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Certified GCP training for Investigators on the Updated ICH GCP guidelines (E6 R2 Update)

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Centre Hospitalier Luxembourg (CHL)

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EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE

What is New in the ICH-GCP Guidelines with Integrated Addendum E6 (R2)?

GCP – Refresher Training for Investigators and Their Staff

What is New in the ICH-GCP Guideline With Integrated Addendum E6 (R2)?

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Introduction (1)

- ICH E6 (R2)
- This revision is an **integrated addendum** to the ICH GCP E6 (R1)
- Adopted by CHMP for release for consultation: 23 **July 2015**
- Public consultation: Aug 2015 – Feb 2016
- Final adoption by CHMP: 15 **December 2016**
- Date for coming into effect: 14 **June 2017**

Introduction (2)

- ICH E6 (R1) Guideline was originally adopted around 20 years ago and still provides an excellent standard for the conduct of clinical trials.
- The recent revision ICH E6 (R2) dated November 1996 is the first update since 1996
- The changes are introduced as an **Integrated Addendum to the** existing ICH E6 (R1) guideline
- This revision provides major additions in Quality Management for the sponsors but also for investigators
- It is the new approved standard for the European Union, Japan, United States, Canada, and Switzerland

Rationale for Updating ICH E6

20 years ago, at the time of ICH E6 (R1) release, clinical trials were **largely paper-based**

Since 1996,

- major **evolutions in technology** happened with an increasing use of **electronic data** in reporting and recording
- scale, complexity, and cost of clinical trials have increased

This revision encourages implementation of improved and **more efficient approaches** to clinical trial design, conduct, oversight, recording and reporting. Standards regarding electronic records and essential documents have also been updated.

E6 (R2): Overview of the Changes (1)

1. Glossary - new definitions

- 1.63 "Certified copy"
- 1.64 "Monitoring plan"
- 1.65 "Validation of Computerized Systems"

2. Principles of GCP - update on sections

- 2.10 media *(used for trial documentation)*
- 2.13 systems *(focus on systems essential to subject protection + reliability of trial results)*

3. IEC - no change

E6 (R2): Overview of the Changes (2)

4. Investigator: update on sections

- 4.2 adequate resources *(delegation and supervision)*
- 4.9 records and reports *(focus on source documents)*

5. Sponsor – *major update on quality management systems !*

6. Essential Documents *(archiving obligations for sponsors and investigators)*

E6 (R2): Impact on Sponsor's Obligations

- **5.0 Quality Management**
  - Risk-based Quality Management System
  - Operational feasibility- Simplification of procedures
- **5.2 CROs** / oversight
- **5.5 Data Handling, Record Keeping**
  - Risk-based validation of electronic systems
  - SOPs and training for using electronic systems
- **5.18 Monitoring**
  - Systematic risk-based approach to monitoring / Monitoring Plan
  - Centralized Monitoring
  - Reporting
- **5.20 Noncompliance**
  - Root cause analysis and CAPA

Changes in Detail: Glossary(1)

- **1.63 Certified Copy**

  A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Draft Guideline on GCP Compliance in relation to TMF (for consultation until 11.07.2017)

"A certified copy is 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 a copy having the exact content and meaning of the original.

Changes in Detail: Glossary(2)

- **1.64 Monitoring Plan**

  A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

- **1.65 Validation of Computerized Systems**

  A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

Changes in Detail: GCP Principles(1)

- **2.10**

  Current text:

  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 referenced in this guideline, irrespective of the type of media used.

Changes in Detail: GCP Principles(2)

- **2.14**

  Current text:

  Systems with procedures that assure the quality of every aspect of the trial should be implemented.

  Addendum:

  Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

Changes in Detail: Investigator Responsibilities (1)

4.2 Adequate Resources:

- **4.2.5**

  The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

- **4.2.6**

  If the investigator / institution retains services of any individual or party to perform trial-related duties and functions, the investigator / Institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Changes in Detail: Investigator Responsibilities (2)

4.9 Records and Reports

- **4.9.0**

  The investigator / institution 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).

Changes in Detail: Essential Documents (1)

The sponsor and investigator / institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of specific documents to the trial.

Changes in Detail: Essential Documents(2)

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 over those data. *(e.g. diary data? Central lab data?)*

When a copy is used to replace an original document (e.g., source documents, CRF), 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.
(How to organise this? For how long? 25 years?)

Conclusions

Quality management has to become truly risk-based

GCP revision should enable sponsors and investigators to conduct trials more efficiently by utilizing new and better technological solutions

GCP revision intends to achieve cost reductions while improving data reliability by the means of better planning and clarity of responsibilities

Data integrity and **subject protection** remain the cornerstones of GCP !

Sponsor Responsibility: Focus on Quality Management

GCP – Refresher Training for Investigators and Their Staff

Sponsor Responsibility: Focus on Quality Management

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- A Case Study
- The additions
- Impact on sponsor's obligations
- How could sponsor efficiently implement GCP addendum
- Challenges
- Conclusion

Indication

- Heart failure in children can be caused, e.g., by "Congestive Heart Failure (CHF)" which means malformations of the heart at birth or by "Dilated Cardiomyopathy (DCM)" which means a weakness of the heart muscle leading to dilation of the heart and resulting difficulties of the heart to pump sufficiently blood into the circulation.
- Heart failure in children is a "rare disease".

Therapy

- “Angiotensin Converting Enzyme Inhibitors (ACE-I)” are a class of drugs which impact the Renin-Angiotensin-Aldosterone System (RAAS), managing the water household in the body and the blood pressure. Therefore drugs belonging to this class are widely used to treat high blood pressure and heart failure in adults since over 30 years.
- First drug of this class was Captopril.
- A known side effect is too strong blood pressure lowering, especially at the first dose

Therapy – The Test Drug(1)

- “Fancypril” is an ACE-I.
- “Fancypril” is a pro-drug which means that it has only a very limited efficacy.
- After absorption into the blood stream it undergoes the first liver passage and there it gets split into metabolites. “Fancyprilat” is the metabolite which has the most therapeutic efficacy.
- The “active drug” arrives at the RAAS in a delayed manner.
- The drug-metabolizing liver capacity matures after birth.

Therapy – The Test Drug(2)

- “Fancypril” is very widely used in adults since over 25 years.
- “Fancypril” is available in form of 2,5 mg, 5 mg, 10 mg and 20 mg tablets for adults.
- “Fancypril” is worldwide administered to children with heart failure without marketing authorisation (“off-label use”) and proved to be efficient in clinical practice.
- For administration to small children 2.5 mg or 5 mg tablets get crashed, dissolved and administered to children as oral solution in mg per kg body weight.

Therapy – The Test Drug(3)

- Oral solutions/syrups are considered “gold standard” galenic forms for small children despite the fact that
  - Dosing is quite unreliable (spitting out, runlet, refusal to take, etc.)
  - Unsafe to produce (water quality, stability)
  - Calculation and volume definition errors
- No reliable pharmacokinetic data of “Fancypril” in children of different age groups available.

Therapy – The Test Drug(4)

- No reliable pharmacodynamic (impact of on RAAS) data of “Fancypril” in children of different age groups available.
- No systematically collected safety data of “Fancypril” in children of different age groups available.
- No reliable data justifying dose titration up to optimal dose of “Fancypril” in children of different age groups available.

Therapy – The Test Drug(5)

- Statistically significantly better accepted and thus more reliable galenic form in small children are “Orodispersible Mini-Tablets (ODMTs)”, proven in adequately powered studies in over 800 children from birth to 6 years testing “acceptability” and “capability to swallow”.
- EMA accepted ODMTs as suitable galenic alternative in their guideline on ethical considerations for clinical trials in children.
- “Fancypril ODMTs” have been developed and proved to be bioequivalent in healthy adults.

Therapy – The Test Drug(6)

- The European Commission has provided a grant to an academic consortium to develop the data required for the marketing application dossier for “Fancypril ODMTs” fulfilling the requirements of the EU Paediatric Regulation.
- According to the Paediatric Regulation the Marketing Authorisation Applicant (MAA) has to agree on a “Paediatric Investigation Plan (PIP)” with the paediatric committee “PDCO” of the EMA and has to deliver the data/results from clinical trials requested in this PIP as a pre-requisite for receiving a marketing authorisation.

The PIP Conditions(1)

- Primary objective: To obtain PK data of “Fancypril” and “Fancyprilat” in 100 patients treated with ODMTs to describe the dose exposure in the paediatric population with DCM, and CHF, respectively.
  - This requires a “PK Profile” (blood sampling at time different time points after ODMT intake) either on the day of the first ODMT intake or later during “steady state”.
  - This requires “population kinetics” (single blood sampling at different time points with clear information on last ODMT intake time points.

  (Efficacy of “Fancypril” can be assumed as known from extended clinical experience and does not need to be demonstrated in this project)

The PIP Conditions(2)

Secondary objectives:

- Demonstrate safety, especially renal safety, of “Fancypril” treatment up to one year in children with DCM and CHF.
  - This requires blood pressure measurement over x h after first and later doses during “Titration” .
  - This requires creatinine, BUN and potassium measurements at very regular intervals, potentially different during the course of the treatment.
- Investigate “Shortening Fraction (SF)” in echocardiography.
  - Investigate the “Acceptability” and “Palatability” of the ODMTs (At first dosing, 1 x during and at the end of an 8-week treatment period)

The PIP Requirements(1)

PDCO concerns:

- Solid dosage forms provide less dosing flexibility than oral solutions:
  - Ensure optimal dosing flexibility with the available 1mg and 0,25mg ODMTs.
  - Give clear dosing (titration) instructions for all age/weight groups.
  - Ensure reliable dosing at each time point during the observation period.
  - Ensure suitable labelling and practical instructions to dosing person.
  - Ensure reliable oversight of drug intake (compliance). (consider that there is only very limited IMP supply available)

The PIP Requirements(2)

PDCO concerns:

- These are very sick children:
  - Ensure a positive benefit-risk balance.
  - Minimise their risks and burden.
  - Ensure optimal flexibility of the investigators in clinical care of these children.
  - Ensure reliable drug accountability.
  - Ensure an appropriate informed consent process according to national legislation.

The PIP Requirements(3)

PDCO concerns:

- PK, PD, safety parameters and potentially routine care will require quite a lot of blood sampling:
  - Ensure that the blood sampling volumes from the EMA guideline on ethical considerations in clinical trials on children is respected at all times

The PIP Requirements(4)

PDCO concerns:

- Pharmacokinetic (PK) assessments need to be very reliable:
  - Blood sampling and sample work-up conditions need to be very clear, reliable and standardised.
  - Temperature-controlled storage and shipment of samples must be ensured at all times.
  - The bioanalytical assay needs to be able to reliably measure these very low plasma levels in very small volumes.

The PIP Requirements(5)

PDCO concerns:

- Pharmacodynamic (PD) and safety parameters should include:
  - PD: Angiotensin I, Plasma Renin, Plasma Renin Activity, Aldosterone, Nt-pro-BNP, (one of these parameters requires sample work-up within 2 minutes after blood withdrawal).
  - Safety:
    - Creatinine, Blood Urea Nitrogen (BUN), Potassium, Microalbuminurea (in urine) at least every 2 weeks during the first 8 weeks of treatment;
    - Blood pressure/heart rate measurement at each visit, especially at the beginning of treatment
    - Haematology (red and white blood count) only at the beginning and end of study)
    - Comprehensive Adverse Event collection and documentation at each visit
    - Clinical Heart Failure Score at each visit

5.0 Quality Management(1)

Sponsor's obligations:

- Implementation of a system to manage quality throughout all stages of the trial process
- Focus on trial activities that are essential to ensure human subjects protection and reliability of trial results
- Design of efficient clinical trial protocols, tools and procedures for data collection and processing as well of information essential to decision making

5.0 Quality Management(2)

Sponsor's obligations:

- The methods used to assure and control quality should be proportionate to the risks inherent in the trial and the importance of the information collected
- All aspects of the trial to be operationally feasible, avoid unnecessary complexity, procedures and data collection.
- Protocols, CRFs, and other operational documents to be clear, concise and consistent.

5.0 QM: Risk-based Approach(1)

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.

5.02 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both system level (e.g., SOPs, computerized systems, personnel) and clinical level (e.g., trial design, data collection, informed consent process)

5.0 QM: Risk-based Approach(2)

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring

b) The extent to which such errors would be detectable

c) The impact of such errors on human subject protection and reliability of study results

5.0 QM: Risk-based Approach(3)

5.0.4 Risk Control

The sponsor should decide which risks to reduce and / or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk.

Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, system safeguards to ensure adherence to SOPs, and training in process and procedures.

5.0 QM: Risk-based Approach(4)

5.0.4 Risk Control (ff)

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 reliability of trial results.

Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0 QM: Risk-based Approach(5)

5.0.5 Risk Communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0 QM: Risk-based Approach(6)

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 and remedial actions taken in the clinical study report.

5.2 Contract Research Organization

5.2.2

Current text:

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

Addendum:

The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions subcontracted to another party by the sponsor's contracted CRO(s).

5.20 Noncompliance

Current text:

Noncompliance with the protocol, SOPs, GCP, and / or applicable regulatory requirement(s) by an investigator / institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

Addendum:

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

Conclusions

Sponsor obligations have been more clearly defined by describing the expected elements of the quality management system.

Risk identification, risk mitigation and implementation of CAPAs are the cornerstones of risk-adapted quality management systems.

Practical Aspects of a Risk-Based Monitoring Approach

GCP – Refresher Training for Investigators and Their Staff

Practical Aspects of a Risk-Based Monitoring Approach

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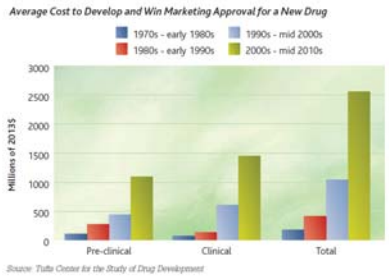
ICH-GCP Gives Flexibility: 5.18.3 Extent and Nature of Monitoring

Current text:

- The sponsor should ensure that the trials are adequately monitored.
- The sponsor should determine the appropriate extent and nature of monitoring.
- The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.
- In general there is a need for on-site monitoring, before, during, and after the trial.; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.
- Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

Reality: Costs have greatly increased



Now it is about 2.5 billion USD!

The Call for a Strategic Change

"By embracing risk-based monitoring, industry is going to become more effective in using what is, in effect, a diminishing resource. We have less money and fewer people, and are continually being required to "do more with less". You can achieve this and work more efficiently if you use a risk-based approach, because your limited resources can be used where you're sure they will deliver the greatest benefit…"

Jane Tucker, formerly GSK

The Call for a Strategic Change

Many initiatives promote this approach:

- FDA' s former Director of Centre for Drug Evaluation and Research (CDER), promoted in 2004 the adoption of quality management approaches and defined "Quality by Design". QbD: drug development begins with the end in mind and includes a structured risk assessment process.
- TransCelerate made Risk-based Monitoring (RBM) to one of their first key initiatives in 2012 to come away from the absolute need for 100% source data verification and standard monitoring frequency in all trials
- ICH took-up this concept to finally enable its broad implementation

5.18.3 Extent and Nature of Monitoring Addendum Text(1):

- *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 efficacy of monitoring.*
- *The sponsor may choose on-site monitoring, a combination of on-site monitoring and centralized monitoring, or, where justified, centralized monitoring.*
- *The sponsor should document the rationale for the chosen monitoring strategy, e.g., in the monitoring plan)*

5.18.3 Extent and Nature of Monitoring Addendum Text(2):

- *On-site monitoring is performed at the sites at which the clinical trial is conducted.*
- *Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).*
- *Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and / or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.*

5.18.3 Extent and Nature of Monitoring Addendum Text(3):

- *Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:*
  a. *Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.*
  b. *Examine data trends such as the range, consistency, and variability of data within and across sites*
  c. *Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.*
  d. *Analyze site characteristics and performance metrics.*
  e. *Select sites and/ or processes for targeted on-site monitoring.*

5.18.6 Monitoring Report Addendum Text(4):

- e) Reports of on-site and / or centralized monitoring 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.
- Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.
- Reporting of centralized monitoring activities should be regular and may be independent from site visits.

Addendum Text (5): 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 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.

How to Get Started?

Definition of « Risk »

Risk of non-compliance with the GCP objectives:

To provide assurance that:

(1) The rights, integrity and confidentiality of trial subjects are protected and their safety is ensured.

(2) Data and reported results are credible.

Pre-requisites for RBM

On-site monitoring alone can never guarantee high clinical trial quality

Requires an overall quality assurance concept including
- Central trial monitoring
- Prompt and pro-active data management
- Trial-specific training

and as applicable
- Reference bodies
- Data monitoring committee
- Audits

Basic Principles for RBM

- Focus on those trial data and information that are essential (‘key data’)
- Extent of monitoring based on the results of a thorough risk analysis
- Monitor’s tasks result from the risk analysis
- Timely central monitoring, with the option to trigger additional site visits (‘for-cause monitoring’)
- Reminder system for outstanding documentation
- The monitors are trained on all relevant aspects identified by the risk analysis

Step 1: Risk Assessment(1)

Use for example the approach presented in the ADAMON project:

I. Assessment of the potential risk associated with the therapeutic intervention

I. Trial specific risk analysis **P = Patient-related indicators**
(e.g., patient population, process of enrolment, study medication, assessments, potential bias
R = Indicators of robustness
("hard" endpoint?, study design?)

III. Classification with respect to the need of on-site monitoring

Step 1: Risk Assessment(2)

Use for example the approach presented in the ADAMON project:

Assessment of Patient-related Indicators:

a. Assessment of the respective risk factor
b. If that risk factor applies: does it mean a higher risk for the patient's safety and/or patient's rights, and/or validity of results?
c. If at least one GCP objective is at risk, which quality management measures will be taken to control the risk?
d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunctions with other measures?

Step 1: Risk Assessment(4)

Use for example the approach presented in the ADAMON project:

Assessment of Indicators of Robustness:

a. Assessment of the respective robustness indicator
b. Has at least one indicator of robustness been answered with "Yes"?

