

Careers for Clinician Investigators

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For the purposes of this article, we define clinical research as that form of medical research that involves human beings as the direct subjects of the research at the individual or a population level. The research may involve the study of biological samples (eg, blood, genes, proteins, and tissue) as a means to understand the individual or the group, but the ultimate objective for the clinical investigator is a better understanding of the diagnosis and treatment of human diseases. Many researchers not trained as physicians perform clinical research; eg, many with PhD degrees work in health services research. The limited scope of this article necessitated that we focus on the physician investigator, henceforth referred to as clinician investigator.

Scope of Clinical Research

The process by which our knowledge of new therapies advances from bench observations to proof-of-concept bedside research and ultimately to widespread regular use in community practice is complex, often chaotic, and usually very inefficient, typically involving several decades of time between an important new basic finding and a useful clinical therapy. To help clarify the conceptual steps involved in generating evidence to inform clinical decision making and healthcare policy, we have used concepts borrowed from continuous quality improvement, particularly the cyclical nature of the process (the Figure).¹ In this model, concepts and new therapies born in the laboratory provide translational investigators with new ideas, molecules, biologicals, devices, and diagnostics to test in early-phase clinical experiments. Promising ideas and technologies next move into larger clinical trials to adequately assess efficacy and safety in selected populations. Results from well-done clinical trials provide the evidence base for recommendations in practice guidelines and performance indicators used as quality measures.² Observational research using practice- and disease-based registries helps define the degree to which clinical trial results have been assimilated into clinical care outside the academic medical center setting. All of this activity depends on a cadre of clinical investigators expert in the various methodologies required to perform the research required at each point in the cycle and capable of working as part of a multidisciplinary team.

Career Options

Career options in clinical investigation are as numerous and broad as are the settings in which a clinical investigator might ultimately choose to work. The employment setting is a simple way to categorize careers in that the setting might also be thought of as a way to view different perspectives on similar-sounding research domains. An academic career typically involves being a member of a medical school faculty, with effort devoted to clinical research and clinical practice, and is the “traditional” career model. This model does not apply to many academics at modern universities because they lack the organizational and quantitative knowledge critical to the performance of clinical research. Similarly, many of the top clinical researchers in the world today do not have traditional academic training.

Increasingly, clinicians in private practice devote some of their time and energy to participating in clinical research. In some areas of medicine, including preventive cardiology, some clinicians forego regular patient care to pursue the practice of site-based clinical research. In such a setting, clinicians see only patients who are participating in research protocols. Careers in government service include being investigators within the National Institutes of Health (NIH), as scientists involved with the regulation of medical products in the Food and Drug Administration, or as health policy investigators in agencies such as the Centers for Medicare and Medicaid Services and the Agency for Healthcare Research and Quality. Industry-based clinical research careers focus on medical product development with opportunities to develop expertise in clinical trials or outcomes research.

Career opportunities also may be defined by the methods or tools used to conduct the research, weighted toward either a clinical or a quantitative focus. Opportunities can focus on understanding patients or on broad policy and public health issues. Perspective and context inform these career choices, some of which are listed in Table 1.

Most broadly defined, clinical researchers are physicians, nurses, pharmacists, or those in other clinical disciplines, many of whom have a graduate degree in a field such as epidemiology, bioinformatics, or biostatistics. Some clinicians obtain advanced training, including advanced degrees, in quantitative areas because this expertise is needed across

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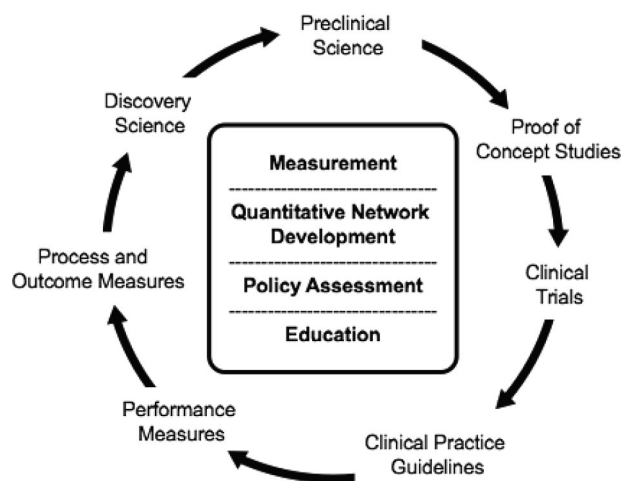


Figure. Cycle of quality. Reprinted from Califf RM. The benefits of moving quality to a national level. *Am Heart J.* 2008;156:1019–1022,¹ copyright © 2008, with permission of Elsevier.

the spectrum of clinical investigation. With or without advanced degrees, clinician investigators must collaborate with researchers skilled in understanding the quantitative underpinnings of research, and serious clinical investigators must be well schooled in the fundamentals of the quantitative issues.

