Managing clinical trials in the Philippines, like all clinical trials done worldwide, requires observing critical processes and timelines to ensure that studies are completed on time as planned. By knowing, understanding and carefully observing and keeping these processes in mind, sponsor companies would have developed over time a clearer and more realistic timeframe of the study process and help manage study expectations. This will impact the trial budget allocated to complete the study and ensure that possible delays are avoided where parallel activities and tasks are done to cut on project timelines.

Conducting clinical studies in the Philippines like other countries in Southeast Asia requires knowledge of current local practices and experience of people in the country since countries differ in their regulatory practices and approval procedures, processes and timelines. In general, the Philippines is one of the countries believed to have a reasonable approval turnaround time for start-up study projects. However, this can still influenced by other factors like the complexity (or difficulty) of the study, the completeness of the documents required, the response rate among study sponsors principal investigators, and regulatory authorities, and the speed and efforts by the local CRO in following up with the different government and other support agencies.

The various players should work in sync to ensure that unnecessary down time is avoided. By experience or intuition, the CRO has an important role by being pro-active and giving that extra service by providing practical advice particularly to foreign study sponsors on local practices in conducting clinical research in the Philippines. The CRO can also provide study sponsors on the effect or influence of cultural differences even among the different social- and sub-groups within the country.

Given these knowledge the study sponsor, nevertheless, can take confidence that the study will be implemented professionally and within international standards.

The Philippines is one of the prime destinations in Southeast Asia for clinical research. It has one of the most number of reported clinical studies performed annually in comparison with its neighboring countries. Other countries with large studies are Singapore, Indonesia and Thailand.

**Contracts & Agreements**

Before any activity is started in processing approval with the various government agencies, it is important that contracts and agreements have already been signed.

It presupposes that the clinical study protocol and the various pre-trial activities outlined were already reviewed and understood and the basic budgets have all been approved. The Contract Service Agreement (CSA) is a common instrument used for this purpose. It identifies not only the tasks and activities with the corresponding budgets and timeframes, it also enumerates the responsibilities and milestones agreed upon by the parties concerned often the study sponsor and the CRO. However, there several other agreement models where parties involved can work on (i.e. a tripartite agreement of the study sponsor, CRO and PI).

Other more specific or limited contracts are available which may only involve a CRO on specific services like regulatory or logistics. Others focuses only on site selection or monitoring.

Whatever the case may be, it is important that all the agreements have already been signed to avoid any confusion in the future. Once agreements are completed, the initial and most important process can be started, i.e., registration of the study with PFDA.

**PFDA Registration**

Applying for PFDA (Philippine Food & Drug Administration) approval to conduct a clinical study in the Philippines is the first crucial step in the chain of activities following along the process in conducting the trial.

The approval process requires the submission of the various documents like the study protocol and design, supporting materials and filled-up application forms.

The PFDA is currently in partnership with ERBs accredited by PHREB (Philippine Health Research Ethics Board) to conduct technical and ethics review of the study protocol. Like most ERB/IRBs worldwide, they are composed of expert professionals and lay people who have interest in the study. Essentially, the ERB focuses on the technical and ethical issues surrounding the study. Once the required safeguards are evaluated the ERB may (or may not) approve the study.

Below is a partial list of ERBs (or ERCs) accredited by PHREB:

**List of Ethics Review Committee**

1. Philippine Heart Center Ethics Review Committee
2. University of the Philippines Manila Research Ethics Board (UPMREB)
4. The Medical City Institutional Review Board
5. Manila Doctors Hospital Institutional Review Board
6. Veterans Memorial Medical Center Institutional Review Board
7. Makati Medical Center Institutional Review Board
8. Davao Doctors Hospital Institutional Review Board
9. Mariano Marcos Memorial Hospital and Medical Center
10. Chong Hua Hospital Institutional Review Board
11. Baguio General Hospital and Medical Center Ethics Review Committee
12. National Kidney and Transplant Institute Research Ethics Committee
13. Lung Center of the Philippines Ethics Review Committee
14. Far Eastern University-Nicanor Reyes Memorial Foundation Institutional Ethics Review Committee
15. University of the East Ramon Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences Ethics Review Committee

1Referred to sometimes as Committee.
These accredited ERBs are located in the major cities and regions all throughout the Philippines. Approvals may be granted for single or multiple sites.