Move to step III:

Classification with respect to the need of on-site monitoring

Step 2: Risk Classification

The potential risk of therapeutic intervention is	Monitoring class	
comparable to that of standard medical care	*K3 - low* If there is no patient-related critical indicator that can be controlled by on-site monitoring and at least one indicator of robustness applies to the trial	*K2 - intermediate* In all other cases
higher than that of standard medical care	*K2 - intermediate* In all other cases	*K1 - high* If there are patient-related critical indicators that require control by on-site monitoring
	K2 - intermediate If there is no patient-related critical indicator that can be controlled by on-site monitoring and at least one indicator of robustness applies to the trial	*K1 - high* In all other cases

Step 3: Decision on Extent of Monitoring(1)

The planned extent of on-site monitoring depends on

1) The risks identified

2) The package of quality assurance measures implemented

To optimise efficiency, on-site monitoring should focus

- on those trial aspects that are critical – in the sense that they jeopardise patient safety, patient rights or data validity – and
- that can be influenced by on-site monitoring and
- that cannot or only at higher cost be influenced by other QM measures

Step 3: Decision on Extent of Monitoring(2)

Monitoring class K1: high risk:

Pre-study Visit	**Obligatory** (if the trial site is not known)
Initiation Visit	**Obligatory**
First Visit	**After recruitment of 1. patient** (100% source data verification (SDV) of all data pertaining to the patient
Further Visits	Verification of key data (100% SDV of all patients) Verification of further data (10% of site's patients or at least one patient is selected (by central office) for 100% SDV. Selected patietns are fully monitored during all subsequent visits. Frequency: Decided in relation to recruitment
Further contacts	Additional telephone and e-mail contacts
Close-out visit	**Obligatory**

Step 3: Decision on Extent of Monitoring(3)

Monitoring class K2: intermediate risk:

Pre-study Visit	**Recommended** (but can be substituted by telephone or contact on congresses, etc.)
Initiation Visit	**Obligatory**
First Visit	**After recruitment of 1 - 2 patients** (100% source data verification (SDV) of of the 2 patients and key data of all further patients who may participate in the trial at the time of the visit.) **Evaluation of the trial site** Assessment of whether the site has sufficient clinical trial and GCP expereince, and the human resources to implement the trial with due diligence - Site without "noticeable problems" - Site with "noticeable problems"

Step 3: Decision on Extent of Monitoring(4)

Monitoring class K2: intermediate risk (ff):

Further Visits	All trial sites are visited on a regular basis. The **frequency of visits** has to be scheduled so that the specified extent of monitoring is adhered to the recruitment .	
	Site without noticeable problems	**Site with noticeable problems**
	Verification of key data -Existence and IC for 100% of patients -Further key data for at elast 20% of the patients at site Verification of further data 1 further randomly selected patient 100% SDV	Verification of key data -Existence and IC for 100% of patients -Further key data for at elast 50% of the patients at site Verification of further data 1 further randomly selected patient 100% SDV
Further contacts	Additional contacts take place as required	
Close-out visit	As required where scheduled monitoring visits still have to be performed or unresolved queries have to be clarified	

Step 3: Decision on Extent of Monitoring(5)

Monitoring class K3: low risk:

Pre-study Visit	Not made
Initiation Visit	**Strongly advised** In exceptional cases replaced by an investigators' meeting and detailed written instructions, e.g. -in trials designed similarly to standard care and involving an estalished trial population if similar trials for the same range of indications have already been implemented in the sites - In trials with a very simple design
Visits	**Each site** is visited **at least once** during the duration of the trial. The order in which the sites are visited is randomly assigned by the central office.
Verification of key data	-Existence and IC for 100% of patients -Further key data for at least 20% of the site's patients
Further contacts	Additional telephone and e-mail contacts as requried
Close-out visit	**Not made**

Step 3: Decision on Extent of On-site Monitoring(6)

Assessment of site-related indicators deciding on the duration of the monitoring visit

a) Technical requirements

b) Personnel requirements

c) Storage requirements

d) Essential documents requirements

e) Material samples

f) Local randomisation

Step 3: Decision on Extent of Central Monitoring(7)

1. **Define frequency and extent of central monitoring**
2. **Elements that should be regularly identified per site, compiled, statistically evaluated, and routinely discussed by a team of CR and DM staff, ("Quality Tolerance Limits") e.g.:**
   - -Number of patients recruited
   - Time to CRF completion overall and during last period
   - % of missing data per CRF page overall and during last period
   - Number of queries per CRF page overall and during last period
   - Time to completion of queries overall and during last period
   - Number of AEs per patient
   - Time to AE completion overall and during last period
   - Time to SAE reporting overall and during last period

Step 3: Decision on Extent of Central Monitoring(8)

3. **Define aspects to be regularly evaluated by the DM/statistical department, e.g.:**

   - Data outliers
   - Unexpected lack of variability in assessments
   - Accumulation of numbers in assessments
   - Type and frequency of protocol deviations
   - Plausibility of visit dates
   - Number of recruited patients in comparison to other sites
   - % of screen failures in comparison to other sites
   - Etc.

Step 4: Define and Present Your Overall Monitoring Strategy in the Monitoring Plan

1. Basic trial conditions and supervision needs (according to structured risk assessment)
2. Prioritisation of supervision needs (key data) and rationale for monitoring strategy
3. Approach to on-line monitoring
4. Approach to central monitoring
5. Quality Tolerance Limits and their review mechanism
6. Roles and responsibilities
7. Applicable SOPs and Work Instructions
8. Communication lines

Conclusions

Risk-based monitoring is a strategic approach to quality management that requires

- careful analysis
- rigorous quality-mindedness of all parties,
- reliable rapid data entry by the site
- on-going alertness of the central team
- readiness to quickly implement corrective actions/changes to the plan

Site Management with Validated Computerized Systems in Europe and US (CRF part 11)

Site management with validated computerized systems.

Agenda points.

- Some requirements (ICH, GAMP, Part 11)
- Why validate
- How is validation organised.
- What needs to be considered for a Site system
- What about data storage.
- Questions

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Site management with validated computerized systems.

What governs!

For computerised systems what is the impact of regulations and guidelines!

Site management with validated computerized systems.

ICH E6(R2) amended text encourage:

- Improved and more efficient approaches to clinical trials.
- Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency.
- A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system = validation.
- The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results (1.65)

Site management with validated computerized systems.

ICH E6(R2) amended text encourage:

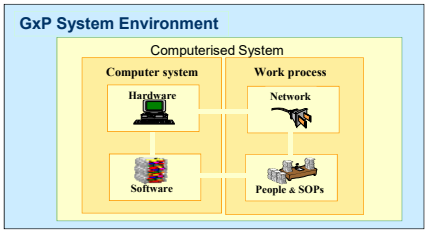
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used (2.10)
- The investigator/institution should 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). (4.9.0)

Site management with validated computerized systems.

System setup, Installation, and Use:

- 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 computerized systems should be clear, and the users should be provided with training in their use.
- A certified copy -irrespective of the type of media used- of the original record that has been verified- i.e., by a dated signature or by generation through a validated process - to have the same information, including data that describe the context, content, and structure, as the original.

A Computerised System



Site management with validated computerized systems.

GAMP 5 + FDA CFR 21 Part 11

The sponsor should identify risks to critical trial processes and data. (Risk Identification- 5.0.2).

GAMP5:

- A pragmatic and practical guidance to achieve compliant computerized systems.
- Focus on risk management-- the higher the risk, the greater the degree of validation and control needed.
- The flexible risk-based approach to compliant GxP regulated computerized systems is based on scalable specification and verification.
- Explains Scrum- a validation concept with flexible timelines and deadlines, small development teams and frequent releases.

Site management with validated computerized systems.

GAMP 5 + FDA CFR 21 Part 11

Combining GAMP 5 and 21 CFR Part 11 in computer system validation (CSV) for systems that are GxP:

- List out the regulations that apply (in the system requirements specification(s)).
- Include requirements that correspond to the regulations.
- Test those requirements – along with all of the others – in the associated qualification phase. (For example, functional requirements to the Operational Qualification (OQ) phase of validation and user requirements to the Performance Qualification (PQ) phase.)

Site management with validated computerized systems.

What does validation do?

- Establishes documented evidence that the computerised system will perform according to specifications and requirements
- Ensures that performance is consistent and reproducible

Validation strives to provide a "high degree of assurance", not perfection or absolute proof.

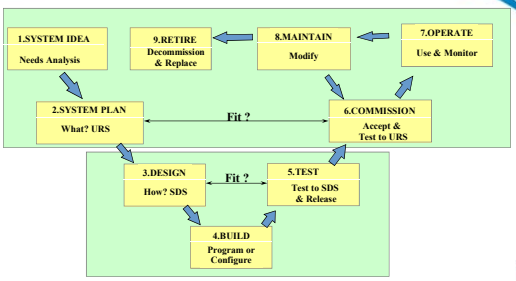
Validation is part of complete System Life Cycle.

- Validation Planning begins early in the system life cycle (shortly after requirements are specified)
- The extent of validation may vary.
- Single Components are not individually validated, they are:
  - reviewed
  - inspected
  - tested
  - controlled or qualified

…… as part of the whole system, depending on type of component.

"Those who fail to plan,…… plan to fail."

System Lifecycle



The benefits of Validation

Direct

- Documentation objectives are identified
- Quality is built into the system
- Regulatory and company requirements are established up front

Indirect

- Easier to maintain
- Improved process control/product quality
- Quicker start-up phase

The RISK of no validation…Data can not be relied upon due to..

- Risk of e-data corruption.
- Missing system control.
- Consequences of changes unknown.
- No control over risk factors.
- Nothing can be based on the results.
- Regulated data on system can be disqualified during any inspection.
- Risk to the patient.

What Systems Need to be Validated?

- Any system where failure or incorrect processing can affect the delivered:
  - Quality
  - Efficacy
  - Safety
- Any system where records hold the information needed for critical activities.

Just monitoring performance is inadequate, but..

- The quality of the validation effort is not necessarily proportional to the amount of paper generated.
- The level of the effort is determined by complexity of the system and the value of the information.

The requirement is that the system is validated, there is no requirement for this to be complicated !

Site management with validated computerized systems

Aspects of E-Systems

Status:
- New systems (retrospective validation is not an option)
- Legacy systems

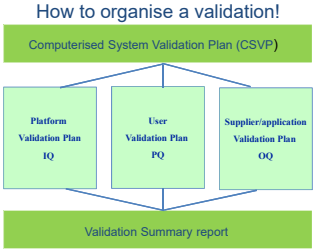
Extend of Use:
- Simple - stand alone systems
- Local networking systems
- International multi-complex systems

Class:
- GxP systems
- GxP supportive systems
- Business critical systems
- Other systems

Security:
- Closed systems, Systems under internal control
- Open systems, Systems interacting with the surrounding world

Site management with validated computerized systems

How to organise a validation!



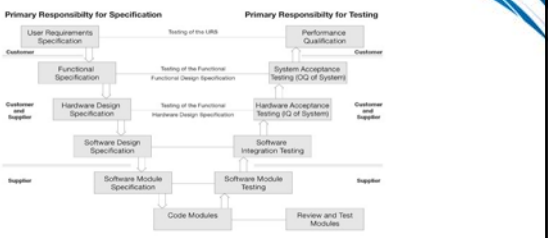
Site management with validated computerized systems

- Validation – the three core elements:

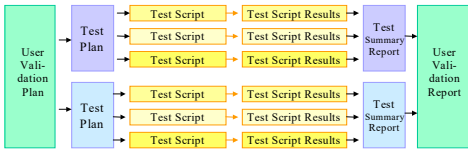
Installation qualification **(IQ)** – confirms complete documentation, proper hardware installation, and software verification according to the manufacturer's specifications.

Operational qualification **(OQ)** – confirms the system operations by testing the design requirements that are traced back to the function specifications.

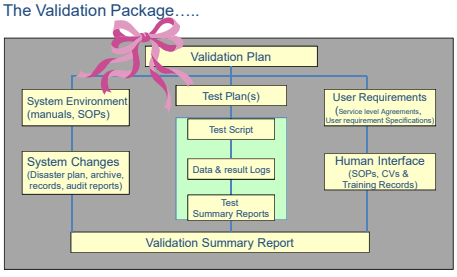
Performance qualification **(PQ)** – confirms that a system is capable of performing or controlling the activities of the process, while operating in a specific environment - responsibility falls on the user.



Key Validation Documents



The Validation Package…..



Site management with validated computerized systems

So what is required for data captured electronically at the investigator site ?

Authorities look at basic principles…
- whether from Sponsor or Investigator.

FDA - Computerised Systems Used in Clinical Trials

Site management with validated computerized systems

How can one assess
a site' electronic systems
&
assure their
reliability and quality?

Site management with validated computerized systems

- Know the expectations and FOKUS…
- The Success criteria for a clinic or a medical team …

…… to get People Healthy!

Site management with validated computerized systems

ICH E6 R2

- Data handling and Record keeping (5.5.3)
  - Originals can be electronic
  - Certified copies can replace originals
  - Certification is produced via a validation process
- Risks to critical study processes should be identified on all levels (facilities/systems/vendors/design/collection..etc.)
- Validation should ensure accuracy, reliability and consistent performance from design till decommissioning
- Focus should be on data integrity especially in case of system changes/upgrades or data migration.
- Sops should support the lifecycle of EDC systems

Critical Areas

Management Control	System Reliability
Personnel Training Docs.	Testing Procedures
Validation / Life Cycle Management	Change Control Logs
System Environment Control Procedures	System Backup
Supplier Contracts	Disaster Recovery Procedures
System Release Procedures	Software QA procedures
Data Integrity	**Auditable Quality**
Data verification & checks Docs.	System Description
System Security (Physical & Logical)	Audit Trail
Data Back-up logs	Doc's & Records - Data Audits
Access Control	Error Tracking

Site management with validated computerized systems

Improving oversight over Site/Hospital e- Systems….what to consider!

First---describe the System including:

- System name
- Developer/supplier
- Version and release date
- Modules applicable

A general principle!

Where the System does not provide the solution then this

must be covered by a practical (described) work-around outside the system.

About Records.

- Are all records stored in the System attributable to the individual patient?
- Can records be retrieved and reviewed?
- Are patient identifiers removed if records are passed on to Sponsors as required by Data Protection Legislation in the respective country?
- Is it possible to see in the System if patient' consent has been given?

About Audit trail:

- Does the System have an audit trail capturing recording date and time, and the identity of the one who entered, changed, or deleted data?
- Does it show the reason for a change?
- Is the audit trail readily available?
- Have you checked the System's audit trail?
  - New information added should not overwrite previous entries.
  - It should not be possible to delete the audit trail without this being detectable.

Rights in the System

- Is the capability to change system data limited to authorised persons and are these notified in case changes are detected?
- Are those who enter data on the system different from those who allocate access rights?
- Are users provided with unique access (passwords etc.) and does the System require renewal at regular intervals?
- Do the access rights match the role/ job functions?
- Is the number of login attempts limited, so that the System locks after a specified no. of attempts?
- Does the System keep a log of unauthorised attempts to access?

NB: whatever method you employ you should make sure it works!

- Can you get an overview over all those who have access to the System, and when and for what role they had access rights .. and if and when these were deactivated.?

Back –up and Control

- Is the system backed up at regular intervals?
- Has the integrity of the back-up been verified?
- Is the back-up data stored on a separate, secure location/server?
- Is the system tested and validated e.g. in relation to changes or upgrades?
- Are there procedures for security and access control?
- Is firewalls and antivirus measures in place?

&

- Is there a procedure for continuing the daily work if the system fails or is inaccessible (business continuity) and has this been tested?

Keeping the Data

- Can you review data in an understandable format?
- Is it possible to print data for e.g. audits or inspection purposes?
- Does this include audit trail and coded data?

&

- Are e-source data used for clinical research retained for the required period?
- Are checks in place to ensure that archived data (and meta-data) is maintained and readable for the retention period.

Electromagnetic Records and Electronic Records Regulation (Japan 2013)

- EDC Management Sheet
  - Sponsors and Marketing Authorization Holders (MAHs) have to prepare and maintain this sheet while using EDC systems.
  - The sheet applies to GCP and Good Post-Marketing Surveillance Practice (GPSP)
  - EDC **is not limited to e CRF but includes other systems as e.g. e LABO**

http://www.pmda.go.jp/operations/shonin/outline/shinrai/shinrai_6/file/08edc_irai.xls

Site management with validated computerized systems

ICH E6 R2

Site essential Documents and Data

- Investigator/institution:
  - should have control over all essential documents and records generated by investigator/institution before, during and after the trial
  - should maintain a record of location
  - storage systems should … irrespective of media used… provide for identification, search and retrieval

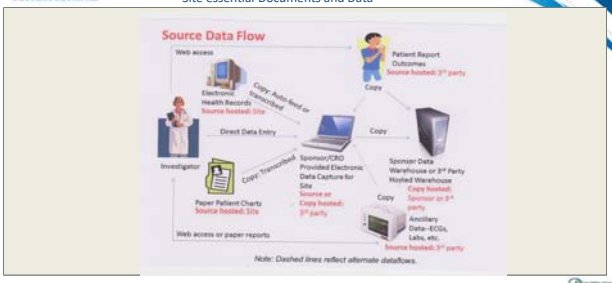
Site management with validated computerized systems

EMA Guidance on E-Master files (commenting ends June 2017)

- Trial subject's medical files should be retained in accordance with national legislation.
- Digitisation of the subject's medical files is acceptable provided the process is validated such that the institution can demonstrate that these are certified copies of the originals which are kept in a format that ensures that the data can be retrieved in the future.
- This will include the relevant documentation contained in the sponsor and investigator TMF **as well as the trial subjects' medical records.**

Site management with validated computerized systems

Site essential Documents and Data



Society for Clinical Data Management White Paper 2014

eSource Principles of Use

The 7 Principles

1. Use solutions that are "fit for purpose"
2. Declare the source
3. Capture the data when first generated
4. Control electronic data
   - As it is investigators primary responsibility for patient care and safety, any data in any form, considered as source data must:
     - ✓ never be under the control of sponsor/CRO
     - ✓ always be accessible to investigator
     - ✓ be under the control of investigator through the legally determined timeframe
5. Leverage automated quality checks
   - eSource being contemporaneous with the event without other documentation use
     - ✓ front end- data verification checks in EDC systems
     - ✓ longitudinal across visits consistency checks
     - ✓ focus on key data elements
6. Control for Quality
7. Conform to regulations and guidelines

Society for Clinical Data Management White Paper 2014

And at all time -- be INSPECTION READY !

Normal day: **Inspection day:**

Just summarising:

- Plan!
- Place a strong focus on the process
- Map the full process flow
- Focus on key parameters
- Consider at what stage data becomes electronic

No chain is stronger than the weakest link!

