SPECIAL CONTRIBUTIONS

Research Fundamentals: I. Getting from Hypothesis to Manuscript: An Overview of the Skills Required for Success in Research

LAWRENCE M. LEWIS, MD, ROGER J. LEWIS, MD, PHD, JOHN G. YOUNGER, MD, MICHAEL CALLAHAM, MD

Abstract. This is the first in a series of articles developed by members of the Society for Academic Emergency Medicine (SAEM) Research Committee. The purpose of this series is to describe a stepwise approach to research, from the inception of a hypothesis to the final publication of a report. This series is written for junior academic emergency physicians (EPs), as well as nonacademic physicians who have an interest in research. This first article presents an overview of the steps involved in performing research and publishing the results, emphasizing the initial steps and the importance of collaboration. **Key words:** research; concepts; hypothesis development; model selection; publication. ACADEMIC EMERGENCY MEDICINE 1998; 5:924–929

GETTING STARTED

In 1988, the Institute of Medicine (IOM) was commissioned by the National Institutes of Health to attempt to identify roadblocks to clinical research.[1] The initial report led to subsequent studies that identified 3 major impediments to initiating clinical research[2]: 1) inadequate training; 2) insufficient time; and 3) inadequate funding. Whether one is a junior faculty member or a more senior EP first entering the research arena, these roadblocks to becoming a productive researcher are common and formidable.

Some investigators are fortunate enough to have received training in the disciplines required for their particular area of research. For young emergency medicine (EM) academicians, research fellowships offer an important opportunity to spend an extended period of dedicated, protected time learning the fundamentals of biomedical research. Several established programs recruit fellows each year, and many EM residencies offer 1- or 2-year training opportunities following residency for individuals interested in developing their research tool kits. It is frequently possible to supplement these focused research experiences with formalized education resulting in an advanced degree. In addition, the early years spent in research training represent an invaluable opportunity to accumulate a body of preliminary data in one's area of interest, a critical prerequisite for the pursuit of extramural funding. Recognition of the importance of dedicated research training led SAEM this year to initiate the Resident Research Year program, one important source of extramural support for the burgeoning investigator.

Regardless of one's prior research training and experience, identifying a mentor is of paramount importance. Mentors help teach necessary skills and often provide support and guidance during an investigator's early development. A good mentor has been described as one who is knowledgeable and influential in his or her field, willing to share, patient, understanding, accessible, willing to commit time, and genuinely interested in the professional development of the protégé.[3]

If there is not a suitable mentor available at your own institution, consider spending time at a center where one is available. The goals of these

From the Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO (LML); the Department of Emergency Medicine, Harbor–UCLA Medical Center, Torrance, CA (RJL); the Department of Emergency Medicine, University of Michigan Medical Center, Ann Arbor, MI (JGY); and the Division of Emergency Medicine, University of California, San Francisco, San Francisco, CA (MC).
Series editor: Roger J. Lewis, MD, PhD, Department of Emergency Medicine, Harbor–UCLA Medical Center, Torrance, CA.
Received April 23, 1998; accepted May 1, 1998.
Address for correspondence and reprints: Lawrence M. Lewis, MD, Director, Emergency Medicine Division, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8072, St. Louis, MO 63110. Fax: 314-362-2495; e-mail: llewis@imgate.wustl.edu

mentoring relationships are similar to those of a fellowship training program, but are more focused and of shorter duration. These "mini-fellowships" can help teach many of the requisite skills for a particular area of investigation. They should allow time to perform pilot studies and to generate preliminary data to help procure funding for future studies.[4] For the junior investigator requiring more in-depth preparation, several academic institutions sponsor full-scale research training programs specifically focusing on patient-oriented research.

Making Time

The second major impediment to research is insufficient time. It takes time to develop the necessary skills required for research, but it also takes time to perform high-quality, meaningful research projects, particularly those involving clinical trials.[2] How to protect adequate time for research, particularly in a specialty as clinically demanding as EM, is a daunting task.

