PHARMASPECIFIC

CONDUCT YOUR CLINICAL STUDY SUCCESSFULLY

Edition 3

To read - Very important

This book is a collective work. You are not allowed to sell it or to include it in offers or otherwise you will be punished by the law of your country. You are free to distribute it to whomever you wish, provided you do not modify it and always refer to Pharmaspecific as the author of this book, and include a link to https://pharmaspecific.com/

Contents

Introduction

I am Vanessa Montanari, Clinical Research Associate, Project Manager and Director, for 9 years, of Pharmaspecific, my own Contract Research Organization (CRO), in clinical research.

After 15 years of experience in clinical research, I had victories and failures. This guide is a summary of the lessons learned from this experience.

This guide will help you to carry out your clinical research projects successfully and in accordance with Good Clinical Practices. If you are a customer or future French customer, you will find all the necessary information including that applicable to France. If you are a foreign customer, you will see the aspect of international studies and also find aspects specific to France.

Good luck for your clinical trials. You can consult our website if necessary (www.pharmaspecific.com), and send me an email to contact@pharmaspecific.fr

Call us directly for any request for quotation on +33 (0) 987046492.

Vanessa Montanari, Director

Who are we?

Founded in 2010, our ISO9001 certified company is located in the Paris region.

Specialists in clinical research, we provide a complete service for the realization and the follow-up of your clinical trials and observational studies.

We are committed to contributing to the success of initiating and monitoring your clinical trials, regardless of therapeutic area, by providing you with efficiency, availability, responsiveness and proactivity.

We collaborate with the pharmaceutical industry (human and veterinary drugs), CROs, Biotechs, hospitals and medical device manufacturers.

a) Our commitments

• Listening and quality assurance of the services provided and the respect of your deadlines.

• Certainty that your studies are rigorously piloted and to obtain quality, totally reliable data.

• Assurance of respect for the rights, security and protection of each participant in the trial.

• Thorough monitoring of your study protocols, in accordance with ICH, European directives and French regulations.

• Continuous improvement of the knowledge and skills of our employees.

• Constant improvement of our processes and services.

• Meeting the requirements of an ultra-regulated environment.

• Confidentiality of data in the course of our work through the establishment of secure and reliable computer systems.

• Possibility for you to manage audits and inspections with confidence.

b) Our ethics

Pharmaspecific expects from each of its employees and regardless of their hierarchical position:

• Ethical behavior and integrity,
• Compliance with laws and regulations against corruption.

That's what you, Pharmaspecific customers and partners, expect from us.
We want every employee, in his or her area of expertise, to take an active part in respecting these guidelines in the implementation of their work.
Violations of these guidelines are not tolerated and will result in sanctions against those affected.

c) Our Quality Policy

In line with our commitment to excellence and reliability of our practices, we organize our development around a clear Quality Policy and organized around the following themes:

1 – Listening: the expectations of our clients, investigators and patients.

2 – Respect:

• of the regulations in force: to meet the legal and regulatory requirements specific to the activity of the company,

• of Good clinical practice in our work (including with investigators and other stakeholders).

3 – A continuous improvement process to ensure the quality of our services, increase our efficiency, maintain the satisfaction of our customers.

4 – The implementation of an ISO9001 certified quality management system in line with the satisfaction and evolution of our various interlocutors.

Find our full Quality Policy in PDF format.

d) Your data under high protection

We take to heart the confidentiality of the industrial and personal data transmitted to us. Thus, we have taken many steps to guarantee you a level of protection of this information.

The hard disks of the computers we use on a daily basis are encrypted.

All our computer equipment is protected by a firewall and our messaging system is secure.

The preservation of documents is secured by the establishment of an archiving system in encrypted mode.

Access to all documents is strictly reserved to authorized personnel.

User rights and authorizations are managed by our IT manager.

The maintenance of our computer equipment is carried out on a regular basis to ensure that the operating systems of the workstations, the antivirus and other protection software as well as the applications, are up-to-date from the point of view of the applicable corrections.

We comply with the following laws: FDA21 CFR11, RGPD.

The physical security of our premises is also strengthened.

e) Our services

Project coordination and management.

A single interlocutor manages your entire project. He is in charge of setting up the project team and the rigorous follow-up of your clinical trial.

- Design and writing of trial documents.
- Global project management.
- Budget management.
- Review of monitoring visit reports.
- Financial management of fees, additional costs of investigative trial sites.
- Control of the distribution of trial materials and documentation.
- Preparation of contracts, negotiation of additional costs

Monitoring

Monitoring is a rigorous control of the accuracy and completeness of the data collected throughout your clinical trial, in accordance with the source documents.

To optimize the initiation of each of your clinical trials, a Clinical Research Associate travels regularly on site to ensure optimal follow-up throughout your study:

- Qualification visit
- Initiation visit
- Monitoring visit
- Audit preparation

Regulatory Affairs

We want your regulatory affairs to be managed optimally. We ensure a rigorous follow-up of your trials for a perfect conformity with the requirements of the sector of the clinical research.

For this, we prepare your files according to the European directives and the regulations in force:

- Submission to the Ethics Committee.
- Submission to the National Council of the College of Physicians.

- Submission to health authorities, such as CA (Competent authority).
- Submission to the CNIL (National Commission on Informatics and Freedoms.

On-site coordination

In order to coordinate and control the realization of the clinical studies, we can provide the investigators with help and support on the trial site.

- Data entry in the CRF books.
- Screening, inclusion and monitoring of patients.
- Logistics management.
- Administrative management.

Patient Fee Management

Compensation for participation in a clinical trial is subject to certain conditions. However, the costs related to this participation are fully reimbursed. As a sponsor, you are not authorized to receive the personal data of patients to make this reimbursement. You must go through a third-party payer (for example the hospital where the patient is treated or a company specialized in the management of patient fees). In general, the hospital does not want to manage this type of services because it is too time consuming for them. This is where Pharmaspecific comes in.

For simplicity, we take in charge the organization and the follow-up of the reimbursements of the patient fees, notably related to the trips, within the framework of their participation in your trial.

- Implementation of the reimbursement procedure and forms
- Administrative management
- Monthly reporting

The GCP Audit

Our auditors are trained in Good Clinical Practices (GCP), experienced and regularly informed about European and US legislation governing GCP.

We carry out quality audits to check that the working methods respect all the regulations in force (local, European, ICH guidelines, Public Health Code ...)

Provision of staff

You would benefit from a staff of experts, project managers, clinical site coordinators, project assistants, data managers, pharmacovigilance managers, statisticians, Medical writers, Regulatory Affairs Officer and Clinical Research Associates for the success of your projects.

- You will be released from your recruitment process.
- You will no longer have any administrative formalities.
- Your expectations will be met by our candidates

Training

Our company is registered as a training organization.

Indeed, we are committed to teaching our knowledge, sharing and transmitting acquired, developed and reinforced skills to clinical research professionals as well as students wishing to access our occupations.

We put our knowledge at the service of others, particularly through our platform of training, events, advice and coaching: www.pharmaspecific-training.com

I – The 10 commandments of the clinical project manager

Are you a Clinical Project Manager or Junior or Experienced Coordinator CRA? Clinical project management consists of planning, organizing, monitoring and controlling all aspects of a clinical study, in order to achieve the objectives while respecting costs and deadlines. I give you here some ways to have an effective project management.

Below are the 10 commandments of the Clinical Project Manager:

1. **Clear objectives, you shall define**

   You shall define clear objectives for your team, i.e. goals to be achieved that will be measurable (that is to say, quantified).

2. **The study, you shall plan**

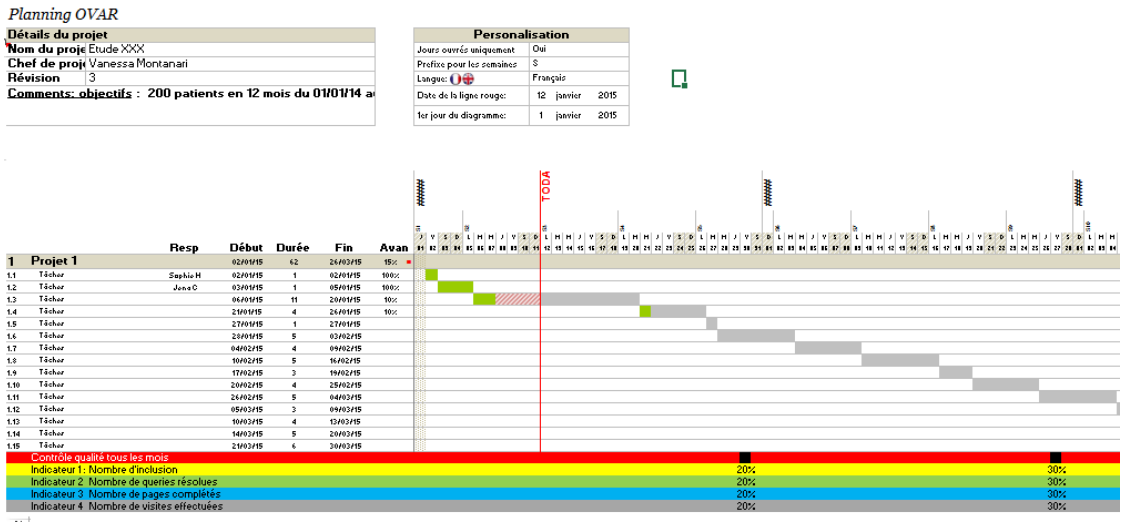
   You shall plan your study and you will distribute this planning to your team. You will indicate on this schedule:

   - The time scale.
     You will split your schedule into several periods (for example, every 3 months) in order to have a readable document for your team.
   - All the tasks to be done to advance the project.
   - The names of the people responsible for these tasks.
     Each member of the team (including the assistant, the data manager, the statistician ...) will thus see his own responsibilities and those of others (even those of the project manager). The goal will be to have transparency on the management of the project. This will increase group cohesion and allow everyone to assess the priorities and impact of each team member on the project.
   - Progress indicators of the study

   Example of progress indicator:
   70% of CRFs monitored, 3 months before base closure
   80% of CRFs monitored, 2 months before base closure
   90% of CRFs monitored, 1 month before base closure
   100% of CRFs monitored, 15 days before base closure

- The quality controls put in place for the project
  For example, checking the% of CRF monitored, every month.

This schedule can be updated monthly and will allow to track and report on project progress at team meetings.



3. A risk management plan, you shall create

You shall create a risk management plan that can evolve over time. You will centralize all possible risks for your project, their possible impact on your project, the probability of occurrence of these risks, the preventive actions that you will implement in case these risks occur and their evolution at the time of writing risk management plan. You must try to foresee all the risks (for example: the absence of a collaborator, the failure of a subcontractor, the lack of inclusion ...). By doing this job, you will be able to solve all kinds of problems more easily because you will have thought about it upstream.

Projet XXXX — V1 du 13 mars 2014

PLAN DE GESTION DES RISQUES

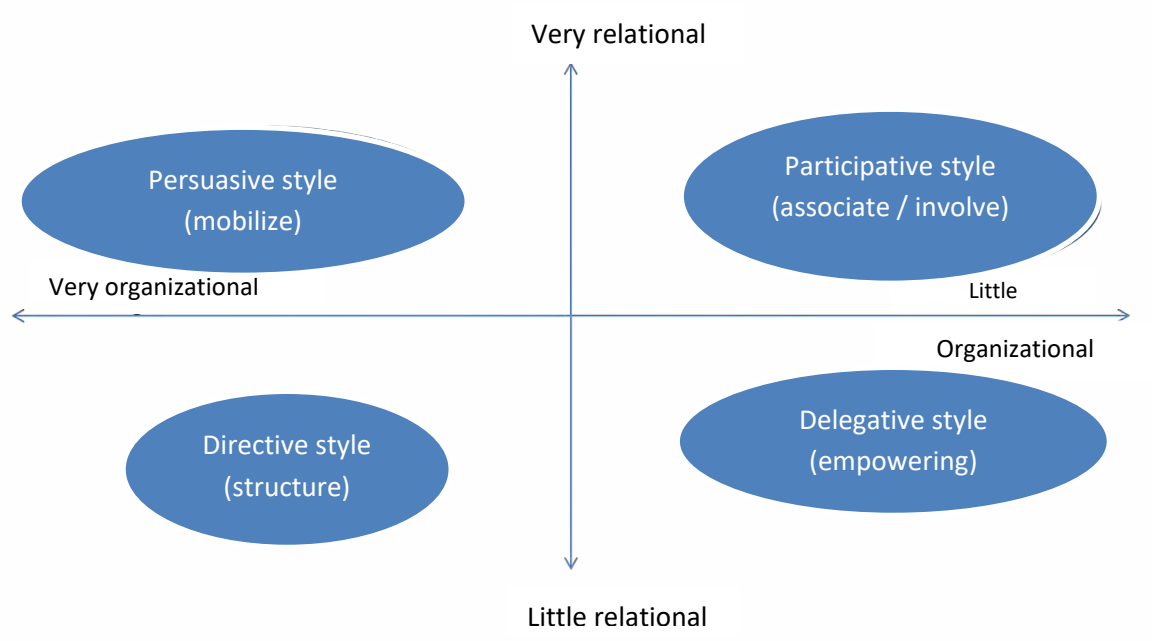
Référence	Date	Description du risque	Impacts	Type de risque	Probabilité	Impact	Poids	Actions préventives engagés	Evolution du risque
1	JJ/MM/YY	Facteur, contexte, Mise à jour du descriptif avec la date de mise à jour	Conséquence si le risque se transforme en événement	Projet, Contractuel, Fonctionnel, Technique, Organisationnel	1à 5	1 à 5	Prob *Impact = 1- 25	Actions engagés Actions différés Pas d'actions pour l'instant	JJ/MM/YYY: + (augmente), - (diminue) =(stable) 0 (clos)
2									

4. The appropriate management style, you shall apply

There are 4 management styles. No management style is better than another. Management styles are more or less well adapted to a collaborator, in

a given situation. You will have to adapt your management style to the members of your team, their autonomy and the situations they go through.

The 4 management styles :



The directive style: Order and organize.

- Your attitude: You are firm and you keep a close eye on the results.
- The advantage: This allows to obtain an immediate result.
- Risk: Your employees may develop a wait-and-see attitude and this can demobilize people of good will.

The persuasive style: Explain and convince.

- Your attitude: You listen to advice and suggestions, while making decisions and explaining them to your team.
- The advantage: This allows to weld the team, to give motivation for the project.
- Risk: This style may still hinder autonomy and initiative because you continue to make all the decisions.

The participative style: Associate and dialogue.

