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# **Updates to ICH E6: What it means for Monitoring**

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# endum to ICH E6 (R1): Guideline for GCP E6 (R2)

## E6 (R1) Document History

First Codification	History	Date	New Codification <b>November 2005</b>
E6	Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.	27 April 1995	E6
E6	Approval by the Steering Committee under <i>Step 4</i> and recommended for adoption to the three ICH regulatory bodies.	1 May 1996	E6

## E6(R1) *Step 4* version

E6	Approval by the Steering Committee of <i>Post-Step 4</i> editorial corrections.	10 June 1996	E6(R1)
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# Addendum to ICH E6 (R1): Guideline for GCP E6 (R2)

## E6 (R2) Document History

### Current E6(R2) Addendum *Step 2* version

Code	History	Date
E6(R2)	<p>Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.</p> <p>Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: <a href="#">Introduction</a>, <a href="#">1.11.1</a>, <a href="#">1.38.1</a>, <a href="#">1.39</a>, <a href="#">1.60.1</a>, <a href="#">2.10</a>, <a href="#">4.2.5</a>, <a href="#">4.2.6</a>, <a href="#">4.9.0</a>, <a href="#">5.0</a>, <a href="#">5.0.1</a>, <a href="#">5.0.2</a>, <a href="#">5.0.3</a>, <a href="#">5.0.4</a>, <a href="#">5.0.5</a>, <a href="#">5.0.6</a>, <a href="#">5.0.7</a>, <a href="#">5.2.1</a>, <a href="#">5.2.2</a>, <a href="#">5.5.3 (b)</a>, <a href="#">5.5.3 (h)</a>, <a href="#">5.18.3</a>, <a href="#">5.18.6 (e)</a>, <a href="#">5.18.7</a>, <a href="#">5.20.1</a>, <a href="#">8.1</a></p>	11 June 2015

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464506.pdf>
- Current Status: Step 2b Review = Released for Review and Comments
- Final E6 (R2) Guidelines slated for **November 2016** after review by RAs in EU, USA, Japan, Canada and Switzerland

## What Are The Changes?

- **Twenty Six Change Elements increase Efficiency and Focus on what is relevant**
  - New Definitions
  - New Responsibilities For Investigator and Sponsor
  - Sponsor's Control of CRF and essential documents
  - Quality Management
  - Vendor Management
  - **Risk Assessment**
  - **Monitoring Plan: definition and implementation**
  - **Introducing Risk Based Monitoring Concept**
  - Changes to IT in Clinical Research: computer validation and electronic records
  - Non-Compliance
  - Extended requirements to minimum contents of TMF

## Glossary Section

### 1.11.1 Certified Copy

- A **paper or electronic copy** of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.

### 1.38.1 Monitoring Plan (in addition to Protocol, SOPs, GCP and Regulations):

- A description of the methods, responsibilities and requirements for monitoring the trial.

### 1.39 Monitoring Report (addition)

- Outcomes of any centralized monitoring should also be reported.

### 1.60.1 Validation of computerized systems

- A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled. **Validation** should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system.

## The Principles of ICH GCP

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

### **ADDENDUM**

- This principle applies to all records (**paper or electronic**) referenced in this guideline.

**2.11** The **confidentiality of records** that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

## Investigator

4.2.5 The investigator is **responsible for supervising any individual or party** to whom the investigator delegates study tasks conducted at the trial site.

4.2.6 If the investigator/institution retains the services of any party to perform study tasks they should ensure this **party is qualified** to perform those study tasks and should implement procedures to ensure the integrity of the study tasks performed and any data generated.

4.9.0 The investigator should maintain adequate and **accurate source documents** and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g., *via* an audit trail).

## Sponsor (1)

### 5.0 Quality Management

The sponsor should implement a **system to manage quality** throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.

Sponsors should focus on trial activities essential to **ensuring human subject protection and the reliability of trial results**. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making.

The **methods used to assure and control the quality of the trial should be proportionate to the risks** inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, case report forms, and other operational documents should be clear, concise and consistent.

The quality management system should use a **risk-based approach...**



## Sponsor (2)

### *5.0.1 Critical Process and Data Identification*

**During protocol development**, the sponsor should identify those **processes and data that are critical** to assure human subject protection and the reliability of study results.

### *5.0.2 Risk Identification*

**Risks to critical study processes and data should be identified.** Risks should be considered at both the system level (e.g., facilities, standard operating procedures, computerized systems, personnel, vendors) and clinical trial level (e.g., investigational product, trial design, data collection and recording).

