CHAPTER 17

Study Management

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17.1. INTRODUCTION

This chapter’s focus is study management of clinical trials conducted in developing regions of the world. Study management is a complex undertaking in any clinical trial, but considerably more so for large, multisite trials being conducted in developing countries. Simply having sites in more than one country (whether developed or developing) means that individual investigational sites may be many hundreds or thousands of miles apart. The contract research organization (CRO) selected to conduct the study has to have a footprint in the selected countries. Unless the sponsor has manufacturing plants in multiple countries, the drug product being tested will have to be shipped into at least one country, which brings travel and customs (import/export) considerations into play. Biological samples collected from many investigational sites will have to be transported to the central laboratory chosen for this trial, which brings considerable logistical challenges. If the countries speak different languages, key documents will need to be translated into each appropriate language.

Cultural differences also need to be considered carefully. These can be much more subtle than language differences (there are often considerable cultural differences in countries that, ostensibly at least, “speak the same language”). Individuals in different cultures can tend to report the same degree of discomfort to a greater or lesser extent, leading to differences in self-reported adverse event occurrences. Some cultures may wish to “please the investigator” more than others, which influences how individuals from that culture interact with the investigator and his or her research staff. This phenomenon can be described in terms of Hofstede’s power distance dimension [1], which is the degree to which individuals within a culture accept or challenge decisions by authority figures. Countries with large positive scores on Hofstede’s power distance index (PDI) are more accepting of power distance: they are comfortable with a greater degree of social and class stratification and in accepting the decisions of authority figures; those with large negative PDI scores prefer small power distance, support minimizing social and class inequalities, and have a greater tendency to challenge authority figures. Countries with high PDI scores include Russia (+154), Arab countries, Bangladesh and China (all with +94), India (+90), and Brazil (+43); countries with low PDI scores include South Africa (−48), Hungary (−62), Jamaica (−67), Costa Rica (−113), and Israel (−214) [2].

Power distance may manifest itself in high-PDI cultures in terms of individuals being less likely to ask questions if they are not sure exactly what
information contained in the informed consent form (ICF) actually means in practical terms for their participation (or otherwise) in the trial, and may therefore be more likely to agree to participate for a given level of uncertainty. All of these complexities in study management mean that advanced, detailed planning is critical, along with the preparation of worst case scenario contingency plans.

Throughout this chapter and the following chapter, examples are cited from several geographical regions: Asia Pacific, Africa, Central and Eastern Europe (CEE), Latin America, and the Middle East. Accordingly, before addressing specific project management issues, an overview of each geographical region is provided.

17.1.1. Asia Pacific

The Asia Pacific region has a very large population, containing the world’s two most populous countries, China (about 1.3 billion) and India (about 1.2 million). Many languages are used, including some with strong regional dialects. There are some general similarities, and also some specific differences that require the sponsor’s attention. With regard to similarities, all countries in the Asia Pacific region require an import license, and often an export license to ship samples or tissue. They all have regulatory or health authorities and site ethics committees, which evaluate and approve protocols, and provide ongoing supervision of the ethical conduct of the clinical trial as it is implemented.

Many physicians have gained clinical trials experience in Europe or the USA. In addition, the Internet facilitates access to global organizations, such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice (GCP) (indicated as ICH-GCP from now on) and other appropriate documentation for physicians to stay current with training on therapeutic areas. Therefore, while the practice of medicine in some of the countries has traditionally been paternalistic, this has been changing over the last several years as more physicians participate in clinical research trials. Nonetheless, a significant challenge in many countries within the Asia Pacific region remains access to medical records. Most individuals own their respective records, carrying them back and forth to physicians.

Many countries means many different regulatory agencies. For example, China’s regulatory agency is the State Food and Drug Association (SFDA). An extensive training program is underway for the SFDA inspectors and there will be increases in inspections in the years to come. The ICH-SFDA
only allows sites that have been approved by the SFDA (trained on GCP) to conduct clinical trials, which can be a limiting factor. In addition, China has very long regulatory timelines.

In India, the Drug Controller General of India (DCGI) is responsible for oversight of any drugs in development. The Central Drugs Standard Control Organization (CDSCO) also regulates clinical trials. South Korea’s agency, the Korean Food & Drug Administration (KFDA), provides oversight to clinical trials and also is responsible for qualifying sites to participate in clinical trials. This country is noteworthy for its very robust regulatory environment.

With regard to differences evident in the region’s countries, healthcare infrastructure and resources vary significantly from country to country. Singapore and South Korea, for example, have more advanced hospital networks, including electronic medical records systems. Standards of care also vary. Therefore, in trials where the test drug is compared with an active control that is the standard of care for the disease or condition of clinical concern, potential variation needs to be addressed. Countries can also differ in their views concerning the appropriateness of specific study designs in certain cases. While major health centers, both public and private, are typically in densely populated urban areas and hence provide access to large patient populations, some of them have very limited infrastructures with regard to the implementation of clinical trials. Conducting appropriate feasibility studies, therefore, becomes particularly important in many instances.

From the CRO perspective, the training for CRO employees has been a (if not the) key factor. By providing training that meets international ICH-GCP standards, acquisition of data of consistent quality with those from other countries is achievable.

17.1.2. Africa, sub-Saharan Africa, and South Africa

Following Asia, Africa is the world’s second largest and second most populated continent. The term sub-Saharan Africa describes the area of the African continent that lies south of the Sahara desert. An estimated 760 million people live in sub-Saharan Africa. This represents around 10 percent of the world’s population, but the region has around two-thirds of all human immunodeficiency virus (HIV) infections, with an estimated 22–27 million people living with HIV infections. An estimated 2000 languages are spoken in Africa, but English is recognized as the language of business in many of its countries.
With the exception of the country of South Africa, the majority of the population in sub-Saharan Africa lives in rural areas, making communication and follow-up challenging when conducting clinical trials. While the increased use of cellular communication has made it somewhat easier to maintain contact with subjects, the lack of adequate infrastructure in the outermost areas (e.g. lack of street names and postal addresses) still causes difficulties. This further emphasizes the need for experienced staff to be used in conducting clinical trials in these regions.

The population of South Africa is around 50 million, and it has 11 official languages, listed in Table 17.1.

<table>
<thead>
<tr>
<th>Language</th>
<th>% of population’s home language</th>
</tr>
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<tbody>
<tr>
<td>Zulu</td>
<td>23.8</td>
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<tr>
<td>Xhosa</td>
<td>17.6</td>
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<tr>
<td>Afrikaans</td>
<td>13.3</td>
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<tr>
<td>Northern Sotho</td>
<td>9.4</td>
</tr>
<tr>
<td>Tswana</td>
<td>8.2</td>
</tr>
<tr>
<td>English</td>
<td>8.2</td>
</tr>
<tr>
<td>Sotho</td>
<td>7.9</td>
</tr>
<tr>
<td>Tsonga</td>
<td>4.4</td>
</tr>
<tr>
<td>Swati</td>
<td>2.7</td>
</tr>
<tr>
<td>Venda</td>
<td>2.3</td>
</tr>
<tr>
<td>Ndebele</td>
<td>1.6</td>
</tr>
<tr>
<td>Other</td>
<td>0.5</td>
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</tbody>
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English is the joint fifth most common home language, but is understood in most urban areas and is the official language of business, government, and media. From a clinical trials perspective, informed consents and patient information leaflets are created in English and translated into at least two other languages, depending on regions. Protocols, investigator’s brochures, and case report forms are not translated and are widely accepted in English.

17.1.3. Central and Eastern Europe

The geographical region called Central and Eastern Europe (CEE) has a combined population of more than 300 million people in 17 countries, 11 of which are members of the European Union (EU). Russia (with a population of 142 million), Ukraine (46 million), and Poland (38 million) account for about 70 percent of the regional population [3]. Like other developing regions containing multiple countries, it is difficult to make sweeping generalizations. However, three qualities of countries in this
region are widely acknowledged: ready access to patients, attractive costs, and high quality. These factors have played a considerable role in the region’s clinical trial success: it now delivers around 20 percent of the global participants in trials. This means that CEE now represents the largest number of global clinical trial initiations outside North America and Western Europe. The ready access to patients noted earlier is exemplified by the observation that recruitment rates per site are much higher in CEE than in any other global region, potentially up to 10 times faster than rates in Western countries. Companies usually position their headquarters for the CEE region in Vienna, Austria.

