Clinical Research Organizations

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8.1 Introduction

Clinical research organizations (CROs) are independent companies that assist sponsors such as pharmaceutical, biotechnology, medical device companies, as well as universities and research organizations by providing trial management services outsourced by the sponsor under a contractual agreement (Gad et al. 2020a, b; Masri et al. 2012). CROs may also be referred to as contract service organization (CSO) or pharmaceutical development organizations. CROs can be traced back to the 1940s and 1950s with founding of companies such as Charles River Laboratories and Huntingdon Life Sciences that provided animals for testing or conducted the testing themselves (Serota 2020a). However, with the increased regulations for pharmaceutical testing of compounds, CROs began to evolve and now serve as a cornerstone of research, supporting sponsors in full-service offerings in the early stages of development through commercialization through the outsourcing of services from the sponsor to the CRO. While sponsors retain responsibility for the conduct of clinical trials, CROs have the ability to provide the essential support services necessary to conduct the trials.

The outsourcing of trial-related duties is largely driven by the need of sponsors to have access to clinical trial staff, trial sites, their generated data, and efficient processes in conducting clinical trials, thereby reducing costs (Rettig 2000; Landhuis 2018; Rose 2008). Specifically, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use defines a CRO as "a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions" (Sfera and Sauber 2019a). This same organization also maintains that although the sponsor may delegate trial-related duties and functions to other entities such as CROs, the sponsor is required to ensure oversight of trial-related duties and functions including those that may be subcontracted to another party by the sponsor's contracted CRO.

Sponsors partner with CROs to further develop a new drug or device from conception to regulatory approval more efficiently than if the sponsor were to conduct the trial activities on their own (Sfera and Sauber 2019a). With the increasing complexity of the regulatory environment governing novel therapeutics such as advanced therapies medicinal products, and cell and gene therapies, CROs play an increasingly important role in helping sponsors develop approval pathways for their drug or device.

Historically, larger pharmaceutical companies conducted these research services internally. However, over time, many of these companies began to outsource these services to CROs who maintain the appropriate trial personnel and overall functionality in order to increase efficiencies and reduce costs of drug or device development (Landhuis 2018). CROs may provide a variety of research services including preclinical research, clinical research, regulatory affairs, clinical trial operations, clinical monitoring, medical monitoring, data management, medical writing, biostatistics, investigational product distribution/tracking, and safety/pharmacovigilance (Gad et al. 2020c; Shih 2015). Larger CROs are likely to be able to provide all these services in a full-service model, while smaller CROs may only provide a few areas, working with vendors to meet the sponsor's other research needs. In fact, there are small CROs that occupy niches in the research field such as specific research functions, serve specific geographic areas, or focus on certain therapeutic areas (Solarin et al. 2020; Gad et al. 2020d).

Some CROs offer additional services such as central imaging review, clinical laboratory, electrocardiogram (ECG) review, biorepositories, and assay development. Centralized evaluation of radiographic images or laboratory assays provides a uniform assessment of these endpoints, minimizing variability introduced by using multiple sites.

CROs may be categorized by geographical coverage, therapeutic area specialization, and size. Some CROs have a global footprint to conduct international trials, while some smaller CROs are limited to a specific country or region of the world. CROs may be specialized in specific disease areas or in healthy volunteers. CROs may be categorized by organization size: large, mid-size, or small (Shih 2015). The size of the CRO is also important not only in its ability to

conduct a trial but also in how the CRO is able to relate and meet the needs of the pharmaceutical or biotechnology partner. Academic research organizations (AROs) are similar to CROs in that they fulfill a function in the conduct of clinical trials; however, they are nonprofit entities and more commonly collaborate with other AROs (Reist et al. 2013).

