The Protocol-Provided Clinical Research Model as an Evolving Research Opportunity for Community-Based Hospitals and Health Care Facilities

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There is an evolving model of protocol-provided clinical research that has become more standardized as a research pathway over the last several decades. This model, with reduced research-specific infrastructure requirements and whose trial processes, management, and business operations are very similar to those of standard-of-care clinical and business operations performed by community-based patient-care facilities, now offers a pathway for traditionally non-university-affiliated “nonacademic” community-based hospitals and health care facilities to enter into the arena of clinical research.

Key words: Academic medical centers (AMCs); Clinical research; Community-based hospitals; Protocol-provided clinical trials; Multicenter trials; Site-based research

Until recently, patient care-related clinical research activities have long been dominated by university-based and university-affiliated academic medical centers or AMCs (9). In the past, this has been an unfortunate limitation for clinical research in general, as the vast majority of clinical patient care in this country occurs not in AMCs, but within community-based, nonacademic hospitals and medical facilities. Thus, large, broad-based cross-sections of potential confirmatory, community-based patient–subject populations have, in the past, been frequently excluded from clinical research activities. This is also unfortunate since community-based hospital administrators and thought leaders have indicated that the ability to offer clinical research options to their patient populations would be an attractive...
and desirable addition to the services they provide their communities (1). However, due to the complex nature of academic-based clinical research pathways and different methodologies for employment of and performance goals for “academic”—as opposed to community-based—physicians, along with financing and management of infrastructure demands for these types of research systems, community-based facilities have historically found it difficult to develop and maintain on-site support for these “classic” types of clinical research pathways.

Over the past decade, there has been a downturn in federal funding and other similar clinical research financial support through classic funding pathways such as the National Institutes of Health (NIH), National Science Foundation (NSF), etc. (4,9). This funding loss has, in turn, led to an erosion of clinical research support for AMCs (4,9). However, over this same period, there has continued to evolve a clinical research model that offers community-based facilities the opportunity to participate in patient-care clinical research activities without having to possess the extensive research infrastructure, special funding pathways, and specialized physician-scientist investigators common to AMCs. This newer model is a pathway of protocol-provided clinical research trials, which has evolved into a well-defined and regulated system that can, if managed correctly, now offer community-based and regional (nonacademic) hospitals and care facilities an entry point into and the ability to participate in this research arena (6,9). Though historically this research model has been offered most frequently by industry-based trial sponsors, this trial design has become progressively more common. Protocol-provided clinical research trials are now being offered to sites through a broader array of differing trial sponsor types, including the NIH and its affiliated organizations, cooperative group networks, and academic-affiliated and community-based research centers and networks.

As a research model, protocol-provided clinical trials are trials in which a group of scientific investigators have already initiated and developed a clinical research question that has evolved into a completed and defined research protocol. Most commonly, such protocol-provided clinical research trials become available when the initiating investigators have already performed extensive initial safety and efficacy or other early phase testing in small numbers of subjects and are now ready to test their clinical hypothesis with large numbers of clinical patient-subjects. The protocol-initiating group, through statistical evaluation and other analytics, has made a determination on the total “n” number needed to attempt to prove or disprove their hypothesis. Frequently, this “n” number can be large, often requiring hundreds or sometimes thousands of patient-subject enrollments. Therefore, to be able to perform this research and achieve total target patient-subject enrollment within a reasonable or accelerated time period, the investigator-initiating group and trial sponsor will need to recruit multiple health care facility sites (multicenter trial) to participate in this research effort. Through a variety of recruitment mechanisms, these protocol developer-sponsors will reach out to multiple health care facilities to determine if they are interested in participating in this research project and serving as a research site for the trial as defined by the provided protocol. After initial confidentiality–nondisclosure agreements and qualifying evaluation, interested medical facilities’ site-based research teams will review the protocol to determine if they have adequate numbers of the patient population being sought, interested physicians of the appropriate specialty, and infrastructures that would be capable of performing the protocol-defined research. Each facility research team, including the potential physician-investigators, will also review the protocol to determine if the trial design is an ethical fit and of potential benefit for their patient population and a
good fit for the facility. As part of this evaluation, potential site physician-investigators will make a determination on their willingness and comfort level in following the requirements of the trial protocol in their patient populations, including protocol-required patient randomizations and other trial elements. After these reviews, if the facility team determines that this trial remains attractive, they will so inform the trial sponsor. With the protocol or subsequently with expressed continued interest, the site will receive a proposed trial site research budget for the facility to evaluate. Such budgets are necessary to appropriately compensate the facility, including participating physicians and other research-related infrastructure, for the performance of non-standard of care (SOC) research trial activities within the facility’s patient population, as such non-SOC activities can never be billed to the patient or their third-party payers but do generate costs to the facility and providers.