Classified as an emerging market region in the past decade, economists predict that growth across most of the region will slow substantially in the next 10 years and follow the steady market with reasonable growth pattern of Western Europe rather than the dynamic high-growth rate of emerging Asia. However, while countries such as the Czech Republic, Poland, and Hungary now adhere to a slower growth mature development model, other areas within the CEE, such as Russia, still exemplify the dynamic growth of an emerging market [4]. Thus, it is difficult to characterize the states as a homogeneous region. Overall, however, the region is still anticipated to experience significant growth in the future.

17.1.4. Latin America

Latin America comprises 21 countries and has a population of 570 million. The two majority languages are Spanish and Portuguese. As in the Asia Pacific region, the major health centers are located in high-density urban areas. Both public and private institutions have developed expertise to conduct large-scale clinical trials. Physicians have trained at high-level medical schools in Europe, the USA, and Latin America. The Internet provides investigators and other clinical trial professionals the opportunity to keep up to date with the global scientific environment.

Countries such as Argentina, Chile, and Brazil have excellent medical infrastructure and well-trained principal investigators, with standards and procedures in hospitals similar to those in the USA, a tradition of Western medicine, and well-established regulations for clinical trials. Some countries have a particularly large population of previously untreated patients since they have no tradition of clinical trials.

While Latin America has a long history in clinical research, starting in about 1950 in Argentina, Brazil, and Mexico, regulations were not initially in place. This has now changed considerably. For example, Brazil and
Argentina have aligned their regulations with 1996 ICH guidelines, placing these countries in the international clinical research community, and more recent adaptations in Chile, Colombia, Peru, and Venezuela have further homogenized the regulatory landscape across Latin American countries.

Brazil is the region’s largest single component and a major pharmaceutical market. The South American region overall is particularly suitable for studies in oncology, cardiovascular, infectious diseases, metabolic disorders, pediatrics, and vaccines, because the incidence and prevalence of those conditions are similar to or greater than those in the USA or Western Europe. More than 80 percent of Latin Americans live in highly urbanized areas, meaning that patients are easily accessible. Many physicians are aware of clinical trials and are keen to participate. In addition, the region has reputable health science and academic institutions, which serve as tremendous resources for conducting clinical trials [3].

A main challenge in conducting clinical trials in Latin America is that the regulatory timelines tend to be longer than in other regions of the world. However, by using the period of time while waiting for regulatory input to help sites develop recruitment strategies, recruitment itself can be very speedy.

17.1.5. The Middle East

With an estimated population of 280 million, and one of the fastest growing in the world, the Middle East is an attractive place to run clinical trials. Countries in this geographical region include Israel, Qatar, Bahrain, Iran, Jordan, United Arab Emirates, Saudi Arabia, Lebanon, Kuwait, Oman, Turkey, Egypt, Iraq, Syria, and Yemen. A growing percentage of the region’s population lives in cities, and urbanization is having a great impact on society and disease trends, with obesity, diabetes, and cardiovascular disease (CVD) being growing problems [5]. CVD, once thought to be confined primarily to industrialized countries, has emerged as a major health threat in many developing countries. CVD, especially coronary heart disease and stroke, now accounts for nearly 30 percent of deaths in low- and middle-income countries each year [6]. The prevalence of gastrointestinal disorders and cancer is also increasing. Populations in the Middle East are clinically naïve, making individuals with diseases and conditions of clinical concern potentially good candidates for clinical trials.

Within the Middle East, Israel, Turkey, Egypt, Jordan, and Saudi Arabia have the most well-established clinical trial regulatory agencies. Egypt, for example, has a well-established pharmaceutical background, and produces
most of the pharmaceuticals used in the country. Israel is forward thinking and innovative, while new healthcare investment is notable in Saudi Arabia. Some countries, e.g. Jordan and Saudi Arabia, have established an agency similar to the US Food and Drug Administration (FDA), and are therefore at the forefront of regulators in the region by establishing procedures acceptable to Western agencies, and Egypt closely follows. Others countries do not have strong regulatory agencies in place. This heterogeneity must be emphasized if a sponsor has a tendency to think of this region in general terms.

Sponsors’ interest in conducting and/or outsourcing trials in the Middle East is relatively recent but growing rapidly. Considerable expansion in Eastern Europe, Latin America, and South East Asia, along with growth in China, has overshadowed growth in this region, which currently accounts for less than 1 percent of global participants in trials. However, accelerated growth is forecast by many observers: in the next 10 years the Middle East may account for up to 5 percent of global participants in trials. This growth, if achieved, would result in a research and development (R&D) flow to the region from the biopharmaceutical industry in excess of US $1 billion [7].

17.2. PLANNING AND PROJECT MANAGEMENT

Once selected to conduct a specific clinical trial, a CRO has to create its own study team for that trial. This team will include the following individuals (the precise names used for these positions may differ somewhat from CRO to CRO, but the functions they perform will essentially be the same):

- investigational site selection specialists
- subject recruitment specialists
- physicians from the therapeutic area in which the drug falls: provide therapeutic expertise whenever necessary
- clinical trial monitors: visit the sites and check that the study protocol is being executed correctly
- medical monitors: physicians (often but not necessarily therapeutic area specialists) who are available to consult on any subject health (safety) concerns
- data managers: responsible for receiving, managing, and storing the data that will eventually be analyzed and interpreted
- project team leaders or managers: coordinate the efforts of all other individuals and specialty areas represented on the team.

In the present context, the term project is used for a new drug that is being developed.
As Turner observed, project management is a critical aspect of the clinical trial process whose importance in successful trial execution cannot be overstated [8]. Just a few components of project management include study budgets, timelines, marshaling and distributing resources, appraising metrics on a continual basis, and facilitating communication to all stakeholders. In addition, project managers must conduct their work against a backdrop of tremendous scientific, technical, and financial risks. Project managers need not be scientists or clinicians by profession, since their specialty is managing a small number of projects, but they often have scientific or medical backgrounds. As Spilker commented, managers are chosen for their administrative ability to move projects ahead rapidly, efficiently, and in the desired direction. Independence and interpersonal skills are key qualities for this specialty [9].

17.3. SELECTION, QUALIFICATION, AND MANAGEMENT OF CONTRACT RESEARCH ORGANIZATIONS

Selection, qualification, and management of CROs are discussed in turn.

17.3.1. Criteria for CRO Selection

Many components and characteristics of a clinical trial affect the choice of the most suitable CRO to conduct the trial. These include: the nature of the trial (design, sample size, etc.); the disease and population for which the investigational drug is intended, and the CRO’s experience with that particular indication and therapeutic area; the resources of the CRO in the countries that are proposed to be included in the study; and competitive advantages that the CRO may be able to offer in complementary ways. The budgets proposed by the CROs bidding for the business of executing the study will certainly be a factor in the sponsor’s choice of CRO, but it is unlikely to be the sole determinant. The sponsor may feel that the services offered by one CRO provide a better chance of successfully completing a study that has particular challenges, and this CRO may be selected even though other companies provided a lower budget in their proposal.

Key knowledge, understanding, and services that the CRO must be able to provide include:

- A feasibility study of the Sponsor’s proposed Study Protocol. This will assess whether the trial as proposed has a high probability of being successfully completed.
Knowledge of the regulatory landscape in each of the countries used, and an awareness of likely challenges and appropriate risk mitigation strategies and solutions. This enables such challenges to be proactively addressed and managed.

The capability to provide appropriate training to principal investigators, coinvestigators, clinical research associates (CRAs), clinical study coordinators, etc. This training will need to focus on ICH-GCP and will need to be undertaken in multiple cultures and languages.

Extending the previous point, the CRO needs to understand how best to implement international ICH-GCP requirements to acquire data that are acceptable to international regulatory agencies, how to fulfill local regulatory requirements and considerations, and how to do this in a culturally sensitive manner.

Ideally, their ability to be a true partner or ally. This can be demonstrated, for example, by making suggestions concerning modifications to the proposed study protocol that increase the probabilities of the trial’s successful execution at scientific, medical, timeline, and cost levels.

The logistics of operationally executing a clinical trial are enormous. Consider a therapeutic confirmatory trial involving 5000 subjects participating at a total of 100 investigational sites spread across several continents. Identifying potential subjects and then recruiting and retaining the required number is one challenge. Shipping the drug products for the clinical trial (the investigational and control drugs) to investigational sites located in various countries spread around the globe is another. Making sure that all necessary data are measured and recorded is a major task, as is managing and storing the data. And the list goes on. Of necessity, this chapter is far from exhaustive in its descriptions of operational aspects of running a clinical trial. Rather, its aim is to give you a feel for some of the challenges encountered, and the ways that organizations that conduct trials function at an operational level.