- Your attitude: You play the role of referee, you share decisions and ideas, you listen and negotiate.
- The advantage: You develop the sense of belonging to the team.
- Risk: Some employees, who need to be framed, will feel overwhelmed.

The delegative style: Delegate and follow

- Your attitude: You almost totally leave the initiative, you validate the proposed solutions, you help punctually and evaluate periodically.
- The advantage: you free yourself from certain tasks, it motivates your employee and increases his experience.
- The risk: You will not know the real difficulties of your employee, which can lead to failure.

Sources: Wikipedia, the 4 styles of management.

5. Your team, you shall empower and autonomy you shall give it

You will need to make your team understand what you expect and how it matters to them and you. For example, you can rephrase and make rephrase to ensure that your request has been understood. Indeed, the same sentence will not be understood in the same way between different people.

You will ensure that the responsibility or the mission is well adapted to the skills of your employee. You will assist in the difficulties and you will make regular checks to verify that the objectives are achieved.

You will have to trust your team and you will not give up if they make mistakes.

You will congratulate the successes because it is encouraging!

6. To your team, you shall delegate

You will need to choose an employee who can perform the task to be delegated and you will clearly communicate the nature of the task. You will have to insist on the result to be obtained, the importance of the task and the time required to complete it. The whole team should be informed about the delegated task, the delegated authority and the new responsibility of your employee in order to give him legitimacy. This will prevent confusion and disputes.

You will not only delegate uninteresting tasks because you will risk demotivating your team. You will not give too much responsibility at the same time and especially not at the last moment.

7. Quality control, you shall do

You will imperatively carry out a quality control on your project (No more than 3 to 4 levels of control, for example: inclusions, CRFs, deviations, the TMF) and you will commit to the frequency and the contents of your control with your team. The results of these controls will be discussed and presented in writing at a monthly team meeting.

You will ask your team to carry out a quality self-control on their work, which they will communicate to you (for example: time spent on site, transmission of monitoring reports).

You will do your own quality self-control that you will communicate to your team. There will also be transparency about your work as a project manager (For example: Respect of the schedule of project meetings, Realization of quality controls).

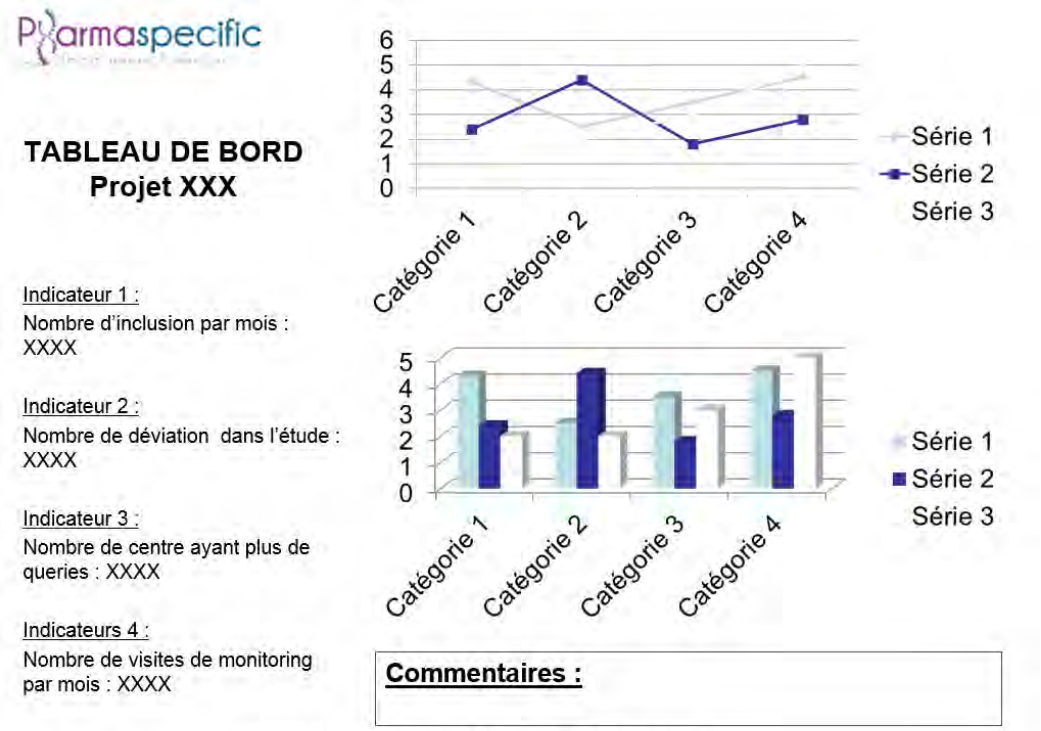
8. Project meetings, you shall organize

Before each meeting, you will send a schedule that you will follow. Meetings should not last more than 1 hour 30 minutes or risk losing your audience.

During these meetings, you will discuss the specific objectives, priorities, organization, potential obstacles of the team members or external stakeholders on the project and the quality controls that have been carried out or to be carried out.

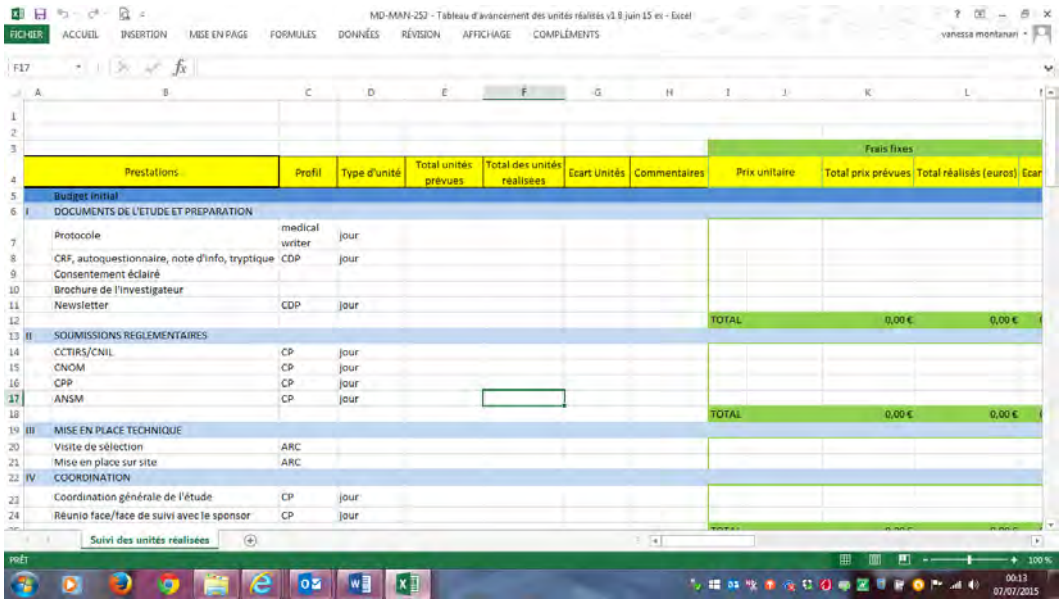
9. A trend chart, you shall create

The trend chart will communicate results about the progress of the project to the team and the line manager. It must be visual (curve) and always contain the same type of information in order to assess the evolution of the project. It will hold in one page to summarize the essential information. It will be colored, to indicate whether the progress indicator is good or not.



10.The budget, you shall track

To track your budget, you will use the specifications, the quote or the contract of your project. You will prepare a table of progress of the budget and you will follow monthly the progress of the consumption of the budget.



The human relationship is an important component of managing a project team. There is of course no secret recipe for managing the human. To succeed in the mission of clinical project manager, it is necessary to communicate as much as possible with your team and with external stakeholders to move together in the same direction.

II – Project management

Of course, before starting a clinical research project, you need an idea, a product or a medicine, a theme. It also requires a protocol that will be written by a medical writer and a medical team who will be the medical reference of the project. We will not discuss these details in this guide otherwise it will be more than 100 pages ☺ We will describe how the project manager should organize himself to carry out his clinical research project.

Human resources

The project manager will have to plan the necessary human resources for the project.
The project manager usually produces a resource management table to evaluate the resources needed and updates it regularly to see the difference between the planned and the real. In the event of discrepancy with the resources provided, the project manager identifies the causes of discrepancies and sets up an action plan (team reframing, new collaborator) in order to stay within the allocated budget and within the allotted time.

Prior to implementation and throughout the project, team members must be trained in study by the project manager or other previously defined stakeholder. The best is to write a project-specific training plan so that you can

train each member of the team in the same way (e.g. new comer). The training plan will include training on the protocol, the product, the therapeutic area ... Of course, everything will have to be documented in training forms.

As a project manager, it is necessary to document the project team members on a form and keep the signed and dated CV of each member of the project team.
In order to maintain continuity in the activities, the project manager can organize handover meetings in the event of staff changes. We recommend documenting this handover meeting on an appropriate form detailing the information provided.

Organization

In general, the project manager organizes the kick-off meeting of the study. All team members, depending on their role, can participate in this meeting. This meeting is documented by sending an agenda to participants and then by attendance certificates, presentation slideshows and the minutes of the meeting.

The kick-off meeting addresses the following specific topics:

- The context of the study, the therapeutic area and the disease studied,
- The study, its issues and its specificities (what makes the difference between this study and another)
- the design of the study,
- the recruitment of physicians,
- data collection (eCRF book / CRF book),
- monitoring,
- objectives in terms of number of patients, deadlines, success factors
- Administrative organisation
- The regulatory steps
- The logistics organization
- The flow of communication between the members of the team (Who will be asked for the technical issues? Who validates what? Who coordinates the teams?)
- Organization and planning

- Responsibilities within the team (the presentation of the teams, the specific roles and responsibilities of each of these people)
- The organization of vigilance
- The list of deliverables to be provided
- Reporting dates and their content
- Risks (preventive actions)
- The key factors of success

The project manager also deals with the creation of documents and tools of the study (CRF, monitoring tools etc ...) He will create the monitoring tables of the study (with the help possibly of an assistant). Nowadays these tables are integrated in a CTMS (Clinical Trial Management System). It is a computerized system for monitoring the progress of the study. CTMS is not mandatory although it is widely used nowadays. Excel tables can do just fine. The project manager creates and updates these monitoring tables with the help of the project team (the CRAs and the project assistant). There are several types of tracking:

- Patient visit tracking table
- SAE tracking table (Serious adverse Events)
- Deviation and violation tracking table
- Monitoring register
- Regulatory submission tracking table
- Table for monitoring the sending and delivery of medications.

We recommend the creation of FAQs accessible to the entire team, so that questions can be listed and found quickly.

It is best if the project manager prepares a project management plan. This plan will present the project, describe the organization, conduct and management of the project. This plan will also have the quality control checklists performed by the project manager during the study.

Throughout the study, the project manager is led to create study management manuals with the help of various stakeholders. He creates if necessary:

- - The monitoring plan (in collaboration with the CRA (s) of the study)

- The data management plan (written by the Data Manager and reviewed / validated by the project manager)

- The statistical plan (written by the statistician and reviewed / validated by the project manager)

Before starting the study, the project manager can set up or follow different types of committees for the study, the most common of which is the Data Safety Monitoring Board (DSMB) or the Independent Data Monitoring Committee (IDMC): This group regularly reviews the study's data regarding the safety of the study, the conduct and progress of the study and, if applicable, the efficacy of the product under study. He gives advice concerning the continuation, the modification or the end of the study.

The project manager is also required to make regulatory submissions and to select the different study CROs (CRF, centralized laboratory, drug storage company ...)

Financial monitoring

The project manager prepares the budget for the study. It is based on the synopsis (number of visits and duration of the study per patient), the objectives in number of patients, the number of trial sites and the duration of the period of inclusion.

This information makes it possible to estimate the number of visits in time and the number of patients enrolled per month and per trial site.

Some costs are easy to anticipate: additional tests, nursing time, physician's time, logistics package, patient travel, equipment rental, CRO budget, pharmacy budget, CIC budget, etc.
The items to be detailed in the budget are as follows:

- Investigative fees per complete patient
- Investigative fees per screen failure (and the number of screen failures to be adjusted maximum per trial site)
- Coordination fees
- Fees for additional tests (independent evaluator, etc ...)
- Hospital overheads (fixed and variable, CIC)
- Material costs (ECG, centrifuges, others)
- Printer costs
- Translation costs
- Reimbursement of travel expenses for patients / others
- Carrier costs

The project manager carries out monthly financial monitoring of the study with the creation of a financial tracking table. It performs a monthly and annual evaluation (preferably in October) of the expenses for the years to come (Last Best Estimate). It also makes a monthly estimate of the human resources needed for the project and for the duration of the project. He centralizes this estimate in the financial tracking table. He tracks the billing of the project and the suppliers that he also centralizes in the financial tracking table.

Quality Control

The project manager is responsible for quality control of the project. He carries out a regular and planned control of the activities. If necessary, a random control can be performed. The project manager uses the quality control

checklist that he has already written and which is in the project management plan.

III – The choice of contractor

Whether you are a CRO, a pharmaceutical laboratory, a biotechnology laboratory, a DM company, you will necessarily need a clinical research contractor during your professional life. We give you 5 tips to choose it:

Make sure your contractor provides quality work

Good clinical practice is clear on this: when performing your clinical trials, you must work within the framework of a suitable quality management system. In case of inspection by the authorities, this point will be checked. Remember to ask your contractor if he has a quality certificate (e.g. ISO9001) even if you do not use his own quality system for your project. You will at least have the assurance that quality is a crucial point for him and that he gives himself the means. If your contractor does not have this type of certificate, find another way to make sure he will provide you with quality work!

Make sure your contractor has a high rate of customer satisfaction

Does the contractor with whom you want to work evaluate the satisfaction rate of his clientele? Is he publishing this result? How can he assure you that you will be likely to be satisfied ... to think about.

Make sure your contractor has enough experience

There are two types of experiences: therapeutic experience and project management experience. Make sure your contractor has both. Remember to ask your contractor for a list of his references.

Do not choose a contractor only on a lower bid

Has the proposed bid taken into account all the parameters in terms of time? Some contractors make a proposal based on an hourly rate only and do not detail the activities. Ask for a detailed assessment (tasks and time) in order to have a clear overall budget. Ask to anticipate the changes according to the number of sites and in case of modification of the protocol. Keep in mind that

most studies will have changes. Having all this information upfront will allow you to better manage your budget and avoid surprises.

Evaluate how important your project is to your contractor and make sure that he is used to finishing the projects he is starting.

If your contractor has other projects that are "more valuable" to him, you may not be satisfied with the level of attention he is paying to your project. So be careful when negotiating (avoid over-charging for example) and check that your contractor will have enough time to manage your project.