Research and development is a large portion of the corporate budget for the pharmaceutical and biotechnology industry. Recently, sponsors (pharmaceutical and biotechnology companies) have been increasingly contracting with third-party vendors such as CROs to perform certain aspects of their research and development, largely to remain profitable and competitive (Landhuis 2018; Buvailo 2020). This is also the result of decreasing returns on late-stage pipeline products. In 2016, for example, the returns for the top 12 pharmaceutical companies declined from 10.1% in 2010 to 3.7% in 2016. In contrast, there were over 1100 CROs internationally in 2013, with the top 10 CROs controlling 57% of the market by 2018, a 12% increase from 2011 (Buvailo 2020). A 2019 report stated that the global CRO industry grew at 10% compound annual growth rate (CAGR) with a projected increase to 12% by 2022 (Buvailo 2020). This is largely due to the growth in the number of biotechnology companies and the number of research projects in the pharmaceutical arena, combined with the number of drug entities in development nearly doubling from 7737 in 2007 to 15,267 in 2018 (Buvailo 2020). On average, large pharmaceutical companies outsource approximately 45% of their research activities to CROs, while small- and medium-sized organizations outsource up to 70% of their activities with some emerging companies outsourcing 90% (Buvailo 2020).

8.2 Business Development

Sponsors typically will issue to CROs a request for proposal (RFP) when a new clinical trial is to be initiated. The RFP includes a synopsis or complete protocol (a road map for the trial) for the research project and an outline of the specific questions that the sponsor would like the CRO to address in their written response (Gad et al. 2020b). A CRO's response typically includes comments on the research proposal, a description of how the study would be operationalized, criteria for site selection, the timelines for trial initiation and conduct, and an estimated study budget (Burks 2020). The sponsor reviews all CRO responses and selects a small number of CROs for an in-person or "virtual" meeting, which is called a bid defense. During the bid defense, a team of individuals from the CRO, each representing a specific area of specialization or function, "defends" the strategy of how the CRO would execute the sponsor's trial according to the proposed clinical protocol (Rose 2008).

The sponsor may have already selected external vendors, representing functions not provided by the CRO. CRO team members may include a regulatory affairs representative, who provides advice in interactions with regulatory agencies; a regulatory submissions person, who interacts with institutional research boards (IRBs) and ethics committees (EC); a project manager, who oversees the research project; a data manager, who oversees data collection, completeness, and data integrity; a medical monitor, a physician who provides medical advice and safety oversight; a safety manager, who oversees safety parameters in the research project; and a biostatistician, who designs the statistical strategy of the trial (Gad et al. 2020c).

A CROs budget proposal in the RFP response provides the sponsor an estimate of the cost of the research project, which will be important to the sponsor's leadership in prioritizing business aims (Gad et al. 2020e). The trial budget typically includes direct and indirect costs. Direct costs are those required to conduct the trial. Indirect costs are those costs that are passed on from sites and other groups involved in the project to cover expenses costs (e.g., expenses of paying site staff, Institutional Review Board costs, visit procedures, etc.). As the project progresses, it is not uncommon that amendments to the project budget are required. The CRO will address changes to the contract through contract amendments.

Following the bid defense meeting, the sponsor will select a CRO to operationalize their project based on the CRO's experience, proposal and

strategy, budget, and alignment with culture/ability to work together with the sponsor (Gad et al. 2020f; CREDEVO 2019). Once the sponsor selects the CRO, the CRO and the sponsor will agree on a final contract and budget for the project, and the CRO generates a scope of work. The scope of work is a document that identifies which tasks of the project will be performed by the CRO, the sponsor, another vendor, or some combination of each. Ultimately, the sponsor is the principal entity responsible for conducting the research project appropriately.

8.2.1 CRO Team Members

A CRO functions as a team. Each member is responsible for a component of the trial, always working in close collaboration with the sponsor. These team members include the following project areas: regulatory affairs, study start-up, medical monitoring, project management, clinical monitoring, data management, safety, and biostatistics (we will review each of these areas in the following paragraphs (Gad et al. 2020f). The CRO may be responsible for these positions, or the sponsor may select other vendors to fulfill certain roles, such as biostatistics, data management, or safety. Project managers are individuals who oversee the trial and function as the central point of communication between CRO team members and the sponsor. Clinical research associates (CRAs) are individuals who function as the main communication liaison between the CRO, sponsor, and the trial site. CRAs conduct the site training and are the first line of contact from the site in the event there are questions regarding the protocol. CRAs also conduct monitoring visits of the trial to ensure the data is complete and captured accurately by comparing source documents (e.g., medical records) with the site's database entries (Serota 2020b; Sfera and Sauber 2019b).