Many sponsors developing drug and biologicals outsource work to CROs. This means that they do not need as many permanent employees, and can hire specialized personnel to conduct their studies on a trial-by-trial basis. Relationships between sponsors and CROs can take many forms, and the nomenclature used by individual sponsors and CROs can vary. Therefore, you may hear different terms in your own work. However, the general picture painted in this chapter should provide a useful roadmap.
Historically, sponsors often hired CROs to carry out a trial exactly as specified in the study protocol that the sponsors had developed. They may also have hired several CROs, each fulfilling some of the overall responsibilities of running the trial. In such contexts, the term service provider was appropriate for the CRO. This trend is changing, and some sponsors and CROs are establishing relationships that are better described as partnerships or alliances, in which sponsors involve CROs early in their clinical development programs and welcome their medical and scientific expertise in the planning and protocol development stages. A single CRO who has provided good consulting at these stages may be given a large role in conducting the trial, or possibly become solely responsible for executing all aspects of the trial. There are mutual benefits. The sponsor gains additional expertise and economy of services, and the CROs obtain more business from a long-term relationship.

### 17.3.2. CRO Qualification

A CRO must meet a very large number of requirements in order to be eligible to fulfill the sponsor’s requirements for some studies, such as large multisite trials being conducted in various developing regions of the world. Some of the most salient requirements are:

- It must have global standard operating procedures (SOPs). There must be documented training set up for these SOPs, and systems audits to make sure all the employees follow them.
- There must be an independent quality assurance (QA) department able to audit the systems and also the sites.
- The staff involved in the trials must have, or receive, training and experience in conducting and monitoring of the trials. This includes training in ICH-GCP, as discussed in the previous section.
- The CRO must have, or have access to, medical personnel who are able to follow medical concerns and issues that may arise before, during, and in follow-up periods after the conduct of a trial.
- The specific know-how of the countries to develop the trial, the therapeutic area, and the indication are essential.
- The CRO must be able to foresee potential issues in the regulatory submission, the recruitment of the patients, and the appropriate conduct of the trial, and have contingency plans.
- It must have a legal structure that takes care of all the legal aspects of the conduct of a trial.
- Most importantly, it must place patient safety as its top priority.
17.3.3. Outsourcing Strategy

A sponsor’s outsourcing strategy (certainly for larger sponsors) typically consists of two phases. In the first step, sponsors will engage in extensive research of many CROs, and then qualification of a small group of CROs that have been carefully chosen according to certain performance criteria of particular importance to the sponsor. These CROs are called preferred providers. Once selected, these preferred providers sign confidentiality agreements with the sponsor. These agreements include a non-disclosure agreement (NDA, not to be confused with the abbreviation for a new drug application) and, thereafter, a master services agreement (MSA), which includes confidentiality provisions. The execution of these high-level confidentiality agreements means that, from that point forward, the sponsor can send any study-specific information in the knowledge that a new individual NDA need not be prepared and executed.

The second step is outsourcing a particular clinical trial. When preferred providers have been selected, the sponsor will look to them first for each individual piece of work. These providers have probably been selected since they are able to do the vast majority of the work the sponsor anticipates needing. However, if they are not able to perform a specific service or fulfill a special need, the sponsor will look to other CROs, or sometimes academic medical centers; for example, when a particular assay is needed and is not provided by the central laboratory services at any of the CRO preferred providers.

For each trial (or, on occasion, each subcomponent service), outsourcing specialists at the sponsor will prepare a request for proposal (RFP). This is discussed in the following section.

17.3.4. Writing Requests for Proposals

RFPs are usually sent to several CROs to enable the outsourcing specialists, and eventually the decision-making study team, to obtain a range of proposals that may differ to some extent in precise operational detail, and are likely to differ in cost. These CROs reply to the RFP by providing (proposing) a detailed plan describing how they would conduct the study, along with a line-by-line list of individual costs, leading to a grand total cost. Preferred providers will already have an MSA in place with the sponsor, and hence issues of confidentiality are already addressed in those cases. However, if the sponsor would like another CRO to provide a proposal (bid) to conduct the trial, a new NDA would need to be executed before the CRO could be sent the RFP and study protocol.
Outsourcing specialists may perform an initial inspection of the proposals submitted by various preferred providers, and then the proposals are forwarded to the study team that has been formed to be in charge of the trial. This team then selects perhaps two or three proposals that look promising, and invites representatives from these CROs to visit their premises for a Bid Defense. In this meeting, the study team asks the CRO representatives many questions, essentially interviewing them in regard to their ability to conduct the trial successfully, and at a price that is acceptable to the sponsor [8].

17.3.5. Managing the CRO/Allying with a CRO

The first part of the title of this section is interesting in the sense that it is perhaps more applicable to the “traditional model” that represented the interaction between a sponsor and a CRO, one in which CROs were hired by sponsors as service providers to provide a specific set of predetermined services. The CRO was not asked to provide medical, scientific, or operational input, but rather was asked to provide the price they would charge the sponsor for completing the requested tasks.

A new model is one in which the CRO functions as a full drug development partner, or ally [8]. In this model a sponsor and its CRO start working together much earlier in the drug development process, ideally as soon as the sponsor conceptualizes a clinical trial. While the sponsor will have expertise in many aspects of study design and operational execution “in house”, a good CRO will also have expertise in all of these aspects and can therefore provide additional (and sometimes unique) beneficial input into the development of a study protocol. Optimizing the protocol before the trial commences can minimize the numbers of protocol amendments and protocol violations (on the part of both subjects and investigators).

In the allying with a CRO model, actual management of the CRO, in the traditional sense of the word management, becomes less onerous for the sponsor: the CRO is seen as a trusted partner that can execute the trial with minimum oversight. The benefits of this model, which has considerable advantages in all clinical trial settings, are perhaps even more powerful when conducting multisite trials in developing countries. Large CROs may have much more extensive footprints in such countries than a sponsor whose R&D and manufacturing facilities may be located in one or two (probably developed) countries. This allows the CRO to provide
detailed advice to the sponsor on many operational aspects of conducting the trial, such as:

- site selection
- selection of the investigator(s) at each site
- subject recruitment and retention strategies
- facilitating transport of subjects to and from the site for each visit required by the trial protocol
- helping couriers to transport biological samples to central laboratories as needed
- facilitating electronic communication channels wherever possible
- facilitating medical (safety) oversight of all subjects participating in the study.

17.3.6. CRO Oversight in the Developing World

Although many companies use regional trials in developing regions to support products on a local basis, it is the ability to use locally generated data to support international regulatory submissions that is of greatest interest. Since ICH-GCP is currently less well known in many developing countries, running trials to the satisfaction of international authorities such as the FDA and the European Medicines Agency (EMA) requires huge training efforts for the local CRAs and principal investigators. CROs with global footprints can be very helpful in this regard, since they are knowledgeable about international standards and have been on the ground in developing regions for a number of years.

Via their chosen CROs, sponsors must also be prepared to make an investment in help call centers, and to ensure that bodies such as institutional review boards are appropriately operating. However, once training programs have been implemented and completed by all necessary parties, investigational sites in many developing regions have access to very large numbers of eligible patients, and can therefore quickly recruit subjects.

17.4. CENTRAL LABORATORY CONSIDERATIONS

The importance of laboratory data becomes extremely clear when one considers the fact that these data account for 70–90 percent of all data contained in marketing approval submissions to regulatory agencies, depending on the therapeutic area. They typically provide the primary scientific data for showing drug safety and efficacy. Appropriate selection of the laboratory or laboratories that will analyze these data is therefore
a critical decision. In single-site studies, the degree of complexity is considerably less than in multinational, multisite studies, and the use of a central laboratory can be a very useful strategy. If a sponsor has selected CRO-preferred providers, it is likely that one or more of these providers will offer central laboratory services. Thus, selection of the central laboratory may well be tied to selection of the provider that will perform the other services (monitoring, project management, data management and analysis, etc.) discussed in Section 17.1.

Most therapeutic confirmatory trials are run at multiple investigative sites, since any one site would not be able to enroll the number of subjects required by the study’s protocol. Central laboratories are analytical laboratories at which biological samples (blood, urine, and many others) collected at all of the investigative sites in a clinical trial are analyzed. This strategy has two important advantages compared with the alternative strategy of using local laboratories located in close proximity to each site:

- Assurance that the laboratory conducting the analyses of the samples is compliant with cGCP is much easier: only one laboratory has to be visited and audited.
- Statistical difficulties associated with analyzing data sets that have been pooled across laboratories are circumvented.

The ability to demonstrate data comparability for laboratory testing results from different centers is a crucial aspect with regard to efficacy, and a key reason for choosing a central laboratory over a local or diagnostic laboratory.