These are the tips we use to choose the best contractors we work with and establish a relationship of trust.

IV – Standard Operating Procedures (SOPs)

According to GCP, the sponsor is responsible for setting up and monitoring a quality system (quality assurance and quality control), including standard operating procedures (SOPs), which ensures that the research is carried out, that the data are generated, documented, recorded and reported in accordance with the protocol, good clinical practice and in compliance with the laws and regulations in force. These are crucial documents for the recognition of your research project by the authorities. We will give you the recipe for SOPs at the top.

A standard operating procedure is a **document** that describes how to carry out an activity according to the "standards" of the company and in compliance with the laws and regulations in force.
In other words, this document describes chronologically the operations that the employee will have to perform, in order to carry out a specific activity.
The procedures can be roughly compared to a "cooking recipe": you can follow each step and thus perform an activity within the company.
For example:
- Procedure to carry out a monitoring visit
- Regulatory Submission Procedure to the Ethics Committee (EC)

In general, SOPs will help you **perform a task or activity independently** when you have a doubt about certain actions in the course of your work or want to understand how an activity is performed.

They will also serve **to train a new comer** to the company.

They will also allow your company **to provide a "consistent result"** because all activities will be done in the same way by each member of the team.

These procedures are also useful for understanding the operation of a complex activity to be performed.

Any member of a team may be involved in writing the procedures. It is interesting that they are **written by the employees**: they are the first

concerned by these documents and can therefore adapt them to the best reality. In addition, this will help to better understand the document.

It is necessary that these procedures be **re-read by other employees**, so that everyone "brings his stone to the building" and brings his own vision.

The key words for writing a SOP are **simplicity** and **efficiency**.

Yes, you must write the procedure with **simple words**, easy to understand for each employee, whether new or not. These words should best describe the action to be performed.

In these procedures, you need to give **enough details, but not too much**, so that they do not become complex and daunting for the reader. Try to keep in mind that a **well-written procedure** is a **source of motivation** for whoever is going to use it.

On the form, try to opt for an **airy layout**, pleasant to read. You can also add **diagrams, drawings** that will help a lot with visual memory.

Another thing is that you can **draw inspiration from other procedures** that already exist within the company to stay compliant.

Here is, for example, the structure of a procedure:

Name of the procedure (e.g. "Monitoring visit procedure")

Created by: (Employee name)

Approved by: (Name of another employee)

1. **Object** (here, you must describe the purpose of the procedure, for example: "This procedure is intended to describe the preparation, implementation and follow-up of a monitoring visit in a trial site")
2. **Scope** (here, you must detail all the activities, operations and / or employees involved in the procedure and determine the limits within which this procedure applies, for example: Monitoring process at the investigation trial site for CRAs, Project Managers, trainees).

3. **Reference documents** (in this section, you can put the titles of the external and internal source documents that you use to write your procedure. For example "Public health code, Article R1123-39")

4. **Associated documents** (here you can indicate which documents or forms are used when performing this procedure. For example "Monitoring visit report")

5. **Definitions** (in this section, you indicate all the definitions of the words that will help in the understanding of the procedure, you can also describe the abbreviations that you used for the writing. For example, "GCP = Good Clinical Practice")

6. **Responsibilities** (here, you define who is responsible for actions related to this procedure "On the side of the sponsor: CRA, project manager / On the side of the trial site: Investigating physician, CRC, pharmacist ...)

7. **Conduct** (Finally, in this section, you get to the heart of the subject, that is to say, you will describe each of the steps required to complete the activity. For example: "The CRA consults the monitoring guide before any action. The CRA contacts the investigator to schedule a monitoring visit. The CRA also contacts the pharmacy and other stakeholders, if necessary. ")

We recommend preparing at a minimum, procedures for the following topics:

- Regulatory submissions
- Quality control (Monitoring)
- Quality Assurance (Audit)
- Project management
- Clinical contract management
- Data Management, Statistics, Medical Writing, Vigilance …

V- Regulatory monitoring

Regulatory monitoring is the anticipatory activity of national or international regulations likely to have an influence on the clinical research activities or the company's strategy.

You must take care of regulatory monitoring in clinical research. We recommend that you complete a monthly tracking table of the regulatory monitoring and check with another employee what updates are to be implemented in the company's procedures and schedule the update date.

It is important to train your team regularly on new updates that have a direct impact on their work.

There are specialized organizations in health regulatory monitoring. Pharmaspecific also uses one of them to ensure that it is up to date for the services provided to its clients.

VI – The protocol deviations

It happens that the protocol is not respected, it is a protocol deviation. These deviations should be avoided as much as this leads to a drop in the quality of the study data. Too many deviations can even lead to the questioning of your study by the authorities. Seeing the price of a study, it would not be pleasant for you or your budget. The project manager and the CRAs must make every effort to maintain good quality of the study data. Below are some tips.

1. **Anticipate problems**

Everything is played out at the time of the feasibility study, the screening visit and the initiation visit. This is where some things can be anticipated. At the time of the screening or initiation visit, the senior CRAs are the most able, thanks to their experience in presenting and identifying future problems (possible risk assessment) on the trial site.

2. **Assist the actors of the trial site and regularly check their understanding of the protocol**

The project manager and his / her team must take the protocol and the CRF to identify with the help of the trial site the procedures that are not part of the current practice and the data that are not usually collected in the service. The project manager can prepare fact sheets or templates of worksheets to avoid any confusions or deviations made by the investigator and his team.

If you are preparing worksheets for the trial sites, do not forget to provide a place for the person who has collected the data to indicate their name, to date and to sign. This document will then serve as source documents.

You can also recommend and help the trial sites to prepare procedures for people whose clinical research is not the primary profession, e.g. nurses. This is even more important if the study includes biological samples that will have to be sent to a centralized laboratory (equipment to use, etc.).

In addition, if the samples are analyzed locally, you can propose to the investigator ready-made prescription templates including all the analyzes

planned by the protocol per visit. It happens, in fact, that certain elements are not analyzed in current practice.

Similarly, see with the investigator and the pharmacist if they do not need a prescription template for the medications allocated to the patient.

Ready-made prescription templates help to avoid errors in writing (dose, time, arm ...)

3. Communicate with the entire care team

Other actors whose clinical research is not the primary role may be involved in the study: nurses, pharmacists, radiologists, ... It is crucial to meet or discuss directly with these stakeholders and to present them the study from the selection of the trial site and especially the importance of collecting the data.

Make sure that all people likely to see the patients in the study are all properly trained in the specific procedures of the study and make sure to answer their questions. Think about staff changes, identify several key players and their back-ups. Also involve potential supervisors, such as health managers, to help put the study in place.

Finally, check that the roles and especially that the tasks are clearly defined in the investigation trial site.

Ask the investigator or his / her Clinical Research Coordinator (CRC) to accompany the first patients from one department to another, in order to remind the actors that they are specific patients and that the study procedures should be applied.

4. Help the trial sites prepare for the patient's arrival

That's it, everyone has been trained, the first patient identified and the visit organized.

Before the start of the study, make sure the CRC or investigator has action checklists to prepare for a visit, during the visit, and after the visit. Thus, at time t, he will only have to follow the checklist and check what he has already done. You can offer your help in the realization of this tool or make sure that these tools are well built.

A few days before the patient's arrival, contact the trial site to verify that everything is going well and that the CRC and the investigator are ready and that they have at their disposal:

- The last version of the consent form and the Patient Information Leaflet if it is the patient's first arrival or if the study has been amended,
- Documents to give to the patient (follow-up booklet, self-questionnaires to be completed, ...)
- All the worksheets for each of the actors involved in the study,
- the possible templates of prescription,
- Biology kits.

You can recommend to the trial site, if it is not used to clinical trials, to plan an "inclusion kit" with all the necessary documents in a package, this way, no more stress, if you have to include urgently a patient, everything is ready and they will not forget anything. You can also ask the trial site to call the patient a few days before his arrival to make sure he will come. This will be the time to remind him to bring back empty study treatments or follow-up booklet, if necessary.

In short, follow the study closely and communicate as much as possible with the investigation trial site, especially when including the first patients.

5. Follow up on the patient's arrival

As soon as the patient has had his first visit, it is better to send a CRA immediately for a first monitoring visit. The CRA will check the source file and work checklists to ensure that everything is in accordance with the study protocol. There will still be time to catch up on possible oversights to prevent this from happening again in the trial site or in other trial sites (feedback).

Finally, the CRA must think of regularly questioning the investigator in order to check that everything is going well and that there is no information that would have escaped him: difficulties that the investigator may encounter or occurrence of a serious adverse event.

6. Set up corrective and preventive or curative actions

Despite all the actions implemented, a protocol deviation occurred. Sometimes the deviation can be "caught up" and the information can still be retrieved. Set up a curative action to solve this problem. This can take different forms: ask the investigator to retrieve the data at a future visit, plan an additional test at the patient's next visit, if it is very urgent, ask that the patient be contacted by phone etc.

The protocol deviation has occurred, but it should not happen again. For that, it is necessary to think of corrective actions. You need to identify the source of the problem and think about a way to resolve the problem. Present the result of your insights to the health care team, the investigator; they will help you evaluate the feasibility of your idea and perhaps improve it.

Finally, you may identify a malfunction during the study that has not yet led to a deviation. Perfect. However, again, you will have to think of preventive actions, to prevent this from happening in the future.

By following these rules, you will avoid protocol deviations at best. This involves a lot of preparation, but it's time you'll earn afterwards. Some sponsors do risk-based monitoring according to the trial site. Indeed, an automatic calculation taking into account several factors, including protocol deviations, to calculate the number of monitoring visits to be performed on the trial site in order to monitor certain trial sites more closely.

VII – Informed consents

The CRAs of your team are responsible for checking informed consents on-site. Here are some tips to give them.

I. How to prepare the monitoring of informed consent form?

That's it, his monitoring visit is booked, this is his first trip to this site. Patient Information Leaflet and informed consent forms will need to be verified. A little advice, if he is traveling for the first time on a site, even if one of his colleagues has already verified the consents in the past, recommend him anyway to review the consents to ensure that he is well authorized to consult patients' files, you never know (no signed consents = no review of medical records by the CRA).

It can be useful for him to check the following information upstream to make sure he does not make mistakes or forget information once on site:

- The number and nature of the consent form (s) and the information letter (s) that should be found on site for each patient. On some studies, several consents may be provided for sub-studies, long-term sample retention, different age groups, different phases of the study or different situations (e.g. in case of inclusion in an emergency situation). Not all patients need to sign all consents. He must check which consents should be signed by which patients.
- The date, the version of the consent form (s) and the information letter (s) that should be found on site for each patient
  Were there any amendments to the protocol? If so, he must check which consent was in effect at the time of inclusion of each patient and which patients are affected by the changes.
- The information to be verified on the Patient Information Leaflet and the informed consent form. These documents may be different depending on the sponsor of the study, the CRO or even the EC who reviewed the document. To be sure not to spend too much time reviewing these documents and not forgetting information, he must plan in advance what information he should check:

- Should the patient and the physician initial each page of the information leaflet and the informed consent form?
- Is there information to complete and which pages (for example: the name of the physician, the contact details of the person to contact, ... This information can be found on the first page, in penultimate, on the last page or anywhere in the consent)?
- Are there boxes to check by the patient? The study may include blood tests or other optional tests. He must note the page where these elements are.

In order to allow your CRA to be as effective as possible once on site, provide your CRA with a monitoring tool including information on the verification of informed consents: date of inclusion of the patient, date of signature of the informed consent (s), version of consent (s), name of the investigator who signed, information to be verified. He will use this tool to retrieve the essential information that will be used to complete a visit report later.

Also, recommend that he prints the approved version of the informed consent forms and Patient Information Leaflet. In case of doubt on site, he will be able to easily access the documents in order to verify the information he is looking for.

II. What to do at the time of the on-site visit?

That's it, he's in front of the informed consent forms and the Patient Information Leaflet, he just has to check them. Consent is the first thing that the CRA monitors, he is not entitled to read patients' medical records if he does not have written proof that the patient has agreed to participate in the study. If he does not have consent, he will not be able to monitor the patient's file.

Here is the information he must check on site:

1. As mentioned above, type of consent, version and date of consent.
2. Number of pages: he must check that all the pages are present. Yes, all. That of the informed consent form and the Patient Information Leaflet.
3. Date of signature of informed consent. He must ensure that the informed consent form has been signed prior to the implementation of any study procedure. The date of signature must be earlier than or equal to the date of the first specific procedure in the study. Similarly, the date of the investigator's signature must be the same as that of the patient.
4. Signing physician: he must ensure that the investigator who signed the informed consent form is properly declared on the delegation log and has been adequately trained in the study protocol.
5. Signing patient: he must make sure that the patient who signed is the patient whose medical record he has and who was enrolled in the study (patient's inclusion number, surname, first name, sometimes, date of birth).
6. Data to be completed / checked: he must verify that the patient has checked the boxes he should check and that all the information has been completed by the patient and the trial site.

Once the informed consent form and the information leaflet have been monitored, he will have to verify that the information is well documented in the patient's source file. In general, the following information must be included to verify that the trial site meets Good Clinical Practice and the law:

- The patient has received the information necessary for his participation in the study by the investigator,

- The patient was able to ask the questions he had and an answer was given to all the questions of the patient,
- The patient had enough time to think about his participation,
- The patient agreed to participate and signed the informed consent form. Specify the signed version and the date of signature,
- The investigator has signed the informed consent form,
- A copy of the signed consent form and the Patient Information Leaflet has been given to the patient (or duplicate in case of duplicate or triplicate forms)

In the case of a study of people who are not in a position to give their informed consent or on minors: he must verify the identity of the signatory of the documentation of the information and the signature of the legal guardian in the source file. In France, both parents must sign the informed consent forms for minors. You will find the terms of consent of persons particularly protected in Article L1122-2 of the Public Health Code.

Your CRA has verified everything and everything is in order. Perfect, he can now open the patient's medical record and start monitoring.

III. Consent does not comply

Consent may not be consistent. What to do? Here are some non-exhaustive examples of what could happen on site.

First, your CRA must try to understand what has happened to prevent this from happening again in the future. He needs to discuss this with the CRC and the investigator and help them find a solution. In the event of non-compliance, he must systematically retrain the investigators and CRCs in the informed consent procedures to prevent this from happening again in the future.

Some non-compliances are not too serious and can be repaired immediately: if this has not been done, the signature of the consent can be documented in the source document a posteriori by the investigator. Be careful, however, to respect the principles of ALCOA.