8.2.2 Regulatory Affairs

Members of the regulatory affairs group provide guidance and strategy to the sponsor on how to proceed with drug or device development. This advice is particularly important for small-to medium-sized pharmaceutical companies or small biotechnology companies who do not have internal regulatory affairs teams. These team members are able to assist the sponsor in navigating the regulatory environment by designing a strategy for drug or device development, which may include writing the Investigational New Drug (IND) application (or equivalent), responding to regulatory agency (such as the Food and Drug Administration (FDA)) inquiries, or attending meetings with the regulatory agency at the sponsor's request. Their advice is particularly important for global trials, where more than one regulatory agency is involved in trial review and approval (FDA 2021).

8.2.3 Investigational New Drug (IND)/Investigational Device Exemption (IDE) Application

Human testing of a new drug cannot begin until there is evidence that the drug product to be used in humans is reasonably safe. This is called the preclinical phase. The preclinical phase typically takes 1–3 years, and the data collected from this phase will be used to move to the IND phase of the trial. The IND phase of the trial will collect the data needed to support the use of the drug product in humans. This phase can take up to 12 years to complete. If the sponsor wishes to begin testing their drug product in humans, a formal IND application is required. The IMD is a similar application for testing medical devices in humans (Babiarz and Pisano 2008).

8.2.4 FDA Meetings

Meetings with the FDA are conducted to review sponsor protocols and provide proposals, provide answers, and resolve scientific issues that impact the development of a pharmaceutical product. These meetings mark the beginning of determining if this product can move forward to the next stage of investigation. There are several meetings that are important in this process: pre-IND meeting, end of phase 2 meetings, special protocol

and ad hoc technical meetings, pre-New Drug Application (NDA) meeting, advisory committee meetings, and labeling meetings. The most important characteristic to remember with all of these meetings with the FDA is that all of these meetings are serious and formal. All discussions are scientific in nature with "scientist to scientist" in many cases (Grignolo and Choe 2008).

8.2.5 Investigator's Brochure (IB)

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data (Chiodin et al. 2019; Sfera and Sauber 2019c).

8.2.6 Annual Reporting

Under the IND, application sponsors are expected to submit brief reports of the progress of the investigations conducted under their respective IND application within 60 days of the anniversary date that the application went into effect. Such reports are submitted annually (Hamrell 2008).

8.2.7 Protocol Development and Amendments

Some sponsors may provide a general protocol synopsis outlining the study title; subject population; planned number of subjects; background and rationale; investigational product; dosing regimen; duration of the study; eligibility criteria; primary, secondary, and exploratory objectives and their corresponding endpoints; and statistical considerations. These synopses may vary in the amount of detail available. The sponsor may request the CRO to develop the formal clinical trial document (protocol), which is typically a collaboration between medical writers, the medical monitor, operations personnel, and statisticians. The sponsor retains responsibility for the protocol development. Once the protocol is final, the sponsor provides approval. Alternatively, some sponsors may have already developed a protocol and request only that the CRO provides comments on the protocol (Green et al. 2012a).

If at any time the protocol requires changes that impact trial conduction, patient safety, etc., an amendment to the protocol will be required. The same quality control process will be employed in the modification of the protocol to ensure that the rights, safety, and well-being of trial patients are not compromised. If immediate altering of a protocol is required for patient safety, then the sponsor can implement these changes in advance of the protocol amendment (Green et al. 2012a; Brody 2016a).