Laboratory selection factors therefore include turn-around time for laboratory results, importance of laboratory data comparability, laboratory quality, performance, and especially in developing countries, cost (including transportation, which is a big component in Asia), and constraining factors (such as inability to export samples easily out of China). Esoteric tests are increasingly being performed in Asia and these may require expertise in setting up and validating new biomarkers for the laboratory, which may limit selection to a few global central laboratories with such capability in Asia. Even when the esoteric tests are not novel, not all laboratories are equipped to support them for varied reasons such as lack of scientific and technical expertise, uneconomic volumes, or simply size and capacity of the laboratory. Central laboratories, especially the large global laboratories, will provide a standardized process for the set-up of the protocol in a laboratory information management system (LIMS) as well as provide a variety of support services including project management, call center support, and logistics.
From an operational execution perspective, the central laboratory chosen for a particular trial can be located many hundreds (or even thousands) of miles from some of the investigational sites, and even in another country or continent. Expedited shipping under very carefully controlled conditions is necessary to ensure that the samples arrive at the central laboratory quickly and safely. Many courier companies specialize in this transportation process.

Using central laboratories can also be considerably more expensive than would be the case if samples were sent to local laboratories close to each investigational site. Indeed, the transportation costs can outweigh the costs of the assays performed by considerable margins. However, obtaining optimum quality laboratory data is critical (as it is for all other data), and the necessary expenditure involved here is well worthwhile.

It is appropriate to acknowledge here that, while there are many advantages to using central laboratories, it is not uncommon to use local laboratories as well as a central laboratory for some studies. For example, when turn-around time is especially crucial (less than 24 hours) or where the requirements are primarily for safety purposes, local laboratories are more often used because of convenience, cost, and practicality.

17.4.1. Sample Shipment and Handling

For central laboratories, product types to be shipped include laboratory samples and laboratory-specific kits. Laboratory samples generally consist of body fluids and extracts (e.g. blood, urine, stools, swabs, DNA, RNA) as well as tissues (raw tissue, tissue blocks, tissue slides). Blood samples remain the most common samples shipped during clinical trials.

Consider shipping and handling requirements in Singapore. While movement of samples within the country is generally straightforward, shipments to other countries for clinical trials are shipped as UN 3373 (biological substance, category B).

While such shipments do not require specific training on the part of the shipper, frozen shipments where dry ice or liquid nitrogen is used do require special handling as these are classified as dangerous goods. Training for handlers includes International Air Transport Association (IATA) Dangerous Goods Regulations, and is carried out by a variety of training centers, logistics/courier companies, and central laboratories.

Shippers must ensure that shipments are prepared in such a manner that they present no hazard to persons or animals. Packaging for UN 3373
shipments generally conforms to Packaging Instruction (PI) 650 of the regulations. Examples include the following:

- **Inner packaging**: This consists of a watertight primary receptacle(s) and watertight secondary packaging. An absorbent material must be placed between these receptacles, and must be able to absorb the entire content of the primary receptacle(s).

- **Outer packaging**: This must be of adequate strength for its capacity, weight, and intended use. It must also be able to pass a “drop test”, i.e. being dropped from a specified height and not sustaining damage to the inner contents.

While exceptional cases (e.g. shipment of whole organs) may require special packaging, the vast majority of diagnostic specimens must be packaged according to the following guidelines:

- **Substances shipped at ambient temperatures or higher**: Primary receptacle materials include glass, metal, and plastic. A positive means of ensuring a leakproof seal, such as heat seal, skirted stopper, or metal crimp seal, must be provided. If screw caps are used they must be reinforced with adhesive tape.

- **Substances shipped refrigerated or frozen** [wet ice, prefrozen packs, carbon dioxide (CO$_2$), solid (dry) ice, or other refrigerants] must be placed outside the secondary packaging(s) or alternatively in an overpack with one or more completed packagings. Interior support must be provided to secure the secondary packaging in the original position after the refrigerant has been dissipated. If ice is used the packing must be leakproof. If CO$_2$ is used as solid dry ice, the outer packaging must permit the release of CO$_2$ gas. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant as well as the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost.

- **Substances shipped in liquid nitrogen**: Plastic that is capable of withstanding very low temperatures must be used instead of glass for the primary packaging. Secondary packaging must also withstand very low temperatures and in most cases will need to be fitted over individual primary receptacles. Requirements for shipment of liquid nitrogen must also be observed. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant as well as the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost.
Lyophilized substances: Primary receptacles must be either flame-sealed glass ampoules or rubber-stoppered glass vials with metal seals. As additional examples of the attention to detail required by the sponsor and the central laboratory, some countries (e.g. Thailand) require material transfer agreements between the institution where samples are being sent and the laboratory where testing is done to be signed. China requires informed consent by patients for whole blood/tissue samples to be sent out of the country before shipping can occur.

17.4.2. Clearing Samples Through Customs

Table 17.2 provides information for South America concerning import, export, and transportation considerations.

For central laboratories, product types to be shipped include laboratory samples and laboratory-specific kits. Laboratory-specific kits refer to

<table>
<thead>
<tr>
<th>Item</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value and weight limitations</td>
<td>While there is no limitation, imported items must have a realistic declared value. If the value is below ZAR500, quick clearance can be arranged and no customs duty or value-added tax (VAT) will apply. Isolates/cultures are considered to be dangerous goods, as is anything shipped on dry ice. Infection shipments require an accompanying Dangerous Goods Declaration Form.</td>
</tr>
<tr>
<td>Documents required</td>
<td>Imported drugs require an approval letter from the Medical Control Council, which serves as an import license. An AWB and Commercial Invoice are required for import and export. All biologicals require an Import/Export permit from the Health Department.</td>
</tr>
<tr>
<td>Services</td>
<td>Premium couriers will export all kits and specimens, including infectious samples and specimens on dry ice. They will re-ice packages as necessary.</td>
</tr>
<tr>
<td>Transit time</td>
<td>24–48 hours (import and export)</td>
</tr>
<tr>
<td>Couriers</td>
<td>Export: World Courier, Marken; Import: World Courier, UPS, DHL, FedEx; Local: TNT</td>
</tr>
<tr>
<td>Dried ice capabilities</td>
<td>Central service: Marken is the preferred service provider, and will supply dry ice upon request (with 24 hours’ notice). Local service: site phones the local TNT depot to order dry ice. A TNT driver will then deliver the dry ice, and wait while the specimens are packed. TNT provides the contact telephone numbers for each country or a dry-ice instruction with the call-by cut-off information.</td>
</tr>
</tbody>
</table>
clinical trial materials (CTMs) used for sample drawing and collection. Other more complex shipment types include medical devices, refrigerated consumables, and investigational drugs, which attract more stringent customs clearance.

As an example, Table 17.3 summarizes the permits required when shipping CTMs out of Singapore, and biological samples from various countries into Singapore.

For kit shipments, integrators such as FedEx and UPS, or express couriers such as Marken, DHL, and TNT, have the ability to do preclearance with a high percentage of shipments without formal inspection, including those countries that require import permits. Customs has the authority to pick randomly any shipment for inspection with no prior notice. When this happens, they have the authority to ask for any supporting documents to satisfy any concerns.

Table 17.3 Permits required to ship clinical trials material (CTM) out of Singapore, and biological samples into Singapore

<table>
<thead>
<tr>
<th>Country</th>
<th>Import of CTM</th>
<th>Ambient (UN 3373 biological substance, category B)</th>
<th>Frozen (UN 3373 biological substance, category B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>×  *</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>China</td>
<td>×</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>India</td>
<td>×</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Indonesia</td>
<td>√</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Japan</td>
<td>√</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Korea</td>
<td>√</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Malaysia</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>New Zealand</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Pakistan</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Philippines</td>
<td>×</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Singapore</td>
<td>N/A</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>√</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Taiwan</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Thailand</td>
<td>√</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Vietnam</td>
<td>√</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

An import permit for medical devices is required. Diagnostic kits with needles could be potentially classified under Medical Device.

N/A: not applicable.

* An Australian Quarantine and Inspection Service (AQIS) permit is required for the import of heparin tubes.
It should be noted that regulatory changes occur for countries over time. Therefore, sponsors are encouraged to reconfirm with central laboratories and courier companies before commencing a study involving sites in any of the countries listed in Table 17.3.

ACKNOWLEDGMENT

The authors gratefully thank Carolyn Moore for her administrative support.

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CHAPTER 18

Study Documents and Logistics


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¶International Corporate Events Network, Johannesburg, South Africa
†Quintiles Latin America, San José, Costa Rica
*Quintiles Africa, Pretoria, South Africa

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18.1. INTRODUCTION

Following on from discussions in the previous chapter, this chapter focuses on key documents that are needed for the clinical trial to be conducted, and then on logistical considerations that need to be addressed to execute all aspects of the study in an optimum manner.