If the trial site's coordinates are missing from the information leaflet or the informed consent form, he must ensure that this information has been given to

the patient and ask the trial site to document it in the source file, respecting the principles of ALCOA.

Has your CRA found two informed consent forms or information leaflets in the patient's medical record? He must ensure that the trial site has given a copy to the patient. If this has not been the case, he must ask the trial site to give it to the patient as soon as possible and to document it in the patient's source file.

Other non-compliances, on the contrary, are more serious and require more attention: the physician did not sign on the same date as the patient or the date of signature of the physician or the patient is missing? He must ensure that the physician has given the information to the patient in accordance with Good Clinical Practice.

If the physician simply forgot to date or sign when the patient arrives or if the patient has forgotten to date, the CRA must ask the investigator to document on the informed consent form and / or source documents that the information was given, the date the information was given and the reason the physician or patient did not sign the informed consent form on the same day, and date the change and initial it .

Similarly, if an undisclosed investigator has signed the informed consent form, your CRA must verify that the investigator was properly trained before signing the informed consent form and that he / she gave the correct information to the patient. Your CRA must ask the trial site to document the investigator's date of training on the training certificates and to update the task delegation form.

If it appears that the signing investigator was not disclosed or trained, that the patient did not have adequate information or no information at all or if the patient did not sign an informed consent form, your CRA must immediately send you the information. This is a major violation of good clinical practice and your CRA must decide what action to take next.

In the case of a non-conforming consent form and if the patient is expected to return to the site, the trial site should ask the patient to indicate what happened on the informed consent form, in writing, to date at the date of the day and sign. For example, in the case of a missing date, the patient must

indicate that he / she has received the necessary information and that he / she has signed the informed consent form and the date on which he / she received the information.

Finally, it may be that by reviewing several informed consent forms, your CRA realizes that the writing of the investigator and the patients is similar or that several patients have the same writing, a close signature, and so on. There may be suspicions of fraud. However, this is not an allegation to be taken lightly. Ask your CRA to contact you to tell you the facts so that you can give him instructions.

These are some helpful tips for verifying informed consent forms. Investigators may find the informed consent procedure cumbersome. Your CRA must be able to explain to them why it is so important that all information is documented: in clinical research, what is not documented has not been done, so it is important to note all stages of informed consent.

VIII – ALCOA

You may have heard about ALCOA, but do you know what exactly that means? ALCOA is an acronym for Attributable, Legible, Contemporaneous, Original and Accurate. Often, international teams use it a lot but it's less the case in France, is it really a new concept? Here are some explanations about this new word: where does it come from? What does it mean concretely and how to apply it?

I. ALCOA, where does it come from?

From the United States, yes! The acronym ALCOA was coined by Dr. Stan Woolen in the early 1990s. The story goes that Dr. Woolen was to make numerous presentations within the FDA department in which he worked. Not used to talk in public, Dr. Woolen set up several techniques to remember what he had to say and organize his speech. One of his techniques was to use acronyms. One day, when he lacked space in one of his slides, he introduced this acronym to remember to mention this notion, ALCOA was easy to remember because it is the name of a company known in United States.

The assembly asked what this "government jargon" was, and since that day Dr. Woolen has repeatedly explained this concept.

The concept of ALCOA, for its part, appears for the first time in a text of the Good Laboratory Practice of the Food and Drug Administration (FDA), 21 CFR 58.130, parts c and e. If you want to know more, you can find the text here.

To date, the concept of ALCOA is included in the last trial version of Good Clinical Practice (GCP) of the International Conference of Harmonization (ICH).

The European Medicines Agency, EMA, has meanwhile added four other concepts to this acronym: Complete, Consistent, Enduring, Available when needed (ALCOACCEA) in a paper of reflection on electronic data sources and transcription of source data in an electronic system (here)

The ALCOA was added recently in the new version of ICH-GCP (R2) international text.

II. ALCOA, what is it?

As mentioned above, ALCOA stands for **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal and **A**ccurate.

a. Attributable :

Attributable means that you must be able to find the source of a datum. It must be possible to find who observed and collected the data, when this data was collected, as well as the source of the data itself: the patient.

Similarly, in case of correction, the person who made this correction must be able to be identified. Of course, the practitioner must be authorized by the investigator to make these changes to the source documents via the task delegation form.

We find this notion in French GCPs:

- Regarding the medical records of patients:

1.19. File of the person who is suitable for the research or medical records [...] The elements appearing in the medical records of a patient hospitalized in a health institution are defined in articles R. 1112-2 and R. 1112-3 of the Public health code.

And article R. 1112-3 of the Public Health Code tells us: "Each document of the file is dated and includes **the patient's identity with his name, first name, date of birth or identification number**, as well as **the identity of the health professional who collected or produced the information**. Medical prescriptions are **dated** with time indication and signed; the name of the **signing physician is mentioned in legible characters**. "

- Regarding data changes

4.9.3. Any change or correction made to a CRF book **is dated and initialed by the investigator or a person designated by him, and must not obscure the original inscription** (i.e. an audit trail must be kept); the reasons for the

changes are indicated if necessary. This applies to changes and corrections made **in any medium** (see 5.18.4)

b. Legible

The data must be legible and remain so in the long run. The data must therefore be collected using a material that allows this legibility in the long term.

French GCPs also mention it on several occasions:

4.9.1. The investigator ensures that the data, provided to the sponsor in the CRF books and required reports, are collected and recorded as and when required, accurately, completely and **legibly**.

8. Essential documents relating to biomedical research: The means used to retain essential documents must allow these documents to remain complete and **legible** throughout the required retention period.

c. Contemporaneous

The data must be contemporaneous, it means that the moment when the data is recorded must correspond to the moment when the data is collected. To document this, obviously, the documents must have a date. If the data is corrected or collected late, this should be adequately justified.

French GCPs tells us well: 4.9.1. The investigator ensures that the data, communicated to the sponsor in the CRF books and the required reports, are collected and recorded **as and when required**.

d. Original

The data must be original, i.e. they must come from the first record of the data: the most reliable. In the case of a copy, the copy must be certified by the person making the copy to document the accuracy of the data.

You will probably notice that this corresponds to the very definition of source documents in French GCPs:

1.17. Source documents: **Original** documents, data and records of interest to the research.

e. Accurate

Finally, the data must be reliable. Of course, the data must be consistent with reality. This reliability is verified during the quality control mentioned by the GCP:

4.9.1. The investigator ensures that the data, provided to the sponsor in the CRF books and required reports, are collected and recorded as and when required, **accurately**, completely and legibly.

5.1.3. Quality control must be implemented at all stages of data processing to ensure that data are reliable and have been processed correctly.

f. Complete, Consistent, Enduring, Available when needed, ….

The EMA has therefore completed the ALCOA by adding that the documents must also be complete at the date of the document review, consistent, sustainable and available as soon as needed in the context of monitoring, audit or inspection.

III. How to apply ALCOA daily?

All study documents must comply with the ALCOA concept: source documents, essential study documents and documents in the CRF books, whether electronic or paper-based.

Here are some examples of everyday applications, particularly by the CRA:

First, the CRA verifies that the data is attributable when reviewing the source data, verifies that the data was collected by a person authorized to participate in the study and therefore, appearing on the delegation worksheet. To be verified, these data must necessarily contain the trace of the person who wrote them. Similarly, each source document must contain the patient's identifier and the date of the data.

When reviewing source documents, CRF books, and essential documents, the CRA ensures that the data is not deleted or obscured, that is, legible. In this case, he trains again the investigator and his team in correction procedures: cross-out the data by ensuring that it remains legible, write the correct data aside, initial and date. French GCPs tell us that the reason for the correction should be indicated if necessary. For example, if the correction is made several months after the initial collection of the data, the corrector must justify this correction (contemporaneous data).

In the case of electronic source documents, an audit trail must be set up in order to follow the corrections made, their author, the date and the reason, this is a point to verify at the beginning of the study.

The CRA must also ensure that the data is legible: the pencil is forbidden on the study documents or medical records because it can be erased with an eraser or simply by the time! If data has been written in pencil, the document must be photocopied, dated, initialed, certified and kept with the original.

The CRA verifies, if possible, that the data has been retranscribed within acceptable timeframes after the data has been issued, that is, that the entry in the eCRF has been made within the time required by the Sponsor's procedures, if applicable and documents the reason in the monitoring report in case of delay.

Finally, the CRA verifies the reliability of the eCRF data during quality control of the source data. To a certain extent, the CRA also verifies the reliability of the source documents. It can unfortunately happen that a member of the investigation team cheats. This case is fortunately rare.

ALCOA is therefore a set of rules to be applied so that the data and documents of a clinical trial are as correct as possible and can be verified long after the end of the trial. Although this system may be perceived as a constraint by some, it is a habit to take to ensure that the clinical trial is going as smoothly as possible. ALCOA does not only concern investigative teams, CRAs, CRCs, Data managers, project managers, statisticians, project assistants, CRF editors, the whole team is concerned.

IX – Serious Adverse Events (SAE/SAES)

We will give you some practical tips on the topic of SAEs. Indeed, as project manager, you must be informed as soon as possible in order to decide to continue the study or not.

Let's talk a little about the practice ... Your CRAs must train the investigation trial sites as soon as they are put in place (investigator and CRC in particular) on the points below. Make sure your CRAs are clear with these notions before the start of the study.

1. **Report immediately the follow-ups of the SAEs as well as the initial SAEs**

When a trial site receives information, even basic on a SAE already reported, it is essential to immediately transmit the follow-up of this SAE! Indeed, it is important to keep in mind that a follow-up of the SAE is as important as the initial SAE report. Some information, which may seem innocuous, can become very important for Vigilance services. So please, report the SAE follow-ups within 24 hours (this is the expected time in the vast majority of clinical trial protocols) as well as the initial SAEs.

2. **Do not wait for the investigator's signature if you know it's a SAE**

Your CRA finds an undisclosed SAE in a file and could not meet with the investigator to discuss it.

Remind him that he can still report the SAE without waiting for vigilance. If modifications have to be made later or if the SAE must be canceled by his investigator, they will be done subsequently!

A SAE must be reported **without delay** within 24 hours of being known (by the investigator or by one of the members of the investigative team)

Does your CRA have no SAE forms for the time being? He can send an email to the Vigilance service in the meantime ☺

3. Report the SAEs if they occur on weekends or on Friday nights!

Your investigator should not wait until the following Monday to report it. Indeed, important things can happen during the weekend and in addition, if the report is not made in time, it will be a violation of the GCP. The principal investigator and the co-investigators must be aware that they must make the report within 24 hours, even during the weekend. The fact that their CRC or CRA is not there is not a reason. Your CRA must really get that message across.

If the trial site does not have the appropriate form, it can report a SAE with a minimum of information and this by email. The trial site indicates:

1. Protocol number
2. Trial site number / name of the principal investigator
3. Patient initials (if allowed by the protocol) / patient number
4. Title of the SAE or symptoms

4. Report the SAEs even if your patient is hospitalized at another hospital and you do not have reports!

Likewise, the trial site can complete the SAE form with the available information. At least one SAE title (e.g. "Symptoms") is required.

5. Grade 4 AEs (adverse events) are potential SAEs

The definition of a grade 4 according to the NCI-CTCAE version 4.03 is: "life-threatening, emergency response indicated".

As a reminder, the definition of an adverse event is as follows:

"In accordance with 1 ° of Article R. 1123-39 of the Public Health Code, any harmful event occurring in a person who is suitable for biomedical research, whether or not this event is related to the research or the product on which carries this research. "

Clearly, an "adverse event" does not necessarily imply a causal relationship with the product under study. It may be a sign, symptom or condition that appears or worsens during the observation period.

As a reminder, the definition of a serious adverse event is as follows:

"In accordance with paragraph 6 of article R. 1123-39 of the Public Health Code, any adverse event or adverse effect that causes death, endangers the life

of the person who is suitable for research, requires hospitalization or the prolongation of the hospitalization, causes a disability or a significant or long-lasting handicap, or results in an anomaly or a congenital malformation, whatever the administered dose. "

It can also be an important medical event (for example, spontaneous or induced abortion).

Life threatening is one of the criteria of a SAE. You need to pay attention to grade 4 AEs (e.g. in Oncology: thrombocytes, PNN, hemoglobin) that need to be reported as SAEs. Check with your investigator and the study's medical monitor to see if they feel there is a real life-threatening problem. It is possible that this can be recognized as an important medical event. The CRA must ask the question and document the response in his report and follow-up letter. He asks the investigator to do the same in his medical records.

6. Severity and causality

For both AEs and SAEs, the investigator should document the severity and causality in the medical record.

1. Severity: that is, Grade 1, 2, 3, 4 (in Oncology) or "Light", "Moderate" or "Severe".
2. Causality: what is it related to: medication under study or something else? And that in a "likely", "possible", "unlikely", "unrelated" way?

This information must be in the medical records accurately and not only in the CRF. The absence of this information in the medical records can be inconvenient, in case of audit or inspection. Your CRA must ensure that what is noted in the CRF is present in the source file.

7. Train your investigators and co-investigators on SAEs

Training the investigators at the initiation is good. Throughout the study, it's even better. We are never too careful. Some bases can be forgotten, especially when it does not happen often. Your CRA ensures that the co-investigators are well aware of how to report the SAEs and the definition of a SAE. The CRA plans to train them in the introductory initiation rather than at the end of initiation: some investigators may wish to shorten the presentation at the end of initiation as soon as they start talking about GCP.

X – Inspections

We will give you practical advice so that this day goes without stress. To help you, we even noted the reference texts.

1. An updated investigator study file

ICH GCP 4.9.4, ICH GCP 8.2.18

The investigator study file contains all the essential documents (protocol, investigator's signature page, updated FDA1572 form, Financial Disclosure signed for all the physicians involved, follow-up letters present ...). The investigator and his team must ensure that it is complete and up-to-date with all versions of the documents. Indeed, this is one of the responsibilities of the investigator. Your CRA can assist the investigator by providing the necessary documents and providing a list of applicable documents. In order to make it easier for the trial sites even if it is not their role, your CRA can store the essential documents in the investigator study file.

2. “Flawless” training certificates, CV and task delegation form

ICH GCP 4.1.1, 4.1.3, 4.2.4

You need to verify that all of your investigators have been trained in all applicable protocol versions, and in the study (for example, to the initiation), that they all have at least a GCP training certificate. All members of the team must have had training appropriate to their task. For each training, a training certificate must be signed in order to document it. Remember, in clinical research, what is not written does not exist;)

You can ensure that all the CVs (dated and signed) of all team members are present (from the investigator to the CRC, through the pathologist, the biologist, the technician, the nurse, the radiologist and the pharmacist). Do not forget any member of the team. If they are involved in the study, then their CV must be present.