### *5.0.3 Risk Evaluation*

The identified **risks should be evaluated** by considering:

- (a) The **likelihood** of errors occurring, given existing risk controls.
- (b) The **impact** of such errors on human subject protection and data integrity.
- (c) The extent to which such errors would be **detectable**.

## Sponsor (3)

### *5.0.4 Risk Control*

The sponsor should **identify those risks that should be reduced (through mitigating actions) and/or can be accepted**. Risk mitigation activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify **systematic** issues that can impact subject safety or data integrity. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

## Sponsor (4)

### *5.0.5 Risk Communication*

The **quality management activities should be documented** and communicated to stakeholders to facilitate risk review and continual improvement during clinical trial execution.

### *5.0.6 Risk Review*

The sponsor should periodically review **risk control measures** to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

### *5.0.7 Risk Reporting*

The sponsor should describe the quality management approach implemented in the trial and **summarize important deviations** from the predefined quality tolerance limits **in the clinical study report** (ICH E3, Section 9.6 Data Quality Assurance).

## Sponsor (5)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

### ADDENDUM

- **The Sponsor should ensure oversight** of any trial-related duties and functions carried out on its behalf.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

### ADDENDUM

- The Sponsor should document **approval of any subcontracting** of trial-related duties and functions by a CRO.

## Sponsor (6)

5.5.3b For **EDC, SOP should cover system setup, installation and use**. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and decommissioning. The responsibilities of the sponsor, investigator and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in the use of the systems.

5.5.3h Ensure the integrity of the data including any data that describe the context, content and structure of the data. This is particularly important when **making changes to the computerized systems**, such as software upgrades or migration of data.

## Sponsor (7) Monitoring

### 5.18.3 Extent and Nature of Monitoring (addition):

- The sponsor should develop a systematic, prioritized, **risk-based approach** to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. A **combination of on-site and centralized monitoring activities** may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the **monitoring plan**).
- *On-site* monitoring is performed at the sites at which the clinical trial is being conducted.
- **Centralized monitoring** is a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner. Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring by such methods as:

## Sponsor (8) Monitoring.

### 5.18.3 Extent and Nature of Monitoring (continued):

- (a) Routine review of submitted data.
- (b) Identification of missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems.
- (c) Using statistical analyses to identify data trends such as the range and consistency of data within and across sites.
- (d) Analyzing site characteristics and performance metrics.
- (e) Selection of sites and/or processes for targeted on-site monitoring.

## Sponsor (9) Monitoring

### 5.18.6 (e) Monitoring report:

- Monitoring results should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up as indicated. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

### 5.18.7 Monitoring plan:

- The sponsor should develop a monitoring plan that is **tailored to the specific human subject protection and data integrity risks of the trial**. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.





## Sponsor (10)

### 5.20.1 Non-Compliance (addendum):

- When significant noncompliance is discovered, the sponsor should perform a **root cause analysis and implement appropriate corrective and preventive actions**. If required by applicable law or regulation the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of the trial protocol or GCP.

## Essential Documents

### 8.1 Essential Documents (Addendum)

- The sponsor and investigator/institution should maintain a **record of the location(s)** of their respective essential documents. The storage system (irrespective of the media used) should provide for document identification, search and retrieval.
- Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential document list. The sponsor and/or investigator/institution should include these as part of the trial master file.
- The sponsor should ensure that the **investigator has control of and continuous access to the CRF** data reported to the sponsor. The sponsor should not have exclusive control of those data.
- When a copy is used to replace an original document, the copy should fulfill the requirements for **certified copies**.
- The investigator/institution should have **control of all essential documents** and records generated by the investigator/institution before, during and after the trial.



# Background

- 100% SDV and monitoring takes time and focus away from more important functions.
- Analysis of warning letters: traditional monitoring practices were inefficient and ineffective - poor data quality and patient safety.
- Using solely a traditional 100% source document verification (SDV) is no longer acceptable in today's technology-rich era.

# Background/Risk Based Monitoring

**Goal:** Achieve patient safety, statistical validity, and correct conclusions of a trial

- The industry is being guided to build better monitoring plans and to apply monitoring resources selectively to address high risk areas.
- Traditional Monitoring does not ensure consistency, quality and safety
- Monitoring costs account for a large portion of the total CRO budget—around 25-35%
- **Suggested solution is RBM**



# FDA Guidance on RBM

- FDA published the final guidance document “Oversight of Clinical Investigations - **A Risk-Based Approach to Monitoring**” in August 2013
- The goal: enhance human subject protection and the quality of data by **focusing sponsor oversight on the most important** aspects of study conduct and reporting.
- Describes strategies for monitoring activities that reflect a modern, **risk-based approach focusing on critical study elements**, and relies on a combination of monitoring activities to oversee a study effectively.