Given the fact that most faculty salaries in EM are paid by clinical revenue, it is unlikely that one can significantly decrease clinical obligations without obtaining funding to offset the cost. One way to obtain some protected time for research is to request the chair or division chief to unburden the investigator from all nonclinical responsibilities. Minimizing lecture load, avoiding administrative tasks, and keeping meetings to a minimum could provide 25% to 30% protected time (based on 28 clinical hours per week and a rotating schedule). Although this may be adequate to initiate a research project, it is not enough time to fully develop an active research program. The only way to obtain sufficient time to be a highly productive investigator is to resolve the third problem of inadequate funding.

How best to structure the time available for research is another important consideration. Some projects can be reasonably accomplished on a 1-day-a-week scheduled routine, others cannot. The type of research project, the availability of special space or equipment, and the need for ancillary personnel all must be considered when scheduling research time. Even the earliest planning phases often require blocks of time to allow reading and thought, unfettered by other concerns and responsibilities. How each investigator decides to structure his or her research time depends on personal preference. It is important for everyone, including EM faculty and outside faculty members, to recognize that tangible results will not occur overnight. A significant investment in time must be made "in good faith" for those with an interest in research and the potential for success.

For optimum utilization of time, the members of the research team should meet to plan out the timetable and agree on the schedule. The principal investigator should assign tasks, along with a preferred completion date, to each member of the research team. One needs to plan for the time required to obtain approval for a proposed study from the required committees, regulatory boards, or agencies, such as the institutional review board (IRB), the animal care committee, or the Food and Drug Administration.

It is a good idea for a senior investigator to periodically monitor progress to ensure that there are no obvious problems impeding the study and to detect unexpected difficulties, such as poor patient enrollment or difficulty collecting complete or accurate data.

Inadequate Funding

The third obstacle to getting started is insufficient funding. There are several causes for lack of funding for clinical research, not the least of which has been a longstanding disproportionate level of funding for nonhuman research at the federal level.[2] Being creative in searching for nontraditional sources of funding and being thorough and timely in reviewing information regarding the availability of grants from traditional sources are important. EM research has traditionally been more likely to be funded through industry and foundations than through federal grants, although a recent survey conducted through SAEM showed that EM investigators have an excellent success rate when they submit applications to federal funding agencies. Intramural funding, especially for pilot or initial studies that have merit and potential for leading to extramural funding, is often available.

Choosing a Question

Choosing a question or problem for investigation often precedes all else, including obtaining protected time. Although this initial step may occur in an almost whimsical fashion, it is a key aspect to meaningful research and as such should receive considerable thought. Selection of the research question will be the subject of an article in this series. The research question posed will often dictate the method of study, the time frame, and the types of resources and personnel required. Five questions should be considered when regarding a research proposal.[5] Is the researcher interested enough in the question to endure the trials and tribulations often encountered in the pursuit of an answer? Is the question of general interest and would the study be relevant to others? Are the time, expertise, and resources available to perform

the study? Can the study be performed ethically? Has the question been asked and answered satisfactorily by others?

This last question brings up the often tedious but necessary step of performing a complete literature search *before* designing and embarking on a research protocol. This serves several purposes besides the obvious one of making certain that the study question has not been thoroughly answered previously. It may also provide information regarding methodology for performing the experiment. If, for example, one wants to study the effectiveness of a new analgesic, reviewing other studies that have evaluated pain relief could provide insight into the preferred scaling systems currently in use.

A thorough literature search can also identify certain individuals or centers with considerable expertise in the area of interest. It is worthwhile discussing the proposal with these individuals to obtain insight not available from reading the literature. Finally, an initial research question may become better defined and appropriately modified based on information gleaned from a search of the pertinent literature.

A sixth question often considered during the selection of a research project, especially among investigators whose salaries are dependent on obtaining grant support, is what funding is available? A researcher in an area that is "hot" in terms of funding is more likely to acquire grant support than one in an area that is currently out of vogue. How does an investigator find where the funding is? One method is to read what has made the list of national health priorities. Federal funds are preferentially allocated to these areas. The *Federal Register* and other services keep the researcher informed of specific funding priorities and programs.