Site management with validated computerized systems

"If you add the support of a computer system to an inappropriate process without changing the process, the results will be as bad as before — but things will probably go wrong faster"

ANNEXES

1/ ICH E6 – Guideline for Good Clinical Practice – European Medicines Agency - 1 December 2016 - EMA/CHMP/ICH/135/1995 - Committee for Human Medicinal Products

2/ Risk analysis in clinical trials regarding the required amount of on-site monitoring form version_final1.0_2009-11-19

3/ APPENDIX 3 - Guidelines for Risk-Adapted Monitoring

4/ eSource Implementation in Clinical Research: A Data Management Perspective – A White Paper – 12 June 2014 – Society for Clinical Data Management

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)

Step 5

Adopted by CHMP for release for consultation	23 July 2015
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Final adoption by CHMP	15 December 2016
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Document History

First Codification	History	Date	New Codification November 2005
E6	Approval by the CPMP under *Step 3* and release for public consultation.	May 1995	E6
E6	Approval by the CPMP under *Step 4* and released for information.	July 1996	E6

***Step 5* corrected version**

E6	Approval by the CPMP of *Post-Step 4* editorial corrections.	July 2002	E6(R1)

Current E6(R2) Addendum *Step 5* version

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

Guideline for good clinical practice E6(R2)

Table of contents

Introduction

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

ADDENDUM

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

This guideline should be read in conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)).

This ICH GCP Guideline Integrated Addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions. In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

1. Glossary

1.1. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3. Amendment (to the protocol)

See Protocol Amendment.

1.4. Applicable regulatory requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5. Approval (in relation to institutional review boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6. Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7. Audit certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8. Audit report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9. Audit trail

Documentation that allows reconstruction of the course of events.

1.10. Blinding/masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11. Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12. Clinical trial/study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13. Clinical trial/study report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14. Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15. Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP)requirements, and the applicable regulatory requirements.

1.16. Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17. Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18. Coordinating committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19. Coordinating investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20. Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21. Direct access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.

1.22. Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23. Essential documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24. Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25. Independent Data-Monitoring Committee (IDMC) (data and safety monitoring board, monitoring committee, data monitoring committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26. Impartial witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27. Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28. Informed consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29. Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30. Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31. Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32. Interim clinical trial/study report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33. Investigational product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34. Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35. Investigator / institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36. Investigator's brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator’s Brochure).

1.37. Legally acceptable representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38. Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39. Monitoring report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs.

1.40. Multicentre trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41. Nonclinical study

Biomedical studies not performed on human subjects.

1.42. Opinion (in relation to independent ethics committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43. Original medical record

See Source Documents.

1.44. Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45. Protocol amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46. Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47. Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48. Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49. Regulatory authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51. Source data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52. Source documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53. Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54. Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55. Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56. Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57. Subject/trial subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58. Subject identification code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59. Trial site

The location(s) where trial-related activities are actually conducted.

1.60. Unexpected adverse drug reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61. Vulnerable subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62. Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

ADDENDUM

1.63. Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

1.64. Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.65. Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration

the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

2. The principles of ICH GCP

2.1.

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2.

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3.

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4.

The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5.

Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6.

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7.

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8.

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10.

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 referenced in this guideline, irrespective of the type of media used.

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).

2.12.

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13.

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ADDENDUM

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

3. Institutional Review Board / Independent Ethics Committee (IRB/IEC)

3.1. Responsibilities

3.1.1.

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2.

The IRB/IEC should obtain the following documents:

- trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.
- The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3.

The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4.

The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5.

The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6.

When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7.

Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8.

The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9.

The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2. Composition, Functions and Operations

3.2.1.

The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

- At least five members.
- At least one member whose primary area of interest is in a nonscientific area.
- At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2.

The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3.

An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4.

Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5.

The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6.

An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3. Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1.

Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2.

Scheduling, notifying its members of, and conducting its meetings.

3.3.3.

Conducting initial and continuing review of trials.

3.3.4.

Determining the frequency of continuing review, as appropriate.

3.3.5.

Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6.

Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7.

Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8.

Specifying that the investigator should promptly report to the IRB/IEC:

- Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).
- Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).
- All adverse drug reactions (ADRs) that are both serious and unexpected.
- New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9.

Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

- Its trial-related decisions/opinions.
- The reasons for its decisions/opinions.
- Procedures for appeal of its decisions/opinions.

3.4. Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. Investigator

4.1. Investigator's Qualifications and Agreements

4.1.1.

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2.

The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3.

The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4.

The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5.

The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2. Adequate Resources

4.2.1.

The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3.

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4.

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

ADDENDUM

4.2.5.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6.

If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.3. Medical Care of Trial Subjects

4.3.1.

A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2.

During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3.

It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4. Communication with IRB/IEC

4.4.1.

Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2.

As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3.

During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5. Compliance with Protocol

4.5.1.

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- to the IRB/IEC for review and approval/favourable opinion, (b) to the sponsor for agreement and, if required,
- to the regulatory authority(ies).

4.6. Investigational Product(s)

4.6.1.

Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2.

Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3.

The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4.

The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5.

The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6.

The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7. Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8. Informed Consent of Trial Subjects

4.8.1.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4.

None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5.

The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all

pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6.

The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7.

Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the trial that are experimental.

- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of trial-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- The expected duration of the subject's participation in the trial. (t) The approximate number of subjects involved in the trial.

4.8.11.

Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12.

When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with

severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13.

Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14.

Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
- The foreseeable risks to the subjects are low.
- The negative impact on the subject's well-being is minimized and low. (d) The trial is not prohibited by law.
- The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15.

In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9. Records and Reports

ADDENDUM

4.9.0.

The investigator/institution 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).

4.9.1.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2.

Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3.

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6.

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7.

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10. Progress Reports

4.10.1.

The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2.

The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11. Safety Reporting

4.11.1.

All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3.

For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12. Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1.

If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2.

If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3.

If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13. Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. Sponsor

ADDENDUM

5.0. Quality management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as 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 as described below.

5.0.1. Critical process and data identification

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

5.0.2. Risk identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3. Risk evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

- The likelihood of errors occurring.
- The extent to which such errors would be detectable.
- The impact of such errors on human subject protection and reliability of trial results.

5.0.4. Risk control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction 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 reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5. Risk communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, 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 and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

5.1. Quality assurance and quality control

5.1.1.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4.

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2. Contract Research Organization (CRO)

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.

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 ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

5.2.3.

Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4.

All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3. Medical expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4. Trial design

5.4.1.

The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2.

For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5. Trial management, data handling, and record keeping

5.5.1.

The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2.

The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and 8.1 of all its meetings.

5.5.3.

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

  ADDENDUM

  The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

- Maintains SOPs for using these systems.

  ADDENDUM

  The SOPs 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 their use.

- Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
- Maintain a security system that prevents unauthorized access to the data. (e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
- Maintain adequate backup of the data.
- Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

ADDENDUM

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

5.5.4.

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5.

The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6.

The sponsor, or other owners of the data, should retain all of the sponsor- specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7.

The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8.

If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9.

If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10.

Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11.

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6. Investigator selection

5.6.1.

The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2.

Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3.

The sponsor should obtain the investigator's/institution's agreement:

- to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);
- to comply with procedures for data recording/reporting;
- to permit monitoring, auditing and inspection (see 4.1.4) and
- to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12). The sponsor and the

investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7. Allocation of responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial- related duties and functions.

5.8. Compensation to subjects and investigators

5.8.1.

If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2.

The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3.

When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9. Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10. Notification/submission to regulatory authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11. Confirmation of review by IRB/IEC

5.11.1.

The sponsor should obtain from the investigator/institution:

- The name and address of the investigator's/institution’s IRB/IEC.
- A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

- Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2.

If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3.

The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12. Information on investigational product(s)

5.12.1.

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2.

The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13. Manufacturing, packaging, labelling, and coding investigational product(s)

5.13.1.

The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2.

The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3.

The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4.

In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5.

If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14. Supplying and handling investigational product(s)

5.14.1.

The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2.

The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3.

The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4.

The sponsor should:

- Ensure timely delivery of investigational product(s) to the investigator(s).
- Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
- Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

- Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5.

The sponsor should:

- Take steps to ensure that the investigational product(s) are stable over the period of use.
- Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15. Record access

5.15.1.

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2.

The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16. Safety information

5.16.1.

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2.

The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17. Adverse drug reaction reporting

5.17.1.

The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2.

Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3.

The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18. Monitoring

5.18.1. Purpose

The purposes of trial monitoring are to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2. Selection and qualifications of monitors

- Monitors should be appointed by the sponsor.
- Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.
- Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3. Extent and nature of monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

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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. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. 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 accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

- identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
- examine data trends such as the range, consistency, and variability of data within and across sites.
- evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
- analyze site characteristics and performance metrics.
- select sites and/or processes for targeted on-site monitoring.

5.18.4. Monitor's responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- Acting as the main line of communication between the sponsor and the investigator.
- Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- Verifying, for the investigational product(s):
  - That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
  - That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
  - That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
  - That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
  - That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
- Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

- Verifying that written informed consent was obtained before each subject's participation in the trial.
- Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
- Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
- Verifying that the investigator is enroling only eligible subjects. (j) Reporting the subject recruitment rate.
- Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
  - The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
  - Any dose and/or therapy modifications are well documented for each of the trial subjects.
  - Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
  - Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
  - All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.
- Informing the investigator of any CRF entry error, omission, or illegibility.
  - The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
- Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).
- Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5. Monitoring procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6. Monitoring report

- The monitor should submit a written report to the sponsor after each trial- site visit or trial-related communication.
- Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.
- Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.
- The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

ADDENDUM

- Reports of on-site and/or centralized monitoring 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. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

ADDENDUM

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.

5.19. Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1. Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2. Selection and qualification of auditors

- The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.
- The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3. Auditing procedures

- The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
- The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).
- The observations and findings of the auditor(s) should be documented.
- To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.
- When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20. Noncompliance

5.20.1.

Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

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If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

5.20.2.

If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21. Premature termination or suspension of a trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and

provided the reason(s) for the termination or suspension by the sponsor or by the investigator / institution, as specified by the applicable regulatory requirement(s).

5.22. Clinical trial/study reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23. Multicentre trials

For multicentre trials, the sponsor should ensure that:

5.23.1.

All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2.

The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3.

The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4.

All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5.

Communication between investigators is facilitated.

6. Clinical trial protocol and protocol amendment(s)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1. General Information

6.1.1.

Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2.

Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3.

Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4.

Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5.

Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6.

Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7.

Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2. Background Information

6.2.1.

Name and description of the investigational product(s).

6.2.2.

A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3.

Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4.

Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5.

A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6.

Description of the population to be studied.

6.2.7.

References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3. Trial objectives and purpose

A detailed description of the objectives and the purpose of the trial.

6.4. Trial design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1.

A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2.

A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3.

A description of the measures taken to minimize/avoid bias, including:

- Randomization.

- Blinding.

6.4.4.

A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5.

The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6.

A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7.

Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8.

Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9.

The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5. Selection and withdrawal of subjects

6.5.1.

Subject inclusion criteria.

6.5.2.

Subject exclusion criteria.

6.5.3.

Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

- When and how to withdraw subjects from the trial/ investigational product treatment.
- The type and timing of the data to be collected for withdrawn subjects.
- Whether and how subjects are to be replaced.

- The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6. Treatment of Subjects

6.6.1.

The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2.

Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3.

Procedures for monitoring subject compliance.

6.7. Assessment of Efficacy

6.7.1.

Specification of the efficacy parameters.

6.7.2.

Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8. Assessment of Safety

6.8.1.

Specification of safety parameters.

6.8.2.

The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3.

Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4.

The type and duration of the follow-up of subjects after adverse events.

6.9. Statistics

6.9.1.

A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2.

The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3.

The level of significance to be used.

6.9.4.

Criteria for the termination of the trial.

6.9.5.

Procedure for accounting for missing, unused, and spurious data.

6.9.6.

Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7.

The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10. Direct access to source data/documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11. Quality control and quality assurance

6.12. Ethics

Description of ethical considerations relating to the trial.

6.13. Data handling and record keeping

6.14. Financing and insurance

Financing and insurance if not addressed in a separate agreement.

6.15. Publication policy

Publication policy, if not addressed in a separate agreement.

6.16. Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. Investigator’s brochure

7.1. Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor- investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2. General considerations

The IB should include:

7.2.1. Title page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired

by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2. Confidentiality statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3. Contents of the investigator's brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1. Table of contents

An example of the Table of Contents is given in Appendix 2

7.3.2. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3. Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4. Physical, chemical, and pharmaceutical properties and formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5. Nonclinical studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

- The information provided may include the following, as appropriate, if known/available:
- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

7.3.5.1. Nonclinical pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

7.3.5.2. Pharmacokinetics and product metabolism in animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

7.3.5.3. Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6. Effects in humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

7.3.6.1. Pharmacokinetics and product metabolism in humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

7.3.6.2. Safety and efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

7.3.6.3. Marketing experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7. Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4. Appendix 1:

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number: Date:

7.5. Appendix 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter

Appendices (if any)

8. Essential documents for the conduct of a clinical trial

8.1. Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

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 (e.g., source documents, CRF), 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.

8.2. Before the clinical phase of the trial commences

During this planning stage the following documents should be generated and should be on file before the trial formally start

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.1	**INVESTIGATOR'S BROCHURE** (where required)	To document that relevant and current scientific Information about the investigational product has been provided to the investigator trial-related injury will be available	x	x
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement	x	x
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT**		X	x
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	- ANY OTHER WRITTEN INFORMATION	To document that subject will be given appropriate written information (content and wording)to support their ability to give fully informed consent	x	x
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.2	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	x	x

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.5	**INSURANCE STATEMENT** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.:	To document agreements		
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO		X	X (where required)
	- sponsor and CRO			X
	- investigator/institution and authority(ies) (where required)		X	X
8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.8	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X
8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial- related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3. During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**
	- protocol amendment(s)
	- revision(s) of:
	  - informed consent form
	  - any other written information to be provided to the subject
	  - advertisement for subject recruitment (if used)
	- any other documents given approval/favourable opinion
	- continuing review of trial (where required)
		To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X
8.3.6	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 8.2.15.)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.20	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

8.4. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.4.7	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	X (if applicable)	X

Risk analysis in clinical trials regarding the required amount of on-site Monitoring

Title of the clinical trial

Sponsor (if applicable)

Coordinating investigator

Version of the risk analysis:

Date:

Risk analysis conducted by:

Name	Date, signature
Name	Date, signature
Name	Date, signature

Risk analysis in clinical trials regarding the required amount of on-site monitoring form version_final1.0_2009-11-19

The form of the risk analysis was developed by members of the project group 'ADAMON Monitoring in IITs' within the project 'Monitoring conform to GCP in non-commercial clinical trials' (project manager: Dr. O. Brosteanu).

The existing form can be used to conduct a risk analysis regarding the required amount of on-site monitoring and to document the result of the assessment. The form can be filled in electronically. The available text field can be extended as needed.

The preparation of this form was supported by the medical platform 'Telematikplattform für medizinische Forschungsnetze e.V.'.

I. Assessment of the potential risk associated with therapeutic intervention

Type of clinical trial	**The potential risk of therapeutic intervention is**
• Trials involving licensed medicinal products: - Phase IV or - Phase IIIb if it relates to the licensed range of indications (allowed are for example moderate dosage modifications, transition from relapse therapy to primary therapy, transition to other disease stages or states of severity, use in new combinations if interactions seem improbable), or - off-label use, e.g. in paediatrics, in oncology (also adults) if this off-label use is established practice, i.e. sufficient published evidence and/or guidelines exist in this respect • Trials involving a CE-certified medical device for the certified range of indications if knowledge derived from controlled trials already exists • Trials involving non-pharmacological therapies if knowledge derived from controlled trials already exists	**Comparable** to that of the standard medical care ☐
• Trials involving licensed medicinal products: - Phase IIb - Phase IIIb, if ▪ such products are used for a new indication or ▪ substantial dosage modifications are made for the licensed indication or ▪ if they are used in combinations for which interactions are suspected • Trials involving a CE-certified medical device: - outside the scope of certification or - within the scope of certification, if no knowledge from controlled trials exists • Trials involving a non-pharmacological therapy, if knowledge from uncontrolled trials are already exists, but not from controlled ones	**Higher** than that of standard medical care ☐
• Phase I, phase I/II, phase II or phase III trials involving an unlicensed drug • Trials involving a medical device prior to CE-certification • Trials involving a non-pharmacological therapy for which only case reports or animal test findings exist	**Markedly higher** than that of standard medical care ☐

II. Trial specific risk analysis

Patient related indicators (P)

P1 Potentially vulnerable population?
a. Will a vulnerable population be included? No ☐ Yes ☐ If 'Yes': specify population _____ If 'Yes': continue with b. *E.g., pregnant women, newborns and infants, geriatric patients, patients with cognitive or psychological disorders.* *Vulnerable populations may be exposed to higher risks, but this is not necessarily always the case.*
b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results? No ☐ Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐ If ,'Yes' was chosen at least ones, continue with c or d.
c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk? _____
d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures? No ☐ Yes ☐

P2 Adult patients who are temporarily not able to give consent?

a. Will adult patients who are temporarily not able to provide their consent be included in the trial?

No ☐ Yes ☐

If 'Yes': specify population _____

If 'Yes': continue with b.

This is generally a critical point in terms of upholding the patient's rights.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P3 Emergency medical treatment

a. Will trial patients be recruited within the scope of emergency medical treatment?

No ☐ Yes ☐

If 'Yes': specify treatment _____

If 'Yes': continue with b.

'*Emergency' defined as:*
– necessity of immediate commencement of therapy (<12 h)
– irrespective of the severity of the disorder.
Consider if problems may occur with:
– informed consent
– assessment of eligibility criteria
– immediate trial-related processes (diagnosis, therapy)

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P4 Eligibility criteria

a. Are there any critical eligibility criteria?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify criteria _____

If 'Yes'": continue with b.

Eligibility criteria are critical if they are
– safety-relevant (i.e., ineligible patient is exposed to a considerably higher risk) or
– relevant for the effectiveness of the therapy (i.e., ineligible patient cannot profit from the therapy) or
– relevant for the validity of the results (e.g., concomitant diseases or medications that can influence the outcome).

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P5 Combination of investigational drugs or therapies

a. **Is there a lack of previous experience on the combination medications and therapies being studied?**

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify drug or therapy _____

If 'Yes': continue with b.

The following aspects have to be considered:
– therapeutic interventions under study,
– but also any basic or background therapies, prescribed, recommended or allowed by the protocol
How likely is it that any combinations affect the patient's status with regard to
– primary or secondary efficacy endpoints or
– safety (e.g., adverse interactions)?
What is the timescale of potential interactions?