# Risk Based Monitoring

- Risk Based Monitoring (RBM):
  - Reduced Source Document Verification (SDV)
  - Targeted Monitoring
  - Triggered Monitoring
  - Clinical Data Review
  - Centralized Data Review
  - On-Site and Remote Monitoring
  - Site Management and Communication
- Optimal RBM strategy incorporate Targeted + Reduced + Triggered Monitoring.
- Why 100% SDV? Do We Really Need it? What Makes it 100%?



# Reduced Source Data Verification

- **Reduced source verification** in the context of overall framework of a cross functional risk-based monitoring methodology:
  - Identify cross functional Key Risk Identifiers (KRI)
  - Framework for monitoring frequency
  - Combine on-site and off-site (remote) monitoring
  - Create/modify Risk Assessment Definitions and provide Risk Assessment Tool – periodic evaluation.
  - Source Document Verification (SDV) vs Clinical Data Review (CDR)
  - Targeted SDV approach



# Monitoring Plan (MP)

- The monitoring plan should be used as a guide by the CRAs and ALL CLINICAL TEAM
- The plan does not replace an understanding of, or adherence to the requirements described in the protocol, ICH/GCP, CRO specific SOPs, and/or Sponsor's SOPs, as applicable
- Any deviations from the MP must be documented, be approved by the Sponsor prior to implementation, unless in response to a safety emergency at an investigator site.





# Training on Monitoring Plan

- Protocol/Study specific procedures and Monitoring Plan
- **Monitoring Plan = Protocol** of Monitoring the Study
  - Visit reports guidelines
  - Follow up letter requirements
  - Monitoring plan training
  - Monitoring Forms
  - CDR tools training
- KRI exercise
- Safety training



# Centralized Monitoring

- Systems:
  - Electronic Data Capture (EDC)
  - IVRS
  - Patient Profiles
  - Clinical Trial Management System (CTMS)
    - Deviation Logs
    - Screening Logs
    - AE Logs
    - ICF Logs
  - Safety Database
  - Medical Review



# On-site and Off-site (Remote) Monitoring

- On-site and off-site monitoring takes place within a framework of cross-functional risk-based monitoring methodology. These activities are part of a larger set of activities intended to provide surveillance of critical data points.
- On-site/Off-site (remote) monitoring supported by:
  - Patient Profiles – CRA & Medical review
  - Review of Site Risk Assessment scores
  - Centralized aggregated listing reviews
  - Statistical assessment of aggregated data, site specific data
  - Clue-point statistical outputs for outlier data
  - Centralized Safety analysis
  - Centralized Medical Reviews

# On-site Reduced Monitoring Approach (Sample)

- CRAs monitor the following:
  - 100% of all ICFs
  - 100% reported SAEs – SAEs meeting reporting definitions per protocol – “Not expected” in patient population; or assessed as “Possible or Probable” in relation to study drug.
  - 100% of eCRF data reviewed against source for the first two subjects enrolled; there after one of every 4 patients or every 6 months (low risk), whichever comes first and depending on ongoing site risk assessment.
  - Identify subjects for 100% SDV and assign selected subject(s) to the CRA. To blind sites to subject selection, request access to multiple subject charts for the on-site visit.



# On site Monitoring

- In addition to 100% SDV on assigned patients, the CRA should attempt to complete at a minimum the following:
  - Review data sourcing for Primary (Secondary?) endpoints via the use of appropriate listings and reports.
  - IP accountability via IWRS to determine appropriate kit assignment for all patients
- CRA completes Monitoring Visit Report **and Risk Assessment** exercise following every on-site and remote monitoring visit.

# Onsite Monitoring: Clinical Document Review

- In addition to 100% SDV for assigned patients and data points, **clinical document review** (CDR).
  - CDR is not a comparison of source data against CRF data but rather a means to evaluate areas that do not have an associated data field in the CRF or a system available for more timely remote review.
  - CDR involves review of source documentation to check quality of source, review protocol compliance, ensure the critical processes and source documentation (e.g. accurate, legible, complete, timely, dated) are adequate, to ascertain Investigator involvement and appropriate delegation, and assess compliance to other areas (e.g. SOPs, ICH GCPs).