8.2.8 Feasibility

Feasibility is the process of confirming if a protocol strategy is possible and makes sense. The conduction of a feasibility assessment is usually one of the first steps in conducting the clinical trial for the CRO (Spilker 2009a). The feasibility analysis helps to identify any challenges a trial could encounter and is critical in determining which regions and sites will be considered for trial participation. The CRO will often utilize

multiple sources of information when conducting the initial feasibility for a trial. Among these materials is a critical review of the published medical literature for the incidence of the disease being studied as well as any geographic or demographic predisposition. Internal CRO databases can also be important sources of information if the CRO has experience in the disease under investigation by the sponsor. External databases are available by subscription and provide detailed information on prior clinical trials (Rajadhyaksha 2010).

If the sponsor permits, sites can be contacted to speak directly with principal investigators about their opinions on the trial design and eligibility criteria and to assess their interest in participating in the trial. Contacting the PIs provides the advantage to the CRO in the ability to gain an understanding of the standard of care therapies at potential sites, the availability of any specific medications, the number and types of patients treated at the site, competing clinical trials, and the sites' standards of care. These latter issues are important in global trials since there may be significant differences in medication availability and standard of care therapies as well as the quality of medical care available.

Using published, proprietary, and general data, the CRO provides an estimate of the screen failure rate for the subject population targeted by the protocol. This requires an understanding of the specific eligibility criteria regarding subjects being approached for the protocol. Using the screen failure rate, the CRO can provide an estimate of the number of subjects with the disorder being studied who will not be eligible to proceed to the trial intervention. The CRO will identify any pertinent eligibility criteria or trial design factors that contribute to the screen failure rate, allowing the sponsor to consider revisions to the trial design, if appropriate.

Using similar data sources, the CRO will generate an enrollment rate for the trial, reported in patients/site/month; aggregate values are calculated for each site and then for the entire trial.

CROs must have a knowledge about the competitive landscape for the specific patient population. This includes both standard of care options and clinical trials in progress and in development. The public website www.clinicaltrials.gov provides a starting point for this evaluation. These values allow the CRO to provide an estimate for the number of clinical sites and countries that are required to complete the trial in a specific time frame. The CRO is also able to provide various scenarios to a sponsor so that the sponsor can view different scenarios that have different numbers of sites and geographic areas, allowing a comparison of timeline and budget considerations.

The importance of a solid feasibility investigation cannot be underestimated as it will provide the approximate number of patients needed, the number of sites needed to enroll the patients, and the time required to enroll the trial. Timelines are critically important for sponsors, and this can affect their ability to obtain external funding from investors and to adhere to their overall product development budgets.

8.2.9 Study Start-Up

Following the conclusion of the site feasibility assessment, the CRO and sponsor identify potential sites to be contacted for official selection for trial participation. The CRA will contact the potential sites to obtain information about the site's PI, their infrastructure, competitive trials status, potential patient population, and their ability to enroll the trial. In many cases, the CRA will need to conduct an on-site evaluation of the site under consideration for inclusion of the trial to ensure the trial has the right infrastructure in place to conduct the trial (Sfera and Sauber 2019b). For many CROs, if the site is well known with recent study experience with the CRO, this process can be waived and a phone assessment conducted with the site. The CRO will provide the site's particular information to the sponsor for review. Sites who meet all the criteria for trial participation are considered qualified or selected. Per regulations, the sponsor is required to formally approve all trial sites for inclusion in the trial. Once approved by the sponsor, the site will begin the start-up activities.

All sites participating in a clinical trial are required to conduct trial activities according to regulatory documents also known as "critical or essential documents" (Sfera and Sauber 2019c; FDA 2018). These essential documents are required to track and evaluate the ethical and procedural conduct of the trial and are filed in the trial master file (TMF). These essential documents illustrate that the trial site, the sponsor, and the CRO have the proper ethical and regulatory approvals to conduct the trial. The collection and submission of these essential documents can be time-consuming and will affect the time required to enroll the first patient. The site's study budget will cover the time and effort of the PI and the internal research team to collect, submit, and provide the documents to the CRO for review and approval for the site to be "activated" and eligible to enroll patients in the trial.

