries (manual and automatic)
	No.	Total number of enrolled patients
	No.	Days to respond to queries

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** database cannot be locked **due to** missing data in the CRF and open queries, **then** delayed statistical analysis **may result.**	
event	*Database cannot be locked*	
cause	*Missing data in the CRF and open queries*	
negative impact	*Delayed statistical analysis*	
KRI	**Long Mean Time for Response to Queries**	
Metric (underlying)	No.	Days to respond to queries
KRI thresholds	Green	< 10
	Yellow	10 - 15
	Red	> 15
Associated metrics (percentage or number)	No.	Long time for data entry after patient visit
	%	Percent of overdue queries

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** the monitors do not confirm the responses to queries in time **due to** lack of resources or other reasons, **then** a delay in database lock and the study completion **may result.**	
event	*Monitors do not confirm the responses to queries in time*	
cause	*Lack of resources or other reasons*	
negative impact	*A delay in database lock and the study completion*	
KRI	**High Percentage of Unverified Queries**	
Metric (underlying)	%	Percentage of unverified queries
KRI thresholds	Green	< 10
	Yellow	10 - 20
	Red	> 20
Associated metrics (percentage or number)	No.	Number of manual queries
	No.	Number of automatic queries
	No.	Number of queries overall

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** site enters many data with mistakes and does not respond to queries in a timely fashion **due to** sloppiness, lack of training, **then** poor data integrity, negative impact on study timelines, incl. DBL impact **may result.**	
event	*Site enters data with mistakes and does not respond to queries in a timely fashion*	
cause	*Sloppiness, lack of training*	
negative impact	*Poor data integrity, negative impact on study timelines, incl. DBL impact*	
KRI	**High Percentage of Total Overdue Queries**	
Metric (underlying)	%	Percentage of queries not responded to within 7 days
KRI thresholds	Green	< 10
	Yellow	10 - 20
	Red	> 20
Associated metrics (percentage or number)	No.	Number of queries overall

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** a SAE underreporting happens **due to** various reasons, **then** poor data integrity, jeopardy of subject safety **may result.**	
event	*SAE underreporting*	
cause	*Various reasons*	
negative impact	*Poor data integrity, jeopardy of subject safety*	
KRI	**Under Reporting of Reported (S)AEs**	
Metric (underlying)	Ratio	Ratio of SAEs at certain sites compared to the overall study per patient visit
KRI thresholds	Green	Within 95% confidence interval
	Yellow	N/A
	Red	Outside 95% confidence interval
Associated metrics (percentage or number)	No.	Number of visits
	No.	Number of AEs

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** high rate of safety events identified **due to** study phase III (use drug for new indication) or other reasons, **then** negative impact on compound's safety profile **may result.**	
event	*High rate of safety events identified*	
cause	*Study phase III (use drug for new indication) or other reasons*	
negative impact	*Compound safety profile*	
KRI	**Over Reporting of Reported (S)AEs**	
Metric (underlying)	No.	SAE per visit
KRI thresholds	Green	0 - 0.15
	Yellow	0.15 - 0.34
	Red	> 0.34
Associated metrics (percentage or number)	No.	Number of visits
	No.	Number of SAEs
	No.	Number of AEs

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** the eCRFs are not monitored regularly according to plan **due to** lack of resources or other reasons, **then** a delayed database lock **may result.**	
event	*eCRFs not monitored regularly*	
cause	*Lack of resources or other reasons (COVID-19)*	
negative impact	*Delayed database lock*	
KRI	**eCRF: too many overdue monitoring pages, eCRF: too many unmonitored pages**	
Metric (underlying)	%	Percent eCRF pages unmonitored
KRI thresholds	Green	10%
	Yellow	10 - 15%
	Red	> 15%
Associated metrics (percentage or number)	No.	eCRFs entered
	No.	Patients enrolled
	No.	eCRFs planned to be entered