You can also compare the CVs and the delegation log. Anyone in this log must have an available CV and a training certificate to the study before starting work on the project. And most importantly, do not forget to put the principal investigator in the log ☺

3. Well-documented and well-stored AEs and SAEs

Decision of Nov. 24, 2006 8.3.16

It is preferable that the link between the study treatments and the adverse events is well reported in the medical records ("possible", "unbound", etc.) or at least in a worksheet listing all the adverse events. Indeed, any information found in the CRF must be in the medical records and in particular this one. Its impact is very important for the safety of the patient.

Your CRA must verify that the SAE forms are properly stored together with the proof of sending (fax or mail). It is not because the form is completed that it was sent ☺

4. Protocol deviations all explained

ICH GCP 4.5.1, 4.5.3; Decision of Nov. 24, 2006 8.3.11

Any protocol deviation must be explained in the medical records. For example, if the patient's compliance is not complete or he does not have tablets. This type of deviation must be explained on the accounting form or in the patient's medical records.

I recommend that you note what corrective and preventive actions have been taken to correct these deviations. The sponsor must assist in the implementation of action and must also retrain trial sites, if necessary. Your CRA must document any additional training or information at the trial site to demonstrate that the sponsor has followed the research properly.

5. Consents

Decision of 24 Nov. 2006 4.8.8. 4.8.6. PHC

In the event of an update of the consents, the last versions of the consents must be signed by the patients of the study and on time (during the visit following the reception of the new consent by the trial site) so that they get to know new security information.

The method of collecting consent must be reported in the medical records. The "modality" is the way the physician has obtained informed consent. A simple sentence such as "Consent Signed Today" to document the collection of

consent is not sufficient. The ideas that must be found in the medical records are as follows:

- The patient was able to ask any desired questions,
- The patient had the time for reflection he needed to make his decision,
- The signature of the consent took place before any procedure of the study,
- A duplicate or copy has been given to the patient.

6. Electronic medical and paper records

FDA 21 CFR part 11

The paper medical reports must be validated by the investigator, that is, dated and signed. If they are medical notes, it must be possible to know who wrote them. Your CRA must make sure it's done. If the trial site has an electronic file, access must be personal and via a login and password. You must be able to see who made the changes, what changes, and when. Otherwise, all reports must be printed and dated and signed by the investigator.

7. Pay attention to the data retrieved in the CRF

MR001 (n° 2018-153 dated on 2018, 3 may 2018)

A classic mistake: some personal data are requested in the CRFs written by US sponsors. For example: race and ethnicity. As a reminder, you can retrieve this type of data only if your protocol provides for it (for a particular reason, for example, to highlight differences between ethnic origins regarding the effectiveness of treatment) and that it has been submitted and accepted by the EC, that the patient is informed through informed consent (i.e. there is a sentence explaining to the patient that his / her ethnic origins will be recovered). Otherwise, do not complete this information at the risk of recovering unauthorized data (MR001 - CNIL text).

8. Note on the medical records or investigator study file

It is possible to make notes on file to explain the deviations and the corrective or preventive actions implemented. You can use them to explain that a

document is out of place and explain where it is located or if it is not applicable. Nevertheless, it should not be abused too much.

9. As a sponsor, simplify the life of the inspector!

You can for example prepare a tool to know the different versions of the applicable documents (consents and protocol for example, and their date of approval by the CA or the EC.) It can be tedious to achieve but it is a document that will allow you to follow up your study well and will facilitate the work of the inspector who will be able to refer to it if a point is not clear.

Conclusion: If you pay attention to all these points throughout the study, your work will be simplified and inspection can only be done serenely.

XI - All recipes to boost inclusions

Are you starting a project in clinical research and you want to reach your goals in terms of patient inclusions? As a project manager, you have or you may have been faced with one or more investigators who do not enroll patients and you want to find solutions to increase inclusions? Here are our recipes to make your project a success.

Above all: AN-TI-CI-PA-TE!

As a project manager, it is important to anticipate the difficulties that the investigators might encounter at the time of the trial's initiation, right from the design phase of the study.

In particular, you can think ahead of time about your action plan and refer to it in your risk management plan.

Step 1: Surround yourself while writing the study documents

- As soon as the protocol is written, consult several experts and opinion leaders on the design and feasibility of the study. Integrate their proposals into the protocol before finalizing it and submitting it to the relevant authorities.
- Plan a recruitment material to present the study to patients and give them the desire to talk to their investigator.

  It may be a poster that the investigator will hang or a flyer to put in his waiting room, a communication on a website or even in the mass media.

  This material will allow your investigator to identify patients he would not have thought of at first or to bring new patients into consultation. Any patient recruitment strategy should be submitted to the EC for opinion as well as the recruitment materials used. Think about it!

- Have a booklet for the investigator. Indicate the title of the study, the primary objective, the inclusion and non-inclusion criteria and any information important for the screening or inclusion of a patient. The investigator can keep this document in his office or in his jacket to remember the study.

Step 2: Plan the right remuneration

- The investigators must be paid at the level of the work provided: the more the study will require an investment in terms of time and resources, the higher the remuneration will have to be. This will have to be negotiated with your trial sites before the contracts are signed. If you expect a remuneration which is too low, there is a risk that the investigators will ultimately not enroll patients in the study.

- The single contract allows additional remuneration for each inclusion and / or if objectives are achieved. This remuneration can be assigned to several recipients.

  Learn about its future and use this new arrangement to encourage your investigators.

Step 3: Select your trial sites

- Select your trial sites through a questionnaire or a feasibility call and then through a screening visit.
- Choose investigators who have proven screening methods and have enrolled patients in similar studies. Check whether your company has already done this type of study or ask the sponsor for a list of former investigators who have worked on similar studies.
- Before going on a screening visit, ask your investigator to check the number of patients who meet the screening criteria in their database. Ask him to prepare this pre-screening list before your meeting, so that you can assess his recruitment potential.
- During the screening visit, make sure that the investigator has the necessary human and material resources to implement the study. Also check with him that he has no other studies going on that could compete with your project. Indeed, he must have time to devote to your clinical trial and his patients must be enrolled in your project only.
- Detail the inclusion and non-inclusion criteria for the investigator. Ask him what criteria might have an impact on his inclusions. It may still be time to change the protocol. Similarly, if the CA or the EC have modification requests, come back to the investigators to check if this will not have a negative effect on their recruitment potential.
- Assess the investigator's motivation. Identify why he wants to participate in the study: the financial aspect, the prestige, the well-being of the patients, the scientific aspect? This will allow you later to find the right arguments to convince him to give time to your project.
- Make sure that the investigator has a good network in his trial site and with other colleagues. Ask him if he regularly communicates with this network, for example at Multidisciplinary Concertation Meetings (RCP). Indeed, he can find, through this, patients that he does not necessarily see himself in consultation.
- Choose the national coordinating investigator for the study. He must have experience in clinical trials and leadership to motivate other principal investigators and encourage them to enroll.
- During your screening visit, if the investigator has promised you to enroll 10 patients, do not hesitate to divide this number by 2 and open other trial sites. He may encounter difficulties that he did not expect (patient refusal, for example). We are never too careful.
- Finally, if you find that your recruitment potential in France is too low, you can propose to the sponsor to open inclusions to other countries. This will allow you to boost inclusions.

Step 4: Encourage sharing of experience

- During meetings for the investigators, always invite the CRCs of the trial sites. They are the actors in the screening and inclusion of patients. Through these meetings, they will be doubly trained to study (the study will also be presented to them during the initiation). They will have the opportunity to exchange with the CRCs of other trial sites and will be able to share their experience and better understand the inclusions.
- Discuss with the trial site team before the initiation of the study: do they need specific tools to facilitate the implementation of this project? Create standard operating procedures and worksheets to assist with this project: they can be used to help note concomitant medications, to report and track adverse events, special prescriptions for the trial to be given to the investigators, specific manuals for CRCs or nurses ... The goal? Avoid having the team encounter difficulties in carrying out the study and that this has an impact on the inclusions.

Step 5: Encourage pre-screening of patients before the initiation and follow the progress of inclusions week after week

Two weeks before the initiation of the study, ask your investigator to prepare another pre-screening list. This will allow them to have a ready subject log and they can begin the inclusions the day after the initiation of the trial site.

- It is worthwhile to plan for the investigators' reminders to quickly identify the difficulties they may encounter and implement the appropriate actions. You will also be able to answer their questions and remind them of the existence of your study.
- Ask for the list of patients in sight and the date of the next visit of these patients. Make note of this information and recontact the trial site the day after the patients come to find out where the screening is.
- Remind regularly inclusion and non-inclusion criteria and procedures to include a patient.
- From time to time, confirm the number of patients that the trial site intended to enroll initially.

Show yourself available to the investigator, he must feel supported and the project team is ready to help him in case of difficulties.

Step 6: Communicate about your study

Write a newsletter. A newsletter is a document that can be sent by email or by mail to the investigators participating in your study. It can contain general information on the study as well as elements concerning the progress of the study: number of open trial sites, number of enrolled patients, the investigators having enrolled the most patients in the study ... You can create, thanks to this document, a competitive dynamic in order to reach a larger number of inclusions.

And if, despite your efforts, your trial sites do not enroll?

Step 7: Identify the cause

When contacting your trial site, discuss with the investigator to understand why he or she does not enroll patients in the study. The causes can be multiple and identifying them will allow you to implement the right solutions.

Step 8: The actions to be implemented

- In case of too restrictive protocol:

Identify precisely what is causing the problem to the investigator. If it turns out that several trial sites are facing the same difficulties, maybe an amendment to the protocol can be discussed.

- In case of lack of eligible patients:

You can suggest to the investigator and his team to get in touch with patient associations to talk to them about the study.

- In case of lack of time or organization:

Perhaps it is possible to make a CRC available to help pre-screen patients who might be enrolled in the study.

- In case of lack of interest or demotivation on the part of the investigator:

Several solutions can be implemented to re-motivate:

- Release pay for the first patients enrolled. Take advantage of a newsletter to announce to all investigators that compensation will start. This may motivate investigators who have already enrolled to enroll

more and investigators who have not enrolled to enroll their first patient.

- Communicate about the study. If you already have results from the study, why not go to the scientific community?

  Learn about the different conferences that take place in your specialty. Often you can submit *Abstracts*. Plan an oral communication or a poster. If your project has been accepted for these conferences, talk to your investigators.

- Propose to the National Coordinating Investigator or a member of the Scientific Committee to contact your investigator. In this way, they will be able to discuss the difficulties together and find appropriate solutions.
- You can also organize a monitoring visit in the presence of a member of the sponsor or the project manager. This will allow the investigator to meet the team members and directly discuss this lack of inclusions.

If your trial site does not enroll despite the actions implemented, it means it will not enroll anymore. You can possibly think of closing this trial site and opening others.

As a project manager, anticipate difficulties and prepare actions upstream by writing them in your risk management plan so you do not get caught off guard.

Your CRA must communicate with your investigators and their teams in order to know as soon as possible the problems encountered and to implement the corrective actions. Finally, he must always remain courteous, available and motivated. He must convince the investigators that it is worth giving time to your project. Remember, his role is also to motivate the team of your trial site, remind them of the study or help them in the implementation of the project.

XII – The expectations of investigators

The role of the CRA is to ensure that the study is conducted in accordance with the protocol, the Good Clinical Practice, the regulations in force as well as the standard operating procedures (SOPs) of the sponsor. You know that good management of a clinical trial depends on many things such as good monitoring tools, good organization and so on. It also involves good communication with the physician and the investigative team.

What you really expect from the investigating physicians in a clinical trial is below.

1. Communication

The key to a well-conducted project is communication! Indeed, it is essential that you keep the investigator regularly informed of the progress of the study.

Your CRA must meet with the investigator at each monitoring visit to discuss the study. However, in his absence he can discuss it with the CRC that deals with the study, the physician will be informed in the follow-up letter of the monitoring visit and also by phone. If your CRA repeatedly cannot see the physician during his on-site visits, he can see with him if it is possible to schedule a telephone appointment.

2. Saving time

Physicians are very busy and have very little free time between consultations, meetings .... So, to lighten their workload, you can help them by anticipating and preparing certain documents.

For example, if a document needs to be created (note on file, for example ...), completed or signed by the investigator, ask your CRAs to prepare them, pre-fill them and send them with the follow-up letter of monitoring, or by email to the hospital CRC, for validation and signature of the physician.

3. Availability and management of logistics

The availability of your CRA is also one of the physician's expectations; especially if he needs information. Good monitoring tools will allow you to quickly and efficiently provide the information requested by the physician (inclusion dates, randomization, monitoring visits, calls, etc.). So, do not underestimate the monitoring tools!

As a sponsor, it is your duty to communicate regularly with the hospital CRC and the physician on the study, either by email, telephone or during on-site visits, in order to contribute to the smooth running of the study.

XIII - Recruitment of investigators

As project manager, you are responsible for recruiting investigating physicians for research. Here are some simple tips to help you find physicians to propose your project. These solutions are more or less expensive and time-consuming, it's up to you to choose the right method and the right time according to your type of project.

1. **One is better served than by oneself.** ☺

Consult the archives of your company. If you have previously worked on research involving the same pathology or area of expertise, then use the names of the physicians who participated in these projects. Make sure that the MR001 regarding the data of these physicians has been respected in your company and then select in priority those who have enrolled patients, you will be more likely to achieve your goals in terms of recruitment;)

2. **Internet, the best tool to find your investigators!**

Look for physicians who are already doing clinical research. You can visit sites that list current or completed clinical trials.

a. The American site clinicaltrials.gov.fr lists trials conducted around the world. You can search by specifying the pathology that your trial is about or the specialty of the physicians you are looking for. Do not forget to specify the country in which you want to initiate your study.
However, all the proposed studies do not indicate the names of the investigators, it will be necessary to search further.https://clinicaltrials.gov/

b. If your study is about cancer, the National Cancer Institute (INCa) offers a register of trials in France. You can select an organ family or a particular organ. http://www.e-cancer.fr/recherche/recherche-clinique/registre-des-essais-cliniques/registre-des-essais-cliniques/recherche-avancee

c. If your study is about AIDS or viral hepatitis, you may find your investigators on the ANRS website. The site proposes the list of the trials carried out by the ANRS in France.http://www.anrs.fr/VIH-SIDA/Clinique/Repertoire-des-etudes-cliniques

d. If your study is about an orphan disease or a rare disease, the ORPHANET portal for rare diseases and orphan drugs offers a list of trials. You can do your research depending on the disease being studied or the gene involved. This site proposes the list of trials in progress in Europe. http://www.orpha.net/consor/cgi-bin/ResearchTrials.php?lng=FR

3. Word of mouth, it works too!

If you have recruited some investigating physicians, put them to work. At the time of a conversation with the investigator, ask him if he knows any physicians who might be interested in this study and would have a good potential for patients to be enrolled. If he refuses to give you their name, ask him if he wants to talk to his colleagues. If he agrees, send him your business card and a presentation form of the study keeping the confidentiality of your project so that he can easily hand them over to his colleagues.

4. Scientific meetings to better recruit …

You can also visit a conference dedicated to the specialty you are looking for. Accompany the scientific team to this conference to propose the study directly to the physicians on the spot.

5. Advertising, why not?

You can also place an ad in the trade press. Contact them, they may agree to write an article about your project. Otherwise, consider contacting their ad network.

6. Your search must be targeted.

Look for physicians at the source: the places where they practice (houses and health centers, specialized services in the given pathology, ...) or associations or networks of physicians.

7. Get help from a specialized contractor.

If you need a large number of investigating physicians, you may want to consider purchasing a roster of physicians from an organization.

XIV - Strategic monitoring visits

a. The screening visit

The purpose of the screening visit is to present the study to the investigator and to evaluate the ability of the trial site to participate in the clinical study under the conditions described in article 1121-13 of the French Public Health Code and Good Clinical Practice.

After receiving the feasibility questionnaire stating that the physician is interested in the clinical study and validation by the project manager, your CRA makes contact by telephone with the investigating trial site to set the date of the screening visit. Your CRA makes an appointment with the CRC, the investigator, the pharmacy (if applicable), the biomedical analysis laboratory and any other service involved in the study.
Your CRA will ask the investigator to check the number of patients who meet the selection criteria in their trial site's database for the screening visit.
The CRA drafts and sends a screening visit confirmation letter to the trial site one week prior to the visit date.

Then, the CRA confirms his arrival by telephone a day before the screening visit.

Your CRA can adapt a screening visit checklist according to the specificities of the protocol (Possible documents to collect, services to visit, ...).

During the screening visit, the CRA aims to:

- present the study protocol to the investigator,

- ensure the motivation, qualification and availability of the investigator of the study,
- check with the investigator the number of patients seen in his department with the given pathology and the number of patients who could be enrolled in the study,

- check in the services that are involved in the project, that the trial site has the technical means, necessary equipment (computers, freezers, room that can be locked for storing equipment, ...) and humans (qualified personnel, in sufficient quantity) necessary to carry out the study.

After the visit, your CRA writes the screening visit report. He reports all points discussed with the investigator, the CRC, the pharmacist, the laboratory manager and any other person encountered during the visit. The report is provided to you as soon as possible for verification.

Potential investigators may participate in the study once you have agreed in writing. This agreement must be given shortly after the screening visit.

b. The site initiation visit

We will detail the site initiation visit (SIV). You will find some tips for your team to make the most of this visit.

1. What is the purpose of a site initiation visit?

The SIV aims to present to the principal investigator, as well as to his entire team (physicians, pharmacists, clinical research nurses (IRCs), CRCs ...) the protocol of the study as well as the information that will be useful to them to enroll, to monitor patients and to carry out the conduct of the trial.

You will need to prepare a presentation beforehand, addressing the following points: protocol, objectives of the study, study design (that is to say, the schedule of visits planned for the patient, with the specific tests to carry out),

the product (s) studied, the patient screening criteria, the procedures for collecting consents, data and adverse events, etc.

This visit will also allow you to retrieve the documents necessary to start the study: CVs (in English and / or in French) dated and signed by the various stakeholders of the study (those mentioned in the "Delegation log" or List of stakeholders on-site), signed agreements, confidentiality agreements, etc.

2. When should a SIV take place?

The SIV is obligatory. It must take place:
After obtaining all the regulatory agreements (favorable opinion of the EC and authorization of the competent authority, and possibly, after obtaining the CCTIRS and the CNIL, according to the type of research), obtaining the certificate by the Sponsor and the receipt of signed financial agreements (hospital, investigators).

But before the initiation, it will be necessary to inform by mail the Hospital Authority (as well as the department of Pharmacy, if applicable) of the conduct of the Research. It will also be necessary to make sure that the material has been sent, and all this, before the inclusion of the first patient in the study.

For trials taking place at the hospital, a SIV to the Pharmacy is also to be expected, for the management of treatment units. Depending on the type of study (phase IV + post-AMM), a SIV by telephone may be possible.

3. How to prepare a SIV?

Before any action, your CRA consults the monitoring guide of the study. You will have taken care to put information that will help in the preparation of this visit.

Then he will contact the investigator and his team to agree on a SIV date. He will take the opportunity to specify the duration, the people to be present, and the reservation of a room.
Importantly, he must ensure the presence of the principal investigator, but also all those who will be involved in the clinical trial (IRCs, CRCs, pharmacists, radiologists, laboratory manager, etc.). These stakeholders will be able to intervene in the collection of consents, the inclusion and the follow-up of the

patients, the filling and the corrections of the CRF books and the realization of the additional tests.

Once the appointment is set, the CRA must send a letter of confirmation by mail and / or email sufficiently in advance (according to the deadlines defined in the Monitoring Guide): this to remind the agenda of the visit (place, date, time, agenda), expected persons and any documents to be provided.
The day before his visit, he must think about making a phone call or sending an email to confirm his arrival (you never know!) And see with the trial site if they have received the necessary documents (investigator study file and pharmacy, study material, treatment ...).

The CRA must consider taking, during this visit, the protocol, copies of blank forms (task delegation, study training forms, etc.), the documents to be sent to the site, the checklist of the investigator study file… and to print multiple copies of the presentation for the benefit of those who may not be present for the duration of the SIV.

4. Once there, how does a SIV take place?

Using the PowerPoint presentation that you have prepared for it, and as noted above, the CRA will need to address the following:

- The study protocol: rationale for study, primary and secondary objectives, evaluation criteria, criteria for inclusion and non-inclusion of patients, study procedure (estimated duration, schedule of visits, etc.)
- The procedure for obtaining and collecting consents
- Inclusion procedures: explanation of the study to the patient, reflection period, signing of several copies of the consent forms and the Patient Information Leaflet (one of which must be given to the patient), possibility of withdrawal of the patient study at any time.
- The product under study: dispensing, preparation, recovery and accounting procedures
- The samples to be taken, their storage, preparation and shipment, as well as the laboratories involved during the study
- Method of collecting, filling and correcting data on paper or via an electronic CRF
- SAEs and their reporting procedures
- Management of treatment discontinuations, unblinding and study outings
- The role and responsibilities of each member of the team
- Monitoring visits: their frequency, duration and progress
- The study file (trial site / pharmacy), its contents and archiving methods
- Other procedures and documents related to the study.

Once the presentation is completed, the CRA will take the time to answer each of the team's questions. If he has no answers to give, do not panic, he will simply explain that he will get information from you and he will come back to them.

He will take many notes during the visit, this will save him time when writing the report ☺

He will benefit from the presence of the investigator and his team to make them sign the monitoring register, the task delegation form ... but also to recover the missing documents.

He will make sure to verify that the trial site possesses the documents necessary for the study, and this, in the good versions! Consent Forms, Patient Information Leaflet, Protocol, Investigator study file or SmPC etc.

Finally, your CRA must think about monitoring the materials and products under study received by the trial site and should not forget to make the team

aware of the auditing and inspection possibilities and remind them of the sponsor's publication rules.

5. And after?

After doing all that, he will have to write the SIV report (in English or French according to the sponsor's procedure), send the follow-up letter and update his monitoring tools. He can then send it to you for review and validation.

c. The follow-up visit (monitoring)

Your project has already started? Your CRAs have monitoring visits to make? We will give you the recipes of a successful monitoring visit that you can share with your CRAs!

A. But first, a reminder of the objectives of a monitoring visit

The monitoring visit, also known as a follow-up visit, has several objectives:

- From a regulatory point of view, it allows to verify and guarantee that the study is conducted in accordance with the protocol (and its amendments if applicable), the Standard Operating Procedures (SOPs) of the sponsor, Good Clinical Practice (GCP) and the legal and regulatory provisions in force.

- From the point of view of the patient, the monitoring visit ensures that the well-being and rights of people who are suitable for research are respected.

- From the point of view of the study, the monitoring visit allows:
  - to verify the quality, reliability and authenticity of the data collected in relation to the source data, in order to obtain reliable and interpretable results,
  - to monitor the progress of the study,
  - to ensure the support and motivation of the research teams,
  - and to ensure good coordination of the study.

For a new study, it is generally recommended to go to the site quickly after the inclusion of the first patient.

Indeed, the CRA has to quickly correct practices that are not compatible with the requirements of the protocol, the regulations in force and GCP, before the trial site enrolls other new patients. The CRA will then be able to make a reminder, if necessary, and a point with the team to find out if they have questions, if they have encountered any particular difficulties or if certain points of the protocol were not sufficiently clear. This is to avoid possible deviations or violations of the protocol in the future, and to ensure compliance with the study procedures.

The other monitoring visits are programmed according to a rhythm that you have defined (all this must be noted in the monitoring guide or "Monitoring plan"). It all depends on the complexity of the trial, patient visits, the pace of patient inclusion, and so on.

In order to carry out the monitoring visits, you will find below some advices, as an indication. However, you will still have to follow the internal procedures that you have put in place.

B. Tip # 1: How to prepare for your visit?

To prepare a monitoring visit is to save time. A good preparation will allow your CRA to forget nothing, and above all, to be efficient and productive when coming on site.

Above all, he must consult the "Monitoring Guide". He must also read it regularly to imbibe it. This guide is a manual created by the project manager, as a project manager, that will know what specific points to check during the visit (consents, eligibility criteria, reporting Serious Adverse Events (SAES), investigator study file ...), the deadlines in which to carry out on-site visits, the deadline for writing the report and the follow-up letter, the procedure to follow when a SAE occurs...

To begin, your CRA will contact the investigator and / or the study coordinator to schedule a monitoring visit. He must also contact the pharmacy and other stakeholders (laboratory, radiologist ...). It is best that he contact them all at the same time, so as not to forget one of them and to be refused a visit to the pharmacy for late call.

The week before his arrival, he sends a letter and / or email confirmation of visit (depending on the trial site) without forgetting the pharmacy (if

applicable). In this letter, mention should be made of the need to make available the source files, the investigator study file (s) and pharmacy binder if applicable, a room or office, and a computer with internet access (if possible).
When he sends his confirmation letter or e-mail, he must think about attaching his last monitoring follow-up letter to remind them of the pending actions. This will save everyone time and they will probably have time to finalize the actions before he comes.

One day before the visit, we recommend that he reminds the trial site of his arrival by phone call and / or email. You are never too careful! It may happen that the files were not brought out because they forgot that the CRA was coming... ☹

Once these actions have been completed, your CRA will be able to prepare for his visit to the office, using the monitoring report and the follow-up letter from the previous visit. He establishes a "checklist" with the essential points to perform, check and / or approach when he comes, as well as documents to recover and / or to provide to the trial site.
Your CRA must write down all the points so you do not forget anything!
Using this list, he will be able to draw up the agenda of the visit.

To optimize his visit, he gathers all the tools he has previously prepared (patient monitoring tools, etc ...). He prints several blank forms that may be needed during the visit: for example, task delegation forms, study training forms, SAE report forms, accounting forms of treatment units, etc. in case some are missing on site, because it is sometimes difficult to print or photocopy documents directly once on site!

C. Tip # 2: How to make a success of your visit?

During the visit, your CRA should consider using a checklist of tasks to be performed on site, as well as a monitoring tool for the review of the CRF and the medical record of each patient. Using this type of tool will save time. It is you, in general, as a project manager who prepares the tools to facilitate the work of your CRA.
The checklist on the tasks to be performed on site will detail the essential points to be made on site, including the verification of the following points:

1. The collection and signing of consent forms and Patient Information Leaflet.

Your CRA must ensure that the consent form is dated and signed by the patient and the investigator.
As a reminder, the signature of the patient must be prior to the first operations relating to the trial. In addition, the investigator who signed must be trained in the study and must be present on the Task Delegation Form and FDA1572 (for an investigational new drug to obtain a new drug approval in the USA) and this investigator must have been declared to the EC.

Your CRA must also ensure:
- the veracity of the patient's information (name, first name, date of birth, address if applicable)
- that the boxes, if there are any, are ticked
- that all pages are present
- That the name of the study in which the patient participates and the date of signature of the consent are mentioned in the patient's medical records. It should also be noted in the medical record that a duplicate or copy has been given to the patient (the investigator also keeps a copy), as well as the method of collecting consent (for example, that the patient was able to ask the necessary questions and he had the time he needed to think about his decision).

2. Inclusion and non-inclusion criteria for each new patient enrolled

3. The rest, that is to say:

The protocol: Your CRA must ensure that the protocol is followed and that there are no deviations or violations, that the treatment regimen is followed, that randomization has been done and the proper medication administered, etc.

The CRF: Your CRA must ensure that the CRF data is consistent with the source data (medical record), that the queries are answered ...
In the case of electronic medical records: Your CRA must be able to access them when they come on site, via their own codes that will be provided by the trial site. If the trial site is unable to provide you with a personal access code, the entire pages of the file must be printed, dated and signed by the investigator to validate the compliance of the documents.

The source documents: Regarding the biology, radiography and other trials performed as part of the study, your CRA must ensure the presence of the review date, a comment and the signature of the investigator. Indeed, this

shows that the investigator did review the results and possible adverse events (AEs) before continuing the study. On this point the opinions are mixed. Indeed, according to the former AFSSAPS (now CA or Competent Authority), this was not mandatory. But a good number of American sponsors require it. Up to you!

The investigator study file: the presence of the necessary documents (updating of the regulatory documents: CV, financial disclosure document, FDA 1572 or "non-IND agreement" for the non-interventional studies etc...) using the checklist of the investigator study file / pharmacy binder that you have provided to your CRA.

The storage and sending of samples: your CRA must collect the temperature records of the place where the samples are stored (freezer or refrigerator), the shipping forms, and check the number of remaining sample kits and their expiry date.

The material of the study: it is necessary to recover the maintenance certificates of the refrigerators, thermometers used for the study ....

The SAE report must be made to your department of vigilance within 24 hours of the investigator's knowledge of the event, by sending a SAE report form by fax or email to vigilance.
A form must be completed and signed by the investigator for each SAE. The following information is indicated by the investigator in the SAE report form: date of occurrence, end date if applicable, concomitant medications, medications administered to resolve the SAE, causal connection, etc.
In the absence of the investigator, the SAE forms will be signed by the study site coordinator until the return of the investigator who will countersign the forms on the current date.
A follow-up of the SAEs must be completed within 24-48 hours in case of new information. Your CRA must make sure this is done on time.