The Regulatory Authority's permission to start a trial is required. If an IND is required for the trial, the sponsor will need to obtain clearance to proceed from the appropriate regulatory agency. In the United States, this would be the FDA, and in Europe, this would be the Medicines and Healthcare Products Regulatory Agency (MHRA) (Brody 2016b). The FDA will provide clearance to proceed to the sponsor. The sponsor then begins the institutional approval process. In some circumstances, while awaiting "notification to proceed" from the regulatory agency, the sponsor may request the site submit the protocol to their IRB prior to the FDA completing their review. This process is termed "at risk" because if additional changes to the protocol are required, the site may need to resubmit the protocol for another review.

Within the overall process of site approvals, some sites may have internal committees involved in the review process. For example, gene therapy trials require Institutional Biosafety Committee (IBC) review (Eisenman 2019). Oncology trials may require institutional scientific committee review. Additionally, sites will have internal committees review the schedule of assessments to determine which ones are standard of care for their institution; this is important in finalizing the budget as only research activities (those that are not standard of care) for the trial will be covered in the study budget.

8.2.10 Site Activation

In conjunction with the collection of all essential documents, the CRA will conduct a site initiation visit, or site training visit with the site. The CRA will train the site on the clinical protocol and all operational activities required to support the execution of the protocol. Once all regulatory approvals have been obtained, all remaining essential documents collected, and the contract and budget finalized/ executed, the site will be approved and "activated" to begin screening patients into the trial (Sfera and Sauber 2019b). Ongoing training will be provided to the site by the CRO if there are any changes to the protocol or any of the trial processes.

8.2.11 Determining the Impact on Timelines

The CRO will leverage its experience with various clinical sites to determine the timelines (Passot 2020). CROs have an understanding of how each site operates, whether they use a central or local IRB, what internal site committees are required for protocol approval, and the requirements for contract and budget negotiations. Using this knowledge, the CRO can anticipate the length of time required for review at each site; the length of time required will vary between regions of the world as well. The CRO will use this information to generate a timeline for trial enrollment, which will impact the overall timeline of the study from study commencement to trial completion. Sponsors will typically request specific dates for the following: first patient first visit (FPFV), last patient first visit (LPFV), and last patient last visit (LPLV). These dates permit sites to better design their budgets and will be important milestones for the success of the sponsor in conducting the trial.

8.3 Project Management

Each study team is led by a project manager, who serves as the central point of contact for all functional areas involved with the research project, including the CRO, sponsor, and other vendors.

The project manager directs the study team through the life cycle of the clinical trial, initially focusing on feasibility and site identification, moving the study through the start-up and site activation phase, progressing to study enrollment and trial conduct, and concluding with study closeout (Serota 2020b; Sfera and Sauber 2019b). The project manager prioritizes communication between the team members of the CRO and sponsor and any external vendors involved in any of these phases of the clinical trial.

The project manager oversees and manages day-to-day trial operations for all functional area deliverables. The project manager ensures all project milestones are met and functional area deliverables are of the highest quality. The project manager will confirm that all team members are trained on the research project and that the documentation of project-specific training is appropriately filed in the trial master file. Project-specific training provides CRO team members with the background information and clinical trial review in order for them to perform their respective job functions appropriately.

The project manager also oversees the development of the study management tools and operational plans for the conduction of the trial. Examples of these documents include enrollment forms, site initiation visit training slides, monitoring plan, communication plan, deviation plan, safety management plan, and data management plan. The project manager is responsible for organizing regularly scheduled, internal, and external team meetings. Internal team meetings allow the CRO employees involved in the project to discuss the current study status of all functional areas. External team meetings include the CRO, the sponsor, and other vendors involved in the trial.

At most CROs, the project manager will be responsible for the financial management of a clinical trial on behalf of the CRO. It is imperative that the project manager is familiar with the duties agreed upon between the CRO and sponsor and ensures that all functional areas are conducting trial activities according to the scope of work that outlines the CRO responsibilities in the trial. Conducting activities not covered under the contract between the CRO and the sponsor are considered "out of scope" activities and not covered for payment by the sponsor. It is critical for the project manager to consult with the functional areas prior to committing to "out of scope" tasks. If the project manager does identify project activities required that are not covered in the existing scope, it is the responsibility of the project manager to discuss with the sponsor prior to conduction of these activities in order to obtain approval to conduct the activities, which may also require trial budget modification.