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P6 Additional medication for concomitant diseases / symptoms

a. Is it likely that patients receive additional medication for concomitant diseases / symptoms?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify diseases/symptoms _____

If 'Yes': continue with b.

The following aspects have to be considered:
– Expected percentage of patients with concomitant diseases / symptoms requiring therapy
– How likely is it that any combinations affect the patient's status with regard to
- *primary or secondary efficacy endpoints or*
- *safety (e.g., adverse interactions)?*

– What is the timescale of potential interactions?

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P7 Limited knowledge about the investigational drug

a. Is there only very limited knowledge about at least one of the investigational drugs?

No ☐ Yes ☐

If 'Yes': specify drug _____

If 'Yes': continue with b.

This can be the case if the drug was only recently licensed. Consider the likelihood of adverse side effects relative to standard medical care.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P8 Additional risks due to investigational therapies

a. Are there any additional risks of the therapies being tested not yet taken into account?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify risk _____

If 'Yes': continue with b.

The risks should always be balanced to the risks associated with standard medical care for the indications in question.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P9 Risks due to other trial related procedures

a. Is there an additional risk associated with trial related procedures (other than the therapy being tested)?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify risk _____

If 'Yes': continue with b.

This risk can relate to diagnostic measures performed in addition to the standard diagnostics for study purposes only.
Timescale of potential risks (e.g. late effects).

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P10 Trial procedures as per protocol are complex and unusual

a. Are study procedures (therapy and / or diagnostics) clinically unusual and complex?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify procedure _____

If 'Yes': continue with b.

Is the on-site implementation of the clinical trial complicated and, at the same time, unusual compared to the standard medical care for the indication in question, e.g., does it include
– several different therapy sections,
– acombination of different therapeutic procedures,
– acomplex diagnostic procedure that deviates from the standard procedure,
– decision trees?
If the standard medical care is already complicated (oncology!) and the trial is designed closely along the lines of the standard medical care, it is not to be classified as 'unusual'!

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P11 Coincidental or deliberate unblinding

a. Is there a risk of coincidental or deliberate unblinding?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify risk _____

If 'Yes': continue with b.

E.g., by obtaining laboratory values from a local laboratory (opening of the emergency envelopes is regarded as fraud, and is not meant here).
Assess the impact of a nonmedically justified unblinding on the credibility of the trial.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P12 Drop-out

a. Is there a risk of (informative) withdrawals or drop-outs?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify risk _____

If 'Yes': continue with b.

Is it expected that patients may withdraw from therapy or follow-up as a result of very positive (or negative) therapeutic effects?
In trials focussing on efficacy differences, informative drop-outs could bias the results.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P13 Sources of bias or variance

a. Are there any sources of bias or variance with regard to the primary endpoint?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify source _____

If 'Yes': continue with b.

This can happen, for instance, if the trial is not randomised or is open label and, at the same time, a 'soft' primary endpoint is being studied (i.e. difficult to objectify, not standardized endpoint).

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P14 Protocol deviations

a. Are there trial protocol deviations that could have a negative impact on patient safety and/or the validity of the trial?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify deviation _____

If 'Yes': continue with b.

This could include:

- *Dosage and application of the investigated product or therapy (dose changes, elimination of individual components, deviation from the specified time schedule)*
- *Concomitant therapies (indicated therapy not given, forbidden therapy implemented, clinically indicated therapy which influences the outcome measures not reported)*
- *Diagnostic measures are not implemented, are technically inadequate or not implemented at the correct time*
- *Visits are not made or not made at the right time*
- *Necessary material (e.g. patient record, diary) are not issued and/or kept incorrectly*

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

P15 Further risks

a. / b. Are there any further risks that could have a negative impact on patient's safety and/or patient's rights and/or data validity, that haven't been answered adequately in questions P1-P14?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If 'Yes': specify risk _____

If ,'Yes' was chosen at least once, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

Patient related indicators:
Summary

Was at least one of the above questions (P1-P15) under point 'd' been answered with 'Yes'?

No ☐ **Yes** ☐

(i.e. at least one patient related indicator is present,
- **that indicate a risk for the GCP objectives and**
- **is to be checked by on-site monitoring)**

Indicators of robustness (R)

R1 Primary endpoint

Is a 'hard' primary endpoint being investigated?

No ☐ Yes ☐

Comment briefly _____

i.e. can the endpoint be investigated in an objective and/or standardised way, e.g.

- *death,*
- *stroke,*
- *titre,*
- *defined laboratory values,*
- *primary endpoint is assessed exclusively by a single reference panel or reference institution.*

R2 Study design

Are the clinical study procedures very simple?

No ☐ Yes ☐

A trial may be considered as having very simple clinical procedures e.g. if

- *the medication or therapy being investigated is only administered once, and/or*
- *very short follow-up time is required, and/or*
- *the extent of documentation required is small.*

Indicators of robustness: summary

Was at least one of the above questions (R1-R2) been answered with 'Yes'?

No ☐ **Yes** ☐

III. Classification with respect to the need of on-site monitoring

Three classes of on-site monitoring are proposed. They differ in terms of the extent of monitoring activities (i.e. the number of patients and trial sites to be monitored) and the minimum frequency of visits to the trial sites. The monitoring strategies are described in detail in the next section.

The classification is based on the clinical trial risk analysis. The following components are taken into account:

(1) The potential risk relative to standard therapy
(2) The patient-related indicators that are classified as critical and can be controlled by on-site monitoring
(3) Indicators of robustness

The site-related indicators necessitate on-site monitoring measures that are performed in conjunction with the visits. Since these are trial site and not patient-related tasks, the indicators are irrelevant for the determination of the extent of monitoring required. They do, however, have to be considered in terms of the length of each monitoring visit.

The following table shows the proposal for categorising clinical trials in terms of on-site monitoring requirements.

The potential risk of therapeutic intervention is	**Monitoring class**	
comparable to that of standard medical care	*K3 - low* If there is no patient-related critical indicator that can be controlled by on-site monitoring and at least one indicator of robustness applies to the trial	*K2 - intermediate* In all other cases
higher than that of standard medical care	*K2 - intermediate* In all other cases	*K1 - high* If there are patient-related critical indicators that require control by on-site monitoring
markedly higher than that of standard medical care	*K2 - intermediate* If there is no patient-related critical indicator that can be controlled by on-site monitoring and at least one indicator of robustness applies to the trial	*K1 - high* In all other cases

IV. Site related indicators (S)

The following list includes the indicators that are relevant for quality assurance measures at trial site level. These indicators are not relevant concerning the selection of the monitoring class, but should be taken into the account in defining the task list of the monitoring.

S1 Technical requirements

a. Are there any technical requirements for the trial sites?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify requirements _____

If 'Yes': continue with b.

E.g., access to diagnostic equipment, refrigerator, centrifuges, emergency equipment.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

S2 Personnel requirements

a. Are there any essential personnel requirements for the trial sites?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify requirements _____

If 'Yes': continue with b.

E.g., access to certain consultation services, trial-specific knowledge or training certificates, training requirements for assessment of the primary endpoint.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

S3 Storage requirements

a. Are there any essential storage requirements for the investigated product?

No ☐ Yes ☐

If 'Yes': specify requirements _____

If 'Yes': continue with b.

It is necessary to analyse whether non-compliance with the storage requirements will actually increase the risk.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

S4 Essential documentation requirements

a. Are there any essential documentation requirements for the investigated product?

No ☐ Yes ☐

If 'No': comment briefly _____

If 'Yes': specify requirements _____

If 'Yes': continue with b.

E.g., controlled substances, anaesthetics.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

S5 Material samples

a. Are there any essential transport and/or storage requirements for material samples?

No ☐ Yes ☐

If 'Yes': specify requirements _____

If 'Yes': continue with b.

Only samples necessary for the primary endpoint or for safety analyses are considered (samples for add-on research projects are not a subject matter of this article).
To which extent is the incorrect handling of samples critical?

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

S6 Local randomisation

a. Is the trial randomised but not blinded, and is randomisation performed locally at the trial sites (e.g. by envelopes)?

No ☐ Yes ☐

If 'Yes': specify randomisation _____

If 'Yes': continue with b.

If central randomisation is not feasible, meticulous checks on randomisation are necessary at the trial sites.

b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results?

No ☐

Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐

If ,'Yes' was chosen at least ones, continue with c or d.

c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk?

_____

d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures?

No ☐ Yes ☐

V. Definition of the key data

The key data comprise the trial data and information that are essential to assess patient safety, well-being and rights, and to achieve the primary and secondary trial objectives.

Key data always include:

- **Existence** of the trial subject
  A check is made to establish whether the trial subject is included in the patient identification list and whether a patient file exists in connection with any list entry.
- **Informed consent documentation**
  A check is made to establish whether a written inform consent form exists, and whether it was filled in correctly, completely and on time.
- **Serious adverse events (SAE)**
  A check is made to establish whether all serious adverse events mentioned in the patient's file are correctly and completely documented and whether they correspond to the trial protocol specifications. Vice versa, a check is also made to establish whether source data exists in respect of all reported SAEs.

The following are also key data, though they have to be specified in the monitoring manual as per the trial protocol:

- **Eligibility criteria**
  In general, eligibility criteria in clinical trials should have been chosen due to their relevance for either safety or efficacy of the trial therapy or due to their relevance for the statistical power of the trial. Thus, all eligibility criteria should be considered as key data. In exceptional cases, it may happen that some inclusion and exclusion criteria do not match the description above – these criteria may be excluded from the key data.
- **Application and dosage** of the investigated product or therapy
- **Primary endpoint**
  The primary endpoint(s) for the clinical trial is/are subjected to a source data verification process. This applies if the parameter(s) was/were assessed at the trial site. If the assessment is done on a centralised basis by a reference panel or institution, the monitoring activity on site referring to the primary endpoint will consist in checking whether the necessary material or the necessary information has been passed on.

Further trial-specific data and information can be included in the key data. These are derived from the trial-specific risk analysis and include, for instance

- **Adverse events** (AEs): In clinical trials with **medicinal products** whose **safety profile (in the range of indications being investigated) is little known**, **AEs** should always be classified as key data.
- Essential **secondary endpoints** (if assessed locally in the trial sites)
- Possibly other aspects ensuing from the risk analysis of **patient-related indicators**

CAVE: Additional data and information should only be treated as key data if they have a decisive impact on patient safety or the informative value of the clinical trial. This necessitates a detailed analysis prior to the planning of the monitoring activities.

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APPENDIX 3

Guidelines for Risk-Adapted Monitoring

Introduction

Monitoring is an essential part of quality management in clinical trials. The purposes of monitoring and the responsibilities of the monitor are specified in the Good Clinical Practice guideline [ICH GCP 5.18]; the necessary scope involved, however, is not clear enough[1]. While it is generally agreed that quality management measures are indispensable, their extent and effective implementation is still a matter of debate.

According to GCP and the latest developments in the regulatory environment, risk-adapted procedures in clinical trials are internationally encouraged, e.g. by the EMA[2] as well as by the FDA[3]. Especially for non-commercial investigator initiated trials, risk-adapted procedures are essential in order to use limited resources in an efficient way. A risk-based approach to monitoring does not suggest any less vigilance in the oversight of clinical investigations. Rather, it steers sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes which are critical to human protection and trial integrity.

On a European level, there are several helpful, well-documented and widely used initiatives running which recommend and evaluate risk-adapted monitoring strategies (the ADAMON[4] Project, the OPTIMON[5] Project, the UK MRC/DH/MHRA Joint Project[6]). The ADAMON and OPTIMON strategies are already partly in use at several CTUs. They both prospectively investigate whether the proposed trial-specific, risk-adapted, reduced on-site monitoring strategy is indeed as effective as an intensive monitoring strategy.

Although it does not address the issue of monitoring and therefore does not directly affect the extent of monitoring activities, the Swiss Human Research Act (HRA) allows for a risk-adapted approach in research in humans according to Art. 65. The Ordinance on Clinical Trials in Human Research (ClinO) and the Ordinance on Human Research with the Exception of Clinical Trials (HRO) even require a risk assessment by evaluating the risks associated with an intervention prior to submission to the competent authorities [ClinO Art. 19, 20, 49, 61, and HRO Art. 7]. The Federal Office of Public Health (FOPH) provides a standardised electronic categorisation tool[7] for sponsors/sponsor-investigators.

In view of these developments and the limited resources within the network, it was decided to adopt the concept of risk-adapted monitoring strategies of the SAKK, which is based on the risk-adapted monitoring strategies proposed by the ADAMON Project. The SAKK concept was adapted to the needs of sponsor-investigators and Swiss legal requirements as of January 2014.

Objectives and Scope

These guidelines describe the risk-adapted monitoring procedures for non-commercial clinical trials, and their scope covers clinical trials as defined by the HRA[8]. Even though this document does not focus on research projects as covered by the HRO, the content may also be applicable. This document was developed by the Quality Assurance Working Group of the Swiss Clinical Trial Organisation (SCTO) to facilitate and harmonise the conduct of multicentre trials, but may also be applied to local mono-centre trials. It is strongly recommended for application to all trials within their scope by all full and associated members of the SCTO. However, the final decision on its implementation lies within the responsibility of each CTU.

1 Refer to ICH GCP 5.18.3

2 Reflection paper on risk based quality management in clinical trials EMA/INS/GCP/394194/2011

3 Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, FDA, August 2013

4 www.adamon.de/ADAMON_EN/Home.aspx
Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials, Brosteanu et al. Clin Trials December 2009; 6: 585–596, first published on November 6, 2009

5 https://ssl2.isped.u-bordeaux2.fr/OPTIMON/default.aspx
Liénard JL, Quinaux E, Fabre-Guillevin E, Piedbois P, Jouhaud A, Decoster G, Buyse M; European Association for Research in Oncology. Impact of on-site initiation visits on study subject recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer. Clin Trials. 2006; 3(5): 486–92

6 www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf
MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, October 2011

7 http://snctp.begasoft.ch/snctp/pages/public/wizard.jsf?lang=en

8 HRA Art. 3 lit. l. Clinical trial means a research project in which persons are prospectively assigned to a health-related intervention in order to investigate its effects on health or on the structure and function of the human body.

Structure

The guidelines for risk-adapted monitoring consist of:

- a categorisation scheme for clinical trials
- a questionnaire for risk analysis with respect to required on-site monitoring
- risk-adapted monitoring strategies for each monitoring category

The templates for monitoring plans for each defined monitoring strategy will follow once experience has been gained with this new procedure.

Review, Updates, Release

The guidelines will be reviewed and updated by the SCTO in collaboration with the CTUs and associated networks if there is any major regulatory change or new evidence as to which monitoring approaches are useful, such as results of the ADAMON Project with quantitative data on the impact of the different monitoring strategies, which are expected in 2015. The relevance and accuracy of the guidelines will be reviewed every two years.

1 Procedures

According to ICH GCP 4.9.1, the investigator is responsible for ensuring that the data reported to the sponsor in the Case Report Form (CRF) are complete and accurate. The sponsor is responsible for implementing and maintaining a quality assurance and quality control system [ICH GCP 5.1].

The best way to control the risks of participating in a clinical trial is to identify and to minimise them with appropriate measures. A risk-adapted monitoring strategy can only be implemented if on-site monitoring with Source Data Verification (SDV) is part of an entire quality management programme, including but not limited to:

- training of trial personnel, pre-trial and initiation visit/teleconference
- review of protocol and related trial documents (e.g. CRF, ICF, etc.) according to Standard Operating Procedures (SOP)
- qualification of sponsors/sponsor-investigators/investigators (education, experience and training)
- validation of database/eCRF and statistical analysis
- central monitoring with resolution of queries
- real-time validation and plausibility checks for trials using an electronic data capturing system
- audit trail of all changes to the data
- safety reporting procedures
- risk-adapted audit strategy

Adherence to GCP guidelines ensures the protection of the three following objectives:

- safety of trial participants
- rights, integrity and confidentiality of trial participants
- data quality (data accuracy and protocol compliance)

Monitoring is the best method of quality control if it has an impact on these objectives, and if other quality management measures are not determined to be more efficient. The efficiency of monitoring can be optimised by focusing on the aspects of a clinical trial that are critical, i.e. that influence participants' rights and well-being and the quality of the data.

1.1 Risk Analysis

The risk of a clinical trial can be assessed by completing a questionnaire (see Figure 1) adapted from the ADAMON Project[9]. Trials are categorised into:

- high risk
- intermediate risk
- low risk

9 Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials. Brosteanu O, Houben P, Ihrig K, Ohmann C, Paulus U, Pfistner B, Schwarz G, Strenge-Hesse A, Zettelmeyer U. Clin Trials. 2009 Dec;6(6):585-96.

Figure 1: Risk Analysis for Risk-adapted Monitoring. (* Copy only: please refer to the excel-tool.)

swiss clinical trial organisation

Insert your Logo here

Risk Analysis for Risk-Adapted Monitoring

Title of Protocol: _____ Sponsor's Name: _____

Principal Investigator: _____ Date: _____

Ethics Committee No.: _____ Signature: _____

Trial Site(s): _____

Project No.: _____ Completed by: _____

Function: _____

Monitoring Class (resulting from the risk analysis below; if no risk analysis has been conducted, a high risk will be assumed) **High Risk**

To complete the questionnaire please use "Tab" for navigation.

Please type **"1"** in the corresponding field.

Potential risk of therapeutic intervention in comparison to standard of medical care

Type of clinical trial	**Comparable** (see also ClinO Art. 19, 20, 61, category A)	
	Higher (see also ClinO Art. 19, 61, category B)	
	Markedly higher (see also ClinO Art. 19, 20, category C)	

Please type **"1"** for Yes and **"0"** for No.

