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Options for Financially Supporting GLP and GCLP Quality Assurance Programs within an Academic Institution

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Abstract

Translational research involves bringing promising candidate drugs, biologics, and medical devices from the research bench into use at the patient's bedside. Many of the pathways taken during this process are governed by federal guidelines and regulations. Academic institutions often are at the forefront of innovative and translational research but lack the controlled environment in which to perform quality-controlled animal and laboratory studies. Such studies should be compliant with good laboratory practice (GLP) and good clinical laboratory practice (GCLP); both of which require the support of Quality Assurance (QA) personnel and a Quality Assurance Unit (QAU). This discussion provides examples of how academic institutions can financially support QA functions for animal and laboratory quality-controlled studies by utilizing: 1) direct funding, 2) indirect sources of funding, 3) University Research Foundations, 4) study sponsor-direct funding, or a combination of these four.

Introduction

With the establishment of the National Center for Advancing Translational Sciences (NCATS) in 2011, the US National Institute of Health (NIH) made a commitment to accelerate the timeline and decrease the cost of translating basic research discoveries from the laboratory bench to clinical applications (1). An increasing number of academic institutions around the country are joining the national movement to advance translational science by focusing research efforts on drug discovery, drug delivery, and device development and testing (2).

The scientific expertise and the intellectual environment present in academia are unique and are very valuable assets for novel product development and testing. Campus facilities now provide support to perform animal and laboratory testing of novel products from preclinical safety evaluations to endpoint assessments of clinical trial specimens. In order to perform such work, academic laboratories must comply with regulations and/or guidelines that define and standardize basic quality principles whereby studies are planned, performed, monitored, recorded, reported, and archived, including the requirement for Quality Assurance (QA) personnel (3). These personnel are crucial to assure the quality of study conduct and study data since these data are used to support human health or environmental safety regulatory decisions. Such quality-controlled animal and laboratory studies are required by Federal authorities and/or sponsors to adhere to good laboratory practice (GLP) regulations (for pre-clinical studies) (4-7) or good clinical laboratory practice (GCLP) guidelines (for endpoint assay studies of clinical trial specimens) (8-10).

GLP governs the processes by which nonclinical safety and toxicology studies perform and demonstrate new product safety (4-7). GCLP guidelines apply those principles, established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from Phase I through Phase III clinical trial specimens, so that consistent and reliable

laboratory results are obtained (8-10). The GCLP standards, although guidelines, are now employed worldwide (11-12) and are vital to the conduct of these laboratory studies, which are not designed to be reported to the physician or the patient and, therefore, are not directly regulated by *Clinical Laboratory Improvement Amendments* in the US (13).

The task of assuring quality is typically associated with the Quality Assurance Unit (QAU). GLP regulations and GCLP guidelines specifically identify the QAU as the entity responsible for inspecting study activities, auditing data to ensure quality and compliance with the pre-established standards, and monitoring quality indicators over time.

Historically, academia has not had dedicated QA personnel and has had difficulty in funding these positions that are necessary to meet the regulatory requirements. More recently, academic institutions have faced the issue of defining what source of funding can be used to support QA personnel efforts, as increased numbers of regulated studies and studies requiring quality standards are being performed by academic investigators (2,14). A working group from the University Specialty Section of the Society of Quality Assurance explored how QA personnel and infrastructures within academia are funded, and a synopsis of the results is presented herein.

Discussion

There are four approaches applicable to funding GLP and GLCP QA programs in academic settings. These include indirect funding, direct funding, university research foundation funding, and study sponsor funding. Combinations of the aforementioned may also occur. The following discusses and analyzes these approaches. Case studies describing each approach are also presented.

Indirect Funding

Supporting a QAU from central funds garnered through indirect cost recovery is one way in which academic institutions are able to conduct regulated studies in compliance with quality standards. In some institutions, indirect costs are provided by a central, inter-departmental structure, such as an Office for Research, to fund QA personnel. Such personnel operate as a shared resource. In this model, the institution has committed to investigators to make QA services for regulated research studies available and to provide funds from indirect cost recovery to support QA activities. This decision is rooted in the concept that providing researchers with guidance for implementing quality standards will not only enhance current research but also will provide the academic institution with a competitive edge for future funding and support an overall heightened quality research culture throughout the institution.

Central funding from such an office can provide additional benefits. First, a centrally funded QAU does not directly answer to any one department and, therefore, avoids potential conflict of interest. This can also protect the QAU from any potential undue pressure by a particular investigator or sponsor. Secondly, centralized and permanent funding of a QAU can provide the institution with an increased level of investment in the quality of the studies being performed and, additionally, can provide a stable source of funding for QA infrastructure.

The indirect funding method also has the advantage of the QA personnel having the ability to work on many different projects. This allows for the development of a skilled, focused, and highly trained QA personnel pool. The drawback of this funding mechanism is that, depending on the amount of regulated work scheduled at the institution, there may not be enough work for a permanent QA position. Figure 1 presents a case-study example of indirect funding of QA.

Figure 1: Case-Study A—Indirect Funding.

The Office of Research Compliance at an academic institution supports a QAU, which is staffed by one full-time employee who reports to the Director of Research Compliance. The employee is responsible for providing QA services for any regulated research projects conducted at the institution. The Office of Research Compliance is centrally funded through recovered indirect costs that the institution receives from sponsored research based on their federally negotiated rate. Funding for the QAU, as well as all personnel in the Office of Research Compliance, is fixed and does not fluctuate based on caseload or the complexity of regulated projects. All projects within each research area of the academic institution have access to the services provided by the QAU at no additional charge.

Direct Funding

Another common option is to have the QAU funded, either partially or in its entirety, through direct costs specified by grants or contracts that support the regulated study. With this option, the budget can be developed in one of two ways. In one approach, the funding to support QA activities is built into the budget of each study as a "QA-specific line item." In this case, the budget includes delineated direct costs for QA personnel, labor, and other QA-related expenses. In the other approach, the budget can be developed in a way that includes QA oversight of particular areas of work. For example, when accounting for the extra cost of running an endpoint assay in GLP/GCLP compliance, an approximate 20% increase can be added to the basic assay cost itemized in the budget calculations in order to fund all QA activities (15). Figure 2 presents a case-study example for direct funding of a QAU.

Figure 2: Case-Study B—Direct Funding.

At a private academic institution, the QAU has its own team overseeing standardization of laboratories that are performing immune-monitoring assays in compliance with GCLP guidance for clinical trials. Grant-funded studies are conducted in compliance with GCLP for both US and international laboratories, many of which are located at academic institutions. To support the quality review required for a GCLP study, a central QA team, supported by the grant's direct costs, oversees this study and provides all aspects of QA services for its duration.

In this direct funding scenario, the study requires QA support that is specific to the study. The budget for these activities can be estimated based upon the required QA resource costs, either as internal QA personnel or external QA contractual personnel. Funding is then built into the direct costs of the regulated study. The advantage of this approach is that funding is not dependent on a commitment at the institutional level and can fluctuate with need.

When using either indirect or direct funding, the option exists to hire outside consultants to fulfill the QA responsibilities. At institutions where there are not enough regulated projects being performed to warrant permanent QA personnel, a qualified QA professional consultant can be hired to fulfill QA responsibilities. Contracting with an outside QA consultant for initial regulated studies may provide a stepping stone to fund an internal unit once the research program becomes established and consistently brings in grants and contracts for regulated research. While using a QA consultant may cost more per study or task than in-house QA personnel, for some institutions, the benefit of not having to establish and fund a full-time position allows them to perform occasional regulated work. These two scenarios are not mutually exclusive, as Figure 3 provides a case-study where elements of both indirect and direct funding can be jointly utilized.

Figure 3: Case Study C—Combination of Direct and Indirect Funding.

An investigator at an academic institution has been approached by a sponsor to perform a GLP-compliant toxicity study. In order to conduct the study, the investigator must implement GLP compliance in her own laboratory and in the animal facility. She works with the institutional officials to hire an externally qualified QA consultant to 1) train staff in GLP compliance, 2) consult on an action plan to implement facility GLP compliance, and 3) perform a pre-study facility audit to assure that the laboratory and the animal facility are GLP-compliant.

The pre-study consultant services are paid from departmental indirect costs. Once the facilities are GLP-compliant, the researcher hires the QA consultant to perform study-specific inspections and audits through direct costs from the sponsor contract.

University Research Foundation Funding

Although University Research Foundations (URFs) vary in their purpose and function from one institution to another, they are an oft-overlooked source of funding that could enable and support the QA function within an institution. URFs are usually operated as 501(c)(3) non-profit organizations separate from the university, and they operate under a Board of Directors or professional Executive Director (16). They typically have their own support staff, which can provide a managerial structure similar to a contract research organization. Foundations often have more flexible funding options than the main institution. The ability to serve as a legal recipient of contracts and grants from industry, public and private non-profits, and government agencies for the performance of research and education allows innovative approaches to QA financial support. As such, URFs are usually an intramural resource that can enable and promote externally funded programs to further the university's research and educational mission.

URFs are often used to enable novel developmental and cutting-edge research, sometimes through start-up companies or

incubator programs, to accelerate growth through access to partnerships, business expertise, funding, facilities, and equipment. The QAU function may be more readily accepted within the innovation culture associated with these types of activities rather than the basic research culture common to historical university research. URFs might more willingly accede to the government oversight and adherence to strict federal regulations. They might also offer flexibility in hiring practices and may be more suitable when QA functions need to fluctuate or are subcontracted to consultants or QA service organizations. Furthermore, depending on the volume of work, permanent QA personnel would not be excluded. Since URFs generally provide cradle-to-grave grant and contract services and a strongly orientation toward client service, QA as a value-added service may provide an excellent managerial fit within the typical university structure and could be set up as a basic service or a fee-for-service system depending upon the foundation's fee structure system. In either scenario, the URF might offer a good financial, managerial, and cultural position from which a QAU could function, support university research needs, and assist in support of GLP compliance by providing test facility management and QA services (16), outlined in the case-study in Figure 4.

Figure 4: Case Study D—Funded by University Research Foundation.

The URF at a local university has, as part of its mission, the goal of making funding and resources available to aid in scientific investigation and research studies. When a researcher is planning to perform the regulated studies, he submits an application to the URF outlining the study protocol, the QA needs, the status of the researcher's program as it currently stands, and an estimate of the level of QA involvement that will be needed.

The URF scientific review board then meets with the researcher to carefully outline all expectations of QA needs before assembling a QA funding package. The final QA funding package would likely include the costs of hiring the consultant to work on compliance aspects of the program and provide independent auditing services.

If the well-funded URF has developed a nearby "technology park" where GLP-compliant facilities are maintained, then after study approval the researcher would be assigned a time when he will be able to use the local facilities to conduct regulated research. Proximity to the academic institution offers ease of travel, and the self-contained facilities have all the QA and auditing functions provided for in-house by knowledgeable and expert staff.

Study Sponsor-Funded QA

For some studies, the term "sponsor" also refers to the entity that requesting the regulated study be performed. If QA oversight for the study is required, the sponsor might choose to either provide their own QA personnel from within their organization or hire an outside independent QA consultant, see Figure 5. In this scenario, the sponsor pays for all QA expenses. While the sponsor will contract with the QA personnel separately from the academic institution, the academic institution may still charge the sponsor for other quality system activities unique to the study being requested if the university is responsible for those charges (i.e., equipment calibrations and archives maintenance). This approach is usually beneficial if the institution only has studies requiring QA oversight from one sponsor for a limited time period. The QA personnel are limited in their scope of work and focus only for those studies specified by the sponsor. This method neither assists in support of a long-term QAU or promotion of an institution-wide quality culture nor provides a support program available to other researchers and research programs.

Figure 5: Case Study E—Sponsor Funded.

At an academic health center, an industry sponsor approached a researcher to use 'cutting-edge' techniques developed in one of the academic labs to study the safety and toxicology of a new potential product. The researcher presents the study protocol to the animal facility administrators and outlines the sponsor's plan to provide all aspects of QA monitoring.

The sponsor provides a monitor who will be welcomed into the facility to do a pre-study inspection of both the animal facility as well as the GLP laboratory. The sponsor then works with the assigned study director to determine the critical phases of the GLP study so that the sponsor-assigned monitor can perform critical phase inspections and compile a final report.

Conclusion

QA funding may be handled through a variety of different mechanisms and must be tailored to the individual academic institutions' goals and infrastructure. However, it is important to note that none of the models described are mutually

exclusive—many institutions select and use parts of each of these models to provide a complete range of services. There are many different scenarios where QA is needed and different funding streams can be utilized.

The core mission of academia often focuses on the dissemination of knowledge, and those institutions, which perform regulated research, are often involved in both enhancing the practice of evidence-based medicine as well as facilitating the translation of scientific ideas from the laboratory bench to the clinic. When an institution has the desire to move forward with such regulated studies, it should be prepared to build and maintain the quality system required to properly conduct these studies, and this includes funding a QAU. The benefits to the institution performing regulated research include increased funding options, the ability to bring discoveries from the bench through pre-clinical studies and possibly on to clinical trials, and the opportunity to teach students, staff, and faculty how to perform regulated research. In the present economy, it may be difficult to find permanent funding for a full time QAU; therefore, all possible resources should be explored to assist in the establishment of compliant research programs.

It should be made clear that the lack of proper quality oversight in the conduct of regulated research can result in severe negative impacts to the study, the institution, the study sponsor, and, potentially, the clinical trial participants. The problems associated with having an inadequate QAU and the necessary resolutions should be noted early in regulated study development. Academia provides some unique challenges in that institutions do not have the typical managerial structure found in clinical research organizations; however, this does not preclude the development of a creative structure tailored to the specific needs and resources of each institution. Currently, there are many institutions in the US successfully performing these studies, and they blend all of these models to achieve compliant research.

Acronyms and Abbreviations

NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health
QA	Quality Assurance
QAU	Quality Assurance Unit
GLP	Good Laboratory Practices
GCLP	Good Clinical Laboratory Practices
URF	University Research Foundation

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