8.3.1 Medical Monitoring

Medical monitors are physicians skilled in the conduct of clinical trials (Riddle 2018). These physicians provide medical support for the internal CRO team and work with the sponsor medical director to conduct the trial safely while maintaining the integrity of the trial. The medical monitors answer questions from sites, CRAs, and internal team members regarding eligibility, study conduct, adverse event term coding, and serious adverse event processing and oversee safety of clinical trial participants. Medical monitors typically provide information regarding the investigational medication, concomitant medications, serious adverse event (SAE) reports, stopping rules, safety review triggers, subject withdrawal, and laboratory alerts. Medical monitors may assist in the preparation for Data and Safety Monitoring Committee (DSMC) meetings. Protocol deviations are unavoidable during the conduct of a clinical trial, and most are discovered retrospectively during the monitoring process (Bhatt 2012). However, occasionally site investigators may request the medical monitor to grant a prospective waiver for a protocol-required assessment. As a rule, prospective waivers for eligibility are generally not granted by the medical monitor and are referred to the sponsor for consideration. Most regulatory agencies and review

boards do not view prospective protocol deviations favorably as the trial has already undergone a thorough and extensive review by the sponsor, CRO, regulatory agencies, and review boards. These requests are best addressed through a protocol amendment (European Commission n.d.).

8.3.2 Clinical Monitoring

Clinical monitoring is a critical process in the conduct of a clinical trial and is fulfilled primarily by the Clinical Research Associate (CRA). The primary role of the CRA is to act as the liaison between the sponsor, CRO, and the sites where the clinical study is taking place. A successful CRA is detail-oriented, highly educated, and able to communicate clearly with all the individual groups. The CRA must review the source documents, which in most cases includes patient medical records, as well as all site study-related/medical documents that support the data generated from the site trial activities as they reflect the protocol requirements. The review of this data is generally conducted via regular visits—virtually or on-site—to ensure that the site is keeping proper records to support the trial and that all trial data is correctly documented. Sites must be sure to maintain the confidentiality of patient records.

As noted earlier, the CRA plays a critical role in the selection of qualified sites. An experienced CRA is valued for their ability to assess the ability of potential sites to conduct the trial according to the clinical protocol. As a representative of the CRO and sponsor, the CRA must ensure he/she is effectively communicating all requirements needed for the site to function at a high level during the trial.

In an effort to promote efficiency, risk-based monitoring (RBM) has been advocated in some instances. RBM in its simplest form is the use of software, data, and analytics to monitor risk and support the clinical decision-making for the trial (FDA 2019). A risk-based approach to monitoring provides a data-driven approach to identifying and correcting issues as they arise. These measures help to mitigate against unexpected findings by review agencies when the investigational medication undergoes review for regulatory approval.

8.3.3 Safety

The sponsor is charged with assuring and monitoring the safety of research subjects on clinical trials. Pharmacovigilance relates to practices used to identify, assess, comprehend, and prevent adverse events or problems associated with an investigational medication or device (Brody 2009). CROs work with the sponsor to develop a safety monitoring plan outlining how the safety processes will be conducted during the trial, including the definitions and reporting guidelines for adverse events, adverse events of special interest (AESI), and serious adverse events (SAE). AEs are untoward medical occurrences in a clinical trial participant and do not necessarily indicate a causal relationship to the investigational product (FDA 2012). AESIs are serious or non-serious AEs of special interest to the sponsor for which ongoing monitoring and quick communication by the site to the sponsor are required. To be considered serious, the AE must meet one or more of the following criteria: results in death, is life-threatening, leads to hospitalization or prolongation of hospitalization, results in significant disability, or a congenital anomaly/birth defect.

