

Emphasizing the Importance of Project Management in CRO's to Achieve Better Clinical Study Outcomes

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Abstract

Accomplishing any jumbled task demands organization, coordination, and discipline. Overseeing a Bioequivalence study is certainly in the same manner, to guarantee that the trial works successfully, good project management is necessary. Project Management in a CRO necessitates competence in a variety of areas, including time, quality, cost, scope, risk management, communications, and sponsor management, and many others. The current review focuses on how to plan each phase of the study and how to create an effective Project Management Plan to reduce the average duration of the study and project management risks. The review also advises to follow a standard operating procedure at all times when conducting Bioequivalence study.

Keywords: Project management Team, Bioavailability/Bioequivalence studies, Contract Research Organisation, Project Management Plan.

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INTRODUCTION

Project Manager

A project manager is a person who works in the field of project management. Regardless of industry, project managers are responsible for the planning, procurement, and execution of a project in any initiative with a specified scope, defined start, and defined conclusion. As project representatives, project managers are the initial point of contact for any difficulties or disputes that arise among the heads of various departments within a company before the matter rises to higher authorities [1].

In a Contract Research organisation (CRO) a key element of communication for project managers is connecting the dots between sites and sponsors that is to relay comments from study locations to the sponsor of the study. Communication is especially crucial when it comes to updating sponsors on recruiting or screening problems at the study location. Study sites should keep track of volunteers, including why the screening failed and whether they contacted them, so that the sponsor may benefit from the information. In certain cases, the sponsor will take that criticism and make protocol changes as a result. They maintain a regular schedule of meetings or emails with the sponsor to report

recruitment updates [2]. When speaking with a sponsor, it's also critical for a project manager to be well-versed in the specifics of a study. The sponsor evaluates how successfully the site or CRO represented the sponsor during the study in post-trial conversations, according to Forte Research.

The project manager should also put in all of the main tasks that need to be completed throughout the study – target dates, descriptions, who they're assigned to, and do weekly progress and project updates. By this, the team is aware of what's going on in each of the projects. One of the greatest ways to avoid delays and difficulties once your trial begins is to create a thorough project plan [3, 4].

Roles of a project manager:

- **Day to Day Monitoring:**

The project manager and the project management team should always check on the project status, to optimize the project's critical paths. They should always facilitate that both internal communications and external communications are up to date. He/she should review incoming work and tasks,

respond to client emails, and communicate with the internal team to get things done.

- **Vendor selection**

Conducting a Bioequivalence study (BES) requires more than simply the study team. Outside vendors are frequently called in to provide expertise in areas like clinical trial technology, such as VMS software and electronic patient-reported outcome (ePRO) technology, and patient recruitment for BES's, etc. It may be the project manager's responsibility to vet these vendors and assist with comparing options.

- **Timeline and budget oversight**

All BES's begin with a set of goals and a budget, yet almost 80% of them are delayed, and many of them go over budget. This is where a project manager's experience may be put to work in holding the study team head up in terms of both time and money spent on the study, as well as managing expectations in the event of changes to the study plan or budget.

- **Machine Utilization**

The project manager and the team should have thorough knowledge about the equipment that is necessary and is used for the Bioequivalence study. Knowing about the equipment can save time. The project management team effectively monitors and reduces the timeline of the project by using software like the phoenix, SAS, LIMS which help in reducing the errors, and using automated machines like SAM HD, etc. in a CRO are helpful to reduce the manual errors along with saving time.

- **Institutional Review Board (IRB) submissions:**

All study materials, including outreach materials, must be evaluated and approved by the IRB. A significant duty that may fall to the project manager is gathering documents from sponsors and vendors and submitting them correctly. Because each IRB is unique, the project manager will need to review past submissions as well as any available submission templates to verify that the IRB's specific requirements for the study are satisfied.

- **Report creation**

BES project managers may be tasked with creating and disseminating reports on different elements of study progress as part of tracking study and remaining on track with schedule and budget.

- **Scheduling meetings**

The main sponsors and heads will need to communicate from time to time to review the progress and obstacles of the study. To ensure that all aspects are covered, the project manager will most likely be in charge of arranging and conducting these sessions. The study sponsor will be happy to receive updates and comments at all times.

