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INVITED MEDICAL REVIEW

Considerations in establishing an oral disease clinical research center

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High quality clinical research is necessary to improve oral health and translate research findings to the practice of dentistry. This has led many academic institutions to consider establishing a formal clinical research center. This is not a trivial undertaking and requires that the center have an appropriate physical infrastructure, trained investigators with recognized expertise in the planning and conduct of high quality clinical research, and very importantly, a financial plan to assure its long-term sustainability. The purpose of this paper is to provide some guidance and practical advice with respect to factors that should be considered in developing and maintaining a successful oral disease clinical research center.

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Introduction

In recent years there has been an increasing recognition that well planned and well conducted clinical research is necessary to significantly advance the practice of dentistry. This research can have a variety of objectives, for example, to investigate the safety and effectiveness of new therapies, to compare the effectiveness of existing therapies, or to facilitate the translation of laboratory findings to clinical practice. The finding of associations between oral diseases and diseases elsewhere in the body has also created a need for prospective, interventional clinical studies to help establish or refute a causal relationship between these diseases. The increase in clinical research activities has been accompanied by the development of more scientifically rigorous study designs and methods of data analysis as well as the establishment of procedures for safeguarding the safety of study subjects.

The increased demand for and visibility of clinical research in dentistry has also nurtured the establishment of formal dental clinical research centers to provide facilities that will accommodate the requisite high level of research. Such centers may be intramural facilities established by governmental agencies or foundations but, more commonly, are centers established within dental academic institutions. It has not always been the case, however, that institutions that have established or are considering establishing a dental clinical research center have appreciated the extent of commitment of space, personnel, and resources required, or have planned for the financial sustainability of the center once it has been built. The purpose of this paper is to provide some guidance and practical advice concerning factors to be taken into account for the development and maintenance of a dental clinical research center. This paper is intended to provide an overview of the subject. While much of the discussion is based on the authors' experience in the United States, the regulatory requirements and standards for the design and conduct of studies cited are derived from a Guideline developed to provide a unified standard for the European Union, Japan, and the United States. Thus, for more detailed information concerning requirements for designing and conducting clinical trials, including such items as investigators' qualifications, human subject protections, data management, and reporting requirements, the reader is referred to the guideline prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (Guideline for Good Clinical Practice., 1996) .

Initial considerations

It is useful to think about the establishment of a clinical research center as having two phases: the first is the allocation of dedicated space and the construction of the

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facility itself; the second is the staffing of the facility and assuring its long-term viability. The decision to proceed with the first phase is generally predicated on the availability of funding sufficient to support construction and is, therefore, usually quite straightforward. It is the second phase that can become problematic, especially when the facility is established within an academic institution. Unlike an intramural research center established by a governmental agency or foundation for which the subsequent operating expenses may be provided for in annual budgets, dental academic institutions may often build clinical research facilities with the intent of attracting funding, especially from industry, that will provide an additional source of revenue for the school. In such cases, sustainability becomes a significant consideration insofar as dental schools generally do not have the funds to provide ongoing operational support for the facility and its personnel. Therefore, they may have established the new facility under the supposition that 'if you build it, they will come' only to subsequently find that they are unable to attract the level of grant support or industry-supported research they had counted on as a new revenue stream. Most frequently, this is because, while the institution might have a state-of-the-art facility and some faculty interested in conducting clinical research, it does not have clinical investigators who are acknowledged experts in the design and conduct of clinical studies and who, therefore, would be sought out by industry to conduct studies on the basis of their accomplishments and reputation.

The role of investigators highly qualified to conduct clinical research cannot be overemphasized as a factor leading to a successful and sustainable research center. The most successful centers have both a breadth and depth of expertise; that is, a critical mass consisting of several investigators in each of several popular disciplines, for example, periodontology, cariology, and oral medicine. While this may present an apparent dilemma for institutions that are considering establishing a clinical research facility but do not yet have investigators with the requisite experience to appeal to industry, it should be recognized that *the conduct of clinical research does not require a dedicated clinical research center*. All successful clinical investigators had to start somewhere. A faculty member interested in developing into a seasoned investigator can participate in courses designed to train clinical investigators to learn elements of study design, data analysis, regulatory requirements, etc. (more about training opportunities to be discussed below) and spend time working with investigators at an established facility to develop skills as a clinical examiner and learn the logistics of conducting clinical trials. With this background, the faculty member can then begin to conduct small studies using existing clinical and laboratory facilities at his or her institution, publish study results and present the research at scientific meetings, and thereby begin to develop a reputation as a clinical investigator. On this basis, it may then be possible to obtain research grants and industry support to conduct larger and more complex studies that will ultimately reach a level that can support a formal clinical research center.

There are additional considerations that an institution should be aware of at the outset. The first is its geographic location, in particular, whether the center would be readily accessible to study monitors. While study monitoring of drug trials is a requirement of regulatory and licensing agencies, companies generally monitor *all* clinical trials and will seek to minimize the travel time, distance and, hence, cost required for monitoring visits. In addition, institutions with high indirect cost rates should be aware that they will be at a disadvantage with respect to equally qualified institutions with considerably lower rates and with commercial contract research organizations.

Research center infrastructure

Clinical facility

The formal clinical research center is a dedicated space developed specifically for this purpose and, ideally, located in a site within the building that is readily accessible to study subjects. If it is anticipated that the majority of study subjects will travel to the center by automobile, it would no doubt facilitate subject recruitment if convenient parking were available as well, although this could be problematic on a university campus. The center's design should take into account the potential requirements for each of the types of studies anticipated and provide for a smooth pattern of patient flow through the facility. A typical dental clinical research center might include the following components:

- Reception area/subject waiting room
- Conference room/subject interview area
- Office space for the center director, clinical research coordinator, and quality assurance monitor
- Work space for subject recruiters, examiners, and study monitors
- Secure, temperature controlled storage facility for clinical supplies
- Secure storage facility for patient records and data
- Minimum of four operatories with dental intraoral imaging capability
- A room in which to conduct medical examinations
- A room for processing clinical specimens, e.g., microbiological, salivary, and/or phlebotomy samples
- A small dental laboratory for the pouring of models, fabrication of *in situ* appliances, etc.
- Instrument sterilization area.

These are meant to be examples of components typically found in a dental clinical research center. The actual configuration will be specific for a given center and will be dependent upon the available space and anticipated use; for example, a room in which to conduct medical examinations might be required for a center that focuses on relationships between oral and other diseases but may not be needed for centers with other emphases.

Personnel

As noted above, the availability of personnel with the appropriate expertise and training is key to the long term success of a clinical research center. For centers located within dental schools, key individuals such as the center director, principal investigators, and study examiners will usually be members of the faculty and have other responsibilities in addition to conducting or administering clinical trials. Similarly, staff members such as research hygienists and dental assistants may participate in patient care elsewhere in the institution. This is particularly true during the early stages of operation of a clinical research center when the volume of studies and level of funding may not be sufficient to support full-time staff. It is not necessarily the case, however, that an excellent clinician will also be an excellent clinical investigator or examiner without training to prepare for these roles. Thus, as part of its commitment to establish a center, it may be necessary for an institution to provide training opportunities for interested faculty in order to establish a core of competent investigators (training and certifying research staff will be discussed in a subsequent section). Personnel required for a mature, fully funded and fully operational dental clinical research center typically include the following:

- Clinical Research Center Director: The individual responsible for overseeing the administration and operations of the Center to assure compliance with all applicable regulatory requirements as well as scientific excellence and efficient use of time and space. He/she should be thoroughly familiar with the basis of sound protocol design and the standards for the conduct of clinical trials specified in the harmonized guideline (Guideline for Good Clinical Practice., 1996), and should have had experience in working on industry-sponsored studies so as to be aware of specific needs of industry.
- Clinical Research Coordinator: A full-time member of the center staff with the responsibility of overseeing the center's operations on a day-to-day basis. This individual should have extensive experience in coordinating industry-sponsored trials as well as trials supported by organizations such as the U.S. National Institutes of Health and the U.K. Medical Research Council.
- Principal Investigators: The individuals responsible for the design, conduct, and reporting of specific studies. They, too, need to have expertise in protocol design, familiarity with the logistics of conducting a clinical trial, and compliance with applicable regulatory requirements.
- Examiners: The individuals responsible for performing the clinical examinations and assessments. They should have the professional credentials and licenses that allow them to work with human subjects. To achieve competence as an examiner requires more than just having knowledge of the disease under study but, rather, involves training in the use of the assessment methods or indices to the point at which consistency and reproducibility in their application is achieved.
- Research Dental Hygienists: Dental hygienists who are knowledgeable in protocol design and the requirements of conducting clinical research.
- Support Staff
    - o Receptionist/Secretary
    - o Dental Assistant(s)
    - o Subject Recruiters
    - o Laboratory technician(s)
    - o Quality assurance monitor

Subject recruiters can play a key role in assuring the success of the research center by assembling needed subject populations in a timely manner and maintaining a data base of subjects suitable for various types of studies. The quality assurance monitor is needed to assure that the facility functions in accordance with all applicable regulatory requirements as well as to assure the accuracy and integrity of the data collected.

Training and certifying research staff

Because clinical research can be very complex, time consuming and expensive, it is critical that the principal investigator, key investigators, and all research staff be trained, and preferably certified, in clinical research. Formal training is becoming a standard for clinical investigators. Study sponsors often prefer to have certified personnel working on their clinical trials because proper execution is dependent on having experienced and qualified investigators and staff. Training and certification also greatly expand career opportunities for clinical investigators and staff.

Courses for principal investigators and other personnel vary from formal master's and doctorate level programs offered at many universities to short online and in-person courses. An example of a short course for investigators and research staff is the annual workshop that is offered in conjunction with the International and/or American Association of Dental Research (IADR/AADR) annual meetings by the Task Force in Design and Analysis in Oral Health Research (http://www.taskforceondesign.org/).

In the U.S., there are a number of opportunities for clinical research staff such as research coordinators, nurses, dental hygienists, and dental assistants to receive training and certification in clinical research. The Association of Clinical Research Professionals (ACRP) and the Society of Clinical Research Associates (SOCRA) are two organizations that provide training and certification. These training and certification opportunities can be accessed online at the websites of these organizations (http://www.acrpnet.org/, http://www.socra.org/) and involves topics such as monitoring to ensure adherence to U.S. Federal Code of Federal Regulations Good Clinical Practice Guidelines, U.S. Food and Drug Regulations, and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guidelines),

completion of case report forms, drug study accountability, informed consent procedures, reporting adverse events, filing and maintenance of required regulatory documents, and other day-to-day activities that are important in maintaining a high quality research environment.

Given the need for clinical trials in a variety of medical disciplines, training opportunities are widely available outside the U.S., as well. For example, the London School of Hygiene and Tropical Medicine offers a postgraduate diploma and MSc in Clinical Trials available by distance learning using the internet.

Human subject protections (good clinical practice)

In planning for and implementing a clinical research center, it is essential that all personnel be fully acquainted with requirements that have been established to assure the safety and wellbeing of subjects participating in clinical trials and that a process be established for the implementation of these requirements. The basis for human subject protections can be found in The Nuremberg Code of 1947, a ten-point statement defining conditions under which medical experiments using human subjects would be permissible (Shuster, 1997). This led to the Helsinki Declaration of the World Medical Association, adopted in 1964 and subsequently amended, which details ethical principles applicable to medical research using human subjects (World Medical Organization, 1996) and is reflected in Good Clinical Practice (GCP) guidelines regulating the proper conduct of clinical trials. Two essential elements of GCP are the review and approval of study protocols by an institutional review board/independent ethics committee (IRB/IEC) and the obtaining of informed consent from participating subjects. The overall role of the IRB/IEC is to review details of proposed studies to safeguard the rights, safety and wellbeing of participating subjects. IRB/IEC approval is required prior to study initiation with review continuing during the period of the trial through the requiring of periodic reports from the investigator. Details concerning the composition, responsibilities, and procedures of the IRB/IEC can be found in section 3 of the Consolidated Guidance (Guideline for Good Clinical Practice, 1996). The requirement of obtaining informed consent is intended to assure that subjects enter the study voluntarily, understand the nature of the study, and know that they can exit the study at any time without penalty. Details concerning informed consent can be found in section 4.8 of the Consolidated Guidance (Guideline for Good Clinical Practice, 1996). Since access to a duly constituted IRB/IEC is a prerequisite for the conduct of clinical trials, planning for a clinical research center should include this as an essential component of the program.

Funding the research center

To be successful, a clinical research center must obtain initial start-up funding and have a plan in place to assure an ongoing stream of revenue for long-term support. All too often, costly clinical research centers are established with the hope of attracting research funding without a realistic assessment of expenses associated with maintaining the facility and personnel costs. Plans for obtaining initial start-up funding and ongoing support are vital for the successful operation of any clinical research center.

There are a variety of funding sources and mechanisms for obtaining support (Pihlstrom and Barnett, 2010). The primary sources for funding clinical research centers include academic institutions such as dental schools, foundations, industry, and the government. Although a research center may conduct research that is exclusively centered on one of these sources of funding, more typically the research reflects a combination of funding resources. For example, a dental school may provide initial start-up funding to support the establishment of clinical facilities and initial salary support for personnel with the expectation that additional support will be obtained from a variety of sources including industry, government or foundations. Institutional or foundation support is usually essential for start-up funding to establish a clinical research center and to provide ongoing 'bridge-funding' during periods when research funding is not available. The importance of a having a plan and firm financial commitments for at least one-year of bridge-funding cannot be overemphasized; it is essential that the physical infrastructure and experienced staff be maintained so that both are available when new funding opportunities arise. Sources of this bridge funding can be an ongoing commitment of the parent institution or university, foundation support, endowments, or profit from industrial research.

Industry and government support is generally only available for specific research projects and not for funding the overall infrastructure and personnel costs of a research center. Government support is available for research that has broad implications for public health and clinical practice while industry support is generally targeted to gaining government approval for marketing devices or drugs, for claim support, or for obtaining professional endorsement by programs under the auspices of national dental associations. Since foundation support is usually limited to funding research that meets a foundation's specific goals, investigators interested in pursuing this funding source should contact foundations that specifically target their area of research.

The main source of government funding for oral health research worldwide is the United States National Institutes of Health (NIH), specifically the National Institute of Dental and Craniofacial Research (NIDCR). All applications for U.S. government funding must be submitted in response to a Funding Opportunity Announcement (FOA) posted on the Grants.gov website (http://www.grants.gov/applicants/find_grant_opportunities.jsp) or the websites of specific granting agencies. Oral health FOAs can be found at three locations: (1) the Grants.gov website, (2) the NIH Guide for Grants and Contracts (http://grants.nih.gov/grants/guide/) and, (3) the NIDCR website (http://

www.nidcr.nih.gov/). Most NIH funding is awarded to U.S. investigators, but the NIH supports research in other countries if resources such as investigator expertise, instrumentation, or patient populations are not available in the U.S and if the findings are applicable to people living in the U.S. Investigators who are interested in obtaining government funding from other countries should consult public health agencies in those countries for funding opportunities.

Government supported research is generally obtained through an investigator-driven grant application process, whereas funding by industry is generally driven by the needs of product development. Accordingly, as noted above, industry seeks to identify study sites that have appropriate expertise and a solid track record of conducting the type of research it needs.

Conducting studies for industry

As noted in the introduction, one of the motivations for institutions to establish a dental clinical research center often is the expectation that it will attract studies from industry and hence serve as an additional source of revenue for the institution. In addition to the requisite personnel, facilities, and regulatory requirements outlined above, there are additional aspects of working with industry that need to be considered in order to establish and maintain a successful research relationship (Barnett, 2002). Some of these that should be considered in developing a clinical research center include the following:

Maintaining confidentiality of study activities

It is important to recognize that the oral care industry is very competitive and, accordingly, make provisions to maintain the confidentiality of each company's activities. This includes not only attention to what investigators might disclose but also to masking specific study activities so that visitors to the center, such as study monitors, will be unable to determine what studies might be underway sponsored by a competitor.

Assuring that appropriate subject populations are available within the promised time frame

The ability to recruit the requisite number of qualifying subjects in a timely fashion is a critical feature of a successful relationship with industry. Companies plan clinical studies to fit into an overall product development time frame with the expectation (and contractual obligation) that they will be completed on the agreed upon date. Therefore, investigators need to provide a realistic projection of the time it will take to assemble the required subject population. It is too often the case that the projections turn out to have been overly optimistic, resulting in a study that drags on long past the expected completion date. This has significant implications as it will upset a company's product development timeline and make the company hesitant to conduct any future studies with the center.

Conducting studies independent of the academic schedule

As noted above, clinical studies for industry are planned in the context of a product development schedule and, moreover, are often of several months' duration. Therefore, if they wish to conduct studies for industry, investigators at a school-based clinical research center should recognize that they cannot be bound to an academic schedule that might include breaks at holiday times and for summer vacation. Clinical trials might be initiated at any time during the year and successful clinical research centers will be responsive to the company's scheduling needs.

Providing adequate work space for clinical study monitors

Investigators conducting clinical trials for industry need to understand the role of study monitors as well as assure that there is adequate work space for the monitors to carry out their assigned duties. The periodic monitoring visits are intended not to influence the results of the trial, as some investigators mistakenly assume, but, rather, are a regulatory requirement to confirm compliance with human subject protections and with the study protocol and record keeping requirements. Details concerning the role of study monitors can be found in section 5.18 of the Consolidated Guidance (Guideline for Good Clinical Practice., 1996).

Establishing a procedure for timely negotiation and approval of research contracts

The days in which a clinical study agreement between a company and an academic site could be concluded with a handshake are long gone. In today's environment, it is necessary to have a contract in place before a study can be initiated. There are few things more frustrating to a company than to have the contract seemingly fall into a 'black hole' at the academic institution with no firm indication of when approval might be granted. Center administrators should assure an efficient procedure for reviewing, negotiating, and approving contracts. Although just one aspect of a clinical research center's capabilities, this is an important factor in establishing the center as a desirable site at which to conduct studies.

It is very important to understand that research contracts and grants are binding agreements between the funding source (e.g. a company or government agency) and the principal investigator's *institution*. As there is some variation between the contractual obligations of grants and those of contracts, investigators must always consult with their university or institutional research office early when developing grant applications or when negotiating with companies for sponsored research. Investigators must have input into certain aspects of the agreement such as the timing of study milestones, subject recruitment, and budget. However, individual investigators should never enter into independent contractual agreements with a funding agency or a sponsor. In fact, independent agreements, whether formal or informal, are generally prohibited by most universities and can result in very serious consequences. In addition, investigators should *never* attempt to bypass their institution's overhead costs or establish private research accounts to fund their research.

Creating credible study budgets for prospective sponsors
Since companies are generally able to estimate study costs based on prior experience, budgets for clinical studies should be based on an approximation of the costs of conducting the study plus a reasonable indirect cost rate. Investigators should avoid the two extremes, that is, presenting an artificially low budget with the expectation that it will help the site 'get' the study or presenting a clearly inflated budget thinking that companies have deep pockets and will not object to the excessive cost. Academic centers need to be cognizant of the impact that their indirect cost rate will have on their ability to attract industry-supported studies. Companies have fiscal restraints and seek to use available research funds in the most effective manner. Therefore, study sites with unusually high indirect cost rates will be at a competitive disadvantage in attracting industry-supported trials.

Summary and conclusions

Since there is clearly an increasing need for well conducted clinical research to advance oral health and expand the field of dentistry, academic institutions may consider establishing a dental clinical research center, both to fulfill this need and to provide an additional source of revenue. This is not a trivial undertaking, however. To be successful, the center must have an appropriate physical facility and investigators with demonstrated expertise as well as a financial plan to assure long-term sustainability.

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