CROs are often the responsible entity for notifying sites of safety concerns, and the sites are typically responsible for notifying their IRB or EC. CROs can also be designated to submit safety reports to regulatory oversight agencies as well. CROs focus on working with sites to facilitate the timely documentation and reporting of adverse events. The reporting timelines are critically important for SAEs. SAEs must be assessed by the PI as related or not related to the study mediation or intervention. The medical monitor will review the SAE narrative, the criteria for seriousness, and the assessments of causality by the PI. The medical monitor will provide an assessment of expectedness of the SAE by reviewing the investigator's brochure (IB) or package insert (Brody 2016c). Expected events are listed in the package insert or are in the reference safety information section of the IB. SAEs that are related and unexpected with respect to the study medication are considered suspected unexpected serious adverse reactions (SUSARs). SUSARs require expedited reporting and have tighter timelines.

CROs frequently oversee the external data monitoring safety board composition and meetings as well as endpoint adjudication committees, if required. As part of their safety oversight responsibilities, CROs will have policies that address tracking of dose limiting toxicities, trial stopping rules, and the implementation of urgent safety measures should a safety issue be identified that needs immediate attention. For global trials, CROs will need to have staff available to provide timely interaction with sites and regulatory oversight entities.

8.3.4 Clinical Data Management (CDM)

CDM is a critical component in clinical research. The function of CDM ensures that the collection and integration of clinical data support the conduct, management, and analysis of the clinical data (Spilker 2009b). The ultimate goal of CDM is that the conclusions of the data support the research that was proposed in the protocol, with particular focus on the primary and secondary endpoints.

Once the protocol is finalized, the protocol-specific data base must be constructed. The method of collecting the trial data that reflects the protocol required information via data entry into trial's case report form, or data collection tool. Most current databases are electronic (electronic data capture, EDC) so that sites can enter source data from the medical record into the database. The database must be secure with password-restricted access and the ability to document the name of individuals making entries as well as the time of the entry. The database must be 21 CFR Part 11 compliant, meaning that electronic records as well as electronic signatures are considered the same as those for paper records and handwritten signatures (FDA 2003). No protected health information is collected in the database, unless specified in the protocol. The entire process of data management is documented in a data management plan. This plan describes the activities to be conducted during data collection and processing.

Data managers, who oversee the function of data management activities, CRAs, and occasionally sponsor representatives have access to the EDC and can issue queries or questions for clarification of data about which they have questions. The site can then address these queries directly. CRO staff work closely with sites to have data entered into the database in a timely manner so that queries can be resolved soon after the data point and that any interim analysis or DSMB meeting can occur.

Data coding is typically overseen by the data management team with assistance by the medical monitor (Babre 2010). Coding is done in compliance with the most recently published version of the MedDRA Term Selection: Points to Consider. The medical monitor may review the coding periodically or at the end of the trial. Final reports are filed in the trial master file, also referred to as the TMF.

8.3.5 Statistics

Biostatisticians provide consultative advice on protocol development, including study design, randomization processes, and questions regarding how clinical trial issues affect statistical analysis (Green et al. 2012b). Biostatisticians take the data collected in the process of clinical data management and use statistical methods to analyze this data. They are responsible for working with the sponsor to generate data sets in the form of tables, figures, and listings to be supplied for interim analyses, trend analyses, safety reviews, regulatory reports, as well as data safety monitoring committees.

When the study is completed, the biostatistician will work with medical writers, the medical monitors, and sponsors to complete the clinical study report (CSR). The CSR is a study document generated at the completion of the trial; the CSR describes the clinical and statistical information required by regulatory authorities in evaluating clinical trial results of an investigational medication or device.