# Remote Monitoring (1)

- Perform eCRF clinical data review for patients and items noted on the Remote Monitoring Checklist.
- The goal of this activity is to:
  - Evaluate the status of site enrollment and compare with information in CTMS
  - Check overall status of eCRF entries and queries
  - Respond to queries directed to the CRA
- Review eCRF data according to remote monitoring checklist, including but not limited to:
  - Verify continued eligibility of enrolled subjects (review of adverse events, concomitant medication, lab values)



## Remote Monitoring (2)

- Assess eligibility of new subjects based on requested documentation
- Determine if SAEs occurred and if so, verify proper reporting (review AEs and Con-Meds in the eCRFs, discuss SAEs with sites)
- Confirm the schedule of events is followed
- Determine if data are timely entered and are complete
- Confirm pages are not inappropriately saved as blank
- Confirm investigator comments are specific and do not require clarification
- Confirm data have been entered in accordance with the eCRF guidelines
- Generate new queries based on review of the data in the eCRF
- Identify issues (e.g., no new data entered, data trends, deviations)



# Remote Monitoring Visit Preparation (1)

- CRA to request necessary documentation from site via fax or scan as applicable:
  - Subject Screening/Enrollment Log
  - Subject ICF Log
  - Local Laboratory Reports for randomized patients
  - Site IP/Subject IP/Accountability Logs
  - Temperature Logs (IP and freezers)
  - Delegation of Authority Log/Staff Training Log/Documentation
  - IRB Submissions/Approvals (if applicable)

# Remote Monitoring Visit Preparation (2)

- Review last on-site and off-site MVR and Risk Assessment to determine any outstanding site issues that can be reviewed/resolved remotely
- Verify latest Enrollment/IVRS Report with EDC Status
- Enter Remote Monitoring Visit (RMV) as planned visit into CTMS
- Send a written confirmation of remote visit including the request for a telephone call with the key personnel ( e.g. PI/SI/SC)



# Remote Monitoring Follow up (1)

- Schedule Follow-up call with key study personnel at site to discuss all critical areas
- Inform key study personnel about key issues and critical information (e.g. Sponsor key messages)
- Review study status and subject enrollment
- Discuss any early discontinuations to ensure proper follow-up and documentation
- Discuss results from remote patient review
- Review any protocol deviations/violations
- Discuss any discrepancies or issues with EDC entry



## Remote Monitoring Follow-up (2)

- Review any new or still unresolved queries (EDC, central lab, CUS)
- Review AE/SAE/Outcome reporting
- Review and follow up on any early withdrawals
- Follow up on ongoing site issues
- Inquire about IP supplies, study equipment and calibration
- Discuss any staff changes and confirm that appropriate training is performed and documented
- Verify that all IRB notifications are made by site, if applicable



## Remote Monitoring Follow up (3)

- Send follow up letter to site summarizing key findings and action items
- Complete Monitoring Visit Report including Site Health Assessment in CTMS and submit for review (together with confirmation and follow up letter to site)
  - **Any critical findings have to be escalated**
- Update CTMS with any new site information as applicable (e.g. new early withdrawals, new staff members)

# Centralized Monitoring

- Ongoing review of the following:
  - Centralized targeted listing reviews
  - Medical review of select patient profiles, safety listings
  - Review of Site Risk Assessment scores
  - Statistical assessment of aggregated data, site specific data
  - Clue-point statistical outputs for outlier data
- When an issue is detected, communicate with CRA potential need for additional monitoring based on a discussion and findings at the last on-site visit



# Risk Assessment and Monitoring Frequency (1)

- The monitoring visit schedule and visit duration is based on the consideration of potential and uncovered risks at the investigator site.
- Risk assessment level for a site may change during the study resulting in changes to the monitoring visit frequency and duration.
  - CRA provides subjective/objective assessment of risk via the CTMS
  - CTMs reviews CRA risk assessment and will be requested to confirm alignment with CRA assessment based on best overall information available. This may include feedback from Centralized Review.
    - When assessed less than high risk, CTM final decision will prevail
    - When any signal of high risk, CTM final decision will prevail



# Risk Assessment and Monitoring Frequency (2)

- **KRI – you can not manage what you can not measure!**
- Until study teams start receiving enough clinical and operational data, couple of months into a study, they can not be objective.
- Until that point, the teams set subjective thresholds based on previous experience, both with individual sites and experience of study team members.
- Once data is accumulated - shift from those pre-set thresholds and adapt to the objective reality of the trial



# High Risk Examples

- Sites are visited ~ every X weeks, or more frequently. High-risk sites may include sites that have:
  - Significant and/or repetitive quality issues, data queries, time to resolution
  - Significant issues or outliers at centralized aggregated and targeted listing review
  - Rapid and/or high enrollment (> X patient per month).
  - High number of Early Withdrawals (EW) or Lost to Follow-ups (LTFU) or missing endpoints data
  - Sites that have a significant number of unreported SAE