Much of the clinical data available to clinician researchers are derived from actual practice, are usually nonrandomized, and are found in a variety of databases of different levels of completeness and quality. The data were typically collected to guide daily care, to report the details of laboratory tests and clinical procedures (such as catheterization, percutaneous coronary intervention, and coronary artery bypass graft surgery), or to provide information for billing purposes through mechanisms such as *International Classification of Diseases*, ninth revision, coding. Outcomes investigators use clinical data to better understand clinical practice; to measure the implementation of a therapy into routine care; to make associations between adherence to certain types of care and clinical outcomes; to assess adverse effects of drugs and devices in larger, more representative populations than were studied in clinical trials; and perhaps to stimulate practice changes by reporting on how actual clinical practice differs from expected. Health services research has emerged as an

Table 1. Clinical Research Career Opportunities

Public health
Epidemiology
Biostatistics
Bioinformatics
Trial design
Trial coordination
Patient enrollment
Outcomes
Quality of life
Cost-effectiveness
Healthcare policy assessment

Table 2. Critical Elements for Success in Developing and Building a Career in Cardiovascular Clinical Research

Strong faculty mentorship
Didactic training in biostatistics, clinical operations, finance, negotiation, and leadership development
Peer-to-peer interactions
Practical experience in both trials and registries to understand, for example, database creation and management, protocol development, Institutional Review Board applications, data collection, event adjudication, site management, statistics, Data And Safety Monitoring Committee management
Involvement in activities that promote collaboration and altruism in clinical research
Support for grant writing and applications
Dedicated training in writing and presentation skills
Exposure to multiple academic collaborators to build relationships and to enhance interpersonal skills

important avenue of investigation at both the local level, where systems can use their own data to inform practice, and broader policy levels, where examples of best practices can be representatively informative or where assessment of very large data sets (eg, Medicare) can underpin national health-care policies. Economic research, which can be considered a part of either outcomes research or health services research, is critical for assessing the societal value of the investment of healthcare dollars in new drugs, devices, and technologies and for framing policy debates by estimating the economic consequences of policy options such as reimbursement strategies.

Elements of Success

Personal Attributes

After 20 years of training fellows at the Duke Clinical Research Institute, we have found that there are critical elements that favor success in clinical research careers; these include both individual and environmental factors (Table 2). The personal characteristics required for a successful clinical research career include the important attributes of intelligence and curiosity but also perseverance, collegiality, and collaboration. The most successful clinical investigators are frequently busy and good clinicians with a healthy sense of skepticism about current dogma and with the quantitative skills needed to structure research questions. Because clinical trial results often fail to demonstrate what was conventionally expected (eg, hormone replacement therapy as a means to reduce cardiac risk among postmenopausal women), humility and a sense of humor can be valuable personality assets. Being able to articulate, both verbally and in writing, the main messages of one's research is a key element for success; an inability to communicate effectively lessens the impact that even intriguing research results might have. Clinical researchers need to be tolerant of the human condition because trying to integrate research projects into busy clinical practices can be frustrating for those doing the research and those providing the clinical care. Successful clinical investigators encourage and foster collaboration and use their negotiating skills to lead groups to work well together.

Table 3. Didactic Training in Clinical Research: Core Elements

Biostatistics (descriptive, estimation, hypothesis testing)
Principles of clinical research (objectives, hypotheses, population, outcomes)
Clinical trials (protocol, sample size, randomization, end points)
Ethical issues (consent, conflict of interest, regulatory issues)
Research management (budget, finances, project management, regulatory, etc)
Epidemiology

Environmental Factors

Successful clinical investigators can emerge from almost any type of clinical environment, including academic and private practices, but the environment is a critical element to consider if there is to be a steady stream of accomplished researchers arising from the ranks. A culture of research emanates from the most successful clinical research training programs. These programs value research, nurture those who perform it, provide resources for its conduct, and create an environment in which clinical investigation is integrated into the fabric of professional life. This latter point addresses the NIH's Roadmap vision and is one of the purposes of the Clinical and Translational Science Awards program: to "create a definable academic home for the discipline of clinical and translational science at institutions across the country."³

Role of Didactic Training

To become leading clinical researchers, clinicians should obtain both didactic and hands-on training as part of their fellowship. Whether they are involved in observational studies or randomized clinical trials, they must understand the scientific issues surrounding the hypothesis being tested, the ethical and regulatory principles governing human experimentation, and the practical aspects of incorporating research into clinical practice. The leading academic research organizations provide much of this training during fellowship, including education about clinical research methods, courses in the responsible conduct of research, experience with the survival skills required for a successful career, a program of formal mentoring, and applied clinical research opportunities.

The traditional view of clinical research was that clinicians concentrated on being excellent clinicians while collaborating statisticians "ran the numbers." Today, this model, which can still be found in certain medical centers, is no longer viable or appropriate. Performing clinical research without specific training and experience in the field is no more acceptable than deciding to add invasive catheterization or cardiac imaging to one's clinical practice repertoire without the requisite training. Table 3 lists the some of the core elements of didactic training in clinical research. Depending on specific career goals, more advanced training might include coursework in computational genomics, proteomics, and metabolomics; informatics; health services research; health economics; pharmacoepidemiology; and more advanced statistics.

At a minimum, clinician investigators need to understand the ethical foundations on which contemporary clinical research is built, including the protection of human subjects and conflict of interest; the latter topic is of increasing interest in the current environment, as some academic institutions sever

all ties between themselves and industry, as congressional and media investigations target physicians who are accused of being less than forthcoming about their industry relationships, and as the public becomes wary of physicians who declare (or fail to declare) a personal financial relationship with a therapy they are testing or recommending.

Clinician investigators also need an understanding of basic research principles such as appropriate study designs and the use of standard statistical techniques and tools. They must understand how to collaborate as equal partners with quantitative scientists. Course work that focuses on essential quantitative tools is very worthwhile; increasingly, clinicians who are serious about an investigative career take the time, typically during fellowship training or the early years of junior faculty life, to pursue an advanced degree such as a Master's or Doctorate in the broad discipline of clinical research. Less common but of great value for selected individuals is to pursue an advanced degree, including a PhD, in biostatistics or bioinformatics. A Master's in Public Health has been a traditional degree for clinical investigators interested in epidemiology or related quantitative fields.

In addition to formal didactic training that stresses the science of clinical investigation, it is helpful for young clinical researchers to dedicate time to learning the practical issues of research management. These topics include basic finance and budgeting, project management, and personnel management. Those working with industry in the development of drugs and devices would also be wise to gain an understanding of federal regulations governing these areas.⁴ All investigators can benefit from polishing the writing and presentation skills required for grants, proposals, and ultimately the publication of results. Investigators who aspire to research leadership positions should consider additional formal education and training in areas such as negotiation, team building, and leadership.

Sources of Funding

One of the critical questions to be asked by any investigator is, how will the research time and work be paid for? The major sources for clinical research funding are the federal government, largely through the various institutes of the NIH; private industry, largely the medical products industry; professional societies; foundations; and other philanthropic sources.⁵ Researchers should consider all potential funding sources but focus on the ones that are most aligned with their professional interests and expertise. The strategies for securing funding differ according to the specific target funding agency, but all depend on an ability to develop and articulate a reasonable study question and appropriate research methods. Please see "Funding Opportunities for Investigators in the Early Stages of Career Development,"⁶ published previously in this series.

NIH grants are broadly categorized by the type of funding mechanism: individual, investigator-initiated research grants (for example, R01), career development awards (K awards), research training (T programs), and program project grants.^{7,8} The K23 program is designed specifically for early career investigators who seek initial training in clinical investigation. These awards typically provide up to 5 years of funding

for career development and require awardees to devote at least 75% of their professional effort to research. These awards allow young investigators to get started with a clinical research project and usually to acquire formal didactic training under the direction of a more senior investigator or mentor. The protected time for research is critical for the development of a research career, especially given the competing demands of clinical practice. The T32 grants are held by an institution to support the training of investigators during their postgraduate time. For the cardiovascular specialist, T32s held by the fellowship institution may provide salary support for fellows preparing for a career in clinical investigation. The R01 is the prototypical NIH grant program that is used to provide support for a specific research project, including a randomized clinical trial or large observational study.⁹ Unfortunately for clinician investigators, the NIH monies dedicated to the extramural funding of clinical research make up a small minority of overall NIH funding. Even the highly publicized funds dedicated to the NIH Roadmap's Clinical and Translational Science Awards amount to only $\approx 1\%$ of the total NIH budget.¹⁰

The American Heart Association is an excellent source of funding for cardiovascular investigators, including new researchers.¹¹ In addition to granting funds for specific research projects, the AHA provides funds to support fellows during their research training and, importantly, offers the Fellow to Faculty Transition Award. This award, similar in intent to the K23 award from the NIH, allows the new faculty member to protect a significant percent of professional effort in an attempt to build a clinical research career. Typically, these awards are for the first 3 to 5 years of faculty time after a cardiovascular fellowship.

The American College of Cardiology (ACC) offers the chance to compete for young investigator awards, most notably the ACC Foundation/Merck Awards, which provide funding for research training and project support during the fellowship years.¹² The ACC also supports several other awards for young investigators, including awards in designated areas such as preventive cardiology, imaging, and women's cardiovascular health.¹³ Additionally, the registries maintained through the National Cardiovascular Data Registry can be a rich source of research material for young investigators working through the ACC.¹⁴

Federal agencies such as the Agency for Healthcare Research and Quality,¹⁵ the Centers for Disease Control and Prevention,¹⁶ the Department of Veterans Affairs,¹⁷ and the Department of Defense¹⁸ are all alternative and very appropriate governmental sources of funding for cardiovascular clinical investigators. Many of their programs are limited in scope, but paying attention to requests for proposals and applications from each of these agencies can provide interested investigators with important peer-reviewed funding opportunities. Likewise, disease-based foundations or philanthropic groups may issue requests for proposals and applications for research grants that are consistent with the missions of their individual organizations.

Most clinician investigators have an interest in novel medical products, including drugs, biologicals, and devices used to diagnose and treat patients who have a variety of

cardiovascular diseases. The medical products industry invests a large amount of time and money in the process of product development as a means of gaining regulatory approval, expanding product label indications, or trying to better understand the appropriate use of their product. Funding opportunities are available by participating as an enrolling center in clinical trials. Investigators typically contract for and are paid to provide specific activities detailed in a protocol. These funds should cover the expense of performing the work required, including hiring a study coordinator at some percent effort, protocol-driven laboratory tests, and other study-related expenses.

The "hands-on" conduct of research has been called site-based research to recognize that the research involves more than an investigator and a subject. Setting up a local organization that can efficiently perform site-based research is a critical skill for the young clinical investigator. There may be funding opportunities through industry to perform substudies within larger studies and some small single-center efforts. Although applying for these funds may not include the peer-review application process, investigators typically need to put forward their proposals in the form of a hypothesis or research question and an associated study design. These applications are usually reviewed within an individual company, but increasingly, industry sponsors are looking to outside experts to review grant applications. A number of young investigator awards sponsored by the industry may provide salary and project support for 1 to 3 years. These awards are usually peer-reviewed applications and may even include a competition involving a presentation to academic leaders in the particular area of interest.

Within cardiovascular medicine, a modest number of academic institutions have developed the infrastructure to support clinical research coordinating centers capable of developing research protocols, coordinating multicenter research activities, analyzing results, and disseminating the information through presentations and peer-reviewed journal publications (a partial listing of such centers is given in Table 4). Faculty working within these academic research organizations may seek funding from either public or private sources, but a key differentiating feature of the academic research organization (compared with the commercial contract research organization) is the independence required from the industry sponsor in the analysis and interpretation of the data and the reporting of results. As technology infrastructures improve through the use of Web-based information platforms, more emphasis can be placed on building academic research organizations within academic health centers and multinational networks of academic research organizations that can collaborate with industry sponsors in conducting large-scale clinical investigation rather than relying on the for-profit contract research organization industry, which has no imperative to either advance the clinical science or publicly share research results.

Formulating Research Questions

The best clinical investigators are active clinicians who identify from their own practice pressing unanswered questions and are capable of formulating those questions into a

Table 4. A Sampling of Global Academic Cardiovascular Collaborators

Canadian VIGOUR Center, Edmonton, Alberta, Canada
Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, Ohio
Duke Clinical Research Institute, Durham, NC
Estudios Cardiológicos Latino América, Sante Fe, Argentina
Flinders Coordinating Centre, Adelaide, Australia
Greenlane Coordinating Centre, Auckland, New Zealand
Henry Ford Hospital, Detroit, Mich
Leuven Coordinating Centre (LCC), Brussels, Belgium
Mayo Clinic, Rochester, Minn
McMaster University, Hamilton, Ontario, Canada
Montreal Heart Institute, Montreal, Quebec, Canada
National Health and Medical Research Council, Sydney, Australia
New York University, New York, NY
Nottingham Clinical Research Ltd, Nottingham, United Kingdom
Singapore Clinical Research Institute, Singapore
Thomas Jefferson University, Philadelphia, Pa
TIMI Study Group, Boston, Mass
Trials Argentina Group Organization, Buenos Aires, Argentina
Uppsala Clinical Research Center, Uppsala, Sweden

research program. Clinical researchers with an appreciation of everyday practice should also be very insightful about the practical aspects of integrating research protocols into routine care. Broadly, clinical research questions can be approached using the tools and methods of observation, controlled experiment, or both.¹⁹