Project Management

Accomplishing any jumbled task demands organization, coordination, and discipline. Overseeing a BES is certainly in the same manner. From eliciting a plan to communicating updates to estimating problems, there are usually a lot of factors involved, and to guarantee that the trial works successfully, good project management is necessary [5].

Project management, according to the Project Management Institute (PMI), is described as "the applicability of knowledge, skills, tools, and methods to project activities to satisfy project requirements." It necessitates competence in a variety of areas, including time, quality, cost, scope, risk management, communications, and sponsor management, and many others. The Project Manager should be an employee of the CRO; the Project Management Team (PMT) should include the Principle Investigator and the Chief Analyst, in other words, the PMT should not include more than 3 members [6].

The BES as any kind of clinical trial is never a project run within a single organization. It includes not less than three organizations when managed by a CRO – the Sponsor, the CRO, and the Clinic (in case the analyst and the statistician are part of the CRO not as employees but per contractual basis. As a type of clinical trial (CT), the bioequivalence study (BES) bears all specific characteristics of a regular clinical trial, while being much less complicated to organize and manage. By all means, though, it is quite healthy to handle the BES as a project, which makes the management at least more structured and well defined. The CRO's always have one objective – to prove the equivalence between the bioavailability of a generic product and its original; its actual clinical part can rarely last more than 17-20 days; the analytical part is in general not more than 2 months and in this sense, the duration of the BES (or the project) from the beginning to its end in most cases should not be longer than 1 year. The outputs are defined as results – bioequivalent, Yes or No. And finally, the results can be attained only following the line of the progressive elaboration – step after step [16].

But the pharmaceutical companies, which are sponsoring these events, are not always happy with the duration and the price they pay to achieve results. In the highly competitive drug development environment, pharmaceutical companies expect to get the results as soon as possible. So, getting a result by one-year duration, the sponsors are ready to jump to the next CRO where they might be promised a much shorter duration of the study. Hence phasing a project with effective project management plan is necessary.

Phasing a project

BES includes the following steps once an invitation from a Sponsor to a CRO for placing an offer is received:

Step No:	Output
I	Offer prepared by CRO
II	The contract between the CRO and the sponsor
III	Set of clinical trial documentation
IV	Ethical Committee application
V	Regulatory application and approval
VI	Clinical part
VII	Analysis of blood samples
VIII	Statistical analysis
IX	Final report preparation and delivery
X	Study archives and final documentation
XI	Study close-down set of documents

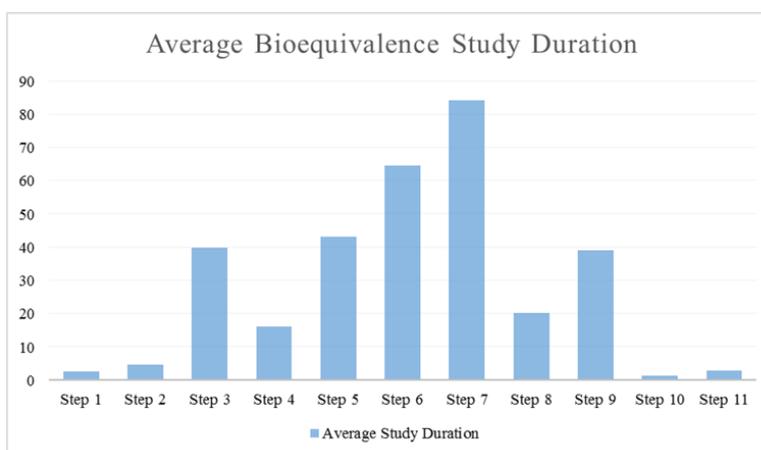


Chart 1: The average duration of each step (days) in a bunch of analysed BESs

The duration of the study mentioned here is 90 days which is an average timeline for the BES. This duration can even sometimes get extended when there is no effective project management plan. After observing the analysis of various BESs, one can have two options either to focus on efforts and pay more attention to the steps that appeared to take the most time (III, V, VI, and VII) or to build from zero, following the PM rules and definitions, implementing the effective project management plan. It is always preferable to take the second method and, rather than trying to shorten the long steps (as the Sponsors desired) [7, 8].

The 5 basic phases of project management are:

The following are the five fundamental phases of project management [9, 10]:

1. Developing a concept: Entails determining whether or not the project is required and identifying key decision-makers.
2. Making a plan: Laying out the work that needs to be done, including prioritizing, budget, timeline, and resources.
3. Task distribution: All teams are informed of their duties and deadlines.