# Medium Risk Examples

- Sites are visited according to average expectations after the site's first X patients are 100% SDV'd (e.g., ~every Y weeks). Medium risk may include sites that have:
  - Few addressable issues with low impact on study outcomes or safety data
  - Consistent enrollment (certain # Patients/ month)
  - Infrequent protocol violations for non-endpoint data, delayed reporting or response on follow-up questions
  - General delay in query response and/ or incomplete resolution
  - No unreported SAE or endpoints but delay in reporting or response to requests from Safety/Medical reviewers



# Low Risk Examples

- Sites visited less frequently after the site's first X patients are 100% SDV'd (e.g. ~every Y months). Low risk sites may include:
  - Sites that have shown consistent adherence to the study protocol (i.e., no protocol deviations other than minor out of window deviations) and have no outstanding high-risk issues noted during the last monitoring visit.
  - Sites that have a low patient recruitment (< Z patients per month).
  - Sites that have had no new recruitment since the previous Interim MV and no outstanding issues requiring follow-up at the site.



# Risk Based Monitoring (RBM)

## High risk

- Significant and/or repetitive quality issues (delayed data entry, etc)
- Significant productivity issues (Missed pts Visits/Timelines not met)
- Significant number of queries
- Significant number of Protocol Deviations
- Rapid/High Enrolment (> # pts / month)
- High Number of EW or LTFU or missing endpoints data
- Significant number of unreported SAE/Study Outcomes
- High score on risk assessment tool

- **MV ~ every 4-8 weeks**
- **Additional time on-site?**
- **Increased SDV%?**

## Medium Risk

- Few addressable issues with low impact on study outcomes or safety data
- Consistent enrolment (# pts/month)
- Infrequent protocol violations for non-endpoint data
- Delayed reporting or response on FU questions
- General delay in query response and/ or incomplete resolution
- No unreported SAE or outcome events but delay in reporting or response to CEC queries

- **MV ~ every 12 weeks**

## Low risk

- excellent study protocol compliance
- no outstanding serious issues noted during the last MV
- anticipated low patient recruitment (< # pt/month).

- **MV ~ every 6 months**



# Triggering Site Visits

- Central and Off-site Monitoring Activities (listings review, deviations review, remote monitoring, etc.), serve as the foundation of monitoring efforts and are complemented by targeted On-site Monitoring Activities based on:
  - a defined risk level,
  - critical process and data,
  - ongoing assessment of Risk Indicators.
  - Ad hoc



# site Communications/Management

- The assigned CRA is the primary contact for the site for routine operational study issues. CRAs are expected to contact their designated sites at minimum (depending on the site needs) # times a month to discuss study issues and remote monitoring/document requests.
- CRAs document significant verbal communications with the site by completing an Ad hoc Report in CTMS.
  - Verbal communication is considered significant if it:
    - 1) dictates an action to be initiated;
    - 2) provides an interpretation and/or clarification of a point of view or idea;
    - 3) provides directions to perform a task.



# Site Health Assessment

#	Remote and On-Site Visit Risk Assessment	Scoring Guidance	Tools for Remote Monitoring
1	Were there ineligible subjects identified since last visit?	3= Yes 1= No	Review Patient Profiles or EDC.
2	Were patients randomized incorrectly since the last visit: I/E, wrong dose assigned; wrong dose distributed	3= Yes 1= No	Review Patient Profiles or EDC.
3	Any new missing endpoint data since the last visit?	3 = Yes 2 = No, but out of window 1 = No	Review Patient Profiles or EDC. Review Study Portal
4	Any new missed clinical outcomes assessments since last visit. Were there Unreported Outcomes noted during the visit?	3= Yes 1= No	Review Patient Profiles - AEs, SAEs, Pes
5	Were there issues with ICF consenting/reconsenting noted during the visit?	3= No pt signature, incorrect ICF, no investigator signature; unconscious pts? 2= Administrative, sign/date corrections, minor NTF 1= No issues	Review ICF log relative to IRB approval dates
6	Any new Withdrawal Consents/LTFU/ since the last visit?	3= Yes 1= No	Review Patient Profiles and IVRS status for study drug discontinuation
7	Reporting and communication with appropriate ethics complete and up to date?	3 = No 2 = Yes, but delay in reporting 1 = Yes	Compliance to local ethics reporting requirements for IND Safety reports or local SAEs, when applicable.