Potential trial participant-related critical indicator

Participant-related indicators (P)	Yes / No	If Yes, specify its nature. Participant safety	Participant rights	Data validity	If Yes, which QA measure can control the risk?	If no QA measure, can monitoring control the risk?
P1 Will a vulnerable population be included?						
P2 Will adult participants who are temporarily unable to provide informed consent be included into the trial?						
P3 Will trial participants be recruited within the scope of emergency medical treatment?						
P4 Are there any critical eligibility criteria?						
P5 Is there a lack of previous experience on the (combination of) medications and/or therapies being studied?						
P6 Is it likely that participants receive additional medication for concomitant diseases/symptoms?						
P7 Is there only very limited knowledge about at least one of the investigational drugs?						
P8 Are there any additional risks of the therapies being tested not yet taken into account?						
P9 Are there any additional risks associated with trial-related procedures (other than the therapy being tested)?						
P10 Are trial procedures (therapy and/or diagnostics) clinically unusual and complex?						
P11 Are there any risks of coincidental or deliberate unblinding?						
P12 Are there any risks of (informative) withdrawals or drop-outs?						
P13 Are there any sources of bias or variance with regard to the primary endpoint?						
P14 Are there any potential trial protocol deviations that could have a negative impact on participant safety and/or the validity of the trial?						
P15 Are there any further risks that could have a negative impact that haven't been answered adequately in questions P1-P14?						
Summary of participant-related indicators						**0**

Robustness-related indicators (R)	Yes / No
R1 Is a "hard" primary endpoint being investigated?	
R2 Are the clinical trial procedures (design) very simple?	
Summary of robustness-related indicators	**0**

Site-related indicators (S) (No influence on risk category.)	Yes / No	If Yes, specify its nature. Participant safety	Participant rights	Data validity	If Yes, which QA measure can control the risk?	If no QA measure, can monitoring control the risk?
S1 Are there any technical requirements for the trial sites?						
S2 Are there any essential personnel requirements for the trial sites?						
S3 Are there any essential storage requirements for the investigated product?						
S4 Are there any essential documentation requirements for the investigated product?						
S5 Are there any essential transport and/or storage requirements for material samples?						
S6 If the trial is randomised but not blinded, is randomisation performed locally at the trial sites (e.g. by envelopes)?						
Summary of site-related indicators						**0**

1.2 Risk-Based Categorisation

The category of a clinical trial is defined according to Table 1 below and determined by the following criteria[10]:

- potential risk of the therapeutic intervention in comparison to standard therapy (critical evaluation of the standard of care has to be performed) and according to ClinO
- trial participant-related indicators that are identified in the risk analysis as critical and that can be controlled by monitoring
- indicators of robustness with respect to protocol compliance or to assessment of the primary endpoint

Site-related indicators evaluated in the risk analysis are not relevant for the definition of the monitoring strategy but can be used to determine whether additional individual site-specific measures or special training are necessary.

10 For details please refer to the Risk Analysis for Risk-Adapted Monitoring, Figure 1.

Table 1: Determination of the monitoring strategy according to the results of the risk analysis

		Potential risk of therapeutic intervention in comparison to standard of medical care		
		comparable [11]	higher [12]	markedly higher [13]
Potential trial participant-related critical indicator	absent	at least one indicator of robustness ↓ **low risk**	independent of the indicators of robustness ↓ **intermediate risk**	at least one indicator of robustness ↓ **intermediate risk**
		no indicator of robustness ↓ **intermediate risk**		no indicator of robustness ↓ **high risk**
	present	independent of the indicators of robustness ↓ **intermediate risk**	independent of the indicators of robustness ↓ **high risk**	independent of the indicators of robustness ↓ **high risk**

11 See also ClinO Art. 19, 20, and 61, category A.
12 See also ClinO Art. 19 and 61, category B.
13 See also ClinO Art. 19 and 20, category C.

1.3 Monitoring Strategies

According to the results of the above-mentioned risk analysis and its categorisation, one of the monitoring strategies described below must be chosen. The selected strategy is adapted to meet the requirements of the specific trial and details described in the trial-specific monitoring plan. Special requirements for specific sites can also be incorporated as needed.

In general, SDV focus on critical data, which are defined as follows:
- existence of the trial participants
- Informed Consent documentation
- eligibility criteria
- application and dosage of the investigated product or therapy
- primary endpoint(s)
- Serious Adverse Events (SAEs)
- further key data derived from the safety analysis (e.g. Adverse Events for products where the safety profile is not well known)

In case of substantial amendments to a clinical trial, a reconsideration of the risk analysis is necessary.

Table 2: Overview of monitoring strategies

		High risk trial	Intermediate risk trial	Low risk trial
Pre-trial visit		Pre-trial visits are recommended, especially if unknown sites are involved. The visit may be conducted on site or remotely.		
Site initiation visit		The site initiation visit will be done on site. All trial team members should be present at the site (principal investigator, his team, pharmacist, specialist, as applicable).	The site initiation visit may be conducted on site or remotely. The principal investigator and his team should be present. In case of a remote initiation, the TMF/ISF should be checked at the first monitoring visit.	
Regular monitoring visit	**Monitoring frequency**	The first regular monitoring visit will generally take place within 1–4 months[14], at the latest after the inclusion of the first trial participant. The next visits will take place according to trial participant recruitment, but generally every 2–8 months.	The first regular monitoring visit should be conducted after the inclusion of the first or second trial participant. The timing and frequency of additional visits depend on the following factors: – site recruitment – extent of monitoring tasks – findings at the site – visit schedule of the participants within the trial In general, visits take place 1–3 times per year.	One regular monitoring visit will take place within one year after the inclusion of the first trial participant.

14 In case of phase 1 trials or first-in-man trials, a more intensive schedule is required.

		High risk trial	Intermediate risk trial	Low risk trial
Regular monitoring visit	**Monitoring frequency**	In case of major or critical findings [15], further visits should be conducted. The timing depends on the findings. Criteria for conducting unplanned monitoring visits and/or additional measures have to be defined in the monitoring plan.		
	Source Data Verification	First trial participant and in addition 10% of all remaining trial participants: – 100% SDV All trial participants: Key data 100%: – existence – Informed Consent – SAEs – eligibility – drug administration – primary endpoint – additional protocol-specific safety parameters	First trial participant: – 100% SDV All trial participants: – existence – Informed Consent Further key data for at least 20 – 50% of trial participants, depending on findings: – SAEs – eligibility – drug administration – primary endpoint – additional protocol-specific safety parameters	All trial participants included at the time of the visit: – existence – Informed Consent First trial participant and at least 20% of trial participants recruited at the time of the visit, as far as available: – SAEs – eligibility – drug administration – primary endpoint – additional protocol-specific safety parameters
	Central monitoring	Some of the consistency checks are performed by the system at the time of data entry. The system should then be used as far as possible by the monitor (or the central data monitor) during the visit to perform further checks and he/she will evaluate if a query has to be issued. The different consistency checks to be performed by the monitor should be defined in the monitoring plan, and the checks to be performed by the system should be defined in the trial-specific Data Management Plan.		Some of the consistency checks are performed by the system at the time of data entry. The different consistency checks to be performed by the monitor should be defined in the monitoring plan, and the checks to be performed by the system should be defined in the trial-specific Data Management Plan.
	Accountability of the Investigational Medicinal Product (if applicable)	Drug accountability will be verified for 100% of all trial participants.	Drug accountability will be verified for 10% of all trial participants (as far as available at the time of the last monitoring visit).	
	Trial Master File (TMF), Investigator Site Files (ISF)	At least once a year a full review of the TMF/ISF should be performed. The monitor should check the completeness of the authorisation list and of the screening, identification and enrolment list as well as the training documentation on a regular basis.		
Close-out visit		A close-out visit is mandatory.	A close-out visit is mandatory, but may be combined with the last regular monitoring visit.	A last visit should take place after closure for accrual and/or end of trial treatment/intervention of the last trial participant at the site.

15 Definition of the findings:

- **Minor**: a GCP, protocol and/or SOP deviation that would not be expected to adversely affect the rights, safety or well-being of participants and/or the quality and integrity of data. However, they are deviations from sponsor or regulatory requirements. Many minor observations may indicate a bad quality and the sum with its consequences might be equal to a major finding. There must be a commitment to take corrective/preventive actions.
- **Major**: a GCP, protocol and/or SOP deviation that might adversely affect the rights, safety or well-being of participants and/or the quality and integrity of data. Major observations are serious deficiencies and high priority items for correction/prevention. Observations classified as major may include those situations where there is a pattern of deviations and/or numerous minor observations.
- **Critical**: a GCP, protocol and/or SOP deviation that adversely affects the rights, safety or well-being of participants and/or the quality and integrity of data. Critical observations are considered totally unacceptable. Fraud belongs to this group. They require immediate attention.

eSource Implementation in Clinical Research: A Data Management Perspective

A White Paper

June 12, 2014

Society for Clinical Data Management

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1. Abstract

Electronic technologies have redefined industries such as banking and commerce. Similarly, advances in technology are bringing massive changes to the healthcare realm, nearing a tipping point for overhauling every aspect of healthcare delivery and records management. As the paper chart is inevitably displaced in the daily practice of healthcare, it follows that the paper case report form (CRF) and paper site source documents for clinical research will also be displaced, ushering in the era of electronic source (eSource) for clinical studies. This transformation presents both opportunity and challenge for data management as we approach the intersection of the delivery of care and clinical research.

To achieve the full potential of eSource in clinical research, the process for data collection must be transformed from the traditional paper CRF collection model and associated paper site source documents to one that optimizes the availability of electronic data records while ensuring that data integrity and patient safety are not compromised. True transformation will preserve the requisite standards of conduct while reinventing the data collection process and governing regulations to fit the new electronic environment. This transformation is sure to surface many challenges—some real and some simply perceived.

The Society for Clinical Data Management (SCDM) has identified constructive principles and best practices for different modalities organized by process, people and technology to address these challenges. We present various data collection modalities of eSource and relevant considerations for successful implementation.

2. Introduction

The earliest attempts of electronic health records (EHR) for clinical care significantly preceded the advent of dedicated electronic data capture (EDC) for clinical research, but both race toward jettisoning paper records and offering the clinician the opportunity to enter data only once and enable its multiple appropriate uses. As is often the case, regulation is informed by these early attempts and must foresee the transformed future and not merely an electronic version of the past.

Electronic Health Records in Clinical Care

The idea of recording patient information electronically instead of on paper—the Electronic Medical Record (EMR)—emerged in the late 1960s, when Larry Weed introduced the concept of the Problem Oriented Medical Record into medical practice.[1] Until then, doctors usually recorded only their diagnoses and treatment. Weed's innovation was to generate a record to allow a third party to independently verify the

[1]Weed LL: Medical Records That Guide and Teach. N Engl J Med 278:593-600, 1968

diagnosis. In 1972, the Regenstreif Institute developed the first medical records system. Although the concept was widely hailed as a major advance in medical practice, physicians did not flock to the technology.[2]

In 1991, the Institute of Medicine, a highly respected think tank in the United States (US), recommended that by the year 2000 every physician should be using computers in their practice to improve patient care and made policy recommendations on how to achieve that goal.[3]

The adoption of eSource from EHRs for clinical research has been slow, in part because implementation of eSource from EHRs is complex. To improve uptake, questions must be answered about what programs should be contemplated and what checks can be implemented to ensure data integrity, protect patient privacy, create audit trails, restrict access appropriately, permit monitoring, and satisfy regulatory inspections.

Historically, clinicians recorded patient data onto paper patient charts and clinical research likewise leveraged paper case report forms. Regulatory inspectors are long accustomed to inspecting such paper records to verify the integrity of reported trial data. Clinicians are now replacing paper patient charts with electronic health records.

A 2012 survey of primary care physicians in 10 countries indicates 69% of US doctors are using EHRs compared to 98% primary care physician EHR use in the Netherlands, 98% in Norway, 97% in New Zealand, 97% in the UK, 92% in Austria, 82% in Germany, 67% in France, 56% in Canada and 41% in Switzerland.[4] A 2010 study on EMR/EHR markets in the Asia Pacific region projected a 7.6 percent compound annual growth rate from $2.3 billion in 2010 to $2.9 billion in 2013, although other predictions suggest much more rapid growth in the region.[5] The 2010 study also suggests emerging markets, such as Malaysia, Thailand, India and China could leapfrog other nations by learning from the experience of other nations and applying innovative approaches such as cloud-based solutions.

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[2] Regenstrief Medical Record System (RMRS) [Internet]. Clinical Informatics Wiki created 27 July 2005. Dean F. Sittig, Ph.D. [updated 2011 Oct 13; cited 2014 Mar 12] [about 4 screens]. Available from: http://clinfowiki.org/wiki/index.php/Regenstrief_Medical_Record_System_(RMRS)

[3] Institute of Medicine Committee on Improving the Patient Record, Division of Health Care Services, Editors: Richard S. Dick, Elaine B. Steen and Don E. Detmer. National Academy Press, Washington, DC, 1997. The Computer-Based Patient Record: An Essential Technology for Health Care, Revised Edition.

[4] C. Schoen, R. Osborn, D. Squires, M. M. Doty, P. Rasmussen, R. Pierson, and S. Applebaum. A Survey of Primary Care Doctors in Ten Countries Shows Progress in Use of Health Information Technology, Less in Other Areas. *Health Affairs* [published online before print 2012 Nov 15; cited 2013 Feb 15] [about 19 screens] Available from: http://content.healthaffairs.org/content/31/12/2805.full?keytype=ref&siteid=healthaff&ijkey=Wx1r2YCsnJVL.

[5] Overview of International EMR/HER Markets, results from a Survey of Leading Health Care Companies. Accenture, [August 2010; cited 2013 Sep 2] [16 pages] Available from: http://www.accenture.com/SiteCollectionDocuments/PDF/Accenture_EMR_Markets_Whitepaper_vfinal.pdf.

The future of EHR in all these nations largely depends on regulatory standards and government support. Thus, clinical research sponsors must know how regulators will judge the acceptance of a site's EHR as a source record as the pool of investigators using paper records shrinks.

Technology and Standardization in Clinical Research

Electronic data capture (EDC) technologies began in the mid-1980s, reaching a tipping point in 2007[6]. Despite the tangible benefits of electronic data capture, the adoption of EDC systems has remained slow in some segments of clinical research. At the end of 2012, only 40% of Phase I clinical trials had adopted EDC[7].

Likewise, Interactive Response Technology (IRT) has proven to be a major force driving innovations in biopharmaceutical research and development because it holds two sets of data vital to the success of a clinical trial: (1) patient information and (2) drug or device supply management information. Its transactional nature is one of the main reasons the technology has seen an increase in adoption. For example, as patients are recruited, the IRT assigns kit numbers and sends drug or device supplies directly to sites. Sites and sponsors/CROs monitor their drug or device inventory via the IRT and react by resupplying or returning supplies based on a number of factors. IRT technology is especially transactional in adaptive trials where changes in treatment arms, drug assignments, and dosage levels are administered by IRT systems in an automated manner.[8]

Electronic Clinical Outcome Assessment (eCOA) has also upped the ante by streamlining patient data collection using modern tools that bypass traditional printed forms. Although less than a decade ago most people accessed the Internet from a desktop computer, today many access it from mobile devices and tablets, making the availability and cost effectiveness of user-friendly Internet-enabled technologies more accessible. Such technologies have the potential to improve data quality by increasing the patient's access and convenience to the collection instrument so their assessment and data entry can be easily accomplished at the prescribed time rather than postponed to a time when their recollection and reporting may be less accurate.

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[6] Connor, Chris. April 2007.Health Industry Insights (an IDC company). Doc #HI206351. U.S. Electronic Data Capture 2006–2011 Spending Forecast and Analysis. See BusinessWire, Electronic Data Capture (EDC) Poised to Disrupt Life Sciences Industry, Say Health Industry Insights. [Internet] [created 2007 May 7; cited 2014 Mar 12] http://www.businesswire.com/news/home/20070507005691/en/Electronic-Data-Capture-EDC-Poised-Disrupt-Life#.UyDGGvldW89.

[7] Challenges and Benefits of EDC Adoption [Internet]. Clinovo, [Created 2013 Apr 26; cited 2014 Mar 12] [about 9 screens]. Available from: http://www.clinovo.com/blog/challenges-and-benefits-of-edc-adoption/.

[8] Bedford, Ph.D., Joesph. Almac Clinical Technologies. The Renaissance in IVR/IWR Systems Use of Interactive Response Technologies is on the Rise. [Internet] [cited 12 Mar 2014] Available from: www.almacgroup.com/wp-content/uploads/IVRIWR-Sytems1.pdf.

As the technologies of EDC, IRT, eCOA and other electronic data capture opportunities gained traction, the ideal of standardization also gained supporters. The potential for sharing data, collaboration, and streamlining processes through the use of electronic data could be achieved if data were standardized in such a way as to support its collection and dissemination. Thus was born the Clinical Data Interchange Standards Consortium's (CDISC) eSource Data Interchange document (eSDI), written with the purpose "to investigate the use of electronic technology in the context of existing regulations for the collection of eSource data (including that from eCOA/ePRO, EHR, EDC) in clinical trials for regulatory submissions by leveraging the power of the CDISC standards, in particular the Operational Data Model (ODM)."[9]

Pace of Regulatory Guidance

The US Food and Drug Administration (FDA) enacted the 21 CFR Part 11 Electronic Records; Electronic Signatures regulation in 1997. The European Union (EU) adopted their electronic signatures Directive in 2001. In the years since, both measures have been evaluated and their regulatory/legal interpretation matured.

As noted by the Clinical Data Interchange Standards Consortium,

> "…if a very strict interpretation of the regulations is taken, it could be argued that some solutions may not meet all of the current regulatory requirements. However, in a time of transition, there is a need to reflect upon the spirit of the regulations (and to keep in mind that some of these regulations were created for paper based documentation only) rather than using a literal interpretation. This view is necessary to adapt to the current environment and thus gain the benefit of new technology, while maintaining the necessary measures to ensure that clinical trial data continues to be of the highest quality and integrity." [10]

To address the more current adoption of technology, in 2010 the European Medicines Agency (EMA) released a Reflection paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Capture Tools in Clinical Trials[11] and in 2011 a

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[9] Clinical Data Interchange Standards Consortium, Electronic Source Data Interchange Group. Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials. [2006 Nov 20; cited 2013 Sep 2]. Available from: http://www.cdisc.org/stuff/contentmgr/files/0/2f6eca8f0df7caac5bbd4fadfd76d575/miscdocs/esdi.pdf.

[10] Clinical Data Interchange Standards Consortium, Electronic Source Data Interchange Group. Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials. [2006 Nov 20; cited 2013 Sep 2]. Available from: http://www.cdisc.org/stuff/contentmgr/files/0/2f6eca8f0df7caac5bbd4fadfd76d575/miscdocs/esdi.pdf.