Steering one's research along the political tides can be tricky, since the time required to do research in an area could eclipse the time period in which it is favored. Nevertheless, there are academic divisions at many medical schools whose research success is at least partially a result of asking this sixth question first.

Choosing an Experimental Model

The best experimental model to answer a question will, to a large degree, be determined by the study question itself, and by the individual expertise and collective resources available at the institution. Thus, the choice between bench research, animal research, or human studies might be dictated by whether the question is best studied in an isolated and more controlled fashion or whether whole organ or systemic effects are required.[6] The decision regarding conducting an animal vs a human trial is based on safety issues and whether an adequate animal model to study the particular question can be designed.[6]

Even after choosing one of these 3 major methodologies, there remain a large number of considerations regarding the best model. An example of how the particular experimental model affects the outcome can be seen in animal hemorrhage research. The early animal model of controlled phlebotomy, followed by fluid resuscitation with no further bleeding,[7,8] leads to very different conclusions regarding the effects of fluid resuscitation than does the current model of continuous hemorrhage during fluid resuscitation.[9,10] In human clinical trials, determining the most appropriate methodology for a particular study can be equally vexing.

Collaboration

At some point during the process of choosing a question or determining the optimal study design, the prospect of collaboration may arise. There are several reasons why collaboration should be encouraged. A multidisciplinary approach to research brings a wider perspective and a greater degree of expertise.[11] Collaboration with investigators from other specialties within one's own institution may lead to increased collegiality, which can spill over into clinical and administrative areas. Also, many of the well-established disciplines have seasoned investigators and significant resources at their disposal, which are often not available to junior or even senior EM investigators.

Collaboration consists of virtually any cooperative effort among individuals and can occur with experts both inside and outside of EM. The first step in planning a collaborative study is to clearly think through what types of collaborators might be desired, and what contributions each type of collaborator might make to the project. Think of all the disciplines that might aid in the proposed study. For example, statisticians can help with determining the required sample size and planning the final data analysis. An expert in psychometrics can help design rating scales for patient use. Also, consider individuals in your own specialty who might bring something positive to the project. Create a list that includes each kind of expert who might make the study better.

Collaborating with experts from many different areas brings a wealth of interactive information to the table, and can help avoid methodologic pitfalls, which may otherwise occur. It is painful to discover, after the study is over, that the methodology chosen is recognized to be outdated or flawed. Widely collaborative efforts may also increase the opportunity for funding and publication. Clinicians involved in bench research should consider collab-

orating with a basic science researcher, not only for additional expertise, but also to help keep the project going during periods of heavier clinical responsibility.

Potential collaborators may be found through colleagues, by reviewing the pertinent scientific literature, by attending lectures, or by consulting faculty directories. Internet discussion lists and the list of award recipients at the grants and contracts office may also be useful. After developing a list of possible collaborators, one should provisionally define each collaborator's role. Who will be the principal investigator? Who will be the first author? Who will help to write the manuscript and who will review it? Who will control the data? If these things are not clear from the start, they are unlikely to become more clear with time.

After each collaborator's role is provisionally defined, the principal investigator should approach each individual with whom collaboration is desired to determine his or her interest in the proposed project, what skills he or she has to offer, how much time he or she has to contribute, what he or she wants in return, and whether the principal investigator's and the collaborator's personal styles are compatible. Many different arrangements are acceptable, so long as they suit everyone's needs in a fair way. The rules for the collaboration, including each investigator's responsibilities and authorship,[12] should be dealt with fairly and communicated clearly from the very first meeting. Since experience and perspective are useful in judging the fairness of a collaborative arrangement, it is good to find a mentor with whom to discuss the planned arrangement, both for scientific merit and for academic fairness.