# Site Health Assessment Tools

db.com/Tasks/Inbox/default.aspx

18	Did any patients discontinue since the last visit?	1		3 = Yes, early study drug discontinuations due to patient preference 1 = No or yes - study drug discontinuation for safety reasons - PI involved
19	Was there a low level of investigator (PI/Sub-I) oversight noted during this visit?	1		3= Lack of oversight impacts outcomes and safety 2= Lack of oversight impacts administrative/operational effectiveness 1= Investigator adequately involved
20	Concerns about staffing or supplies / equipment: Amt of staff turn-over Staff training needs Inappropriate delegation of responsibilities adequacy, maintenance, calibration of supplies/equipment (CUS, Central lab kits)	1		3 = High concern (high staff turnover; staff training not ensured; Inappropriate delegation of responsibilities) 2 = Moderate concern (key site personnel available to provide training, support for re-supplies required; maintenance documents provided upon request) 1= No/little concern (little staff turnaround, timely supplies management handled site staff)
21	Site staff unaware of latest Sponsor Key Messages	1		3 = Yes, PI/SC unaware latest Sponsor Key Message 2 = Yes, PI/SC aware but required additional clarification 1 = Site staff fully aware of latest messaging
22	Timeliness of CRF entry	1		3 = data only entered upon request 2= consistently >14 days after visit completion; or incomplete data 1 = consistently within 7 days after visit completion;
23	Issues with site access to study systems?	1		3= Yes, CRA to assist w access 2= Yes, but access information forgotten; delayed entry (IVRS, EDC) 1 = No issues noted
24	Were there issues with site file and eTMF completeness relative to expected available site documents?	1		3 = Yes, IRB submissions/approvals for protocol, consents, SAEs, and IND Safety Update not complete; 1572s not complete 2 = Operational documentation not available (Delegation Logs, Screening logs, etc) 1 = File needs minimal updating

Total score: 126  
Risk Level:

**CRA's risk assessment**

**CRA Assessed Risk level**

Medium

**CRA's Comments**

[Redacted comment text]

**CTM's risk assessment**

**CTM Assessed Risk level**

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**CTM's Comments**

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# Evolution of MV Schedule/Budget: Traditional

Study assumptions:

Start Up: Start to FPFV: 3 mo

FPFV – LPLV (enrollment): 7,5 mo

LPLV – LPLV (Follow up): 4,5 mo

LPLV – Close Out: 3 mo

Length of patient participation: 4,5 mo

# of Sites: 100

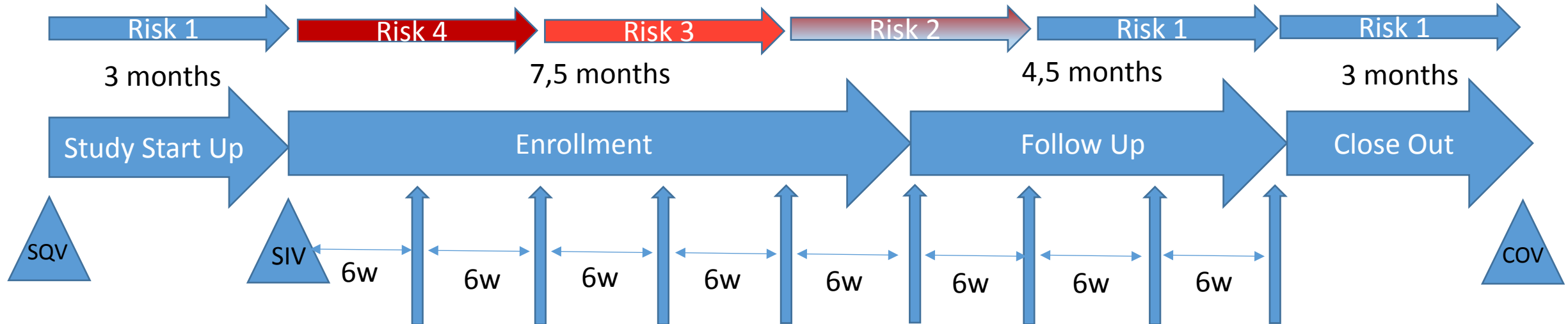
SDV 100%

Visit Time = Prep (4H)+Travel (12H)+Onsite (8H)+Follow Up (4H) = 28H

CRA time = \$100/hour

Cost per MV = \$2,800 + \$600 Travel Costs = \$3,400

Monitoring Visits Budget = **\$340,000** Excluded SQV, SIV, COV



# Evolution of MV Schedule/Budget: Rational

Study assumptions:

Start Up: Start to FPFV: 3 mo

FPFV – LPFV (enrollment): 7,5 mo

LPFV – LPLV (Follow up): 4,5 mo

LPLV – Close Out: 3 mo

Length of patient participation: 4,5 mo

# of Sites: 100

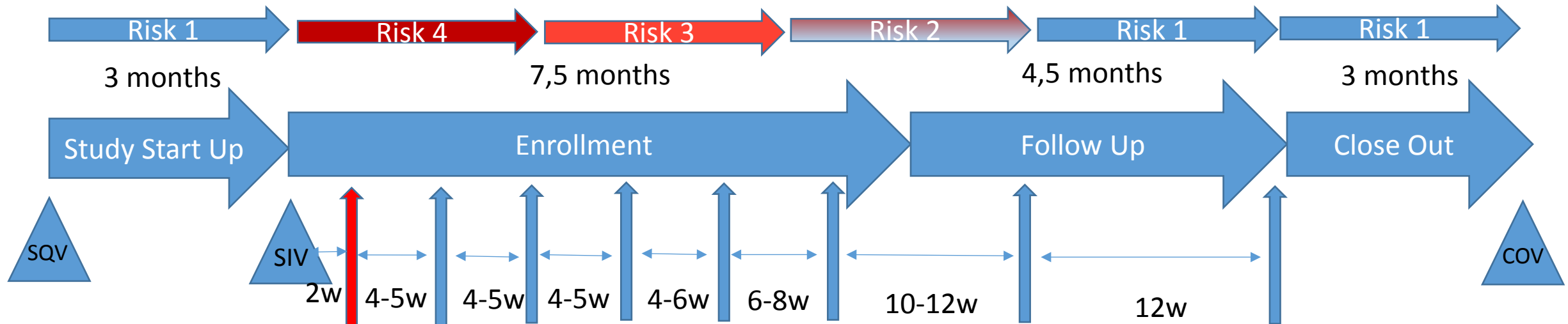
SDV 100%

Visit Time = Prep (4H)+Travel (12H)+Onsite (8H)+Follow Up (4H) = 28H

CRA time = \$100/hour

Cost per MV = \$2,800 + \$600 Travel Costs = \$3,400

Monitoring Visits Budget = **\$340,000** Excluded SQV, SIV, COV



# Evolution of MV Schedule/Budget: RBM

Study assumptions:

Start Up: Start to FPFV: 3 mo

FPFV – LPFV (enrollment): 7,5 mo

LPFV – LPLV (Follow up): 4,5 mo

LPLV – Close Out: 3 mo

# IMVs: 5; # RMVs: 5

# of Sites: 100

SDV **60%**

Visit Time = Prep (4H)+Travel (12H)+Onsite (8H)+Follow Up (4H) = 28H

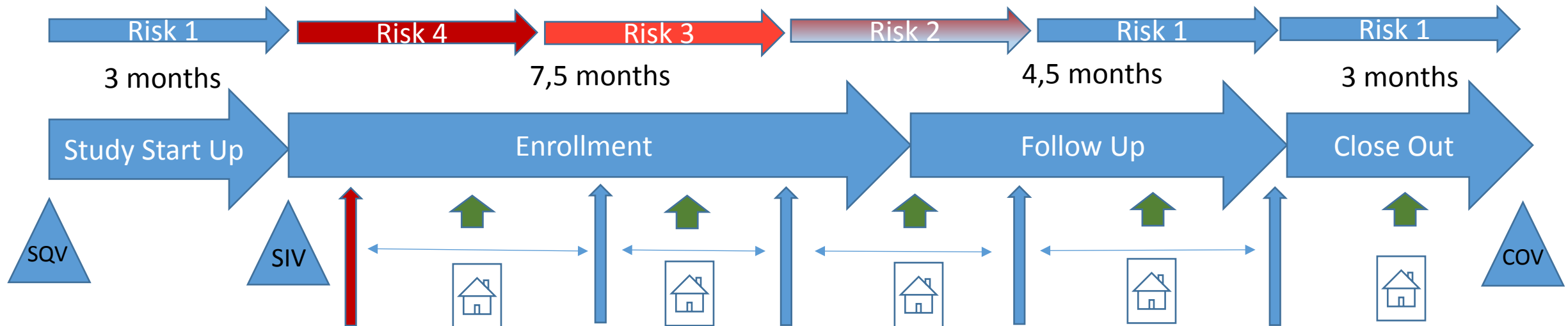
CRA time = \$100/hour

Cost per IMV = \$2,800 + Travel Costs (\$600) = **\$3,400**

RMV Cost = Prep (2H) + On phone (4H) + Follow up (2H) = 8H or **\$800**

Overall Monitoring Budget = 100\*(\$3,400\*5 + \$800\*5)= **\$210,000** -  
Excluded SQV, SIV, COV