In many cases, questions for clarification are raised by the Board and or pursuits brought in the Philippines an .

1. pending questions and issues are cleared, the Board may approve the study and endorse the study back to the PFDA. Upon accepting the endorsement, the PFDA begins processing the application for the issuance of the Approval to Conduct Clinical Trial.

Institutional Review Board (IRB) of the trial site may require review and study approvals as well besides that of the PFDA. This is on top of the review being conducted by the ERB assigned by the PFDA for purposes of approving the conduct of the clinical study. The study must pass both ERB reviews as a pre-requisite before the study can be started. A separate fee is required for both reviews.

Depending on the complexity of the study and the number of pending questions not fully answered satisfactorily, the whole approval process can take from somewhere between 2-6 months.

Investigational Medicinal Product (IMP)

With the PFDA approval of the study, the CRO starts with the processing of the Import License (IL) for the IMP. The application requires the submission of the PFDA Permit and other documents to conduct the trial. This is true with products coming from Study Sponsors outside the Philippines. Application is not required for investigational medicinal products sourced locally.

As with all imported items brought in the Philippines an Import License is filed with the PFDA and eventually submitted as supporting document with the Bureau Of Customs (BOC). Together with the application form, the company applying for the IL must submit a pro-forma invoice showing detailed information about the importing institution and product to be used for the clinical study. A pro-forma Invoice is usually prepared by the Study Sponsor. Great care must be exercised in accurately filling out the information as even a slight deviation from the actual product information in the pro-forma invoice may delay clearing by the BOC or total rejection of the whole lot.

The whole process from filing the application to the release of the Import Permit by the PFDA takes about 2-3 weeks.

Once the IL is released, the company concerned can start the process of importing the product, first, by advising the Study Sponsor to ship out the IMP. Local customs brokers who are appointed to facilitate release of the product must be accredited by the BOC.

Shipment of IMP

Once shipment is made by the Study Sponsor, the IMP is expected to arrive within a few days in the Philippines. However, the shipment time depends of the country of origin - longer for countries in the western hemisphere than those coming from nearby Asian countries.

In many cases, shipment arrives within 2-3 days by air - the preferred mode. Upon arrival the shipment go through BOC clearing for release. Couriers often have end-to-end service which includes forwarding services bringing the shipment to its final destination. Releasing shipment from BOC requires that all pertinent papers are in order.

It is important that the importing company chooses a reliable courier to ensure immediate release of the IMP from the BOC. Usually, release is done within the day of receiving the products. For IMPs requiring special storage within certain temperatures, the release is critical because a delay could compromise the integrity of the IMP. This means extra effort in ensuring that the temperature of IMP pack is maintained within the specified temperature range.

In these situations a temperature log is required the moment the IMP leaves the Study Sponsor’s warehouse until it arrives at its final destination which is usually the Study Site where the IMP will be stored in biological refrigerators or similar controlled facility. For multiple Sites the IMP can be transferred accordingly through interconnecting transport system granting that the Study Site is ready to receive the products.

Experienced CROs understand the importance of this process and have Cold Chain policies and procedure to cover processing to ensure that the integrity of the IMP is preserved.

Site Initiation Visit (SIV)

In the Philippines like most countries, a study is heralded by a Site Initiation Visit (SIV). However, this assumes that a Site Qualification Visit (SQV) has already been performed and the Study Site already passed the criteria and finally selected. The SIV allows for all involved in the study to ask questions regarding the study protocol. In this meeting, it is assumed however that all concerned (especially the Principal Investigator or PI) have already read and understood the study protocol.

In the meeting, a representative from the Study Sponsor is present to provide further technical input and answer other related questions in regard to the trial.