The ability to easily integrate such trial budgets into their usual business and financial operations can be a very functional option for community-based hospitals and health care facilities. Protocol-provided clinical trial budgets are generally negotiated and contracted in a fashion similar to other “vendor” negotiations and agreements and thus are familiar to health care facility administrations and financial personnel. Such trial budgets are predominantly “pay-for-performance” in design, with a trial protocol design and site budget proposal that comes as part of the trial contracting process. The site budget proposal has been formulated by the initiating trial protocol developers and/or trial sponsor or other trial leadership group, but these site budget proposals are subject to negotiation by each potential participating facility research site in similar fashion to any other vendor-associated contract-budget proposal. The majority of trial payments to the participating site (other than start-up costs, institutional overhead, etc.) are subject-related, “pay-for-performance” invoice-directed payments. Thus, each time the participating health care site successfully completes a subject’s trial enrollment activities and submits the appropriate documentation with an accompanying invoice for those non-SOC, trial-directed, performance-related activities (including non-SOC physician and staff research time and effort services and other trial-related goods and services) through the appropriate pathway, a payment is subsequently received by the participating facility site (pay-for-performance). This is a system that is very similar, both clinically and financially, to current standard-of-care patient treatments and services, except that invoicing for all trial-related non-SOC services rendered is submitted to trial sponsors instead of the patient or SOC third-party payers. Therefore, the clinical trial financial performance system is very familiar to community-based health care facilities and can be performed by the facility’s financial team without undergoing an extensive readjustment or expansion. Also, such trials do not require on-site presence of physician-scientist investigators to initiate trial proposals, protocols, and grant applications seen at university and academic centers, as the trial protocol has been developed off-site. Likewise, there is no requirement for an on-site facility “grants” office to develop and manage investigator-initiated trial grant proposals and awards because trial funding is through a pay-for-performance platform provided by the trial sponsor and negotiated through the facility business office. The absence of such special pathway requirements further reduces the “institutional overhead” expenses and infrastructure requirements for performing these trials and makes this trial pathway more attractive to community-based and regional hospitals and health care facilities that may not have affiliations with traditional academic or university centers.

An additional benefit of the “pay-for-performance” methodology for compensating medical facilities for their trial-related performance efforts is that the participating facility
can rapidly begin to develop and financially underwrite a research infrastructure platform through this funding pattern and expand this service through ongoing participation in such trial opportunities (9). Over time, as this infrastructure grows and the facility physicians who are participating in such trial activities become more comfortable in this research environment, there is an opportunity for such infrastructure to evolve into the realm of addressing research questions specifically of interest to that facility and physician investigators or clinical community by utilizing the now existing research platform to begin to develop facility-based investigator-initiated trial proposals (9).

Some have questioned whether this evolving protocol-provided trial pathway receives adequate oversight and supervision and provides adequate protection for human subjects. For protocol-provided clinical trials, supervision, oversight, and management generally originate with the site where the protocol and trial plan were first initiated, usually termed the “lead site” or coordinating center. Increasingly, if the trial target subject “n” number to enroll is very large, thus requiring large numbers of sites, sometimes in the hundreds of sites nationally or even internationally, trial sponsors or lead sites may seek the assistance of companies commonly referred to as contract research organizations (CROs), which can be recruited to assist or take the lead in supervision and management of these large numbers of trial sites (5,9). As noted previously, in multicenter trials, each potential facility site goes through a pretrial “vetting” process, usually known as a feasibility or qualifying selection review, during which the lead site or CRO evaluates the capabilities of the potential site to successfully perform all the trial-related tasks for a particular study, and the site, in turn, evaluates the elements of the trial. For sites thus selected, the lead site or CRO will then supervise and monitor all aspects of pretrial, trial-related, and posttrial activities, including all trial-related activities of the research team and site physician investigators. Such monitoring and supervision includes regulatory issues, protocol compliance, adverse event reporting, and all other aspects of trial activities. All site trial team members must follow all federal and other guidelines and rules pertaining to research and must undergo extensive and periodic training and certification in topics such as trial ethics, good clinical practice, and other aspects of trial-related activities. Supervision and monitoring also includes continuous central monitoring and site reporting along with periodic on-site visits and review by trial auditors and monitors, periodic site reporting and reviews, etc.

As in all research that involves human subjects in the US, all participating sites and trial leadership in this research pathway are also governed by an array of federal regulations and oversight agencies. These include governance under the Federal Policy for the Protection of Human Subjects (HHS, 45 CFR part 46), generally known as the “Common Rule,” which requires, among other items, institutional review board (IRB) oversight and informed subject consent for all trials involving human subjects or their information as well as adherence to other aspects of human research subject protection (11). Activities of site physician investigators, research teams, and all other trial management entities are also governed and monitored under federal rules such as federal antikickback statutes, Stark laws, federal false claims acts, and CMS physician payments “sunshine act” reporting (9,10). Trials involving investigational devices or pharmaceuticals will be subject to additional oversight requirements through the U.S. Food and Drug Administration (FDA) (12). Additionally, almost all human clinical trials in the US are required to be registered with and periodically report to the National Library of Medicine/National Institutes of Health monitoring site www.clinicaltrials.gov (2). A full description of the total package of oversight, monitoring, and supervision for multicenter,
protocol-provided clinical trials would constitute one or more entire articles in and of itself, but such oversight and monitoring is extensive and continuous.