An increasing number of clinical practices today have electronic databases of patient information, and many practices participate in national registries such as the National Cardiovascular Data Registry and Get With the Guidelines. These databases can provide the opportunity for researchers to examine questions relevant to routine practice that would be difficult or even impossible to study with a randomized clinical trial. For example, what is the association between evidence-based prescribing and mortality among patients with non-ST-segment elevation acute coronary syndromes?²⁰ Using local databases such as a cardiac catheterization database allows clinical investigators to quickly obtain preliminary information on timely topics for which randomized trials have not yet been performed.²¹ These initial studies can then serve as the basis of the hypothesis-testing randomized clinical trial.

Observational studies have the advantages of most accurately reflecting routine clinical patients and practices and of being less costly than randomized clinical trials. They can be less reliable as a means of comparing therapies that have not been tested in a randomized trial because it is not possible to be certain that all treatment selection bias has been controlled in the analysis. On the other hand, observational studies are typically performed rapidly (assuming the data have already been collected for some other purpose), provide insights into broad patient populations and practice patterns, generate preliminary information (hypothesis-generating) about therapeutic comparisons, track the adoption of new therapies and

techniques, and provide insight into unusual side effects of therapies, particularly among groups of patients who may have been excluded from randomized clinical trials.

The randomized clinical trial is the best research tool when an investigator is interested in directly comparing the outcomes (both positive and negative) of a therapy (drug, biological, or device) or an intervention with a different therapy, intervention, or placebo. Randomization is used to balance the groups and to reduce the likelihood of bias in treatment selection.

An area of investigation that is growing in importance and popularity is quality and practice improvement.²² Investigators working in these areas, commonly thought of as the second block of translation (T2 block), are interested in moving from the “what to do” questions that have been put forward, eg, by practice guidelines, to the “how to do it” questions of implementation. Examples of research being conducted in this area include projects centering on the timeliness of reperfusion therapy for acute myocardial infarction. National efforts involving both the AHA (Mission Lifeline) and the ACC (Door to Balloon) coordinate endeavors among multiple investigators. There are also examples of local efforts involving cities, regions, and states.^{23–25}

Challenges and Opportunities

Although there are many challenges for cardiovascular fellows considering a career in clinical investigation, there are opportunities as well. Among the challenges that make it difficult to recruit and retain talented research professionals are the clinical cardiovascular workforce shortage,²⁶ the requirement for additional time for research training, the accrual of substantial educational debt, and salary disparities between academic and private practices. For clinical investigators who also spend time in clinical practice, the competing demand of generating clinical volume and income is apparent in both the university and private practice settings.

Medical school education in the United States typically leaves a student ill prepared for understanding the quantitative issues of clinical practice, including an appreciation of the need for evidence rather than reliance on pathophysiologically based reasoning. Fellowship programs have a limited amount of time available for dedicated research. This crucial period is further threatened by the desire to increase clinical training in newer techniques such as multi-modality imaging and the care of patients with advanced heart failure. Because there are fewer training dollars from the clinical practice at universities, months devoted to research are further curtailed, and clinical training time is expanded. Mentors for clinical investigators are in short supply during residency and fellowship training, and those who are available to mentor are under pressure to produce clinical revenue, reducing the time they are able to devote to developing the next generation of investigators. The increasing salary disparity between academic and private practice also contributes to the exit of faculty, especially early- and mid-career faculty, from the ranks of available academic mentors.

The commercialization of clinical research, including the rise of for-profit contract research organizations, has raised serious questions about the ethics and organization of clinical

research.²⁷ Clinical investigation should focus on advancing medical knowledge and improving health care. Although a profit structure that encourages innovation is critical to the development of new medical products, a research system that views the sale of research services as the endgame warrants serious societal conversation.

Conclusions

Despite all these challenges, however, prospects abound for talented cardiovascular fellows who wish to commit to a career in clinical research. The explosion in biological understanding has created almost limitless opportunities for curious, motivated, passionate investigators to take new knowledge and move it into the clinic and eventually into populations through the conduct of clinical investigation. Few careers in cardiovascular medicine are more satisfying than one that takes a clinical observation or problem and then carefully unravels it and tests hypotheses to understand how knowledge might be advanced. Bringing to our patients new therapies or technologies that have been proven through clinical trials to have value is enormously satisfying. In this brief overview, we have provided some guidance on how we view the process of training and early career development for clinician investigators.

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Disclosures

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