While clinical trials are designed to meet global International Conference on Harmonisation good clinical practice (ICH-GCP) standards in almost all countries around the world, local interpretations can vary and each country has its own procedures that need to be followed. The logistical challenges of running multinational trials are therefore considerable, and are likely to be more so in developing regions. It is therefore important to know the country-specific pathways that need to be followed during the start-up and maintenance phases, and the close-out of the study. It is important to have a balance of coordination and the right mixture of local/regional knowledge and global knowledge, and the establishment of good working relationships with local regulatory authorities is very important.

18.2. WRITING THE STUDY PROTOCOL

A study protocol includes precise accounts of the design, methodology, and statistical analysis considerations necessary to conduct the trial and analyze data collected. Frequently, most of the discussions concerning the statistical analyses to be performed are presented in an associated statistical analysis plan (SAP). If this approach is taken the study’s SAP should be prepared at the same time as the protocol. Study design and statistical analysis are inextricably linked, and the design of the trial determines the appropriate mode of analysis. Therefore, writing the protocol and the SAP together is both feasible and good practice (although it must be acknowledged that, in reality, the SAP is often written at a later date).

The study protocol is “the most important document in clinical trials, since it ensures the quality and integrity of the clinical investigation in terms of its planning, execution, conduct, and the analysis of the data” [1]. The study protocol is a comprehensive plan of action that contains, for example, information concerning the goals of the study, details of subject recruitment, details of safety monitoring, and all aspects of design, methodology, and analysis. Input is therefore required, for example, from clinical scientists, medical safety officers, study managers, data managers, and statisticians. Consequently, while one clinical scientist or medical writer may take
primary responsibility for its preparation, many members of the study team make important contributions.

Buncher and Tsay listed just some of the detailed requirements of a study protocol [2]:

- **Primary and secondary objectives**: These are stated as precisely as possible.
- **Measures of efficacy**: The criteria to be used to determine efficacy are provided.
- **Statistical analysis**: The precise analytical strategy needs to be detailed, here and/or in an associated SAP.
- **Diagnosis of the disease or condition**: When subjects are required to have the disease or condition for which the drug is intended, precise diagnostic criteria are provided.
- **Inclusion and exclusion criteria**: These provide detailed criteria for subject eligibility for participation in the trial.
- **Clinical and laboratory procedures**: Full details of the nature and timing of all procedures and tests are provided.
- **Drug treatment schedule**: Route of administration, dosage, and dosing regimen are detailed. This information is also provided for the control treatments.

### 18.2.1. Inclusion and Exclusion Criteria

A study’s inclusion and exclusion criteria govern the subjects who may be admitted to the study, and they are listed in detail in the protocol. Criteria for inclusion in the study include items such as the following:

- reliable evidence of a diagnosis of the disease or condition of clinical concern
- being within a specified age range
- willingness to take measures to prevent pregnancies during the course of treatment (this can apply to male and female subjects).

Criteria for exclusion from the study include:

- taking certain medications for other reasons and which therefore cannot safely be stopped during the trial
- participation in another clinical trial within so many months prior to the commencement of this study
- liver or kidney disease.

Meeting all the inclusion criteria allows a subject to be considered as a study participant, but it is not sufficient. In addition, an individual must not meet any of the exclusion criteria. Inclusion and exclusion criteria precisely
define the nature of the subject sample that participates in a clinical trial. Accordingly, they also define the study population to which statistical inferences may be made. That is, the inclusion and exclusion criteria define the study population to which the results of the trial can reasonably be generalized.

18.2.2. The Trial’s Primary Objective

Clinical protocols should be clear, concise, unambiguous, and as short as possible while maintaining scientific integrity. However, this ideal is all too often not achieved [3]. One challenge is to “maintain a balance between brevity and completeness” [2]. All necessary procedural information must be included to allow the investigators to implement the protocol exactly as intended. However, as the length of the protocol increases, the chances of its being read throughout decreases. Clarity and conciseness are therefore beneficial characteristics of the protocol.

One aspect of conciseness is actually a study design feature. For many reasons, it is a very good idea to limit the number of primary objectives in a study, ideally to one but perhaps to two (many protocols contain far more objectives than are actually necessary to address the goals of the particular study). The designs used in most clinical trials are relatively simple. Clinical trials are certainly complex, but this complexity is not a direct function of the nature of the designs employed. Rather, it originates from other factors such as “ethics, biology, logistics, and execution” [4]. The logistics and execution can be particularly complex for trials where some or all of the investigational sites are located in developing countries.

18.3. WRITING THE INVESTIGATOR’S BROCHURE

Each drug has an investigator’s brochure (IB) that is created for the use of investigators running clinical trials, and which is reviewed by institutional review boards (IRBs) and regulatory agencies [5]. The IB can be regarded as the repository of everything that is known about the drug, including non-clinical and clinical information, manufacturing details, and any adverse events that investigators should be particularly watchful for during clinical trials (i.e. adverse events of special interest). These brochures are often collated and then smoothed together by a medical writer using sections prepared by various experts within a biopharmaceutical company. Early information will focus on non-clinical investigations and the preparation of the drug compound used in that research. As the drug’s clinical
development program commences, information will be added on clinical pharmacology, including pharmacokinetics, pharmacodynamics, adverse events, and human responses to the drug. For this document, constant updating and revision is to be expected. Each sponsor will have a policy governing how often these updates should occur. Typically, this would be once a year as a basic rule, with the proviso that more immediate updates should occur if new information that needs to be communicated to investigators, IRBs, and regulatory agencies arises.

As a drug progresses through many preapproval clinical trials, more and more information becomes available. Once marketed, postmarketing trials may be conducted to gain additional information about the drug’s safety and effectiveness. For example, relatively small studies may be conducted in certain populations that were not heavily represented in preapproval trials and, at the other end of the scale, very large therapeutic use trials may be conducted to study the drug’s safety and effectiveness under “real-world” conditions. Large-scale comparative effectiveness trials may also be conducted, something that is likely to increase as comparative effective research becomes more routinely performed to provide third party payers with information on how best (often defined in terms of how cost-effectively) safe and effective pharmacotherapy can be implemented.

Whatever the research question being asked and answered by a trial, additional safety data continue to accrue. This is an extremely important facet of postmarketing studies since, even though great care has been paid to documenting a drug’s safety in preapproval trials, those safety data are limited by the fact that, in a typical clinical development program, only some 5000–10,000 subjects will participate. While this provides a large enough database to identify adverse events that are relatively common, it is probabilistically very unlikely that rare adverse advents will be seen. As the Institute of Medicine has noted, “The [marketing] approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do not obviate continuing formal evaluations after approval” [6]. Typically, a sponsor will declare a cut-off date for the collection of safety data to be reported in an annual update. This may be, perhaps, two to three months before the completed update is due. This allows time for these data to be analyzed and described in the updated IB (data collected in that two- to three-month period will be included in the following year’s update).

Non-clinical data are very important, and can be very informative in clinical situations. For example, the best (and sometimes only) data available
to investigators for certain potential occurrences come from animals: these include data on reproductive toxicology and genotoxicity. However, as more and more clinical data become available, the relative importance of non-clinical data is likely to decline in the eyes of investigators conducting clinical trials: they are most interested in all available clinical data, and particularly safety data collected to that point. To prevent the size of the IB continually increasing, some sponsors ask the IB writers commensurately to decrease the space allotted to non-clinical data. However, this is not always done, which means that investigators are sent larger and larger documents. While this may initially seem a good thing, since more information is available to the investigator, investigators should read the entire document before commencing the trial at their particular investigative site and, arguably, the larger the IB the less the chance that this will occur.

18.3.1. ICH Position on the Nature and Content of an Investigator’s Brochure

ICH considers that the information presented in an IB should be concise, simple, objective, balanced, and non-promotional. It should enable a physician who may wish to participate in a specific clinical trial to understand all content, and to make an informed decision, in an unbiased manner, concerning the benefit–risk and the appropriateness of the proposed trial.

18.3.2. Typical Content of an Investigator’s Brochure

While each sponsor can effectively structure an IB according to its own document standards and guidelines, the need to include certain key information tends to make them relatively similar. A hypothetical table of contents might be:

- Executive Summary
- Table of Contents
- Abbreviations and Descriptions Table
- Pharmacokinetic and Pharmacodynamic Information on Drug ABC123
- Rationale for Use of ABC123 for XYZ Indication
- Physicochemical Properties of ABC123 and Formulation Information
- Pharmaceutics
- List of Excipients Used in Addition to Active Pharmaceutical Product
- Manufacturing, Storage, and Handling
- Non-Clinical Studies Conducted to Date
- Clinical Studies Conducted to Date
18.3.3. One Comprehensive Brochure or Several Separate Ones?