Start of Study

Once the SIV is completed, recruitment of subjects can officially start. They undergo an orientation and medical interview to determine their suitability to join the study and screened based on the Inclusion/Exclusion criteria as defined by the study protocol. Subjects or volunteers may not be enrolled in the study for several reasons. Among others, this may be because the patient’s safety may be compromised, the patient’s existing medical condition could be exacerbated by the drug, or for the simple reason that the drug under study is contraindicated to the said condition. Other practical considerations are based on the ability of the patient to participate and continue the study because of distance, religious constraints, personal beliefs, culture clash or lack of support from family or relatives. However, once the patient or subject passes the initial screening, patients have to be consented.

The PI gets to consenting patients/subjects to the study by asking them to sign the Informed Consent Form (ICF). Without the ICF, any procedures to be done to the subject cannot be started. Once ICF is signed, the PI can get patient/subject to undergo further medical evaluation. This often involves getting standard medical baselines through laboratory tests and procedures (e.g. CBC, x-ray) as required.

The Philippines is regarded as a rich source for patients because of its large population (i.e., 100 million). However, patients or subject population depends on the disease or medical condition being investigated on which means the prevalence rate for such conditions. Certain conditions are race-specific or are not common among certain ethnic groups or race. Or, certain diseases are common only in certain geographical areas, for example, infectious diseases of which the infecting organism thrive only in certain environment (e.g. TB or malaria).

After all preparatory work is done, dosing starts according to the prescribed dose and predetermined schedules or visits. This schedule depends on frequency outlined in the study protocol. Some studies require patients to be confined in a medical facility like a hospital for closer monitoring. Others are asked to visit the facility or site on scheduled times. Studies can be as short as an overnight stay in a hospital or visits spaced out for specified number of years.
Site Monitoring & Data Collection

The end point of any clinical study is data (information). Without the data, the study is of no value. Therefore, the accuracy and integrity of the data collected is of primary concern and importance. Some Sponsors provide training and usage of an Electronic Data Capture (EDC) proprietary to the study or the company. Preferably, data entry must be done immediately and retrieved in real time for analysis and interpretation. Source documents must be kept in order and stored at the Site for future audit if the need arises. For speed, however, the EDC can be used to get immediate information or feedback.

One of the main functions of a CRO is to monitor the progress of the study and to ensure that the Study Site closely adheres to the study protocol. This includes validating of data, checking for errors and notifying the PI immediately in order to avoid similar errors from happening as the study progresses. Incomplete, inconsistent and erroneous data entries or omissions are some of the most common errors observed in the course of monitoring the study.

Of concern for both the PI and CRO is the emergence of possible Serious Adverse Effects (SAEs) in the course of the study. These observations must be reported immediately and proper standard of care intervention given at the discretion and supervision of the Primary Investigator.

Closing Out & Data Lock

Closing a study starts formally by doing a data lock. The step requires that no further changes, entries, or revisions will be made on the data. The data eventually will be evaluated by a biostatistician for analysis and significance based on the endpoint or parameters set and objectives established at the beginning of the study.

Data at this stage would have been reviewed and audited for accuracy to ensure that data are devoid of any inconsistencies and errors.

Reporting

Reporting the results of the study is also as challenging as conducting the study. The PI is assigned to make the study report. While there are standard reporting standards, some Sponsors may provide a template as a guide for PIs in developing the report. This helps reporting to be comparable as studies may be done in several sites or from different countries.

The report may be published in medical journals as decided, approved or allowed by the Study Sponsor. The study report becomes part of the documents that the Sponsor use in supporting and substantiating the clinical safety and efficacy of the drug under study. They become part of the compiled reports gathered for finally registering the company for eventual launch or commercialization.

Conclusions

Managing clinical studies in the Philippines follows the same stringent criteria and procedures used and outlined in the manual of Good Clinical Practice (GCP).

In keeping with international standards, the Philippines observe and adhere to this guideline. All personnel involved in the clinical study must undergo the training program and be GCP certified. Quality assurance is maintained all throughout the clinical study process to ensure integrity and validity of data to be obtained.

A general process overview is shown as follows: