

## **Quality Agreements: Contractual Commitments by CROs to Deliver High-Quality Work**

**By Tom McGrady and Susan Callery-D'Amico**

### **Introduction**

Regulated companies have been using formal agreements for years to define the respective quality roles, responsibilities, specifications and key performance indicators between organizations. For companies that outsource manufacturing operations, the FDA and other health authorities routinely review evidence of formal Quality Agreements during inspections. Prior to formal guidance from health authorities, many companies adopted the use of Quality Agreements as best practice, resulting in each company independently developing their own processes and templates.

The need for Quality Agreements can be traced to the ICH guidance documents *Q9 Quality Risk Management (ICH Q9)*, which recommends supplier evaluation through audits and supplier Quality Agreements, and *Q10 Pharmaceutical Quality Systems (ICH Q10)*, which states that the control and review of any outsourced activity are ultimately the responsibility of the sponsor. The tenets of these ICH guidance documents for industry are to build quality into processes and products (Quality by Design) rather than relying on end-product testing or inspection (Quality by Inspection).

It was not until May 2013 that the FDA issued a draft guidance, entitled *Contract Manufacturing Arrangement for Drugs: Quality Agreements*. In the absence of a requirement for quality agreements between study sponsors (Sponsors) and contract research organizations (CROs), we can look to this draft guidance and the ICH guidance documents.

In this article, the following questions will be addressed:

- What is the regulatory basis for Quality Agreements and where can we find current guidance?
- What is the definition of a Quality Agreement?
- What are the essential elements of a Quality Agreement and the typical process flow between the Sponsor and the CRO or other contracted entity?
- Where does the Quality Agreement fit into the matrix of contractual agreements and the Sponsor's supplier qualification program?

Within the last few years, the implementation of Quality by Design (QbD) concepts within clinical research has generated wide interest. With the promise of understanding and controlling process variability with a "right first time" approach, it is easy to understand why adoption of QbD concepts is gaining traction with both Sponsors and contract research organizations (CROs). To understand how the generation, approval and management of formal Quality Agreements can be viewed as an element of building quality and efficiency into clinical trials, it is important to understand the genesis of QbD concepts specific to selecting and qualifying suppliers.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidances are based on the concepts first defined in International Standards Organization (ISO) 9000. The current version of ISO 9001:2008, Section 7.4 Purchasing states:

*The organization shall evaluate and select suppliers based on their ability to supply product in accordance with the organization's requirements. Criteria for selection, evaluation, and re-evaluation shall be established. Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained.*

Within the FDA, the Center for Device and Radiological Health (CDRH) adopted the quality management system (QMS) approach with the issuance in 1997 of medical device Good Manufacturing Practice (GMP) in 21 CFR Part 820. Section 820.50, Purchasing Controls, which mandates supplier qualification:

*Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received products and services conform to specified requirements. (a) Evaluation of suppliers, contractors and consultants. Each manufacturer shall establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors and consultants.*

A formal risk assessment and evaluation of suppliers and contract manufacturers, as defined in ICH Q9 and ICH Q10, recommends a three-step approach to the management of outsourced activities and purchased materials:

- **Step 1.** Conduct a supplier evaluation and perform a risk review based on the results. Based on the risk review, determine the extent of controls needed and build this into the agreement.
- **Step 2.** Develop and approve a formal written agreement between the parties.
- **Step 3.** Continuously monitor and evaluate performance to identify continuous improvement opportunities.

Good Clinical Practice (GCP) and FDA regulations allow the transfer of responsibility to a CRO under CFR 312.52. The CRO then becomes a regulated entity along with the Sponsor; however, the Sponsor is not relieved of responsibility and is still expected to provide adequate governance and oversight to ensure data integrity and safety of study participants. The device regulations do not address this transfer of responsibility, so device Sponsors are directly responsible for all activities contracted to outside parties.

As defined in CFR 312.52, all transfers of obligations must be documented in writing to describe how responsibilities are assumed by the CRO. To satisfy this requirement, a Clinical Services Agreement, CRO Master Agreement, or similar agreement, including respective responsibilities (including those for quality), may be employed. Quality Agreements are required (or "expected" in the U.S.) for providers of GMP products and services. In the EU, the recent *Guidelines on Good Distribution Practice of Medicinal Products for Human Use (07 MARCH 2013)* requires Quality Agreements with providers of GDP services.

ICH E6 *Guideline for Good Clinical Practice* requires an agreement but does not say it has to take the form of a separate Quality Agreement. To satisfy the requirements in ICH E6 5.1.4 and 5.2.2, a Clinical Services Agreement, CRO Master Agreement, or similar agreement that specifies contractor responsibilities is typically used:

**5.1.4** Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

**5.2.2** Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

Recently, regulatory guidance for formal Quality Agreements in related areas has come from both the U.S. and EU. In the EU, the new *Guidelines on Good Distribution Practice (GDP) of Medicinal Products for Human Use (07 MARCH 2013)* requires Quality Agreements with

providers of GDP services. In the U.S. and for providers of GMP products and services, the FDA issued a Guidance for Industry in May 2013, entitled: *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. This Guidance defines a Quality Agreement as:

*A comprehensive written agreement that defines and establishes the obligations and responsibilities of the Quality Unit of each of the parties involved.*

The term "Agreement" is generally defined as a negotiated and legally enforceable understanding between two or more legally competent parties, in this case, the Sponsor and the CRO.

A Quality Agreement may also be referred to as a "Technical Agreement" (e.g., in the EU), "Quality Technical Agreement," or "Quality Manual."

## **Essential Elements**

Appendix 1 presents an actual Quality Agreement template that can be adapted. The core sections consist of the following:

### **Purpose/Scope**

This section provides a high-level description and scope of the products and/or services to be provided by the supplier. When a contractor provides personnel to the Sponsor to be integrated within the Sponsor's organization, a formal Quality Agreement may not be warranted, since the Sponsor normally assumes responsibility for training the staff on its SOPs, and all the activities are under the umbrella of the Sponsor's quality management system.

When the relationship is elevated to a functional service provider (FSP) or full CRO model, a Quality Agreement becomes necessary. The CRO's work may be performed under its own QMS (with Sponsor oversight). Or, responsibility for quality may be split between parties, so it becomes necessary to define which QMS applies where.

### **Definitions**

This section includes definitions and acronyms to guarantee that both parties have the same interpretation of quality terminology. For example, the immediate corrective action taken to correct a nonconformance or deviation at one company might be identified using different terminology than at another. Also, companies often use the terms for quality control (QC) and quality assurance (QA) with different meanings.

### **Sponsor Evaluation of the CRO**

The supplier evaluation process does not stop after the initial qualification audit but continues with the ongoing monitoring of the CRO's performance against delivery requirements. The parties must agree upon the quality objectives and key performance indicators against predetermined performance metrics, and how often they are reported. The sponsor will need this information to coincide with scheduled management review meetings, where this information will be presented to senior management. All identified nonconformances and Corrective Actions / Preventive Actions (CAPA) should be cross-referenced to the CRO's quality record file and, in the case of CAPAs, the CRO should focus not only on immediate corrective actions but also on preventive actions to improve the capabilities of their processes.

The sponsor's rights to audit the CRO are defined by the following topics:

- Requirement for prior notification and length of audit

- Facilities, records, files, SOPs, etc. within scope of the evaluation
- Corrective and/or preventive action for any identified audit observation
- Escalation process
- For cause audits in cases of scientific fraud or misconduct, nonconformances, deviations or Corrective and Preventive Actions (CAPAs), adverse events/serious adverse events

### **Timely Notifications and Communications**

This section describes the plan for communications between the parties. To facilitate communications, the primary points of contact for each critical functional area are defined in an appendix or attachment to the Quality Agreement, including each person's name, title, electronic mail address, and telephone number. The addendum must be revised each time a primary point of contact changes.

This section also defines expectations for notification timeliness. For example, it is quite common for the CRO to notify the Sponsor within a defined time period when a regulatory inspection agency visits. The timelines for reporting nonconformances, deviations or CAPAs must also be defined, as well as changes to standard operating procedures, quality processes, or upgrades to computer-related systems that support quality processes.

This section also outlines dispute resolution steps, including the steps taken to escalate issues to senior management and the roles and responsibilities between the organizations. Typically, the Quality Agreement will defer to and reference the corresponding section of the Master Service Agreement, which defines in much greater detail the dispute resolution process.

### **Quality Responsibilities**

The most important section of any Quality Agreement is the division of quality roles and responsibilities between the parties. For each service or product provided, this section delineates accountability for the quality requirements pertaining to each GCP requirement (federal, state or local) and quality management system component.

The quality system elements that must be covered include document control, record control, training, nonconformance/CAPA, supplier qualification, and internal/external audits. The roles, responsibilities and processes for the following must be identified:

- Management of the Trial Master File (TMF) and essential documents before, during and after the clinical phase of the trial
- Reporting Adverse Events and Serious Adverse Events, including definitions of listed events, timeliness and roles/responsibilities
- Monitoring plan of investigator sites and distribution of visit reports (site initiation, interim monitoring, and close-out)
- Selection and training of site monitors
- Regulatory filings, including Investigator's Brochure, Form FDA 1572, Patient Narratives, Clinical Study Reports, etc.
- Information systems that will be used for a Clinical Trial Management System (CTMS), electronic Trial Master File (eTMF), Electronic Data Capture (EDC), electronic Learning Management System (eLMS), etc.

### **Change Management and Revisions**

This section describes how to keep the Quality Agreement and appendices current when the

service/product offerings, regulatory requirements, or responsible personnel change. Typically, either party can initiate a change. This section outlines the steps between the respective organizations to update, review, approve and implement a new revision.

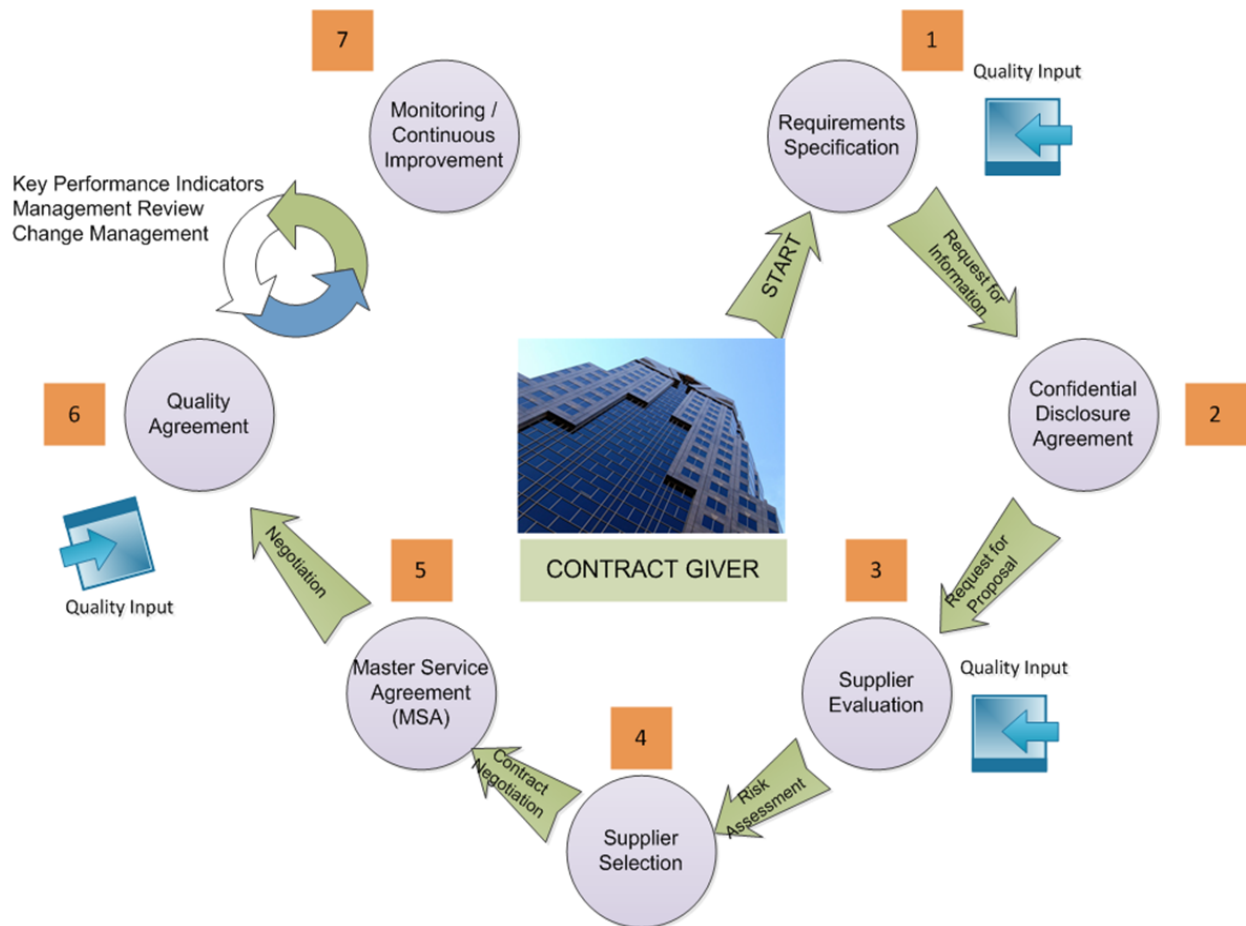
**Process Flow**

It is important to incorporate quality concepts and engage a representative from the Quality organization at select points in the procurement process (Figure 1). For example, when the requirements are being defined, a representative from the Quality organization should be consulted to help answer the following questions:

- What quality management systems are involved?
- For each quality management system, what are the requirements for the CRO?
- What are the inputs and outputs for each quality management system element?

The Quality representative will also help identify those CROs that have already been vetted through the quality part of the supplier qualification process and the current status of each. This information may help determine a short list of those CROs that appear to best satisfy the requirements.

**Figure 1. Procurement Process**



For those CROs that make the short list, the Sponsor verifies that a current, approved confidential disclosure agreement (CDA) is in place prior to conducting a quality evaluation by the Quality Assurance function to determine:

- Current regulatory status of the company (site licenses, registrations, recent inspection results, etc.)
- Formal, written standard operating procedures and objective evidence of compliance
- Quality organizational structure and capabilities
- Maturity level of the quality management systems and interfaces with customers, including feedback and continuous improvement
- Capability of processes, infrastructure and personnel to support the outsourced work

From the results of this quality evaluation, a risk assessment is conducted to itemize and quantify the known risks for each supplier. For example, a supplier might have an off-site data center for disaster recovery in the same neighborhood as the main site, which is thus susceptible to the same environmental risks. For each identified risk, potential controls and risk mitigation strategies must be identified. If the Sponsor hosts bid-defense meetings, team members can ask very specific questions related to quality.

The Master Service Agreement (MSA) may provide an overview of the quality requirements of the relationship, but the Quality Agreement should be a separate document. The MSA contains confidential commercial terms, so access is usually restricted within both organizations. In contrast, the Quality Agreement must be readily available throughout both organizations so it can serve as a seamless guide between the quality processes of the two organizations.

Regulatory authorities normally do not request and review commercial contracts but will request and review evidence of a formal Quality Agreement.

While the signed MSA seldom changes, the Quality Agreement is a living document, subject to updates in areas such as:

- Regulations, guidelines and standards
- Quality management system requirements
- Quality specifications and related quality KPIs
- Key contact personnel

When implementing or significantly revising a Quality Agreement, formal training of all appropriate personnel should be conducted and documented. Given the frequency of these changes and the need for broad access, version control is very difficult unless the document is maintained with a single electronic point of access for each party.

As with any quality system requirement, it is best to define the quality agreement process within a standard operating procedure (SOP), using a pre-approved Quality Agreement template for each category of supplier. For example, separate Quality Agreement templates might be developed for:

- Nonclinical development laboratories
- Clinical monitoring
- Clinical operations
- Medical writing
- Investigative material packaging and distribution
- Pharmacovigilance

## **Conclusion**

A written Quality Agreement serves as a significant tool to build quality into a relationship between the respective parties by defining the roles and responsibilities for all quality elements within the quality management system. A separate Quality Agreement is best practice and should be available to all personnel in both organizations that are involved in the conduct of a clinical trial. Making the effort upfront to clearly delineate expectations of each party will promote transparency, open communication, and consistency that will carry forward through the entire lifecycle of the product or service. By building quality into clinical trials, data integrity and subject protection can be achieved in a more efficient and controlled manner.

## **Disclaimer**

The views expressed in this article are solely those of the authors and not necessarily the views of the companies or institutions at which they are employed.

## **Acknowledgment**

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## **References**

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonized Tripartite Guideline; Pharmaceutical Quality System Q10; current Step 4 version dated 4 June 2008

Title 21-Food and Drugs; Chapter I-Food and Drug Administration; Department of Health and Human Services; Subchapter H-Medical Devices; Part 820 Quality System Regulation

Guidance for Industry; Contract Manufacturing Arrangements for Drugs: Quality Agreements; Draft Guidance, May 2013

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonised Tripartite Guideline; Guideline for Good Clinical Practice E6(R1); current Step 4 version dated 10 June 1996

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## APPENDIX 1

### **SAMPLE GCP QUALITY AGREEMENT TEMPLATE**

*(Note: the agreement must comply with each company's requirements and specific language)*

Between

**The Contract Giver/Contracting Entity:**

**{include company name/address here}**

and

**The Contract Acceptor/Contractor:**

**{include company name/address here}**

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5.0	CHANGE HISTORY
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The Contract Giver/Contracting Entity ("CE") and the Contract Acceptor/Contractor ("CO") agree as follows:

#### **1.0 OVERVIEW/PURPOSE**

- 1.1 CE and CO have entered into a {enter as appropriate: "Collaboration," "Master", "Service", "Business"} Agreement effective mmddyy ({enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement) for certain Products, including {enter description, as applicable}. In furtherance thereof and to define the interaction between CO Quality Assurance and CE Product Quality with respect to clinical study activities, CO and CE are entering into this GCP Quality Agreement (this "Agreement"). Each capitalized term used but not defined herein shall have the meaning ascribed thereto in the {enter as appropriate: "Collaboration", "Master", "Service", "Business"} Agreement. CE and CO may each be referred to herein individually as a "Party" and collectively as the "Parties".
- 1.2 This Agreement will be effective as of the date of final signature on the Agreement ("Effective Date") and will expire automatically with expiration or termination of the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement, except for provisions which, by their nature, are intended to survive.
- 1.3 In the event of a conflict between any of the provisions of this Agreement and the {enter as applicable: the ""Collaboration", "Master", "Service",



"Business"} Agreement in the terms non-quality related topics, the terms of the {enter as applicable: the ""Collaboration", "Master", "Service", "Business"} Agreement shall override the terms in this Agreement. In the event of a conflict between any of the provisions of this Agreement and the {enter as applicable: the ""Collaboration", "Master", "Service", "Business"} Agreement in the terms quality related topics, the terms of this Agreement shall override the terms in the {enter as applicable: the ""Collaboration", "Master", "Service", "Business"} Agreement.

- 1.4 Basic responsibilities of the Parties are identified in Attachment 2, Responsibility Table.

## 2.0 TERMS/DEFINITIONS

**Adverse Event (AE)** – Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the use of the investigational medicinal product.

**Clinical Study** – Any human clinical trial of {enter program description} that is subject to the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement, and refers to a Phase I Clinical Study, Phase II Clinical Study, Phase III Clinical Study, or Phase IV Clinical Study.

**Other Party** – The Party that is not the Responsible Party.

**Program (s)** {may include Program title} – any activity related to a Clinical Study conducted by either Party.

**Regulatory Filings** – IND and BLA submissions, including any supplements or modifications thereto.

**Responsible Party** – The Party that is responsible under this Agreement or the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement for a particular activity related to a Clinical Study. The Responsible Party may delegate certain Clinical Study activities to a Service Provider.

**Serious Adverse Event (SAE)** – An AE is classified as a SAE if it meets any one of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event requiring expedited reporting by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

**Serious Breach** – A breach of GCP or the protocol that is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial and the breach could be relevant to trial subjects in the UK.

**Standard Operating Procedures (SOPs)** regarding the performance of clinical studies in accordance with GCP.

**Service Provider** – Any Third Party retained by either of the Parties in accordance with this Agreement to perform one or more study-related activities or duties.

**Study Management Team (SMT)** – Multi-disciplinary Team consisting of members from the CE and CO responsible for Study Management activities.

**Testing** - Uniform chemical and biological testing procedures and equipment within the laboratories.

**Trial Master File (TMF)** - A Trial Master File contains essential documents for a clinical trial that may be subject to regulatory agency oversight. The Trial Master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements. OR

The collection of artifacts that enables us to evaluate the conduct of the clinical study, the integrity of the data and the compliance with GCP and all applicable regulatory requirements.

Standards for the management of the TMF artifacts that individually and collectively permit the reconstruction an evaluation of the conduct of a clinical study and the quality of the data produced.

### **3.0 COMPLIANCE REQUIREMENTS**

#### **3.1 General**

- 3.1.1 This Agreement may be revised “as needed” or whenever the {enter as appropriate: “Collaboration”, “Master”, “Service”, “Business”} Agreement is renegotiated. All changes in this Agreement must be documented, reviewed and approved in writing by both Parties. Notwithstanding this Section 3.1.1, Attachment 1: Contact Information may be updated as needed from time to time by written notice to the other Party.
- 3.1.2 Disputes or conflicts will be settled, if possible, through good faith negotiations between the Parties, in a timely and equitable manner in compliance with all applicable quality and regulatory requirements. Resolutions will be documented and signed by both Parties. If resolution cannot be reached, the issue will be referred to the Executive Officers in accordance with {enter as appropriate: “Collaboration”, “Master”, “Service”, “Business”} Agreement.
- 3.1.3 All Clinical Studies shall be implemented in accordance with the GCPs and all applicable Laws. The Parties or their Service Providers will have the appropriate SOPs in place to carry out these activities.
- 3.1.4 The Responsible Party will not subcontract or delegate work related to implementation of Clinical Studies (including but not limited to study activation and monitoring, clinical laboratory testing, data management, medical writing, regulatory affairs and pharmacovigilance) to a Service Provider without prior written approval from the Other Party and except in accordance with the applicable provisions of the {enter as appropriate: “Collaboration”, “Master”, “Service”, “Business”} Agreement.
  - 3.1.4.1 The Responsible Party that subcontracts or delegates work to a Service Provider is responsible for assuring work is conducted in accordance with the GCPs and all applicable Laws.

- 3.1.4.2 The Responsible Party that subcontracts or delegates work to a Service Provider is responsible, notwithstanding such subcontracting, for all activities assigned the Responsible Party in this Agreement.
- 3.1.5 The Responsible Party will conduct and maintain operations in compliance with applicable Laws, including current applicable environmental and occupational health and safety laws and regulations.

### **3.2 Regulatory Filings**

- 3.2.1 The Responsible Party for Regulatory Filings will maintain such Regulatory Filings in a manner that allows visibility to the other Party, in accordance with the {enter as appropriate: "Collaboration", "Master", "Service", "Business"} Agreement.
- 3.2.2 Both Parties are responsible to review designated Regulatory Filings prior to submission (e.g. protocols and amendments, responses to Health Authorities, Annual Reports).

### **3.3 GCP Audits**

#### **3.3.1 General**

- 3.3.1.1 An audit plan will be prepared and agreed to by both Parties and must be implemented by the Responsible Party for each Clinical Study. The Responsible Party will make copies of audit plans available to the Other Party at the beginning of each clinical study and updates will be provided as they occur during the study.
- 3.3.1.2 Each Party must notify the Other Party within one (1) business day of critical observations from audits. Critical observations are defined in the Party's or the Service Provider's SOPs.
- 3.3.1.3 An audit summary report will be provided to the Other Party within thirty (30) calendar days after completion of the audit.
- 3.3.1.4 Audit responses to critical observations will be submitted to the Other Party within five (5) business days of receipt.

#### **3.3.2 Directed/For Cause Audits**

- 3.3.2.1 If a directed or for-cause audit is required specific to a {enter program description} Program activity, the Party leading the audit (i.e., the Responsible Party) will inform the Other Party in advance of the scheduled audit at the applicable site/facility. The Other Party will have the option of attending the audit. The results of the audit will be provided to the Other Party within thirty (30) calendar days after the Responsible Party's completion of the audit.
- 3.3.2.2 SOPs of the Responsible Party or the applicable Service Provider will be used as the audit standard. In general, audits will generally require two to four days on site at the site/facility.
- 3.3.2.3 The Responsible Party will, within one (1) business day, communicate to each Party's regulatory affairs department any
  - 3.3.2.3.1 suspected scientific misconduct or fraud
  - 3.3.2.3.2 In studies where there are clinical sites in the United Kingdom (UK), evidence of a Serious Breach to

ensure that the Regulatory Authorities are notified as dictated by Law.

### **3.4 GCP Audits – Other Party**

- 3.4.1 Each Party shall have the right (upon reasonable notice during reasonable business hours) to conduct annual quality assurance audits with respect to the {enter program description} Program of the Other Party, including with respect to the Other Party's Service Providers, to verify compliance with GCP and applicable Laws. The number of participants and days will follow industry standards (typically two persons over two days). Additionally, "for-cause" audits may occur at any time in the event of a compliance issue.
- 3.4.2 Each Party may conduct annual audits of the Other Party's laboratories or, if subcontracted by the Other Party, the Service Provider's laboratories performing clinical sample analysis relating to a {enter program description} Program and any documentation/records related thereto to verify compliance with SOPs and applicable Laws. Audits may occur more frequently in the event of a compliance/technical/scientific issue ("For Cause"). All audits conducted by each Party at the Other Party's or the Service Provider's facilities will occur upon reasonable notice and during normal business hours.
- 3.4.3 The Party managing the Clinical Study (i.e., the Responsible Party) will conduct or allow the Other Party to conduct routine audits of {enter program description} Program clinical investigator sites following the established audit plan, as set forth in more detail in Section 3.5 below.

### **3.5 GCP Audits - Investigator Sites**

- 3.5.1 Investigator site audit timing is dependent on enrollment and other factors, such as identification of significant GCP compliance issues. A minimum of {X%} of investigator sites will be audited for each {enter program description} Program.
- 3.5.2 Investigator sites should be notified that audit findings may be shared with the Other Party. Appropriate agreements should be obtained prior to audit to ensure accessibility to the investigator site and distribution of the findings to the Other Party. The Responsible Party's SOPs or the Service Provider's SOPs will be used as the audit standard. In general, audits will require two (2) to three (3) days on site at the investigator site.

### **3.6 GCP Audits – Service Providers**

- 3.6.1 The Responsible Party may delegate or subcontract certain responsibilities for a {enter program description} Program to one or more Service Providers approved by the Responsible Party. The responsibilities delegated will be called out clearly in an appropriate service contract between the Responsible Party and the Service Provider. This documentation will be shared with the Other Party.
- 3.6.2 Audits of Service Providers may be performed by the Party that has contracted with such Service Provider (i.e. the Responsible Party), the Other Party on behalf of the Responsible Party, or jointly by both Parties. In general, audits will require two (2) to three (3) days on site at the Service Provider's facilities.
- 3.6.3 Service Providers for the {enter program description} Program shall have a qualification assessment or audit prior to use. If a qualification assessment is performed prior to use of a Service

Provider, the first audit shall occur within three to six months of the initiation of a new protocol. Service Providers shall be audited per the audit plan utilizing a risk based analysis with input from the SMT.

3.6.4 Service Providers should be notified of the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement and that audit findings may be shared with the Other Party. Appropriate agreements should be obtained prior to audit to ensure accessibility to the Service Provider's facilities, study documentation and allowance for distribution of the findings to the Other Party. The Responsible Party's SOPs will be used as the audit standard. In general, audits require two (2) to three (3) days on site at the Service Provider's facilities.

### 3.7 **GCP Audits - Clinical Study Report**

3.7.1 The Party responsible for the development of the clinical study report (CSR) will conduct a routine CSR audit in accordance with the Responsible Party's SOPs or the Service Provider's SOPs with such Responsible Party's SOPs after the joint SMT has reviewed the document and all of the SMT's comments are addressed.

3.7.2 The audit may be performed by the Responsible Party or by a Service Provider. The Responsible Party will still maintain responsibility for ensuring the audit of the CSR is performed.

3.7.3 In cases where a CSR will not be pursued for regulatory submission, the Responsible Party's SMT may deem the audit of a CSR unnecessary. Documentation of the rationale for not conducting a CSR audit will be maintained in the Trial Master File in accordance with ICH Guidance for Industry E6 (Good Clinical Practice).

3.7.4 The Party responsible for providing the data for the CSR is responsible for ensuring raw data, applicable technical reports, any statistical tables and listings generated for the development of the CSR, and any other publication, may be audited or quality control reviewed, following such Responsible Party's SOPs or the Service Provider's SOPs.

### 3.8 **GCP Audits - Other Audits**

3.8.1 The results of any other GCP audits (i.e., data listings, regulatory submissions, etc.) specific to the Programs will be provided by the Party responsible for the audit to the Other Party as the audits occur.

### 3.9 **Regulatory Inspections**

3.9.1 Each Party shall provide the Other Party, within two (2) business days of the event, notice of any Regulatory Authority inspection of any {enter program description} Program study manager, clinical investigator site, or Service Provider. Notification shall be made by phone and email per the contact information set forth in Attachment 1. At the conclusion of the inspection, the Responsible Party will provide a written summary of any inspection findings to the Other Party, from the inspected party.

3.9.2 In the case of a {enter program description} Program, study-specific inspection of the managing Party by a Regulatory Authority, the Party being inspected shall notify the Other Party of the inspection within two (2) business days before the inspection occurs. At the conclusion of the inspection, the inspected Party will provide a summary of any inspection findings relating to the {enter program description} Program to the Other Party. Copies of FDA-483s, warning letters and the like will be provided by the inspected Party to the Other Party

within two (2) business days after receipt by the inspected Party. The Other Party will have the opportunity to review and comment on any Regulatory Authority findings or subsequent responses if the 483 or warning letter impacts the {enter program description} Program.

3.9.3 The Other Party, if applicable, shall have the right to be present, but not participate in direct interactions, during such Regulatory Authority inspection, as further described in the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement.

**3.10 Documentation**

3.10.1 Each Party will retain Quality Assurance records in compliance with all applicable Laws, but at minimum for a period of {X} years.

**3.11 Debarment**

3.11.1 The debarment provisions in the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement shall apply to this Agreement.

**3.12 Jurisdiction**

3.12.1 The provisions in the {enter as applicable: the "Collaboration", "Master", "Service", "Business"} Agreement regarding the place of jurisdiction shall apply to this Agreement.

**4.0 SIGNATURES**

Contract Giver		Contract Acceptor	
By		By	
Printed Name		Printed Name	
Title		Title	
Date		Date	
By		By	
Printed Name		Printed Name	
Title		Title	
Date		Date	

**5.0 CHANGE HISTORY**

Version	Description and reason for change
1.0	{add description of change and reason for change}

**ATTACHMENT 1**

**CONTACT INFORMATION**

<b>Function/ Department</b>	<b>Contract Giver</b>	<b>Contract Acceptor</b>
GCP Quality Assurance	Insert Name/Title, phone # and E-Mail of CE Contact Name/Title: Phone: EMail:	Insert Name/Title, phone # and E-Mail of CO Contact Name/Title: Phone: Email:
Regulatory Affairs	Insert Name/Title, phone # and E-Mail of CE Contact Name/Title: Phone: EMail:	Insert Name/Title, phone # and E-Mail of CO Contact Name/Title: Phone: EMail:

**ATTACHMENT 2**

**RESPONSIBILITY TABLE**

<b>Task</b>	<b>Contract Giver</b>	<b>Contract Acceptor</b>
Registration agency liaison		
Supply of all necessary technical and regulatory documentation		
Supplier qualification of Contract Acceptor		
Audits of any Service Providers		