There are, as noted earlier, other available pathways for site-based funded clinical research activities. The most common alternative pathway is that of on-site “investigator-initiated” research (termed earlier in this article as the “classic” pathway). For the nonacademic-affiliated, community-based, or regional facility that is just deciding to enter into the clinical research arena or that does not already have an infrastructure-rich research system, this pathway has some significant disadvantages as compared to the protocol-provided trial pathway. Developing an on-site investigator-initiated trial pathway first requires the presence of experienced clinician-scientist investigators who are motivated to develop novel clinical research ideas, mold these novel ideas into a workable trial hypothesis, then advance these into a protocol and budget proposal, document all of this in a rigorous “grant proposal” application process, and finally submit these proposals to a grant-providing organization or foundation (such as the NIH, NSF, or private research foundations) as a grant application for a possible funding grant. This method of research funding is frequently a long developmental process, often covering several years from initiation until a grant application is submitted and then approved or rejected. Also, in the US, only a fraction of grant applications (often as low as 10–20%) are awarded a financial grant (7). The investigator-initiated clinical research pathway requires a highly motivated clinician-scientist investigator (usually an M.D. or M.D.-Ph.D.) who has extensive training and experience in all aspects of clinical research and a history of success in grant writing and grant applications, as grants are more commonly awarded to those investigators who have had previous successful grant applications. These grant-writing clinician-scientist investigators will generally need significant “protected” time during which to develop their research proposal submissions. At a nonacademic, community-based hospital or facility, protected time translates into time in which the clinician is not performing standard of care clinical activities (in essence, being paid to not see patients). The need for funding “protected time” and the large infrastructure (grant-writing and submission, grant acquisition and management, etc.) associated cost requirements are some of the reasons for the high institutional overhead fees that university and “academic” institutions apply to their research trial activities.

Additionally, the types of trials that are created by investigator initiation can vary widely. Such efforts can range from early stage research activities, such as “proof-of-concept” or “pilot” studies, to true “translational” or other early phase projects to later stage efforts. Depending on the research project design, the development and execution of the trial may require input by and participation from other professionals such as biostatisticians, computer programmers, epidemiologists, pharmacologists, geneticists, etc., thus adding additional trial system costs (3). The increased variability of these trial designs can also significantly increase the general infrastructure demands, again adding additional costs to support these varying trial types. Investigator-designed trials also require that the investigator or team that designs the trial be experienced enough in all aspects of clinical research to avoid committing critical mistakes in trial design that can lead to loss of funding and/or nonpublishable data or that the facility have available a knowledgeable feasibility review committee (8) to perform this function (an additional cost and infrastructure requirement). These types of trials, once initiated, can require a lengthy period (frequently many years) from inception to completion with the necessity that the participating team members remain funded throughout this entire
period. Additionally, for facilities that do not have large patient populations with the target disease or condition being investigated, completion may require the additional complication and expense of developing research networking collaborations with other facilities willing to participate in the trial effort.

These issues represent just some of the hurdles involved in developing an on-site investigator-initiated research pathway. Therefore, for the nonacademic community-based or regional hospital without an extensive research infrastructure or an affiliation with an academic medical center that can provide such services, investigator-initiated clinical research activities are probably not an optimal starting point for facilities just entering the clinical research arena. For all of the above reasons, the protocol-provided, pay-for-performance, clinical trial design will frequently be the least infrastructure-demanding, most cost-effective entry point for facilities just starting up a clinical trials team and clinical trials activities.

To summarize, community-based, nonacademic-affiliated medical facilities have historically found themselves unable to develop and support on-site the more “classic” model of investigator-initiated, grant-seeking clinical research trials. There are multiple reasons for this. But overall, the investigator-initiated trial pathway—with its requirements for extensive and specialized research infrastructure to assist with trial creation, development, and management, including an aggressive grant-seeking infrastructure—and the need for specialized physician-scientist investigators with requirements for significant protected non-SOC clinical time make the investigator-initiated trial pathway a poor fit for the nonacademic-affiliated, community-based hospital or medical facility without an established research program. However, the evolution of the protocol-provided model of clinical research, with functional elements very similar to the clinical and business operations of community-based facilities and without requirements for the extensive, on-site specialized research infrastructure as noted above, can potentially provide a much better fit within the operational framework of the community-based, nonacademic medical facility. Since it would seem beneficial for research trials to be able to access broader, more representative cross-sectional patient-subject populations, and since community-based hospital and facility leaders find it desirable for their facilities to be able to offer research trial services to their patient populations, the protocol-provided clinical research pathway is a model that seems worthy of investigation by facilities that desire to develop a new research infrastructure pathway for their facility and their patients.

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REFERENCES