Once a fair collaboration is organized, some additional work on the part of the principal investigator will help ensure that openness and fairness are maintained. Make sure each key collaborator understands and is comfortable with his or her commitment, expected contribution, and expected recognition. Summarize all this briefly on paper, recognizing that things can change as the project evolves. The most important point, on which agreement should be sought early, is who will be in charge of making final decisions should things change. What if one participant doesn't contribute much at all? Someone should have the last word, and everyone should agree to this in advance. It need not be formal or legalistic, but it helps if everyone has the same expectations from the beginning.

Collaboration with residents and medical students should be held to the same criteria for fairness as are other collaborative relationships. But there is another, equally compelling concern when collaborating with students or residents. As senior investigators in EM, we must maintain and communicate the highest ethical standards in our research; including honesty, respect for others, scholarly competence, and stewardship of resources.[13]

FINE-TUNING

The stage is now set to fine-tune the study plan. Procuring necessary space, support personnel, and equipment, and developing a budget for the study should take place at this stage. The entire research team should meet, and the principal investigator should delegate responsibilities to each team member. The group should talk through the planned study procedures to uncover previously unrecognized problems. These steps are important for detecting potential difficulties, whether in a clinical trial, a study using an animal model, or a bench research project.

Before the project can be started, the proposal must be submitted to the appropriate oversight committee(s) and approved. In the case of human clinical trials, this is usually the IRB or human studies committee. Animal studies are usually referred to an animal care and use committee. If the project requires the use of hazardous materials or various drugs or devices, there are usually additional agencies or committees that must approve the project.

Sadly, history has shown a great need for such oversight,[14-16] but the experience of working with such committees can be frustrating. It is frequently useful to approach someone on the appropriate committee prior to finalizing the design of the project, to obtain advice on whether the study design will likely be approved or ought to be modified. This can save an enormous amount of time and energy.

When filling out application forms, follow the directions. Be simple, specific, and complete. Make yourself available to answer any questions and, if additional information or specific revisions are required, respond promptly with exactly what is asked for, no more and no less. If the recommended changes might jeopardize the scientific quality or feasibility of the project, call the committee chair and discuss the issues directly with him or her.

Once approval by the required committees or agencies is obtained, walk through the experimental protocol to make certain that it works. Pilot studies are particularly helpful in animal studies or investigations requiring models of injury or illness where they may demonstrate that certain parts of the protocol require revision. If revisions are required, another pilot study should be performed until the research team is convinced of the feasibility of the protocol. Any nontrivial revisions

must be communicated to the committee(s) that approved the study.

Data Acquisition and Analysis

The methods of data acquisition, the actual data points to be measured, and the data collection forms themselves should be agreed upon prior to performing the experiments. The data to be collected should be highly structured, consisting of numerical values or discrete categories. Free-form text or "fill-in-the-blank" information is almost impossible to analyze, and little or no such information should be put on the data collection form. In all but the smallest studies, the data should be stored in an electronic database program. Although spreadsheet programs can be used for small databases, this should not be done in studies involving an appreciable amount of data. In general, the statistician who will analyze the data should be involved in the design of both the data collection form and the database.

The planned data analysis should be developed in collaboration with a statistician prior to initiating the study. In fact, for good reason, many statisticians are reluctant to be involved in data analysis when they have not had prior input into the study. Poor study design cannot be corrected by good data analysis. It is important to define 1 primary endpoint. Although tempting, measuring every possible data point and looking for possible relationships after the experimental period is over should be strongly discouraged. This type of data snooping or dredging can be very misleading,[17] yielding unexpected and inexplicable relationships in the data that are unlikely to be real. Another important step in which a statistician's input is often necessary is determining the appropriate sample size. An adequate sample size will help to prevent type II errors from occurring.[18,19]

Data preservation is also important to consider at this point. All data sheets, consent forms, and computer data should be kept for at least 7 years after publication, and longer for studies that involve children.