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** high screen failure rate **due to** various reasons, **then** a study duration impact **may result.**	
event	*High screen failure rate*	
cause	*Various reasons*	
negative impact	*Study duration impact*	
KRI	**High Ratio of Screen Failures**	
Metric (underlying)	%	Percentage of screen failures
KRI thresholds	Green	< 10%
	Yellow	10 - 20%
	Red	> 20%
Associated metrics (percentage or number)	No.	Number of Screening Failures
	No.	Number of enrolled patients

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** the time between patient visit and data entry is too long **due to** lack of resources or high number of patients enrolled, **then** patient safety and database closure **may be** jeopardized**.**	
event	*Time between patient visit and data entry too long*	
cause	*Lack of resources or high number of enrolled patients*	
negative impact	*Patient safety and/or database closure*	
KRI	**Critical Data Entry Time is Too Long**	
Metric (underlying)	Days	Time between patient visit and data entry
KRI thresholds	Green	< 3 days
	Yellow	3 - 5 days
	Red	> 5 days
Associated metrics (percentage or number)	No.	Patients enrolled

RISK-BASED QUALITY MANAGEMENT
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Risk Statement	**If** the study drug is not being dispensed properly **due to** misunderstanding of the dispensing instructions or any other reason, **then** patient safety or the drug efficacy **may be** negatively impacted**.**	
event	*Study drug not being dispensed properly*	
cause	*Misunderstanding of the dispensing instructions or any other*	
negative impact	*Patient safety of study drug efficacy*	
KRI	**Inappropriate IP Administration (Dose/Timing Dispensing Error)**	
Metric (underlying)	%	Study drug underdosing/study drug overdosing
KRI thresholds	Green	+/- 10%
	Yellow	+/- 10 - 15%
	Red	> +/- 15%
Associated metrics (percentage or number)	No.	Tablets dispensed
	No.	Tablets returned
	%	Compliance

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** only a fraction of the screened patients is enrolled into the study **due to** a high rate of screening failures, **then** the non-acceptance of the investigational product as the treatment of choice by health authorities **may result.**	
event	*Only a fraction of the screened patients is enrolled into the study*	
cause	*A high rate of screening failures*	
negative impact	*The non-acceptance of the investigational product as the treatment of choice by health authorities*	
KRI	**Patients Screened: Too Low % of Target Achieved**	
Metric (underlying)	%	Screen failure rate
KRI thresholds	Green	< 10%
	Yellow	10 - 20%
	Red	> 20%
Associated metrics (percentage or number)	No.	Number of screening failures
	No.	Number of enrolled patients

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** many patients drop out during the study **due to** various reasons, **then** non-acceptance of the study results by health authorities **may result.**	
event	*Many patients drop out*	
cause	*Various reasons*	
negative impact	*Non-acceptance of the study results by health authorities*	
KRI	**Low Ratio of Subjects who Completed the Study**	
Metric (underlying)	%	Ratio of drop out cases
KRI thresholds	Green	< 3%
	Yellow	≥ 3 - 5%
	Red	> 5%
Associated metrics (percentage or number)	No.	Number of drop outs due to AEs
	No.	Number of enrolled patients
	No.	Number of lost to follow up
	No.	Number of informed consent withdrawn

RISK-BASED QUALITY MANAGEMENT
GOLDEN KRI SET FOR CLINICAL TRIALS

Risk Statement	**If** the rate of manual queries is too high **due to** low number of EDC built-in edit checks, **then** increase in workload for site staff and internal staff **may result.**	
event	*Rate of manual queries*	
cause	*Low number of EDC built-in edit checks*	
negative impact	*Increase in workload for external and internal staff*	
KRI	**High Rate of Manual Queries**	
Metric (underlying)	%	Rate of manual queries/patient
KRI thresholds	Green	< 2%
	Yellow	≥ 2 - 4%
	Red	> 4%
Associated metrics (percentage or number)	%	Automatic queries
	No.	Queries
	No.	Manual queries

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