If a drug is being considered for more than one indication, or prepared in various formulations, it is possible to create a set of individualized IBs, each one being tailored to a specific indication and/or formulation. If this strategy is followed, there would certainly become repetition in each version, but each version would also contain information uniquely informative to investigators conducting relevant trials. The investigators’ “IB reading burden” would therefore be lessened.

While this is arguably a very good approach, the logistics are considerably more complex for the sponsor. Any new information that is relevant in every case (fundamental safety information, for example) needs to be inserted into every individualized IB. In addition, since various IBs could be updated at different times, version control becomes more important than ever. Accordingly, many sponsors maintain just one IB per drug.

18.4. INFORMED CONSENT AND THE INFORMED CONSENT FORM

The purpose of the clinical development program is to establish whether or not the drug is effective, and best way to do so is to conduct a randomized controlled trial using the drug and a comparator treatment. Often, the comparator is a placebo. One potential ethical concern with giving some subjects a placebo while others receive the active treatment is that those receiving the placebo are being done a “disservice” since they do not stand to gain any benefit from the test drug. However, there are well-established guidelines and procedures that enable investigators largely to overcome any ethical objections to the conduct of randomized trials. At the
time of a trial’s conduct, it is not known for certain whether the investiga-
tional drug is actually more effective than the placebo; that is, a state of
equipoise exists. If it were known for sure that the test drug is more effi-
cacious (and safe), it would indeed be unethical to deprive the subjects
receiving placebo of therapeutic benefit since the trial would not provide
any new information.

A cornerstone of conducting ethical trials is the process of informed
consent. It is incumbent on sponsors and investigators to provide all
potential subjects with an informed consent form (ICF) that explains the
risks to the individual, the potential benefits at the public health level should
the drug be found to be efficacious and safe, and full details of all procedures
involved in the trial. Investigators should not simply be satisfied with the
required signature from individuals consenting to participate in the trial:
they should answer any and all questions each person has. Going one step
further, some clinical trialists advocate that a “comprehension test” should
be administered to individuals prior to their signing the form to ensure (to
the greatest degree possible) that they truly understand the benefits and risks
of their participation in the study. The informed consent process is
undertaken to ensure that subject participation is undertaken in an informed
and voluntary manner.

The US Food and Drug Administration (FDA) and other regulatory
bodies elsewhere in the developed world have been encouraging more trials
in developing regions (for diseases that are not of neglect). Such studies
present challenges, opportunities, and barriers that are different from those
in developed countries and regions. Consider the case of South Africa, and
the example of recruiting pediatric subjects. There is a need to conduct
studies in geographical regions in which the disease or condition of clinical
interest is prevalent. The continent of Africa offers opportunities in
vaccines, used either as preventive or curative measures. To satisfy regulators
in the USA, there is an increased need for studies in black children. To meet
these FDA requirements, sponsors must look outside the USA to recruit
enough subjects. Historically, there have been few data on pediatric clinical
pharmacology, hence the need to study drugs in a pediatric population to
determine the most appropriate dosing levels from both safety and efficacy
perspectives.

18.4.1. Recruitment of Pediatric Subjects

Recruitment is done primarily through doctors who work in clinics.
Recruitment through word of mouth is also strong, for example with
vaccines, because parents and community elders are keen to have all the children in their community group vaccinated.

18.4.2. Informed Consent

Adherence to the most stringent requirements is essential for ensuring that the informed consent process complies with the essential criteria for obtaining true informed consent. These include voluntary participation, the provision of complete and accurate information to the subject, and evidence of comprehension of this information by the subject.

Considerations to be taken into account when obtaining informed consent in African study populations include the language of consent, cultural sensitivity, sensitivity to potential illiteracy, and any specific considerations for pediatric subjects. These include the concept of community-based informed consent, which must be given by the local tribal elders as well as the child’s parent(s).

When obtaining informed consent from African clinical trial subjects who speak an indigenous language, the following considerations are essential:

- ICFs are translated by certified/accredited translation agencies.
- When no translation agency is available for a specific language, a quality control procedure must be put in place to ensure the quality, completeness, and accuracy of the translation.
- If utilized, interpreters must be trained in the relevant medical terminology and be conversant with subtle aspects of the local language(s) usage by subjects (e.g. idioms, symbols, and metaphors).
- Comprehension of the information by potential subjects must be appropriately assessed, and individuals must not be enrolled in the study unless a predetermined level of comprehension is demonstrated.

The informed consent process needs to be sensitive to country- and/or tribal-specific beliefs and practices, examples of which include:

- respect for the elderly
- gender-related practices/beliefs
- disease-associated stigmatization
- autonomy of married female subjects
- role of tribal chiefs in the community
- awareness of superstitions possibly associated with the disease/therapeutic area under investigation and certain medical procedures (e.g. blood draws).
To address the issue of potential illiteracy, the following procedures can be helpful:

- If the illiterate person is competent to provide informed consent, it has to be orally obtained in his or her own language, the trial subject should make their mark on the ICF, and the person obtaining informed consent from them should sign the ICF.

- This process must be witnessed by a literate person who should also sign the ICF to attest to the fact that this process was followed.

- The witness should be independent of the study itself but may be from the site (such as another doctor or nurse) if a large medical center, and can also be someone who would otherwise qualify as a legally acceptable representative (LAR).

- Before obtaining informed consent from parents or legal guardians of pediatric subjects, regulatory requirements pertaining to legal guardianship, unmarried parents, cases where one parent is deceased, parents who are minors, parents who are illiterate, and the need for one or both parents to provide consent need to be ascertained and adhered to. In addition, a means to confirm the identity of legal guardians needs to be determined in advance.

18.5. CHEMISTRY, MANUFACTURING, AND CONTROLS

Chemistry, manufacturing, and controls (CMC) address issues related to drug identity, manufacturing control, and analysis. Drug manufacturing and processing procedures need to ensure that the compound is stable and can be consistently made to high standards.

The drug manufacturing process is much more complex than typically realized. As Monkhouse observed, “The difficulty of converting a laboratory concept into a consistent and well-characterized medical product that can be mass produced has been highly under-rated” [7]. In addition, while the approved drug must be manufactured on a commercial scale, smaller amounts are required throughout non-clinical and clinical development programs. Moreover, if there are any chemistry and manufacturing differences between the nature of the investigational drug proposed for clinical use and the drug product that was used in the animal toxicology trials that formed the basis for the sponsor’s conclusion that it was safe to proceed to clinical studies, these need to be described in the investigational new drug (IND) application. If there are any such differences, the sponsor should discuss if and how these differences might affect the safety profile of the clinical drug product.
18.5.1. Manufacturing Drug Products for Non-Clinical Development

In early phases of non-clinical development, relatively small amounts of the drug product (test material) are needed, and manufacturing focuses on laboratory, small-scale synthesis of the drug substance. At this stage, the quantities needed are in the gram range. Studies do not need to be conducted to current good laboratory practice (cGLP) standards, and the drug compound does not need to be manufactured to current good manufacturing practice (cGMP) standards. However, both cGLP and cGMP standards must be met by later non-clinical studies.

18.5.2. Manufacturing Drug Products for Clinical Trials

Drug products include both the new investigative drug and the control materials, i.e. a placebo or an active comparator drug that will be administered to the control group. These materials need to be manufactured in a way that allows their double-blinded use in randomized, concurrently controlled, double-blinded clinical trials.

When an active drug is used as the comparator, an interesting challenge arises. It is conventional that the active comparator chosen is the gold standard of care at that time, and that, in the test treatment arm, the investigational drug is given as an “add-on” to the standard of care. However, this simple statement belies the complexity of defining the gold standard in each case [8]. Of many relevant issues, the pertinent question here is: Are there different gold standards in different countries? If so, which one should be chosen in multicenter trials being conducted in countries with differing views?

The manufacturing process of blinding makes the drug product and the comparator product appear the same. This involves two steps:

- making the test drug and the comparator drug as similar as possible in appearance (e.g. color and shape, if they are tablets) and other pertinent characteristics (e.g. taste and smell)
- packaging them in such a way that they cannot be distinguished by the package in which they are supplied to investigators.