During the monitoring visit, your CRA must verify in the patient's medical records that:
- Any adverse event that meets the definition of SAE has been reported within 24 hours after the investigator becomes aware of it.
- The statement was made by an investigator declared in the task delegation form and trained in the study.

- The statement has been appropriately documented (laboratory reports, trials ... dated, signed and commented).
- The form information is correct.
- The SAE was followed (as soon as the patient's condition was changed) and the follow-up was performed by an investigator declared and trained to study.

If your CRA highlights a SAE in the patient's medical record and this SAE has not been reported by the investigator, the CRA must complete and submit the form on the day of the visit. He must also retrain the investigator to the reporting of SAEs ☺
If the investigator refuses to report a SAE or is not available to report the SAE, your CRA must report the SAE, by completing the form provided for this purpose. No way to wait when it comes to SAEs!

D. Tip # 3: and for Pharmacy?

During the visit, check the following points:

- medication management: accounting, compliance, dispensing (number of medications sent to the trial site, administered to patients, remaining, expiry dates, etc.)
- answers to queries
- the place of storage of the medication: recovery of the temperature readings from the date of reception of the medications or since the last visit. Verify that the medications have been kept at the correct temperature, in accordance with the protocol, the investigator's brochure or the Summary of Product Characteristics (SmCP).
- the pharmacy binder: presence and update of essential documents using the checklist.

After the quality control of your CRA, the pharmacist proceeds to the destruction of used and / or expired medications according to the SOPs of your company: your CRA must not forget to recover the certificates of destruction, which must be dated and signed by the Pharmacist.
Attention, in case of studies on a cytotoxic medication, the trial site can demand to destroy the medications after their administration without waiting for his arrival as explained here.

E. Tip # 4: At the end of the visit ...

At the end of the visit and depending on the availability of the investigator, your CRA should try to talk with him (or if necessary with the trial site's CRC), to discuss the progress of the study, difficulties encountered (inform them of any errors, omissions or illegible data in the CRFs) during the trial and for the signature of documents if necessary.

For any deviation or violation of the protocol, GCPs, legislation in force or the SOPs of the study, your CRA makes a reminder of these points by retraining the investigator and his team, during his visit but also in the follow-up mail of the monitoring visit. Make sure he documented all this in his monitoring report.

Your CRAs must gather all their monitoring notes on the same type of form to avoid scattering. Indeed, it will allow them to find their notes in one place and save time when writing their report. The evolution of correction requests and problems will be followed on this form until full resolution.

F. At the end of the monitoring visit

Following this visit, your CRA will have to write:
- a monitoring report, in English or French according to the procedure of the sponsor, for sending and checking to your project manager,
- a follow-up letter to evoke the various points seen during the visit, the queries to correct and possibly the actions to be carried out on this subject.

When he returns to the office, your CRA should not forget to update his own tools: tracking tables of patient visits, tracking tables of SAEs, tracking table of deviations and violations to the protocol, study documents using information gathered during his on-site monitoring visit.

For centralized monitoring, also plan a tracking table of centralized monitoring: this will allow you to quickly see where your CRA is and quickly access certain information, without having to look in the reports or follow-up letters.

d. The remote monitoring

In recent years and with the expansion of the eCRF, pharmaceutical companies are increasingly focusing on remote monitoring and putting in place tools to

help the CRA implement it. Some see a new way of creating a relationship of trust with the investigating trial site by making it more accountable for the collection of data for which it is responsible, while others see only a new way to reduce the costs of monitoring for the pharmaceutical company.

The remote monitoring… what is it?

Remote monitoring consists of a remote review of certain data, which of course implies the use of an electronic CRF (eCRF). Once the trial site staff has entered the data into the eCRF, the CRA checks for consistency and validates it as a "data reviewed". To verify the coherence of the data is simply to verify, for example, that a patient defined as "masculine" does not have as medical antecedent a hysterectomy...
This review is done every week or as soon as the data are entered during the screening period in order to be able to identify possible screening failures and especially to avoid incorrectly enrolled patients.
All the data entered in the eCRF are reviewed in this way, and some can be verified by comparison with other electronic systems used in the study:
- Laboratory results review system (date of birth, date of visit, patient weight, patient's gender...)
- System for the dispensing of the medication under study (date of dispensation, arm allocated to the patient if applicable, number of batches dispensed to the patient, weight of the patient if applicable)

When a data does not seem consistent or different from that found on another system, a query can be issued and allow the Study Site Coordinator (CRC) to check and correct (or not) the data.

And the "real" monitoring ... what does it become?

Monitoring is the review of data collected by the investigating trial site where the study is conducted, by comparison between the Clinical Report Form and the "source data" (patient record, clinical report, medical notes ...). Remote monitoring does not replace this part of the monitoring but simplifies it by eliminating input errors well before the CRA comes to the trial site.

During his monitoring, the CRA can therefore concentrate on verifying the veracity of the data, and devote himself to other activities related to monitoring such as the training of study staff, the review and collection of essential documents or the review of follow-up letters for serious adverse events.

Some protocols establish a focused review only on certain data from the study (endpoint, safety, efficacy criteria). The review is therefore no longer on 100% of the data but only on so-called "target" data. In this case we are on "target source data verification". The review of other data is then essentially done remotely.

Balance Benefits / Risks of this type of monitoring:

- ✓ The sponsor-trial site relationship (CRA-CRC) is deepened by a more regular contact.
- ✓ The trial site is more responsible for entering data knowing that they will be checked quickly.
- ✓ Rapidly identified errors are quickly corrected and even avoided in future entries.
- ✓ The trial site better understands the sponsor's expectations regarding this entry and the mode of collaboration is improved.
- ✓ The CRA knows what type of collaboration will be in place with the trial site, given the pace of data entry and accuracy, he can steer his collaboration by being more insistent on monitoring or on the contrary much less.
- ✓ The costs are reduced by reducing the number of visits on the trial site: indeed, the equation is simple, more time on trial site therefore more data reviewed therefore fewer additional visits to complete the review of all data.

Remote monitoring is an effective new way to remotely review data. Comparative studies have shown that the level of risk of error remains unchanged between a conventional monitoring with a 100% data review and a remote monitoring with a targeted data verification.

At a time when all our actions are related to electronics and computer networks (remote races, remote sports, soon remote medicine ...) cybermonitoring finds its place and still has a lot of ways to develop!

e. The risk-based monitoring

In recent years, we have witnessed a real change in how to monitor a clinical trial on an international scale.

Indeed, a new risk-based approach has been incorporated into Good Clinical Practice (GCP, ICH GCP, section 5.1) and the European Directive 2005/28 / EC. We speak of "Risk-based monitoring".

1. Regulatory context

In Europe, GCPs have imposed themselves on all clinical trials involving a medicinal product for human use by European Directives 2001/20 / EC and 2005/28 / EC (GCPs were transposed into French law by the decision of 24 November 2006). They integrate many notions, including that of monitoring.
Definition of monitoring (from the Decision of 24 November 2006): "*Activity consisting of monitoring the progress of a biomedical research and ensuring that it is conducted and that the data are collected and reported in accordance with the protocol, the standard operating procedures, GCPs and the laws and regulations in force* "
Monitoring of all on-site source files has long been considered the standard approach applied by CRAs. But in recent years, a new trend is emerging.
In 2013, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) published a guide ("*Oversight of clinical investigations - a risk based approach to monitoring*" and "*Electronic source data in clinical investigations",* respectively).) and a discussion paper ("*Reflection Paper on Risk Based Quality Management in clinical trials*", downloadable here), encouraging the pharmaceutical industry to consider a new monitoring approach, the Risk-based monitoring (RBM).
This approach was created as a result of significant deficiencies in the monitoring of clinical trials despite 100% of Source Data Verification (SDV) on site. The FDA and EMA therefore recommended a more centralized approach to monitoring, including many performance indicators to identify problems at the research site, and to limit the amount of SDV performed.

The RBM therefore integrates the concept of risk incurred by the participant and consists in adapting the pace of the CRA monitoring visits according to this risk.

2. What is Risk Based Monitoring (RBM)?

Unlike "standard" monitoring, which consists of verifying 100% of the source data and identifying source data transcription errors in the paper or electronic CRF, Risk-Based Monitoring (RBM) wishes to optimize and reduce monitoring.
The intensity of the verification of the data on site will therefore be adapted to the level of risk, pre-established from the beginning of the study in the "Risk Management Plan". This will, among other things, optimize on-site monitoring, thus reducing the time spent on the trial site, and consequently the cost allocated to monitoring (almost 30% of the budget of a study is dedicated to monitoring!).

This includes "Remote monitoring" (see the previous chapter).
It should be noted that verifications of consents, eligibility criteria, and security data (SAEs) remain unchanged during on-site monitoring.

In its guide, the FDA encourages sponsors to "perform aggregate statistical analyzes of study data to identify sites that are out of line with others." In other words, the sponsor can identify trial sites whose data differ considerably from others thanks to statistical algorithms. The sponsor will seek to detect incompatible information generated by a trial site, compared to data produced by all other sites participating in the clinical trial.
For example, if a trial site makes the same mistakes on several patients enrolled or, when on the contrary, a trial site never makes mistakes, the sponsor must be able to identify it by means of his software. Thus, the sponsor evaluates the consistency of the data of each trial site and detects the abnormal data to identify the specific problems of each trial site.
By identifying data discrepancies, the sponsor will be able to trigger an on-site monitoring visit, or guide the CRA on such or such points to check during his next on-site visit.

Preventing and identifying risks (error detection, carelessness, fraud, falsification) as early as possible through statistics can anticipate and correct the problem before it gets worse.

3. Application of the RBM in the AP-HP (Assistance Publique - Hôpitaux de Paris)

Since 2003, the AP-HP has applied risk-based monitoring, depending on the type of clinical trial (with or without drugs) and depending on the phase of the study concerned, especially for budgetary reasons.
Below you will find 3 grids that the AP-HP uses to define the level of monitoring (A, B, C, or D, D being the highest level) of a clinical trial:

Monitoring level tailored to the risks & constraints added by the research (AP-HP, since 2003) – drug clinical trials

Risk level	Drug clinical trials	Level of monitoring
A		Consent
B	**Phase 4 : licensed drugs in their indication** (comparative effectiveness research, optimization, observational) Phase 3 : Combination of licensed drugs in their indication	Basic data* in all patients + monitoring of all relevant data in a few dossiers
C	**Phase 3 : new drug under development or licensed drug in new indication**	Basic data* in all patients + monitoring of all relevant data of 10-20% of Case Report Forms
D	**Phase 1 or 2 : new drug under development**	**100% of Case Report Forms**

* Consent, Serious Adverse Event (SAE), eligibility, primary endpoint…

Monitoring level tailored to the risks & constraints added by the research (AP-HP, since 2003) – non drug trials

Risk level	Gene or cell therapy	Physiopathology, imagery	Psychiatry	Radiotherapy isotopes, surgery	Medical device (MD)
A		None invasive, e.g. blood puncture, imagery without injection of contrast agent	Non risky use of patient questionnaires	Routine technique or surgery, non severe biopsy (skin, ganglion)	The risk depends : • Of the grade of the MD (I, IIa, IIb, III) • Whether invasive or not • Whether use in or outside the approved indication • Of the novelty of use in practice • Whether availability of the CE conformity marking
B		Slightly invasive procedure Imagery with injection of contrast agent	Use of patient questionnaires with a risk of destabilizing the patients	Generalization of a new or recent technique	
C		Invasive procedure		Learning phase of a new technique	
D	Gene or cell therapy			New technique	

Monitoring level tailored to the risks & constraints added by the research (AP-HP, since 2003): What is monitored ?

Risk level →	A	B	C	D
Initial meeting, commitment to comply with good clinical practice (GCP)	X	X	X	X
Monitoring of consent	X	X	X	X
Monitoring of SAE	X	X	X	X
Basic monitoring (6 points)	-	X	X	X
Monitoring of primary endpoint	-	X	X	X
Monitoring of selected secondary endpoints	-	-	X	X
% of CRF monitored at 100%*	-	1st/centre 1st/investigator	10 - 20 %	100 %

* Important data

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

4. Skills Required for the CRA

In the RBM, the CRA will integrate the data quality review as a whole. For this, the CRA will have to improve and / or reinforce some of his skills:
- Use statistical software to identify data discrepancies;
- Interpret these discrepancies, i.e., have an overview of the study data: assess all the data of a site, compared to those of the other sites to see if any errors are recurrent, and therefore correct them as quickly as possible.
- Perform monitoring and remotely (by phone, remote monitoring, ...)
- Write tools to help decision-making based on types of risk
- Write a risk management plan

Initial or continuing training in clinical research will need to adapt to allow CRAs to acquire these new skills.

It has been shown that a high frequency of on-site monitoring does not necessarily lead to better data quality of the trial. By providing more clarity and efficiency, Risk-Based Monitoring will be the new standard to be adopted by all CRAs. The new generation of CRA will have to develop new skills to perform this type of monitoring in the right conditions: proactivity, statistical and analytical skills, etc.
The integration of statistical software into risk-based monitoring will therefore be essential for the sponsor to prevent potential risks, and to help improve the efficiency of his monitoring process as well as the quality and reliability of his clinical data.

Sources:

- Journal of clinical research best practices, Vol. 9, N°9, September 2013, « Adaptive monitoring : Risk-based monitoring and beyond » by Michael Rosenberg
- « Competencies for the changing role of the clinical study monitor : implementing a risk-based approach to monitoring », April 29, 2014 by Charlene Stubbs et al.
- http://www.cluepoints.com/solutions/reduce-regulatory-submission-risk
- http://www.fcrin.org/

f. The drafting of the monitoring report

Your CRAs have a monitoring report to write. Here are our 8 essential points for a top-notch monitoring report.

The texts below are strictly for example. Each CRA has his writing style. The idea is to find the important information and answer the following questions when your CRAs write a report: who, what, when, how? As a project manager, we recommend that you submit an annotated monitoring report to your CRAs to better understand your expectations, if you have not done so yet. In addition, recommend that they regularly refer to the monitoring plan, which will give them many elements to improve the quality of their report.

The monitoring reports are written in the 3rd person of the singular (ex The CRA has reviewed the CRF n ° 4, 5, 6).

1. **Enrolled Patients and consents**

In this part, your CRA specifies how many patients are enrolled in the trial site and where they are in their progress in the study (in monitoring, ongoing patients ...). He must also be specific about the date of signing the consent and by whom.