4. Project tracking: Comparing actual project status and progress to the initial plan and making necessary adjustments.
5. Evaluating: Emphasising project success and lessons learned for future projects.

Project initiation

Previous project management studies/papers have indicated that the time spent on trial start and preparation was quite short. Furthermore, the research revealed that the longer duration of the subsequent phases, as well as the poor profit rate, are mostly the result of incorrect initiation and bad planning. The initiative of the project's framework is crucial for BESs. And because of the project's low degree of complicity and the shared experience between projects (studies), once prepared project framework can be used for other studies and if required it can be modified for the other projects. This project framework is independent of steps I and II of BES. But if possible in an effective project management plan the above two steps can be regulated [8].

The planning phase has been probably one of the most seriously affected phases in Project

Management. Once you've created a project management plan, you may use it as a template for future projects. The main factors that should be taken care of are– the environmental factors and the organizational assets [11]. The Work Break-down Structure is an important component of the work that has a beneficial impact on managers and other sponsors in a CRO. It is also crucial for the CRO to describe very precisely the activities and to estimate the corresponding resources and duration of the BES. The planning phase should also include which are extremely important – cost estimating, risk identification, risk response planning [14].

• Bioequivalence Study protocol

All the above issues discussed (excluding the cost-related issues) become part of the study protocol (SP). From any standpoint, this is the most significant document for the project. It covers directly all steps from VI through XI and indirectly steps IV and V. In this regard, it is critical to involve the Project Management Team as early as feasible in the project cycle, make the protocol the team's first and most significant proposal, and disclose the drafts and versions of the protocol to sponsor as soon as possible (from those who can have an access to such document). The widely (and appropriately) disclosed SP makes the rest of the project a straightforward routine task. The SP is also used after the project has been completed to help identify a project that has been done. It also serves as a foundation for monitoring and quality control. SP can also be called a “Trial management plan” and it is the component that requires the most of our time and work.

Based on this understanding one has to provide maximum time or increase duration of Step III, as shown in **Chart 2**. And also notice that once prepared SP template can be exercised for further projects, due to similarity between the BESs. So initially the SP step takes more duration but gradually, the time can be decreased [8].

Project Execution

The execution of a BES includes step III, excluding the SP and step IV through X [8, 11]. The analysis of the execution has shown the following:

- The SP determines the execution time in step VI, and the number of blood samples to be analyzed and the analytical equipment utilized in step VII;
- Step III's execution section involves the creation of all documents except the SP and is mostly reliant on the CRO's efforts and organization, as well as communication patterns between the Project Team and Project Management team. The success of stages IV and V is determined by these actions;
- Steps IV and V are dependent on Step III, but they are also susceptible to barriers, which cannot be controlled (regulatory and legislation changes) or can be controlled to a certain extent by paying reasonable attention to the issues related to sponsors. These phases are defined in terms of duration as shown in **chart 2 and 3**;
- Step VI can be extended by poor planning, a lack of communication of the study protocol and project management plan, and other factors. However, once started, it is set in time, and any exclusion is a severe breach of the SP, which can result in a failed clinical study;
- Step VII can be extended for the same reasons as step VI, as well as by poor laboratory organization, laboratory equipment failure, and issues with lab employees. The use of modern equipment can reduce the amount of time it takes to analyze a sample. In any case, once the organization and equipment are optimized, it is more or less fixed. Step VIII is almost constant, but it is good if the time required for statistical analysis is decreased.
- Steps IX and X are completely reliant on appropriate management within CRO and administration, as well as adequate planning.
- If all the steps are scheduled according to the Project Management Plan the average duration of the study can be reduced as shown in **chart 2**.