[11] European Medicines Agency, 9 June 2010; EMA/INS/GCP/454280/2010; GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. [2010 Jun 9; cited 2013 Sep 2] Available from:

draft Reflection paper on the Use of Interactive Response Technologies (Interactive Voice/Web Response Systems) in Clinical Trials[12]. Per the 2010 Reflection paper,

> "Collection of accurate clinical trial data is essential for compliance with Good Clinical Practice (CPMP/ICH/GCP/135/95)[13]. With increasing use of information technology in pharmaceutical development there is a need to have clear guidance on the use of electronic source data and transcribed data and the principles that should apply to them. This is necessary in order to ensure that the processes can be used and accepted with confidence when such requirements are complied with, and that the benefits that these systems offer can be fully utilized."

The US FDA issued Guidance for Industry on Computerized Systems used in Clinical Investigations (CSUCI) in 1999[14] and updated it in 2007.[15] Per CSUCI,

> "The computerized system applies to records in electronic form that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained, or submitted to the FDA. Because the source data are necessary for the reconstruction and evaluation of the study to determine the safety of food and color additives and safety and effectiveness of new human and animal drugs, and medical devices, this guidance is intended to assist in ensuring confidence in the reliability, quality, and integrity of electronic source data and source documentation (i.e., electronic records)."

The US FDA has also issued two guidance drafts: in January 2011 the Guidance for Industry on Electronic Source Documentation in Clinical Investigations[16] and a revision draft in November 2012 entitled Guidance for Industry on Electronic Source Data in Clinical Investigations.[17]

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http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.

[12] European Medicines Agency, 5 August 2011; EMA/INS/GCP/600788/2011; Compliance and Inspection. Reflection paper on the use of interactive response technologies (Interactive Voice/Web Response Systems) in Clinical Trials DRAFT. [5 Aug 2011; cited 2013 Sep 2] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110227.pdf.

[13] Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Volume 3C Efficacy, Rules Governing Medicinal Products in the European Union.

[14] FDA, US Department of Health and Human Services, Office of the Commissioner, April 1999, Guidance for Industry Computerized Systems Used in Clinical investigations.

[15] FDA, US Department of Health and Human Services, Office of the Commissioner, May 2007, Guidance for Industry Computerized Systems Used in Clinical investigations. [2007 May; cited 2013 Sep 2] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf.

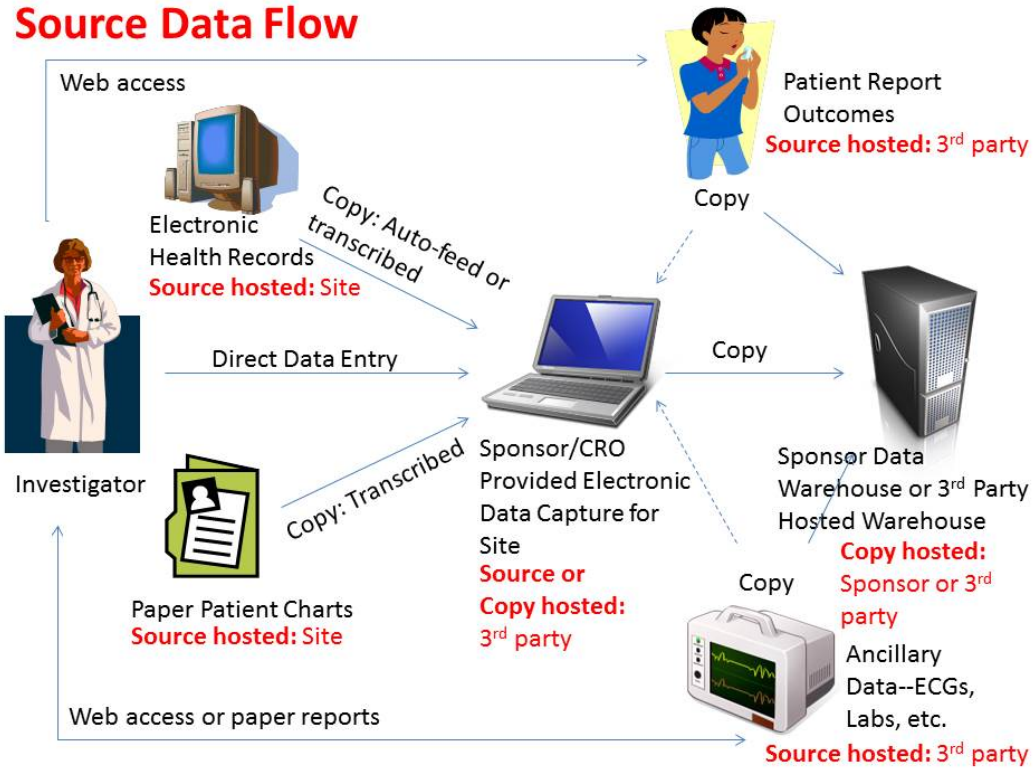
[16] FDA, US Department of Health and Human Services, January 2011, Guidance for Industry Electronic Source Documentation in Clinical Investigations DRAFT GUIDANCE.

[17] FDA, US Department of Health and Human Services, November 2012, Guidance for Industry Electronic Source Data in Clinical Investigations DRAFT GUIDANCE.

The aforementioned guidance documents are aimed at describing what is expected to ensure eSource is a reliable and trustworthy source. The regulations point toward the desire to realize the potential benefits of electronic source yet the practical application of it falters over the exact wording of the regulations. Implementation activities grind to a halt with spiraling analysis of the needed software features and debate over regulatory interpretation. The result is a delay in the timely, appropriate and compliant introduction of new technology, when, in fact, what is needed is to consider the "spirit" of the regulations authored for a world using traditional paper CRFs combined with the content from more recently drafted guidance documents for electronic source.

3. eSource Principles of Use

When electronic source is properly implemented, it offers many benefits not possible with paper source records. The following principles are intended to guide organizations in an optimal, efficient and compliant implementation of eSource as denoted in Figure 1.



Note: Dashed lines reflect alternate dataflows.

Figure 1: Source Dataflow

Principle 1: Use solutions that are "fit for purpose"

Any electronic solution for source documentation should align with the needs of the trial. The gamut of functionality of eSource solutions is broad. Factors to consider include the modality, improved accuracy/data quality, efficiency, type of study, patient population, location of study/hospital and cultural considerations, site sophistication, program

consistency, timeliness of entry, protocol adherence and timeliness of availability (e.g., safety monitoring). Systems that are robust may be "overkill" and not practical for some trials; others may be too basic to capture the necessary information. To avoid any technological pitfalls that would make the use of eSource obsolete, the capability of the eSource solution to export data into a format that will easily integrate into the electronic data capture solution must be understood. The choice of the solution should be confirmed by all internal sponsor stakeholders and key opinion leaders.

Principle 2: Declare the source

Data in a trial may be generated from a mix of paper sources and electronic sources. Per the CDISC glossary, source data is information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).[18] All computerized systems and data sources that a sponsor mandates for all sites (e.g., eCOA/ePRO, EDC) should be identified in the protocol. To capture other patient data, sites may elect to use eSource or paper source or a combination. The sponsor-mandated source decision will be documented in a data management plan or its equivalent. Sites must consistently document and apply their chosen method of source documentation for all patients. A source data location list should be maintained as part of the investigator's trial file. The investigator's primary responsibility is to patient care and safety. It is critical that the chain of custody of data from all sources through the final analyses data sets is properly documented and consistently applied such as in a dataflow document. The FDA Guidance for Industry Electronic Source Data in Clinical Investigations[19] emphasizes the role of data element identifiers including originator as key elements in documenting eSource.

Principle 3: Capture data when first generated

For the many benefits it provides over paper records that are later data entered into a computer system, clinical data should be captured electronically by study site personnel or by patients (when eDiaries are being used) at the point of data generation to help:

- avoid transcription (and inherent errors) from paper records
- enable timely data review by the principal investigator
- enable timely data review by sponsor safety reviewers

[18] CDISC Clinical Research Glossary. Version 8.0 [Internet] [2009 Dec; cited 12 Mar 2014] [51 pages] Available from: http://www.cdisc.org/stuff/contentmgr/files/0/be650811feb46f381f0af41ca40ade2e/misc/cdisc_2009_glossary.pdf.

[19] FDA, US Department of Health and Human Services, September 2013, Guidance for Industry Electronic Source Data in Clinical Investigations. Procedural. [2013 Sep; cited Sep 2013] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf.

- enable real-time data quality checking
- capture a more accurate and complete audit trail
- reduce the volume of records to be source data verified or reviewed

Some of these benefits are achieved merely by capturing the data electronically when it is first generated as long as the data capture system properly manages the electronic records. However, some benefits are enabled only if the source is integrated with the sponsor's/CRO's clinical system. The sponsor's/CRO's real time safety review is enabled only if the electronic source is tightly coupled to the sponsor's/CRO's EDC system as the most robust real-time data quality checking is often only programmed into the sponsor's/CRO's systems.

Data captured at point of care may require a change in workflow at the site. To promote adoption of eSource, this new workflow should be efficient for the site. Mobile data collection is ideal.

Principle 4: Control electronic data

In the world of paper records, it is easy to understand the physical control that an investigator has over the paper source records at their site. The records still require proper management to remain effectively controlled but only transcribed copies are sent to the sponsor/CRO and the original source records physically remain at the site under a combination of physical (e.g., locked file cabinets) and procedural (e.g., restricted distribution of keys) controls implemented by the investigator. However, a true validation of data equivalence end to end (source to sponsor/CRO analyses database) was never truly feasible in the paper world. It was also never truly possible to know if a paper document was destroyed because a remaining audit trail would not be guaranteed.

In the world of electronic records, it is possible to control the integrity of data seen or modified by many parties over the lifetime of the record or we would not have the e-commerce solutions that drive so much of the global economy today. However, appropriate control of electronic records requires a very thoughtful implementation of a system of controls working together, some procedural (e.g., segregation of duties, standard operating procedures), some physical (e.g., different server locations to establish redundancy) and some electronic (e.g., computer security rights and roles). It may take significant effort to validate and commensurate inspection activity to verify such control systems are operating as designed.

In the context of a sponsor/CRO EDC system, the system may be used purely for transcription/transfer from an investigator-controlled source (paper or electronic) or as the source itself, if the data are entered directly in the sponsor/CRO EDC. It is important to acknowledge that just as source may be a certified copy or a transcription this does not mean that every transcription is and should be treated as source as prescribed by predicate rules. Three principles must always be followed as it is the principal investigator's primary responsibility for patient care and safety. Any data in any form to be considered source data:

(1) must never be under the control of the sponsor/CRO,

(2) must always be accessible to the investigator, and
(3) must be under the control of the investigator through the legally determined timeframe.

Only a clinical investigator or delegated site staff should perform modifications or corrections to eCRF data. Modifications or corrections must be traceable by data element identifiers reflecting date, time, originator and reason for change. Ideally the eCRFs are kept at the site in an independent way (i.e., independent of a sponsor or CRO-controlled system). A fully independent trusted third party may be an alternative, but the definition of "independent" has not crystallized yet.

The investigator should have not only access but also sole control of content of the eCRF. The site's eSource should not be changed without the express consent of the investigator as well as traceability of any changes easily identifiable by inspectors. Sites should have access and control of eSource to know what they have sent to the sponsor. This can be accomplished via a trusted third-party information technology (IT) organization with no data management responsibilities. Decommissioning any EDC system should follow chain of custody methods to show traceable data from the hosted venue to sites. Decommissioning should follow investigator confirmation of archiving to assure that direct access by the investigator never lapses.

In legacy EDC environments, where software programs ran on the sponsor's/CRO's computers (thick client) located at a clinical investigation site and the data was stored on electronic media at the same site, the perception may have existed that the electronic records were under the investigator's direct control. However, if such systems ever exchanged removable media, were linked directly to sponsor's/CRO's systems to transfer records or update software, or the sponsor/CRO provided the software or any administration of the system, then the effective control of those records depended on a validated system of controls.

The same state exists when computers and media are located away from the investigator's premises—as so many Internet-enabled applications function today—except that the physical and procedure controls are often implemented by neutral IT third parties contracted to perform such duties. Whether such third party is contracted by the investigator or the sponsor/CRO should be immaterial if the system of controls is effective. Theoretically, the more parties engaged to perform independent roles in such a system of controls, the more clear segregation of duties likely exists, minimizing the ability of any one party to subvert the system of controls. While no shortcut for designing an effective system of controls exists, any techniques that implement greater segregation of duties should inspire more confidence in the effectiveness of the control system.

Principle 5: Leverage automated quality checks

Given that eSource is collected contemporaneously with the event without other documentation, the most effective way to ensure data integrity is to program front-end data verification checks (i.e., front-end validation checks) into the data capture system. Front-end edits allow the end user, patient or principal investigator, to verify the

accuracy or intent of the entry real time. Additionally, edit checks should look longitudinally across visits to ensure that consistent data are being captured. In the instances when the entry is an upload by a device or machine (e.g., blood pressure cuff), both the validation of the device/machine by the site and the validation of the transfer system by the site and sponsor/CRO is key to ensuring data integrity. In the legacy transcription world, verification checks post data submission are routine to check for transcription errors; however, in an eSource scenario, verification checks post eSource submission should be limited to checks across multiple sources, header data, etc. To be the most efficient, front-end validation checks should focus on key data elements that will be analyzed.

Principle 6: Control for quality

As part of the quality controls on data retrieved from eSource, system and user controls should be in place and appropriately documented to ensure all data collected from eSource meet ALCOA+CCEA (attributable, legible, contemporaneous, original, accurate plus complete, consistent, enduring, and available).

ALCOA+CCEA on eSource includes these elements:

- Data are captured in the eSource in such a way that they are **attributable**. The eSource system or device should capture information about who made the entry, or from what other electronic source it was derived. To facilitate a secure and auditable electronic system, security roles and user accounts should be created for each individual given access to the system. It is up to the sponsor and/or designated personnel to create and maintain these roles and accounts within the system and validate they function as intended. The investigational site should be properly trained and is responsible to ensure investigators and site employees use unique access to the EDC system and do not share user account information to avoid fraud or harm to any subjects. Sites should understand how the security controls work.
- Data are **legible** and in the appropriate language required by the local regulatory authorities, and, where applicable, conform to industry data format standards recognized and used by that regulatory authority, such as ODM, CDASH, CDISC Controlled Terminology, or SDTM.
- Data are **contemporaneous** so that it is known when the measurement or observation was made and when it was recorded in the eSource. If there was a time lag between the measurement and the time it was recorded in eSource, this should be recorded in the eSource with the data, or detectable from the audit trail. (See Principle 3: Capture data when first generated.)
- For the data to be considered eSource, they should be **originally recorded** or recorded as a certified copy in the system or device that is considered the source. If the eSource is another system, such as an electronic health record, or a device that captures data, adequate metadata to clearly identify the source should be transmitted along with the data. (See Principle 3: Capture data when first generated.)
- To ensure data are **accurate**, there should be known quality controls on the originating source, including validation of any processes, programs or systems

that transfer data from one source to another, acceptable calibration practices and documentation on devices that capture data automatically, operation of data capture devices by trained personnel, and procedures that describe these controls and the proper operation of the device.

- To ensure data are **complete**, a validated transfer process should be employed and additionally programmed edit checks can be automatically run to confirm that all data expected for mandatory data fields in a study have been retrieved from the electronic source. (See Principle 5: Leverage automated quality checks.)
- Programmed edit checks can also be employed to ensure **consistency** within and across data from various electronic sources. (See Principle 5: Leverage automated quality checks.)
- Process and technical controls should be in place to ensure that clinical records collected from an electronic source will **endure**; that is, that those records are maintained for as long as specified in applicable record retention requirements. Maintenance of such records should be accounted for in an organization's backup and recovery plans and procedures.
- Electronic records and their source should be maintained in such a way that they are **available** for review, and in a format that is suitable for review by a human for as long as the applicable record retentions requirements endure. This could be done by storing the records on enduring media (e.g., disc or tape) in a system-agnostic format (e.g., portable document format (PDF), extensible markup language (XML)).

Principle 7: Conform to regulations and guidelines

Understanding that regulatory bodies do not regulate various investigator eSource solutions used as part of source data collection in clinical trials, investigator eSource data capture systems should align with the spirit of US FDA 21 CFR Part 11 as much as possible. Sections of the regulation address the need for accurate, controlled recordkeeping of subjects' information in sponsor/CRO electronic data capture systems whether used as direct data entry systems (eSource) or holding transcribed data. Given these sponsor/CRO systems will rely on information contained in investigator eSource solutions, the same practices should be applied wherever possible. Sponsors/CROs need to define a process to determine the EHR's trustworthiness/access such as using the eClinical Forum's site checklist[20] for EHR reliability assessment that is under development.

[20] EHRCR (Electronic Health Records for Clinical Research) Project Team, eClinical Forum (www.ehrcr.org). June 2011. Release 1.0. Practical Considerations for Clinical Trial Sites using Electronic Health Records (EHRs) Certified for Clinical Research; Addressing Regulatory Considerations. Release 1.0. [Internet] [2011 Jun 1; cited 2014 Mar 12] [24 pages]. Available from: http://eclinicalforum.org/ehrcrproject/en-us/documents.aspx.

Like any paper-based system, investigators participating in clinical trials and using eSource for patient charting (e.g., EHRs) are expected to follow the retention requirements outlined in ICH E6 Section 8 and US FDA 21 CFR Part 314 and Part 312 regulations. Sites using eSource must understand the dataflow and how it meets the US FDA 21 CFR Part 312.62(b) obligations of maintaining case histories under this dataflow. Other guidance documents such as CDISC's eSDI, FDA's Guidance for Industry Electronic Source Data in Clinical Investigations[21] and EMA's Reflection paper on eSource[22] provide key input to expectations for sites and sponsors/CROs.

As a part of good software development life cycle (SDLC) practices, clinical researchers should encourage their eSource providers (e.g., EHRs) to implement the following recommendations wherever possible:

- controlled access
- appropriate, documented training of users, administrators, and developers of the eSource system
- written policies holding individuals accountable for information contained within the eSource application to which their signatures were applied
- requirements related to electronic signature compliance
- audit trails (user, date/time of data change, reason for change (if applicable), and all previous entries not obscured)
- documented system validation including system users, for example researchers, participating in user acceptance testing.

Sponsor/CRO data managers have the right skills and are in the best position to advise their organizations on a risk-based approach to evaluating sites' data systems to ensure they are meeting SDLC practices (checklists, defining roles and responsibilities, etc.).

4. Data Collection Modalities

While applying the above principles, consideration should also be given to challenges and solutions that are specific to a given eSource modality. The following sections address the most common eSource data collection modalities: third-party data, eCOA, EDC and EHRs.