For example:

Patient 01:

Signature of the general consent v1.0 of August 17, 2016, by the patient and Dr. Dupont on May 17, 2016.

Signature of pharmacokinetic consent v1.0 of August 17, 2016 by the patient and Dr. Dupont on May 17, 2016.

The patient is currently undergoing treatment at V1 visit (July 16, 2016).

2. **CRF and source folder**

Here, he must specify the items he has checked and if he has reviewed all the queries.

For example:

Patient 01:

Monitoring visits V1 (total verification), V2 (total verification), V3 (partial verification), AE (partial verification), Concurrent treatment (partial verification)

On this day, the queries have all been reviewed, corrected and monitored.

3. SAEs

As a first step, it is important to confirm whether or not there were any SAE on the trial site. He must also state whether they were reported on time or not.

A monitoring of SAEs and FUs (follow-up) of SAEs must be done within his report, he must also specify if he has monitored the data related to this SAE or this FU of SAEs. He can write sentences of the type:

« Patient 001: SAE "hospitalization for back pain" was reported by Professor XXX dated XXX "The SAE has not been reported within 24 hours to the pharmacovigilance service. On XXX, the CRA monitored all SAE data. The follow-up of the SAE must be postponed upon receipt of new information by the investigator. The investigator, the co-investigators and the CRC have been retrained to the management and SAE report. This major deviation has been reported to the Clinical Project Manager on the day of the visit »

4. The deviations

Any deviations found during his visit should be reported in his monitoring report. He must also make distinctions between minor, major deviations as well as violations of the GCP or protocol. He must also specify, the reasons for these deviations and what the investigator has put in place to prevent this from happening again (preventive actions) and what they have put in place to correct the deviation (corrective actions).

For example:

Minor deviation: The ECG was not performed during the V1 visit. The CRC failed to perform this test because it was not reported on the working document he usually uses for the study. The working document used by the CRC has been modified by the CRC so that this type of error cannot be

repeated. In addition, the CRA rechecked the working documents to ensure that all tests of the study were well reported. The investigator and the CRC were retrained on the different tests needed for the study. A reminder sheet has been sent to the team for reference.

In general, the deviations are classified as follows:

Minor deviations: requirements, practices or processes that are not likely to affect the rights, safety or welfare of subjects or the quality and integrity of the data.

Major deviations: requirements, practices or processes that may affect the rights, security or welfare of the subjects or the quality and integrity of the data.

Violations (critical): requirements, practices or processes that affect the rights, security or welfare of subjects or the quality and integrity of the data.

In practice, as a Clinical Project Manager, we recommend that you create a listing that clarifies the type of deviations that you will consider minor, major, or critical that CRAs can refer to.

5. **<u>The "issues" that is to say problems or malfunctions</u>**

Throughout his report, the CRA must describe the problems and ways to resolve them. In general, he must report at the end of the report, the summary of all "issues" that occurred during the visit, as well as the "issues" unresolved during the previous visit.

We recommend you give a number to each "issue" and keep this number in time, it will allow you to better follow the issues and to quickly realize if he has done a wrong handling (example deleting an unresolved "issue") or if the "issue" is very old. Issues should normally be resolved from one visit to the other. It is not always easy according to the different activities to be treated or the goodwill of the investigation team. However, your CRA must be proactive and try to resolve all issues before his next monitoring visit.

For example:

Date	Problems	Comments	Resolution date
17May2016	***The ECG was not performed during the V1 visit. The CRC failed to perform this test because it was not reported on the working document he usually uses for the study.***	***The working document used by the CRC needs to be modified. The CRA must recheck the working documents at the next visit. The investigator and the CRC will have to be retrained on the different tests necessary for the study. A reminder sheet will be sent to the team when sending the monitoring follow-up letter.***	Pending

6. The contents of the investigator study file

He must summarize the missing documents from the checklist of the investigator study file.

"For example: The investigator study file is stored in a locked cabinet. It has been updated by the CRA today.

The following documents were stored in the study file:

-

-

-

The following documents are currently missing and will have to be transmitted before the next monitoring visit.

-

-

-

All missing documents will of course have to be included in the list of "issues" so that he does not forget to manage this "issue".

7. The medications

The CRA must report if he has gone to the pharmacy. He reports in his report the number of medications received, used since the last visit. It specifies if the account is good. He can also talk about the patient's compliance and calculate it. He can talk about destroyed medications, outdated medications. He also specifies whether the medications have been stored correctly and the temperature readings checked.

For example:

The CRA visited the pharmacy on May 17, 2016. The CRA reviewed the temperature readings in the ambient from February 14, 2016 at noon to May 17, 2016 at noon. No temperature excursions were observed.

Medication Accounting:

5 vials (Expiry Date: July 7, 2018) have been received since the last visit.

4 vials were used (destroyed on 17 May 2016, a certificate of destruction was provided).

Rest 1 bottle (Expiration date: July 7, 2018) to date.

An urgent order was made by the pharmacist. The CRA has retrained the pharmacist on the need for regular medication orders.

8. The material of the study

Your CRA may specify the number of lab kits remaining in the trial site.

For example:

There are :

- ***0 kit: Screening***
- ***1 kit: V1 (Expiration date May 22, 2019)***
- ***1 kit: V2 (Expiration date May 22, 2019)***

An order for kits was made by the CRA on the day of the visit.

Writing a complete report is crucial for the follow-up of an investigation trial site, your CRA must write it so that any other CRA can resume his work and understand what it is. He must be precise about who, what, when, how?

As a reminder in case of inspection or audit, the reports will be scrutinized, so stay rigorous and vigilant when checking these reports.

XIV - Reimbursement of expenses incurred by patients

As a project manager, you will have to budget the reimbursement of patient fees in the beginning of the study by choosing a contractor. During the initiation, your CRA will need to address this aspect with the trial site.

But the patient reimbursement, how does it work? Who manages it?

The reimbursement of expenses in a clinical study is an obligation of the Public Health Code.

1. What is the difference between "reimbursement" and "compensation"?

Reimbursement and compensation are two terms to be distinguished. We talk about "compensation" when the sponsor pays money to healthy volunteers, or to patients whose pathology is unrelated to research.

The compensation is the same for all participants in a study. It is neither a salary nor a fee and compensates for the constraints suffered by participating volunteers. For example, hospitalization or the performance of unpleasant or painful acts.

The amount and the terms of compensation must be recorded in the protocol, in the consent and the Patient Information Leaflet. They are communicated to the EC for approval. It is prohibited for vulnerable people (minors, persons under guardianship, prisoners ...)

"Reimbursement" refers to patients participating in an interventional clinical trial protocol. By accepting to participate, the patient will have additional tests defined by the protocol, requiring on-site travel, and therefore additional expenses compared to a "classic" follow-up. These expenses concern transport (taxi, VSL, personal vehicle, etc.), but can also take into account housing or catering. The types of expenses reimbursed as well as their ceilings are defined by the sponsor and sent to the company providing the patient reimbursement service with which he has contracted.

2. What do the texts of French laws say?

« No remuneration can be allocated to the person who is suitable for an experiment on his person, the collection of elements of his body or the collection of his products.», Article 16-6 of Civil Code.

« Biomedical research does not give rise to any direct or indirect financial compensation for those who are suitable, except for the reimbursement of expenses incurred and, where appropriate, compensation for the constraints incurred (...)», Article L1121-11 of the Public Health Code.

Currently, regulatory texts address the issue of compensation. As mentioned above, compensation is paid by the sponsor and is capped at 4500 euros for 12 consecutive months (amount defined by the Ministerial Decree of April 25, 2006), in order to avoid any excess "in the light of the fundamental principle of no merchandising of the body and to avoid a possible accumulation of risk ". Moreover, these people are registered by the investigator in the National Patient Database, instituted by the Huriet-Sérusclat Law. This database guarantees the safety of people because it ensures compliance with the exclusion period of the patient (that is to say his non-participation in other biomedical research) but also that of the ceiling of the patient. compensation. This database is accessible by investigators only.

With regard to reimbursements, the only regulatory text on the subject is in MR-001 (Decision No. 2018-153 of May 3, 2018 approving a reference methodology relating to the processing of personal data implemented in the research framework in the field of health with the consent of the person concerned (MR-001) and repealing the deliberation n ° 2016-262 of July 21, 2016.

The General Data Protection Regulation (RGPD: No. 2016-679) is also used in the context of the management of personal data.

3. How does this happen in France?

According to the decision of November 24, 2006 setting the rules of Good Clinical Practice for biomedical research on drugs for human use, the sponsor must have no access to the patient's personal data. This is why patients are identified by a number as soon as the consent is signed. To guarantee their security and the confidentiality of their data, the sponsors must therefore go through a CRO (independent of the project team), which will have the sole right to access the confidential data of the patient (names, first names, address ,

written on the claim forms and on all supporting documents such as invoices, or on the RIB or gray cards for example, provided by the hospital). You and your CRA will obviously have to validate the visits made, but it is the CRO who will make the reimbursements.

4. Would it be easier to set a package for patients in the same study?

In order to facilitate the management of the budget for the project manager of the study, one might ask if a package covering all expenses related to the protocol for the patient could be planned.

Packages may apply for compensations, but not for reimbursements. Patients coming from all parts of France, and trial sites being most often located in large cities, it seems difficult to concretize this idea. Indeed, travel expenses are very variable from one patient to another. They can be from a few tens of euros to hundreds of euros for a single trip. There is therefore a huge variability within the same group of patients for the same study, and this could be a barrier for a patient to participate.

Moreover, it would be against the law. Take for example, a package of 50 € per patient. If the actual cost of the trip for the patient is greater than this amount, the patient must cover his own costs. However, the Public health code provides that the patient is reimbursed for all costs. A flat-rate reimbursement (greater than the amount actually incurred by the research participant) could be re-qualified as a "disguised" compensatory allowance, prohibited.

It is therefore preferable to do it on a case by case basis in the interest of the patient, but also to avoid possible abuses.

Patient reimbursement is a subject we do not necessarily think about when we are a project manager. It is important to think about it from the beginning of the study, not to exceed his budget, but also to reimburse patients as soon as possible.

5. How long should patient data be kept as part of the patient reimbursement?

Expense reports received and invoices from transport companies or patients are accounting documents and must be kept in accordance with the commercial code. These data must be kept for a period that does not exceed

that required for the fulfillment of the assignment (i.e. reimbursement). Once the payment is made, the contractor should delete the data. However, he must keep the accounting documents for tax monitoring, up to 6 years after the end of the financial year.

According to deliberation n ° 2018-153 of May 3, 2018 approving a reference methodology relating to the processing of personal data implemented in the context of health research with the consent of the person concerned (MR-001) and repealing the deliberation n ° 2016-262 of July 21, 2016.

Subcontractors, acting on behalf of the person in charge of treatment and not having the quality of place of research, can be addressees of the administrative data of identification of the persons suitable for the research (name, first name, postal address, electronic and telephone numbers, bank details) in strict compliance with the following cumulative conditions:

The purpose of access to personal data is to enable:

- reimbursement of transport costs and / or the payment of compensation

The data are kept by the subcontractor for a period that does not exceed that required for the performance of his assignments;

A correspondence table, specific to the accomplishment of these assignments, is established and kept securely by the subcontractor.

Conclusion

This guide is a summary of the last articles of our blog (www.blogdelarechercheclinique.com) on the subject of monitoring and project management, as well as some of our internal procedures. We only addressed our core business. We hope that it has been useful to you and that it will allow you to better manage your clinical study.

My greatest satisfaction is to see the clinical projects we take care of, advanced and smile on the faces of our partners. When the product finally arrives on the market, we are happy to have participated in the progress of science. It is for us a result.

Click on the following links to stay connected to the Clinical Research Blog and Pharmaspecific:

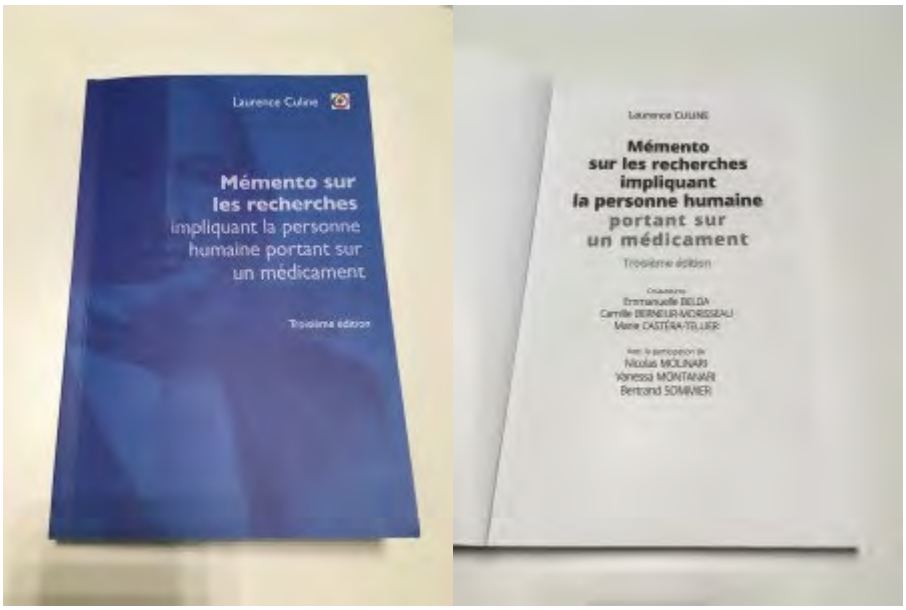
- Youtube: https://www.youtube.com/channel/UC6P9d1aaNVAYjGdQ5rg8uPA
- Instagram : https://www.instagram.com/blogrechercheclinique/
- Facebook : https://www.facebook.com/blogdelarechercheclinique
- Twitter : https://twitter.com/pharmaspecific
- Viadeo : http://fr.viadeo.com/fr/company/pharmaspecific
- Linkedin : https://fr.linkedin.com/company/Pharmaspecific

Send me a contact request via LinkedIn, we will be connected and you will receive all my news: https://www.linkedin.com/in/vanessamontanari/

Buy the memento on the research involving the human person concerning a medicine - Laurence Culine - 3rd edition - Self-publishing - January 2019 - 30 euros of which I am co-author (In French only).

I detail the content of this book on my YouTube channel, it's a must-have: https://youtu.be/sw4OO4VhX5c

To order, please contact Laurence Culine on the following email: memento.rc@gmail.com, inform that you come from me.



You can distribute this guide to whomever you want, as long as you do not modify it and quote www.pharmaspecific.com

Pharmaspecific
www.pharmaspecific.com