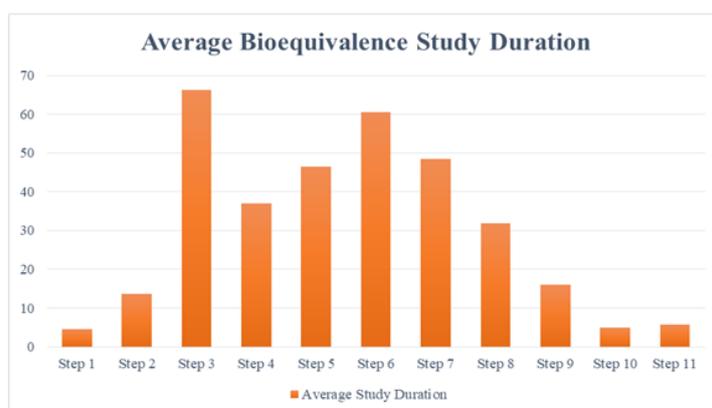


Chart 2: Average duration of each phase (days) for BESs following analysis

If all steps are planned accordingly to the PM rules and follow SOP etc; then one can observe a decrease in the duration of the Bioequivalence study (70 days).

Comparison of duration before and after the study analysis and the results are graphically presented on Chart 3.

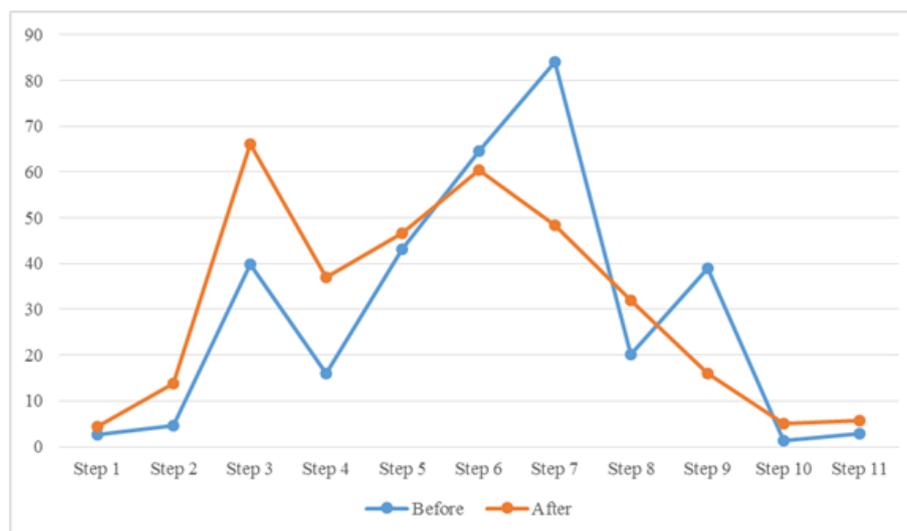


Chart 3: Comparison of steps/phases average duration (days) before and after the analysis

Close-down

The process of closing a BES requires careful planning and supervision. Once a standard operating procedure is authorized, the time it takes to complete this step is nearly fixed, because any difference in any direction will result in a deviation of the processes. One should necessarily follow the standard operating procedure [11].

Standard Operating Procedure of roles and responsibilities of a Project Management Team during a BES

The procedure is applicable for allotment of study number, communication of the project information to the concerned departments, to maintain the client correspondence, projects planning, tracking, and close-out for clinical studies [12].

1. The responsible role of the Project manager or the members of the project management team is to allot the study number to each project after confirmation from the sponsor.
2. The project manager or the member from the project management team should communicate the scope to the concerned departments before the study initiation regarding information about the project and should also coordinate technical discussions with the sponsor representative and concerned department heads and investigators periodically.
3. The PMT should also initiate the project contract/master service agreement (MSA) and confidentiality disclosure agreement (CDA) process with the sponsor representative after technical discussions.
4. The project contract should address the following details- protocol development, analytical development/ validation, clinical phase/ conduct, bio-sample analysis, clinical study report/summary report.
5. The PMT should also conduct an internal meeting with the concerned department heads/ investigators before initiation of the first project of a new sponsor to discuss the scope of the project, MSA, CDA, and any other agreements (except the financial agreements) if required.
6. The project management team after allotment of the study number should communicate any changes in the scope of the project works to the department head and also ensure that all amendments are communicated to the person to whom the initial project information sheet has been issued.
7. Once the project scope has been described and their dependencies are identified, fix the milestones for different stages of the projects and plan the phase duration.
8. It's good to prepare a detailed project tracking excel sheet for tracking the progress of the project.
9. Review the progress after dividing the project execution into phases with clear completion dates for each phase. It's always best for the project management personnel to follow up on the ongoing projects as per tracking/ schedule and update the project tracking sheets.
10. It's the primary duty of the project management team to inform the sponsor if there are any changes in the project completion date and notify the project extension and closure and they have to consider the project is completed after the formal acceptance of the final report by the sponsor.

11. The main important duty is each communication with the sponsor should be filed and kept for further reference.

After the project

A project review meeting should be conducted which should include required significant sponsors. This meeting should be scheduled when that the whole project plan is being created itself, so it is a part of the project wrap-up that is expected. A pre-meeting survey or questionnaire to collect feedback on what went well, what didn't, and what may be done better next time must be sent, which might be helpful for future projects [13].

Communication tips for project management

One of a project manager's most essential responsibilities is to communicate effectively and clearly with various sponsors. Make a list of sponsors for each particular project, outlining what kind of updates they'll need and how frequently they'll need to be updated. Knowing your sponsors is essential for efficient communication, just as it is for any other type of communication. Some sponsors, for example, prefer a weekly summary email instead of a weekly teleconference, or vice versa. In the RACI (Responsible, accountable, consulted, and informed) project management technique, sponsors will be divided into four groups based on their project engagement and communication needs [14, 15].

Responsible: This is the sponsor who will be performing the real work on this section of the project and will be the main point of contact for communication. If the project manager is compiling outreach materials to submit to IRB, for example, the person responsible may be the marketing team's lead or a BES recruiting company's contact.

Accountable: This individual, who is usually the manager of the person responsible for the project, may want to be involved in certain but not all project updates. If the person responsible has to get clearance from their manager, they will usually do so before sharing information with you.

Consulted: Additional sponsors who offer an opinion on a project. Inquire with the person in charge about to include the "consulted" group in your communications.

Informed: People who are merely kept informed on the project's progress.

IRB submission tips

Before the study starts IRB must approve the procedure and materials. In this case, previous submissions to IRB will always guide to the new submission. If applying to the IRB is completely new to

the project manager then it is advisable talking with the IRB administrator before submitting your materials to IRB. IRB administrators may answer any concerns they have about the submission procedure, as well as assist them in filling in gaps or making adjustments to ensure a smooth and efficient process. It's good to check thoroughly the documents before forwarding them to the IRB. It saves time because every time making a change and sending it back, increases the duration for materials to be authorized. CROs, sites, or sponsors submitting documentation to the IRB should have a quality control system (QC) in place to ensure that all requirements are met. Also, having a team meeting to review the documentation requirements and check that all essential material is being supplied in the proper format on time is preferable to having just one person accountable for the submissions. Though the project manager is ultimately responsible for the IRB submission, he or she should strive to engage additional team members to assist with quality assurance before submitting papers to the IRB [14, 15].

Risk management in PMT

In addition to laying down who and what is involved in each stage of your project, it's also a good idea to assess the risks associated. Any study has varying degrees of risk. Making a strategy for what you'll do if something goes wrong may help you relax. PMT should make the best judgment about the probability of each risk occurring and its impact on the project [2, 15]. A few examples to start with include:

1. IRB approval delays
2. Patient recruitment delays
3. Staff turnover
4. Changes to the Study protocol

PMT should assess the risk based on past experiences. Spend time with your team's other members before the project begins to discuss anticipated risks, how you've dealt with them in the past, and ways to reduce their impact - or, if feasible, avoid them entirely [4].

CONCLUSION

The Project Management Team acts as a point of contact for both the study team and the sponsors. PMT holds the most essential responsibilities in a CRO and they are involved in every area of the project from the beginning including, vendor selection, timelines and budget oversight, IRB submissions, preparation of reports, day-to-day monitoring, clinic, and machine utilization, and scheduling meeting. They are in charge for overseeing the operation at the study location by offering guidance and instruction. The Project Management Body of Knowledge (PMBOK) and GCP/ICH norms and regulations should be followed by

a project management implementer in the BES area. The development of the project's framework is crucial for BESs, an effective project management plan aids to reduce the duration of a BES. Furthermore, PMT is involved in risk assessment and effective management of timeline by using quality automated machines that reduce manual errors, both of which are crucial for any organization's success. Any CRO, which would like to improve its performance, should invest in Project Management. Finally, the project management approach can assist the CRO in providing higher quality services at a lower, competitive price while maintaining or even increasing the profit margins.

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