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[21] FDA, US Department of Health and Human Services, September 2013, Guidance for Industry Electronic Source Data in Clinical Investigations. Procedural. [2013 Sep; cited Sep 2013] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf.

[22] European Medicines Agency, 9 June 2010; EMA/INS/GCP/454280/2010; GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. [2010 Jun 9; cited 2013 Sep 2] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.

Third-Party Generated Sources (Central Laboratories, ECG Data, IRT, etc.)

We define third-party data sources as those electronic sources not controlled by the entity that requires the data to perform analysis and reporting for a clinical trial. Certain third party data, such as laboratory data and electrocardiograms (ECG), were among the first electronic sources adopted. Using these data as eSource has been successful because the processes to handle eSource from these organizations are well established; the technology is mature and data standards are available.

The influence of third-party data sources will continue to increase as technologies continue to advance, making data available much more quickly. The varied sources producing these critical data for research are not all necessarily regulated by government authorities. Organizations relying on these data to demonstrate effectiveness, safety, metabolic behavior, and/or post-marketing outcomes have adopted best practices to receive, exchange, manage, track, and store electronic data from third-party sources thereby demonstrating control and traceability. Regardless of the specific third-party data source, processes and principles for handling and maintaining these data should be consistent.

Process

- **Planning:** Before clinical trial data are collected in any third-party data source, planning activities need to take place. The entity managing the data source and the recipient of the data to be collected must agree on their roles and responsibilities during the life cycle of data acquisition, management, and archival. The overall dataflow, chain of custody, transmission data structures (naming conventions, data attributes, etc.) and issue resolution should be clearly documented in the Data Management Plan (DMP) or related documents. (See Principle 2 Declare the source.)
- **Executing:** Executing third-party data acquisition and management should be in accordance with the approved plan. It is recommended that test data from the third-party data source be transmitted to the receiving entity to verify the data structures as well as the data extract and transfer process (including appropriate security measures to protect the data during the transmission). The receiving entity should execute a complete and thorough check to ensure that data from all sources are reconcilable and suitable for analysis. At minimum the subject and visit identifiers must be reconciled. Checking of safety and efficacy data across different data sources to ensure consistency of data handling may also be necessary. All programmatic checks and manual data review should be documented as part of the DMP or edit specifications documents. (See Principle 5: Leverage automated quality checks.)

  During the course of study data collection requirements may change as a result of a protocol amendment. The DMP and the data transfer specification should be updated accordingly if the changes result in new data present for only a subset of subjects (i.e., subjects already beyond the point in the study when the new or modified data are collected). A specific description of the expected disparity

should be documented in the DMP. Implementation of such middle-study change will require close collaboration by all parties.

In any scenario involving third-party generated data, it is critical that any data corrections deemed necessary are made at the source and not to subsequent copies of the data.

People

Depending on the organization and structure of companies, the people involved in the exchange of third-party data can vary. We outline the key functional roles that should be engaged in the life cycle of a clinical trial using third-party data: More than one of these roles may be held by the same individual in an organization, and the roles focus on the recipient entity.

- **Project Manager:** The Project Manager role may also be referred to as the Vendor Manager who oversees all aspects related to the third-party deliverables including contract, budget, meetings and minutes, data transfers, and archive documents at end of the study. The Project Manager will often liaise with the corresponding vendor's Project Manager to assure alignment of expectations.
- **Data Manager:** The Data Manager role focuses on the actual study data received from the third-party data source. The Data Manager owns and executes against the approved DMP and liaises with the corresponding data management personnel at the third-party vendor. The Data Manager provides information to the Project Manager pertaining to progress of activities against milestones and deliverables, impacts on specific changes and timely communication about any potential issues/challenges that may impact the ability to deliver data for the analysis and reporting of the trial. Documentation of data handling procedures and any deviations are the responsibility of the Data Manager.

Technology

As technology develops the number of third-party data sources is ever increasing. Below is a representation of some of the more notable sources commonly used.

Laboratory Data

As the most mature use of eSource, central laboratory services have been successfully used to analyze clinical safety (hematology, chemistry and urinalysis) and bioanalytical samples from clinical trials for decades. Why have they been so successful? The instruments are fully automated to perform the assays and to generate data. Data standards and control terminologies are well defined. Laboratory data are commonly included in regulatory submissions to support marketing applications. The laboratory instruments used to generate data for clinical trials must be US FDA 21 CFR Part 11 compliant and validated. Laboratory data can be accessible through Laboratory Information Management Systems (LIMS) by laboratory personnel or via a web-based portal to the physician and project team. The data are exported from the LIMS database and transferred to the sponsor/CRO through secure means for analysis and reporting. When central laboratory services are used, the investigative sites should intend to use the central laboratory for

regular, scheduled or non-emergency unscheduled blood draws. It is understood that some sites are required to use a local lab (e.g., a university site). The same requirements put forth to the central laboratory should be adhered to by the local laboratory. In the case of an emergency situation for patient safety reason and a local laboratory has to be used, a duplicate sample should be obtained and sent to the central lab for confirmatory analysis. (See Principle 6: Control for quality.)

Electrocardiogram (ECG) Data

Another commonly used electronic source in clinical trials is the collection of electrocardiogram (ECG) data to evaluate cardiac safety. Central vendors usually provide ECG machines to investigational sites participating in a trial. ECG tracings and Holter ECG measurements are periodically transmitted to central readers usually at the end of each day. The cardiologist at the central facility conducts the reading and provides ECG parameters and interpretation to the sponsor/CRO as electronic data files. For submission to the US FDA, electronic ECG waveform files in XML format may be also required. It is important to ensure that the ECG machines are compatible with the FDA data warehouse requirements. When a central reader is used to assess ECG results, sites should be cautioned not to use local ECG machines since it would be difficult to digitize paper tracing to combine the results with the rest of the data.

Interactive Response Technology (IRT)

Interactive Response Technologies (IRT) traditionally referred to as Interactive Voice/Web Response Systems (IVRS/IWRS) have long been in use in clinical research. The typical purpose of IRT has been to randomize patients and manage clinical drug supply. Because this paper focuses on eSource, we only examine the electronic data collection and use of such data to support regulatory submission.

IRT, like other electronic data collection systems, provides secure log on, audit trail, and transaction logging. To support clinical operational, demographic, enrollment and drug accountability, information is often collected real time in IRT while the subject is on site. The relevant data can be extracted from the IRT system and transferred as datasets to the sponsor/CRO or be integrated directly with other clinical data collection systems such as EDC. Integrating IRT with EDC allows the subject eCRF to be automatically populated with data, avoiding duplicate data entry of demographics, drug accountability, and other information, thus alleviating the need for reconciliation of data from two different sources. For EDC data collection where IRT is not integrated with EDC and is not electronic, a paper log is used as official source. In such a case, duplicate data collection may result in discrepancy between the EDC and IRT data. It is important that the official source be declared whether or not IRT is integrated with EDC. (See Principle 2 Declare the source and Principle 6: Control for quality.)

Sponsors should consider the complexity of data integration within the two systems early in the study setup. Since IRT integration must be completed before the EDC system can be used, it is paramount that all tasks are accounted for in the project timelines and robust project management is applied. Integration can be either one direction or both directions. One-way integration is to populate IRT data into

appropriate eCRF forms and data fields. Two-way integration will also include automated data transfer from EDC to the IRT system. It would be advantageous to use a system that provides internal integration between IRT and EDC modules.

In addition to the previously discussed electronic sources (Lab, ECG and IRT) there are many other types of data that are generated electronically and transferred directly as data files from third-party vendors. Examples of such third-party data include polysomnography (PSG) sleep data, neurocognitive test data, radiology and MRI image data, PET scan data, and pharmacogenomics data. The same considerations apply to these additional electronic source data. Imaging data are usually processed by a medical specialist. Sponsors/CROs may only receive data for overall interpretations or key parameters for reporting and submission. All third-party data will need to be reconciled with the data collected on the CRF to ensure integrity and consistency.

Electronic Clinical Outcome Assessment (eCOA, eDiaries, ClinRO, ObsRO) to Capture Patient-Reported Data

Electronic Clinical Outcome Assessment (eCOA) systems also known as Electronic Patient Reported Data systems are unique when contrasted with other sponsor/CRO-provided electronic data capture in that these patient-centric data collection methods capture the source data directly from the patients. Unlike EDC, an eCOA setup may require psychometric and cognitive validation of the instrument or questionnaire. Additionally, eCOA allows direct transfer of data generated from other patient devices such as personal glucometers and peak-flow meters.

In the context of this paper, eCOA includes collection of both the copyrighted, validated instruments such as Quality of Life SF-36, Montgomery-Asberg Depression Rating Scale, and so on, as well as any diary data collected directly from the patients. The data collected in this context are the eSource data.

In today's clinical research industry, eCOA system development is typically a joint effort between the sponsor and a sponsor-sourced third-party eCOA provider. A data collection modality such as a smartphone, tablet, etc., can be provisioned and provided to the patients, investigators, or the caregivers or alternatively, they can bring their own device. The data are electronically entered and edit checks executed at the time of data entry. Once data are successfully entered, they are transferred to the third-party eCOA provider's database server where the eSource can be accessed by the sites and sponsor/CRO personnel according to and based upon their role within the trial. At the end of the trial, the eSource is copied on a durable media (e.g., DVDs) and sent to the clinical sites and sponsor/CRO. Upon confirmation that the eSource is in the sites' possession, the third-party eCOA provider decommissions and archives the eCOA database. The diagram below represents the key aspects of an eCOA setup.

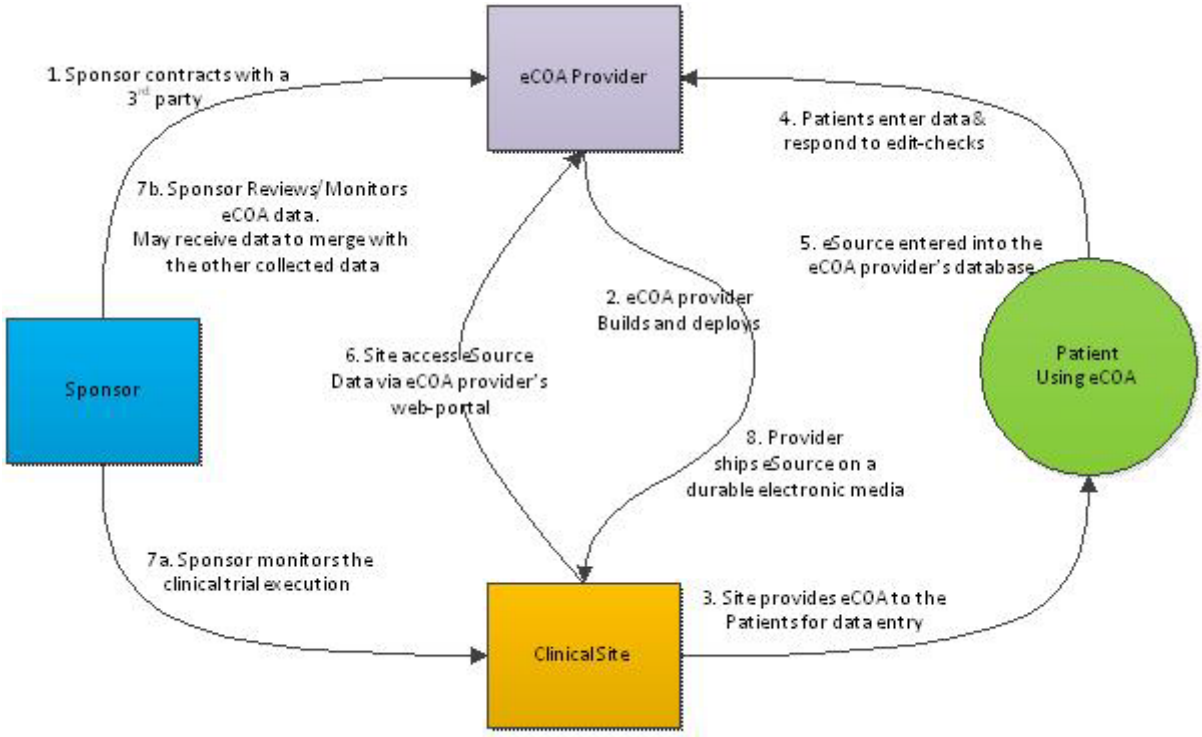

Figure 2: Electronic Clinical Outcome Assessment (eCOA)—Traditional Setup

Process

- **Planning**: Sponsors should define all patient data collection instruments early in the clinical trial planning stages. All eCOA data to be collected must be driven by the clinical trial protocol and be fit for purpose. In certain cases, it may be necessary to implement additional rigor to the measurement validation such as cognitive debriefing or linguistic validation. If a copyrighted measure is used, an approval to use it should be obtained. These activities require working with one or more external providers and can add additional timeline risks to eCOA deployment. (See Principle 1: Use solutions that are "fit for purpose".)
- **Regulation**: Although we do not intend to discuss all the specifics of the current and active regulations that cover electronic data capture, it is to be noted that the US FDA 21 CFR Part 11 and the FDA's Guidance for the Industry: Patient Reported Outcome Measures: Use in Medicinal Product Development to Support the Labeling Claims (Dec 2009)[23] apply. (See Principle 6: Control for quality and Principle 7: Conform to regulations and guidelines.)
- **Dataflow:** Due to practical reasons, at the time of protocol writing, the eCOA dataflow may not be completely known; however, the sponsor Data Management

[23] FDA, US Department of Health and Human Services, December 2009, Guidance for the Industry: Patient Reported Outcome Measures: Use in Medicinal Product Development to Support the Labeling Claims [2009 Dec; cited 2013 Sep 2] Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

Plan (DMP) should clearly articulate the description and flow of the patient-reported data that is captured as eSource. In other words, it should describe how the eSource data would be electronically transferred from the patients' hand-held devices to the eCOA provider's data center and integrated with other clinical data collected through the EDC system by the sponsor/CRO. It is important to note that eSource data once transferred from the eCOA device, resides at the third-party server, and the sponsors/CROs only get a copy of the data for processing. eSource is not *moved* to the sponsor/CRO.

People

- **Sites**: Clinical investigators should have access to the eCOA data at all times. It is important to note that unlike other eCRF data that is transcribed from a source document and entered into the sponsor/CRO-provided EDC system, eCOA data is the eSource and therefore the site investigator's approval of the accuracy of eCOA data captured is not required. Nevertheless eCOA data should be monitored by the sites to ensure patients' safety at all times. The eCOA system should be developed to send alerts to site personnel and clinical safety monitors when peculiar eCOA data pointing to a safety concern is entered. (See Principle 4: Control electronic data.)
- **Sponsor/CRO:** The eSource data collected via the eCOA system is unlike any other transcribed eCRF data and therefore should not be queried and cleaned in the same manner. Sponsor/CRO review and query of the source data should be planned in advance and be kept at a minimum, for example, subject identifiers or seeking clarification on data points that may point to safety issues. Most, if not all, data entry errors should be caught during the electronic capture of the eCOA data, however in those rare instances where an erroneous data point needs to be updated, the sponsor/CRO should follow the eCOA provider's data correction process, which should have a provision for the site's review and approval. Electronic prompts, flags and data quality checks should be used to minimize errors and omissions at the time of data entry[24]. (See Principle 5: Leverage automated quality checks.) Due to the element of "recall bias", data entry time windows should be established and queries should be created as close to reporting of the event as possible. Because the key benefit of eCOA is improved data quality, sponsors/CROs also should carefully weigh the downside of allowing lengthy retrospective data entry periods. Due to the lack of traceability or audit trails outside a controlled system, when eCOA is used, sponsors/CROs should not allow capture of the same eCOA data via other paper source; for example, data transcribed on paper and brought to the site. Lastly, it is important to note that although an eCOA implementation contract is established between the sponsor/CRO and the eCOA provider, the contract terms should clearly lay

[24] FDA, US Department of Health and Human Services, November 2012, Guidance for Industry Electronic Source Data in Clinical Investigations DRAFT GUIDANCE. Lines 215-216.

out the independence of the eCOA provider for hosting the eSource data and that source data is in the exclusive control of the investigator[25] (See Principle 5: Leverage automated quality checks, Principle 3: Capture data when first generated and Principle 2: Declare the source.)

- **eCOA Vendors:** eCOA vendors play a key role in ensuring the independent nature of eSource data. eCOA providers should have a documented process and procedural controls to demonstrate that all data edits or corrections are documented and approved by site personnel. This should be in addition to the audit trail, which should be part of the system. eCOA vendors must ensure the availability and accessibility of eSource data by the sites and the sponsor/CRO at all times. They should publish the system maintenance periods and communicate any downtime periods to site and sponsor/CRO personnel. Vendors should also provide documentation including a dataflow to the site with regard to how sites meet US FDA 21 CFR Part 312.62(b) to maintain case histories using this method. (See Principle 4: Control electronic data, Principle 3: Capture data when first generated and Principle 6 Control for quality.)

Technology

- **Modality independent eCOA:** Continued pressures on cost containment within the clinical research industry as well as rapid adoption of consumer mobile smartphones and tablets are creating opportunities for sponsors/CROs and eCOA vendors to look for ways to reduce costs by utilizing the patient's own mobile phone, laptop, and tablet to collect eCOA data. According to the Nielsen Survey, overall smartphone penetration in the US grew from 45% in the fourth quarter of 2011 to 60% in the fourth quarter of 2012. Smartphone penetration among people who recently bought a mobile phone stood at a whopping 77% in the fourth quarter of 2012.[26]

  Although smartphone adoption opens up new doors and opportunities to implement more cost-effective eCOA data collection, it also raises unique challenges. First and foremost, the eCOA instrument's validity on different mobile platforms as well as rendering on different screen sizes becomes a big question. Secondly, this can introduce operational management challenges at the site where a site would now have to ensure each device make/model/operating system meets the requirements to be used as an eCOA device.

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[25] European Medicines Agency, 9 June 2010; EMA/INS/GCP/454280/2010; GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. Topic 3: Control. [2010 Jun 9; cited 2013 Sep 2] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.

[26] The Nielsen Company (www.nielsen.com). Mobile Insight Q4, 2012.

Even with the aforementioned challenges, which are directed more toward copyrighted, validated scales and instruments, modality-independence can be a solution for post-marketing trials or to capture simple patient diaries. Therefore, a "fit for purpose" approach is warranted. (See Principle 1: Use solutions that are "fit for purpose".)

Sponsors should discuss any modality-agnostic eCOA data capture ideas within their program with regulatory agencies as early as possible, for example at the End of Phase II meeting. eCOA vendors and sponsors/CROs should ensure that the data collected from different modalities reside in one centralized database.

Sponsor/CRO Electronic Data Capture

Using EDC as an eSource system requires a paradigm shift from the current transcription into EDC being used today in the majority of studies. When using EDC as eSource, Principle 4 Control electronic data, can be satisfied via the rights/roles/privileges functionality inherent in the EDC system. Multiple aspects of process, people and technology changes outlined below must be in place for EDC to be considered eSource.

Process

- **Point of Care**– eSource requires contemporaneous recording. However, depending on the procedure or when enrollment is determined, direct data entry may not be possible (e.g., enrollment based on an investigator's decision during an open surgical procedure). In this situation, routine paper source guidelines are to be followed. In general, the site should indicate which data points are transcribed from original paper source documentation versus data points that are eSource. One example of how to achieve this is to use a direct data capture system that allows fields to be flagged if they are sourced from paper. Any application that can be used on a mobile device should increase the site's interest in Direct Data Entry into EDC. (See Principle 3: Capture data when first generated.)
- **Data entry instructions** are critical and could be in the form of completion guidelines or help menus built into the electronic system.

People

- **Investigational/Clinical Site**
    - **Clinical Coordinator Experience**: As eSource becomes a more common practice for capturing data, the opportunity to lose data due to incorrect readings, typographical errors, or common mistakes increasingly becomes a major concern. If the correct data are not captured or entered during the interview with the subject, that information may be lost permanently. Due to this, sites instructed to capture clinical data in an eSource system should make special considerations to have an experienced coordinator, nurse, or designee perform or oversee the data entry to ensure data are captured accurately and represent the status of the subject during the

interview period. The person assessing the patient should be the person entering the information or overseeing and/or reviewing the entry of the information into the electronic system storing the clinical data.

- **Technical Ability**: When considering executing clinical research where the eCRFs will be source data; special consideration should be taken to ensure the investigational site can accommodate capturing data electronically at the point of care. Sites should be assessed on their ability to enter data in real time and a thorough assessment of their ability to connect to the EDC system during a patient interview should occur prior to selecting the site as part of the study. If reliable connectivity is not available, an alternative method of capturing data manually and performing data entry at a later time should be considered. Assessments should reflect the local feasibility of the modality employed. A checklist for appropriate assessment areas is recommended to maintain consistency when assessing multiple sites.

- **Sponsor/CRO Monitors**

  - **Traditional Monitoring**: Although eSource may make some forms of source obsolete, sponsors and their designated staff should be vigilant to maintain compliance by recognizing when clinical data capture is part of another source system (laboratory devices, medical records, patient charts, etc.). In this case, traditional source document verification should be performed on critical data points that affect the primary endpoints, secondary endpoints, and safety results of the subject. Processes to verify the existence of patients should continue to be used.
  - **Remote Monitoring**: A truly electronic source clinical study leaves little to no paper for a monitor to reference on a traditional monitoring visit. Given this drastic change in their traditional monitoring processes, monitors should now view remote monitoring as their optimal solution. Remote monitoring (along with Targeted Source Document Verification (TSDV) or Risk-Based Monitoring (RBM)) allows the monitor to review data for potential queries, discrepancies, etc., without the additional resource, travel, and financial burden previously considered routine. For additional details on remote monitoring, see the FDAs Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring [27]
  - **Reliance on Data Quality Checks**: As monitors shift from paper to eSource, their reliance on clinical edit checks becomes significantly more

[27] FDA, US Department of Health and Human Services, August 2013, Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring. Procedural. [2013 Aug; cited 2 Sep 2013] Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf.

important. With the appropriate edit checks, the burden on monitors and data management should be reduced throughout the life of the study allowing for faster database locks, shortened clinical study closeout, and reduced travel required throughout the study. (See Principle 5: Leverage automated quality checks.)

Technology

- **Data Quality Checks (Edit Checks)**: Given that the EDC system will now be the source for clinical data, there is very little room for error. As research moves to eSource, edit checks become very important for the quality of data being captured. Edit checks should be in place and thoroughly tested prior to subject enrollment to ensure that as data is being captured, the edit checks are executing and responding with the appropriate query, range check, format checks, and so on.
- **Data Access**: Traditionally, EDC systems are web-based systems. In a true eSource environment, care must be taken to ensure that the data capture system is "live" and accessible to the clinician during the subject visit regardless of Internet access. For example, in a study using EDC as eSource, the data capture interface needs to be available during all parts of the subject interview and visit. In most instances, it should be mobile to capture data at the point of care.
- **Connectivity to External Systems**: The sponsor/CRO should also consider alternative (fail-safe) methods of capturing data in the event the EDC system cannot be accessed during a subject's visit period. In the case of time-critical data (i.e., SAE reporting), a backup may be necessary in the event of a system failure. This will allow data to be stored and entered at a later date when the system is fully restored.
- **Enduring**: Backups of EDC are necessary to ensure no loss of eSource data. Each company should have a risk-based approach as to how frequent servers are backed up given this is the only copy of the data. (See Principle 6: Control for quality.)

Site Controlled EHRs

In the EHR operating paradigm the segregation of duties is quite clear. The clinician, the clinician's practice or institution own and manage the EHR for the primary purpose of providing direct care to their patients. Those business practices are governed by different regulations but still require similar control systems to manage the records and assure they substantiate the history of care. (See Principle 4: Control electronic data.)

Given the relatively nascent nature of EHRs, there are myriad implementations and the global marketplace has yet to settle on a stable, effective solution to exchange EHR's clinical data with clinical research. Thus, it is likely that for some time investigators will manually have to transcribe data captured in an EHR into the clinical research data capture tools, be they paper or EDC technology. A direct feed from the EHR to the EDC tool is currently limited to a few real-life examples. This paper entertains both paradigms. (See Principle 3: Capture data when first generated.)

Transcribed EHR to EDC

In this transcribed scenario EHR functions similarly to the paper patient chart and thus the roles of the sponsor/CRO clinical trial monitor and regulatory inspector change very little. They still require the ability to read patient records to verify the transcription of data (into paper CRFs or the sponsor/CRO EDC system) is accurate. The primary difference is simply that they require different training to effectively and appropriately access the EHR rather than the traditional paper records.

To meet regulatory expectations, if the EHR is used in any capacity, the subject's records from the EHR should be accessible to the monitor and inspector either through direct access or together with site staff. Such obligations need to be clear when screening investigators/sites for clinical trials and supported in the research contracts. It should be noted that in the certified copy paradigm, the certified copy coexists with the eSource. Any changes to the data should be made at the eSource, that is, in the EHR. Understanding the starting point for sponsors/CROs to evaluate sites' systems is key to appropriate evaluations. (See Principle7: Conform to regulations and guidelines.)

Can We Eliminate Manual Transcription from EHRs?

Given that manual transcription of data from an investigator's EHR to a sponsor's/CRO's data capture system replicates many of the risks of manual transcription from paper records, FDA guidance[28] acknowledges that transcribing data from an EHR onto either paper or electronic CRFs is not the goal of eSource technology. The more favorable alternative would be direct/auto transfer of relevant EHR data to the sponsor's/CRO's clinical research systems. One problem is the limited "ability to communicate and exchange data accurately, effectively, securely, and consistently with different information technology systems, software applications, and networks in various settings… such that clinical or operational purpose and meaning of the data are preserved and unaltered". [29]

However, this is not as simple as exchanging data. The CRF logically guides the clinician to what data to collect at each visit and supports capture and reporting of adverse events. Thus, replacing the CRF requires substantial process integration as well as data exchange. In an effort to support data transfer from EHRs for research purposes, CDISC and IHE (Integrating the Healthcare Enterprise) developed an integration profile to collect and transfer key clinical trial data already existing in the EHR to an EDC. Demonstrations/pilots at Healthcare Information and Management Systems Society (HIMSS) and Drug Industry Association (DIA) conferences have been

[28] FDA, US Department of Health and Human Services, September 2013, Guidance for Industry Electronic Source Data in Clinical Investigations. Procedural. [2013 Sep; cited Sep 2013] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf.

[29] FDA, US Department of Health and Human Services, February 2012 [Revised February 2014], Guidance for Industry Providing Regulatory Submissions in Electronic Format-Standardized Study Data. Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf.

successful and one EHR vendor expanded on that concept to integrate their hospital EHR with their clinical research data capture tool. The premise is to populate the CRF with data collected in the EHR, surfacing the CRF within the EHR. There is still a person verifying the data for research is correct and then it is also archived as the certified copy of eSource and saved per legal requirements. Updates to the EHR are resent to the CRF and archive.

Interoperable EHR/EDC

Process

- During the design of the eCRF, the data manager must work with technology colleagues to identify which elements are to be entered by site staff, and which elements will be extracted and transferred to the eCRF electronically so that the database can be set up to accept transfers from the EHR system to populate the CRF. This mapping exercise is facilitated if the EHR vendor can produce Health Level Seven (HL7) v.2 output (e.g., Continuity of Care Document (CCD)) and has experience with integration profiles such as Retrieve Form for Data Capture (RFD). In addition, documented processes for handling amendments and other changes that can affect the fields collected in the EHR system and the eCRF must be in place. (See Impact of Amendments section.)
- Documentation must be kept that outlines what fields on the CRF are manually entered by the site versus what fields are electronically transferred from the EHR to the eCRF. The DMP is the most likely place to document these study-level conventions, and additionally a site-level source document is needed to identify how the site will capture source (eSource-EHR, direct data entry into EDC tool or paper transcription). (See Principle 2: Declare the source.)
- At database lock, a process to disable further transfers from site EHR systems must be implemented in addition to the traditional locking of case books. It is recommended that a process to verify all EHR data has been transferred to the EDC system, if the EDC/EHR integration does not already provide this information.

People

- As in any change management, behaviors will be the hardest to modify. Site personnel such as study coordinators and principal investigators will be more willing to adopt a model that closely integrates their EHR with an EDC tool, thus providing one familiar interface and allowing for a shorter adoption curve. However, if the tool is not customized to the site's workflow, the adoption/satisfaction rate will be low. Fewer mouse clicks to navigate and visibility to patient status at all times will facilitate workflow. Functionality that supports both the patient's healthcare activities and research requirements is key.
- Given the highly technical nature of the integrations, an alternative model with a third party may be the most effective in setting up the transfers versus site personnel. A new role of central monitor would also benefit from a direct feed from an EHR to an EDC in that source document verification (SDV) at the site location would be dramatically reduced and remote monitoring enabled.

Additionally, with EHR access, remote monitoring or inspections to ensure completeness of the CRF records would be possible.

Technology

- Technology solutions are only possible when the content to share is semantically interoperable. Standards are critical to enable data sharing between systems. Even if each system brings different standards to the table, they can be mapped for integration. When there are no standards, customization becomes too prohibitive for interoperability. For healthcare, Health Level 7 (HL7) is the standard; for research it is CDISC. The CDISC Biomedical Research Integrated Domain Group (BRIDG) model brings the two together by starting with concept modeling to ensure semantics are correct.
- When importing data from an EHR system into an EDC system consider:
    - The vendor of the EHR system at each site (some vendors have built-in integration functionality, some have customized integrations), how the system handles exporting information, and the capacity of your EDC system to handle the load transactions from multiple sites on an ongoing basis.
    - Traceability should be maintained between the EHR system and the sponsor/CRO database. (See Principle 6: Control for quality.)
    - The sponsor's/CRO's database must be designed to accept and denote multiple data entry methods: direct site data entry, transfer from EHR systems and other external sources to support the collection of eCOA or central laboratory data.
- Edit check design
    - Consistency checks on the data transferred from the EHR must be handled differently than those designed strictly for use on data captured in EDC. Consider employing analytical tools to look for corroborating evidence within the case report form if data anomalies are detected. For example, treatments associated with a given condition reported as a clinical finding. (See Principle 5: Leverage automated quality checks.)
    - Data quality checks take on more significance for data collected via the EHR and transferred to the EDC system. Checks for missing information, inconsistent dates, and so on, should be included in the overall data management plan. (See Principle 5: Leverage automated quality checks.)

This section explored an interoperable EHR/EDC however the same principles and best practices apply to a tablet-to-EDC model. This model is an interim solution in which a third-party IT vendor supplies the site with a tablet to collect eSource that could directly feed a copy to both an EDC system while providing an archivable file to store in an EHR (e.g., PDF). This interim eSource solution requires an investigator-controlled database hosted by a neutral third-party IT organization for the eSource collected in the tablet. Data management activities are limited to checks programmed on the EDC system.

Impact of Amendments on EHR, Edits, etc.

Amendments to protocols pose a challenge similar to those encountered with the current state. Changes still need to be managed through a robust change control process. The difference is that the site or perhaps a data broker would now be included in the technology changes as the mapping from EHR to EDC would be necessary. For edits, the changes would still be added to the EDC as they are today—contained solely within the sponsor/CRO realm.

5. Future Directions

The future of leveraging eSource efficiently lies in integrating the modalities described in this paper.

Standards, both format and content, are the key to integration and eSource information sharing. Standards organizations such as Integrating the Healthcare Enterprise and CDISC are working on profiles to enable data sharing across multiple sources. Without standards, an integrated future is limited and would require extensive custom mapping.

Technology advances and regulatory encouragement have converged to move the clinical trial industry to the tipping point for more widely adopting eSource. Progressive organizations that are preparing now for adopting eSource must assess the challenges that will impact their processes, people and technologies.

Process

- eSource turns the paradigm of the paper process for clinical trials on its head. To continue progress and realize the full benefit of eSource, we must change our mindset from the old paradigm of paper to the new paradigm of data integration throughout the trial. Every facet of the process must be evaluated and we must be ready to adapt or retire existing processes, and adopt or create new processes.
- The Data Management Plan will become even more critical to the success of data management as the dataflow becomes more complex and the chain of custody and traceability become automated. DMPs should be authored by a data manager who fully understands the dataflow, data sources, and the procedural adjustments needed for each type of source. For example, the data verification process needed for data that have been collected from an eSource through 100% electronic transfer would be very different than for data collected in EDC through manual transcription.
- Dataflow and chain of custody will affect our approach to Risk-Based Monitoring as well. For example, source data verification will be obsolete in a 100% electronic transfer of data from an EHR, whereas in a process where the site is performing manual transcription from the EHR to an EDC system, RBM would include some level of defined source data verification. Dataflow will help focus on what controls and processes are required to ensure data integrity.

People

- In all of the role changes from data manager to monitor to project manager, the role of the data manager remains vital and crucial to the task of providing a data set that is fit for analysis. Data managers must understand the complete life cycle and flow of data, from the point of collection through the point of reporting. Their role will include managing the dataflow and integration of data from various sources in such a way that data integrity and traceability are maintained.
- The data manager's role will evolve from one of being primarily a data reviewer, to one of managing the processes and technologies that allow eSource to become integrated in the clinical trial process. As the focus of monitoring shifts from source data verification to ensuring site compliance with the protocol and with Good Clinical Practice, the data manager will be crucial to the development of technology and process solutions to support risk-based monitoring.
- Although technologies and processes will certainly evolve over time, the underlying responsibility of data management remains the same: to deliver a set of data that are reliable and fit for use. We must be ready to meet the challenges of our responsibilities in a rapidly changing technology landscape that is unlikely to stop evolving any time soon.

Technology

- Emerging technologies are and will continue to be the driver for the availability and adoption of eSource in clinical trials. It is impossible to predict what future technologies will be developed to support eSource. To ensure eSource for clinical trials is maintained under appropriate controls, standards and processes must be continuously assessed and adapted. The concepts and principles presented in this paper form a solid foundation ready to be adapted and leveraged across trials as new eSource technologies evolve.
- Validation of the integrations between the site EHR and the sponsor/CRO data collection system is important. Validation processes should be based on the type of integration. Given that each EHR is different and has numerous upgrades/releases, one way to significantly reduce the validation of the transfer process would be to include a human verification step of the data auto-populating the eCRF—essentially a manual validation with each population. For example, if a common integration with the sponsor/CRO data collection system is possible with an EHR product, one validation per EHR system can be applied to all sites using that particular EHR system. Otherwise, develop a strategy to ensure the integrations are working as expected with each site. In a future-looking option, this may best be done with a newly formed type of entity called a data broker. This data broker could act as an intermediary for EHRs and EDCs for all clinical researchers. The data broker would validate the transfer process and keep up to date with any new releases of EHR software that might impact validation. They would also map core data fields (CDASH) from an EHR to a CRF and the clinical researcher

would buy these services. The data broker could also be an archivist for the site (a role in RFD) and could operate in a community cloud where multiple sponsors/CROs could access the shared validation or mapping information. The study archived data could reside in a private cloud for the site with view-only access for sponsors/CROs or inspectors thus meeting the requirement that the sponsor does not have control of the source data.

- An unconventional but effective approach to further segregate controls would be to have commercial software (the application, not a person) digitally sign all records as they are written to a database which would prevent the investigator, sponsor/CRO or any third party from creating or modifying data outside of the commercial software without detection.
- Organizations also need to address data integrity considerations when collecting data through various eSource technologies. Although validation of the actual eSource technology at the site may be out of the scope of responsibility for sponsors/CROs—just as validating a paper source process would be—the processes for capturing data from the eSource will need to be validated, and the methodology of validation will differ based on the modality.
- Assessing the value and appropriateness of a new technology is also challenging and its mere existence should not translate into its adoption, or that it should be implemented for every trial—there is no “one size fits all” in selecting eSource modalities to use in a trial. Each clinical program and trial must be individually evaluated to determine which eSource technologies should be leveraged.

6. Conclusion

The benefits of eSource are far reaching. In the scenario of direct patient data capture, an eSource is virtually the only method that assures contemporaneous data capture with corresponding audit trails to assure the principal investigator, sponsor/CRO and regulators that data were captured in compliance with the protocol and data handling instructions. When data are captured outside the confines of a site visit, and hence outside the direct control of site personnel, protocol adherence should be a critical concern. In such a setting, eSources such as eCOA become significant adherence and risk mitigation instruments.

Across all aspects of source data generation, paper can no longer be considered the “gold standard.” Demanding high-quality data should be the gold standard—a modality that can help improve it should be the right choice. The minimization of transcriptions (and inherent errors), the data association to individuals and timestamps offered by audit trails, the data validation enabled by automated system queries and the potential for virtually instant safety review to protect human health are more than adequate justifications to establish eSource as the new “gold standard.”

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