8.3.6 Quality Assurance

CROs conduct their operations to meet the requirements of international regulatory agencies as established by the World Health Organization (WHO),

European Union (EU), US Code of Federal Regulations (CFR), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), with emphasis on ICH Good Clinical Practice (GCP). In addition, each site must conduct the trial in an ethical manner in compliance with the protocol and under the approvals of national and institutional regulatory agencies. The sponsor is responsible for the oversight of the trial operations, and quality assurance is a means to ensure this occurs (Green et al. 2012c). It is important that the clinical trial be conducted in compliance with regulatory guidelines so that the conclusions of the trial can be regarded as valid. CROs have internal quality assurance groups that function to oversee these aspects of the trial. When the matter can be addressed by the clinical trial team, the issue may be resolved through discussion with the site to review the issue and to identify ways to prevent it from occurring again. For recurrent issues, a correct action plan may be implemented to formally outline the problem and the corrective actions required. When matters are more serious, the quality assurance team also serves as escalation point should the CRO team members and the sponsor have differences of opinions regarding any matter that could potentially affect the quality of the trial.

8.3.7 Risk Management/Risk Mitigation

Risk mitigation or risk management in clinical research is the process of evaluating opportunities and threats to the execution of a clinical protocol. The primary focus of risk management is to ensure that the rights and well-being of clinical trial patients are protected (Brody 2009). Some of the most egregious issues with failures of clinical trials revolve around the lack of appropriate planning in advance for investigator noncompliance with the clinical protocol. The most recurring issues requiring oversight are in the areas of protocol compliance, incorrect informed consent procedures, inadequate record keeping, and inadequate investigational product accountability. Sporadic issues include problems with screening or enrolling patients on the trial.

Risk mitigation will always be a challenge that needs continual review and time to ensure that patients are supported throughout their participation in the clinical trial. In addition, this process also ensures that the protocol primary and secondary endpoints are protected.

Risk mitigation is an important function of CROs. When the trial begins, the CRO and sponsor will review the protocol and identify risks to the successful conduct of the trial along with prospectively identified mitigation measures. Patient recruitment and retention measures may require modification if the trial fails to meet enrollment goals. Mitigation measures have been particularly important during the COVID-19 pandemic that affected many countries throughout the world, requiring novel methods for clinical monitoring and modifications of timelines due to delays in protocol review by regulatory boards and clinic closures.

8.3.8 Recruitment and Retention

The success of clinical trials hinges on the ability to enroll eligible subjects in a timely manner and to ensure that they can complete the trial to the point that they are evaluable for protocol objectives (Hulley et al. 2007; Spilker 2009c). CROs have expertise in this area based on their experience in the therapeutic area, their data on prior trials in this indication, their usage of social media, and their relationships with sites and patient advocacy groups. Most CROs will have patient recruitment teams that focus on these measures and can develop print- and web-based methodologies. Strategies to improve patient education, increase trial compliance, and enhance patient engagement prove valuable in these efforts. CROs will typically have experience in reviewing clinical trials from a patient perspective so that the trial is written to be minimally cumbersome for patients.

Recently, the FDA has focused on enrolling diverse clinical trial populations where possible (FDA 2020). This diversity allows the sponsor to collect additional data by gender, race, and ethnicity as there may be variations in pharmacokinetic (PK) and pharmacodynamic (PD) assessments. In addition, a recent publication

reported that 96.3% of subjects in phase III cancer clinical trials had good performance status (Jaoude et al. 2020). Thus, others have called for enrolling research subjects with lower performance scores to reflect real-world patient populations more accurately. Similarly, given the improved treatments available for HIV and with an increasing number having undetectable viral loads, there has been a focused effort to enroll HIV-positive patients when this diagnosis will not alter patient safety or affect trial endpoints (Dirix et al. 2020). However, sponsors may be hesitant as these subjects with lower performance scores may adversely affect the ability for the trial to assess safety and efficacy.

8.4 Conclusion

CROs are playing an increasingly important role in drug development, collaborating as full-service or partial service partners with pharmaceutical or biotechnology sponsors, to allow the sponsor to conduct their trials expeditiously, safely, in compliance with GCP, and in concordance with pertinent regulatory authorities. What began as a small industry in the 1940s has grown into a significant entity in the clinical research industry with the expectation of a valued section of up to 90 billion by 2026.

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