**38%**

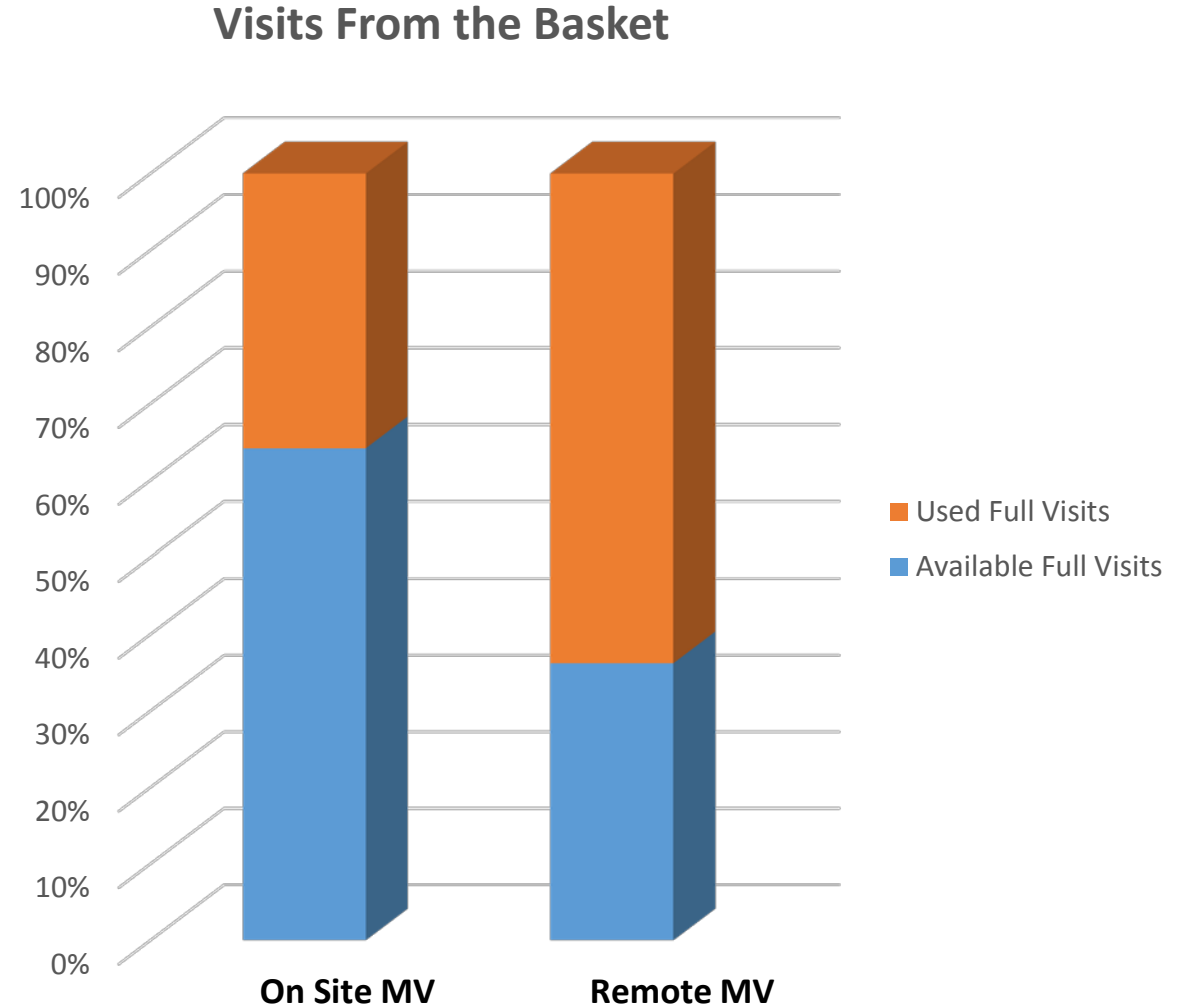


**Visits frequency and choice of the visit mode depends on Site Health Assessment score and Central Monitoring Triggers**



# “Out of the Basket” Methodology

- Combination of Remote and On-Site Monitoring
- Triggered, Targeted and Focused Monitoring
- Visits only when and where needed
- **“Out of the Basket” Methodology**





CONFIDENCE  
PHARMACEUTICAL  
RESEARCH

**THANK YOU FOR YOUR ATTENTION !**

- **Questions?**
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