While a relatively small amount of clinical drug products may be required for early-phase trials, later-phase trials can require considerable amounts, and therefore their manufacture is not a trivial undertaking. In addition, while the majority of blinded trials are conducted using solid dosage forms, blinding can also be needed for other drug forms, such as oral liquid
formulations, injectable solutions, ointments, and metered dose inhalers. Since protein biologicals are typically administered by injection, manufacturing clinical drug products in this case can be a challenge.

The content of a package that contains clinical drug products cannot be deduced from the package itself. This presents special challenges. Once packaged, clinical drug products need to be distributed to all of the investigational sites participating in a trial. Given that many multicenter trials may now use sites in various countries, this adds several degrees of potential complexity to the process. If international shipping is required, each country’s customs (import/export) authorities may need to be appraised of the drug products’ entry into that country.

18.6. DRUG SUPPLY AND LABELING

Consider the example of South Africa. There, an investigational medicine must be properly labeled and the package must convey certain information adequately:

• the clinical trial to be conducted
• the medicine to be used
• the subject (identified in code form) to whom the medicine is to be administered
• the name and address of the premises where the clinical trial is to be carried out.

Labels are required in clearly legible, indelible letters in English and at least one other official language.

The Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (GCP) require that the sponsor is responsible for supplying the principal investigator with the investigational product(s). The sponsor should not supply an investigator/institution with the investigational product(s) until it has obtained all required documentation, e.g. approval from the appropriate ethics committee, the Medicines Control Council (MCC), and other applicable regulatory authorities.

The sponsor has many responsibilities, including:

• ensuring that written procedures include instructions that the investigator/institution should follow for handling and storage of investigational product(s) for the trial, and appropriate documentation; the procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused investigational product(s) to the sponsor (or alternative
disposition if authorized by the sponsor and in compliance with the MCC-approved protocol and/or where available, applicable regulatory requirements)
• ensuring timely delivery of investigational product(s) to the principal investigator(s)
• maintaining records that document shipment, receipt, disposition, return, and destruction of the investigational product(s)
• maintaining a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim)
• maintaining a system for the disposition of unused investigational product(s) and for the documentation of this disposition. Disposal must be done according to MCC regulation
• taking steps to ensure that the investigational product(s) is stable over the period of use
• maintaining sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintaining records of batch sample analyses and characteristics; to the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

The IP labeling requirements for countries in Africa have many similarities, but also some unique differences that require extensive knowledge of local regulations from country to country, and the ability to keep up with changes in regulations. For example, some countries, such as Namibia, require instructions on how to use the investigational product and/or route of administration, while others, such as Tanzania, do not.

### 18.6.1. Logistics of Clearing Customs

Consider the example of Latin America. Rules for importing investigational products and supplies to emerging markets are dependent on local regulations, which can vary greatly from country to country. The more mature the country is, the more likely it is that the regulatory agency will request an import license. Typically, this import license is requested to accompany the submission to conduct the trial. In many countries, the regulatory agency requests a declaration of the total amount of drug and supplies that will be imported and, with every shipment, they discount the approved amount. In cases where additional drug or supplies are required,
a new import license must be requested. Additional procedures may be necessary for psychotropics or narcotics. Approval from the US Drug Enforcement Agency (DEA) and potentially additional permits are required in some countries.

The process of clearing customs can vary from country to country. A local expert needs to review the airway bills to make sure they comply with the local regulation. Such localized knowledge is the key to speeding up the customs release process.

18.6.2. Shipment and Cold Chain

Consider again the example of Latin America. In customs offices there are temperature-controlled facilities, such as cold rooms and ambient temperature rooms. The way drugs are imported depends on the type and specifications of the drugs. These include:

- ambient temperature drugs
- refrigerated drugs (vaccines, biologicals, etc.)
- frozen drugs (some vaccines).

The control employed during transportation also depends on the type of drug. For example, drugs that can be transported as ambient controlled drugs may not require monitoring during transportation. This will depend on the drug stability. Different strategies are applicable to refrigerated drugs. They may be shipped with different types of temperature monitoring devices (Temp-tails® is one such device) in order to track temperature deviations during shipping, and sometimes in validated coolers that control temperature for a specific length of time. In cases where the drug does not arrive in an appropriately controlled manner, the sponsor is made aware and the stability of the drug is reviewed; the monitoring of the temperature will allow the sponsor to compare these potential exclusions with stability data to make a decision to retain or release the drug.

It is important that sponsors establish and maintain a depot in these countries. This will ensure that the stability of the drug is appropriately addressed, and all GMPs are followed.

18.7. INTERACTIVE VOICE RESPONSE TECHNOLOGY

The software that enables the randomizing of subjects into clinical trials and dispensing medication to them in a blinded fashion is commonly known as an interactive voice response system (IVRS). With the increasing use of the web over the last few years, it is also referred to as an interactive
web response system (IWRS) or interactive response technology (IRT). While some clinical trials still use paper-based systems, the majority of them now mandate the need for preconfigured, validated software to reduce human error, which could put the subjects and/or the trial itself at risk.

The process starts with the client identifying the specific requirements of the clinical trial. While some of the requirements are clear and universal (e.g. study design), many are very customer specific. Examples include how and where study drug (and control drug) should be dispensed and the study reports needed to monitor the trial. Once the specification process is completed, a telephone and/or web interface is built through a rigorous, quality-controlled process. A validated system is made available to the client and the investigator sites, with a typical timeline for this being 10–12 weeks. Users are sent secure envelopes which contain the unique identification information (ID) and password that are needed to access the system. In recent years, vendors have begun to use secure e-mail or web-based processes to distribute confidential user account information.

Once the sites receive the envelopes and the system is active, they start using the system for every transaction that they need to perform. A transaction may be in the form of randomizing the subject, dispensing them medication, or managing drug supplies (for the sponsor). With proactive system design, it is possible to reduce the drug wastage in a clinical trial to an absolute minimum by deftly managing the drug inventory.

Special attention needs to be paid to developing an IRT system that is primarily going to be utilized by sites in developing countries. Some of the unique problems that need to be addressed are:

- **Local language translation:** Most countries have a local language with which the investigator is comfortable. It is often necessary to translate all the phrases that are used by the system into the local language for the phone and the web. In a lot of countries, even the smallest of variations can lead to a very different meaning for the word, and even the way the word is pronounced can have different meanings. It is extremely important, therefore, to use a vendor who is very experienced in the local language and uses talented individuals who are experienced enough to notice the nuanced differences. The use of companies certified in medical translations for both the system and any supporting user documentation is also necessary

- **Web availability:** While Internet access is now fairly widely prevalent in developing countries, there still remain some pockets where it is not easily accessible. While more than 80 percent of users in the Western
world utilize and prefer the web over the telephone interface, the percentage may not be as high in the developing countries. Therefore, the telephone infrastructure that is set up needs to be robust and sophisticated to support the volumes.

- **Telecom infrastructure**: Unique attention needs to be paid to each country when deploying the telecom lines. The challenges include having rotary telephones, long lead times in obtaining toll free numbers, and sometimes the inability to obtain toll free numbers at all to dial out of country. The infrastructure also needs to account for possible line outages and hence needs to have built-in redundancy. There are some hospitals where all physicians do not have access to independent telephone lines, and hence the physical logistics might need to be worked out on a case-by-case basis. While mobile phone technology has alleviated some of these challenges, the need to provide free telephone access to sites is still an important consideration.

- **Patient scheduling**: In several countries, patients are brought to the hospital (investigational site) by social workers from quite far away. Should an issue prevent a successful visit when planned, a return visit might not be possible during the visit window. Such possibilities need to be kept in mind when designing the drug supply strategy of the trial. They also emphasize the criticality of system availability and accessibility, as described in previous points.

- **Drug supply management**: There are several countries where the time taken to ship the drug and clear it through customs is significant and needs to be taken into account when attempting just-in-time drug supplies. The increasing number of clinical trials for biologicals that have specific temperature controls that must be monitored, in addition to more stringent storage requirements, compounds this requirement. In addition to leveraging IRT technology, many sponsors choose to use local country drug depots or regional warehouses to facilitate this process. Finding the right balance of how much clinical supply to have available at sites versus in warehouses or depots requires experienced vendors working with appropriate technology to determine this based on initial assumptions and continuous refining and monitoring of these assumptions throughout the life of the trial.

Another feature that IRT technology provides is the ability to provide capping for situations where naïve subject populations have the potential to enroll quickly, while also utilizing the system to maintain potential stratifications or substudy attributes. Having immediate access to enrollment rates,
subject visits, and subject terminations assists with the monitoring plans as well as ensuring that adequate clinical supplies are available.

Once all these factors have been taken into account and a system has been designed by an experienced IRT provider, the compliance and commitment levels in investigators using the system are typically no different than seen in the West. Currently, IRT technology is enabling the seamless execution of hundreds of trials in developing countries. Since a significant part of the overall subject population in large trials will be coming from these countries, sponsors and vendors will need to be able to adapt their processes and systems to country-specific challenges, and to create a solution that meets the requirements of the trial in that country. The quality and experience of sites and sponsors working in these emerging markets is improving every year, with more and more trials being successfully completed.

18.8. INVESTIGATORS’ MEETING

While certain small trials can be conducted at one investigative site, it is much more common in large trials to see multicenter trials, and hence to have multiple principal investigators. Given that the expertise and previous experiences of these investigators will not be identical, the sponsor must work diligently to enable them all (to the greatest extent possible) to conduct every aspect of the trial in the standardized manner detailed in the study’s protocol. Spilker provided some examples of areas in which principal investigators, and their study staff, may need training [5]:

- accurate implementation of inclusion/exclusion criteria such that (only) subjects who are appropriate for the trial are enrolled
- fully understanding (and accepting) the need for adherence to all study protocol procedures
- understanding cGCP
- completing case report forms (CRFs) accurately and completely, and making (and documenting) changes if and when necessary
- collecting, processing, storing, and shipping any biological samples (e.g. blood and urine) in a uniform manner
- diagnosing and rating the nature and severity of adverse events, and particularly adverse events of special interest, accurately, and in a uniform manner across all sites
- reporting these adverse events uniformly across all sites
- developing strategies for communication between sites and the sponsor [and the contract research organization (CRO) representing the sponsor].
Various strategies exist for implementing investigator training. One option is for all investigators to attend a training session, or investigator meeting, run by the CRO or possibly by a professional training organization. In trials for which the sites are in close proximity, it may be logistically possible to run just one meeting. However, particularly in the case of therapeutic confirmatory trials, the sites may be spread across a country, and even across various continents. In these cases, it may be advantageous to run several meetings. In this case, attention must be paid to standardizing the training course itself. Having the same trainers running multiple meetings is ideal, but when the investigators speak many different languages, this can be a challenge.

An alternative option is for the trainers to visit each site to conduct training. As in the previous strategy, more sites and greater geographical diversity make this potentially more challenging. At one time, it was considered somewhat of a perk for investigators to attend meetings, since they were often held at luxurious settings in exotic locations. This is much less the case now. In addition, some potential investigators would much rather have trainers come to visit them, since this is more time efficient for their busy schedules.

A third strategy is running web-based meetings. This can involve training modules that investigators and their staff must complete, and also interactive web-based sessions, potentially using video capabilities as well as just on-screen materials. Whichever method is chosen by the sponsor and/or their CRO, the more thorough the training, the more likely it is that investigators and their staff will implement the study protocol correctly.

18.8.1. Investigators’ Meetings in Africa

The continent of Africa is associated for many individuals with images of many tribes and their differing traditional cultures. African tribe culture is distinguished by its great diversity of social patterns. For example, there are the anthropologist-termed hunter–gatherer tribes, as well as more technologically advanced pastoralist and horticulturalist tribes. In addition, African tribe culture is characterized by a great diversity of religions, ranging from animism to monotheistic religions such as Christianity, Judaism, and Islam. Furthermore, African tribe culture has a great diversity of visual arts and music.

Given this cultural diversity, planning investigator meetings (and many other meetings) need to take account of various factors, including:

- suitability of venue
- accommodation
The majority of physicians are well traveled and used to attending meetings both locally and internationally. Some of them may have qualified or gained previous experience overseas. However, for health workers from rural areas, who often have very limited financial resources, particular care must be taken when choosing a venue. Access, distance to be traveled, and mode of transport must be considered. Appropriate accommodation must be provided (a five-star hotel, which may be attractive to some attendees, may be too intimidating for rural health workers). Single accommodation is normally booked for out-of-town delegates, unless a different request is made in advance (e.g. many married couples work together on trials). However, some of the rural health workers prefer to share accommodation with one or more of their colleagues.

The country of South Africa is multilingual. Besides the 11 officially recognized languages, many others (e.g. African, European, and Asian languages) are spoken as the country lies at the crossroads of southern Africa. English is generally understood across the country, being the language of business, politics, and the media, and the country’s lingua franca. However, despite this, it ranks only joint fifth out of 11 as a home language.

The continent of Africa has four major language families and over 2000 existing languages. The largest language family in Africa is Niger–Congo, with over 1400 languages, illustrating the great diversity of African tribe culture. Certain parts of Africa speak French or Portuguese. When organizing meetings in certain parts of Africa, interpretation facilities becomes a necessity, which is a cost factor in meeting planning.

Delegate dietary requests typically fall into four categories:

- halaal
- vegetarian
- kosher
- no special dietary request.
Halaal and vegetarian requests are increasing. Most hotels are able to accommodate such requests. In certain rural areas, however, special dietary requests have to be flown in, again adding to the overall cost of the meeting.

With regard to transportation, doctors typically have some form of personal transport and are able to reach airports, hospitals, and venues by themselves. Out-of-town delegates sometimes have to arrive earlier and/or leave earlier owing to inconvenient flights. In the poorer rural areas, workers have to take taxis, walk, or make other arrangements. This can delay their arrival at the meetings, and these timing factors must be taken into account. Timing considerations are also necessary in the context of religion. Members of certain religions pray at certain times, and this must be taken into account when planning flights and commencement times of meeting. Religious holidays must also be considered.

Documentation intended to facilitate the on-time running of the meeting must be prepared in a thoughtful manner. Different cultures have differing perceptions of time, with some adhering more than others to the perception typical in Western cultures, and hence at Western investigational sites and meetings. Requests for acknowledgements and information from delegates and attendees should be sent out in plenty of time, and a reply date that is earlier than might otherwise be used requested. Postage can be unreliable, and so it is advisable to fax and/or e-mail correspondence and follow-up with a telephone call to ensure that the person concerned has received the information. “Personal reminder” telephone calls made before the meeting date are very important to prevent absenteeism.

At the meeting itself, advance planning must take into account the technological requirements of meeting sessions. Frequently, training takes place on personal computers, and web meetings run over the Internet are also common. Therefore, the meeting facility needs to be appropriately connected to the Internet, and computers provided for attendees who may not own one, or may find that transporting one they own from a distance is impractical.

18.9. ELECTRICAL GENERATORS AND POWER ISSUES

Any site is vulnerable to power outages, including those in Latin America. Latin American sites are very heterogeneous, with clinical trials being conducted in a variety of environments ranging from very large hospitals, private or public, to small offices where an independent investigator conducts the trial. Investigators who perform trials in hospitals always
have back-up generators available as part of the site’s infrastructure. However, this is often not the case for independent investigators at smaller sites. In these instances, other precautions must be considered, including:
• maintaining a supply of batteries for air conditioning and the refrigerator in which the drug is kept
• subcontracting a laboratory that does have back-up capabilities for storing blood samples when needed
• arrangements for handling emergencies in hospitals located near the independent investigator’s office that has the required infrastructure.

When smaller sites become more proficient at conducting trials, and wish to continue to develop their revenue stream from this activity, they may decide to invest in a back-up generator.

18.10. TRANSLATIONS

In the planning of a clinical research trial, it is critical to take into account the logistics of the translations, and to ensure optimum quality of the translation itself. In Latin America, regulatory documents and clinical study documents must be submitted to the regulatory authorities in the legal language per country, and must be understandable by the site staff and subjects. The clinical team must determine the following on a country-by-country basis:
• the type of translation required: certified/qualified
• what documents require translation: considerations include determining which documents are required by regulators in the local region and in what language(s), when documents need to be submitted to them, when they need to be delivered to the site for use as recruitment tools, and when they will be needed for subject use
• which documents require back-translation
• which documents do not require translation.

A successful translation process requires all parties to be familiar with the timelines for securing translation, reviews, and back-translations ready on time. On average, the overall process can take from four to six weeks.

The level of translator depends on the nature of the document, which can require a certified or a qualified translator. One of these levels will always be required and, depending on the importance of the document, it may have one or two quality review steps. Even though most of the countries in Latin America use the Spanish language, there are notable variations in the words and expressions. Therefore, a native person from
each country must make sure that the document’s Spanish is appropriately tailored.

The other important language is Portuguese, as spoken in Brazil. Occasionally, it may be necessary to use some dialects, and to have documents submitted and approved in other languages depending on the target population of the study. For example, in some countries there may be large immigrant groups that contain many potential subjects. Therefore, providing documents in their native language may be very helpful.

ACKNOWLEDGMENT

The authors gratefully thank Carolyn Moore for her administrative support.

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