Manuscript Preparation

Once the study is complete, the data are collected, and the results are analyzed, the study is ready for presentation. This may be accomplished in an oral abstract presentation, in written form, or both. A future article in this research series will be devoted to manuscript preparation and submission. Even if you have completed a high-quality study, it is important to prepare the manuscript in a style consistent with the journal in which you desire to publish and to submit to a journal whose readership will be interested in your results. When in doubt, be succinct. It is also useful to have a more senior faculty member critique the manuscript prior to submitting it. Pay attention to reviewers' comments, address them directly, and don't take them personally. In most cases the manuscript is substantially improved as a result of the review process.

Judging the Quality of Research

What defines "success" in research? The definition probably depends on your perspective. One measure of success is obtaining a satisfactory answer to the research question. To a first-time author, success might mean getting the manuscript accepted for publication, and many academic centers use the number of publications as a benchmark of success. Where the articles are published and the number of citations they receive are other markers of success.

Grant support is another tool used to measure success in research. Large grants have the additional benefit of making others aware of this success. This awareness reaps additional benefits, which help to ensure continued success, in much the same way a successful athletic program attracts money and talent and becomes self-perpetuating.

What is good research? Is it any research that increases our knowledge base? In the final analysis, any research that enhances our ability to prevent illness or injury, to improve the quality or decrease the cost of care, or to improve the lives of our patients should be considered great research.

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Statistical Methodology: VI. Mathematical Modeling of the Electrocardiogram Using Factor Analysis

DAVID M. SCHRECK, MD, MS, VICTOR J. TRICARICO, MD, JOSEPH D. FRANK, MS, LAWRENCE E. THIELEN, BS, PARAG CHHIBBER, CRISTIAN BROTEA, IAN B. LEBER, MD

Abstract. The ECG is a 12-lead-vector system and is known to contain redundant information. Factor analysis (FA) is a statistical technique that improves measured data and eliminates redundancy by identifying a minimum number of factors accounting for variance in the data set. **Objective:** To identify the minimum number of lead-vectors required to predict the 12-lead ECG. **Methods:** A total of 104 ECGs were obtained from 24 normal men, 22 normal women, and 28 men and 30 women with variable pathologies. Each ECG lead was simultaneously acquired and digitized, resulting in a voltage–time data array stored for mathematical analysis. Each array was factor-analyzed to identify the minimum number of lead-vectors spanning the ECG data space. The 12-lead ECG was then predicted from this minimum lead-vector set. ANOVA was used to test for statistical significance between normal and pathologic data groups. **Results:** FA revealed that 3 lead-vectors accounted for 99.12% ± 0.92% (95% CI ± 0.18%) of the variance contained in the 12-lead ECG voltage–time data for all 104 cases. There were no statistically significant differences between men and women (99.25% ± 0.66% vs 98.98 ± 1.11%; p = 0.139). Statistically significant differences were noted between normal and acute myocardial infarction ECGs (99.5% ± 0.27% vs 98.66 ± 1.25%; p = 0.00003). The measured and predicted leads were almost identical. A 3-dimensional spatial ECG derived from the 3-lead-vector set resulted in variable curved surfaces that differed by pathology. **Conclusions:** The 12-lead ECG can be derived from only 3 measured leads and graphed as a 3-D spatial ECG. This type of data processing may lead to instantaneous acquisition and may enhance the diagnostic capability of the ECG from routine bedside telemetry equipment. **Key words:** mathematical modeling; electrocardiogram; factor analysis; statistics. ACADEMIC EMERGENCY MEDICINE 1998; 5:929–934

From Muhlenberg Regional Medical Center, Plainfield, NJ (DMS, VJT); Robert Wood Johnson Medical School, New Brunswick, NJ (DMS, IBL); and Stevens Institute of Technology, Hoboken, NJ (DMS, PC, CB). Current affiliations: University of Pittsburgh School of Medicine, Pittsburgh, PA (IBL); and University of Medicine and Dentistry of New Jersey–Newark, Newark, NJ (CB).
Series editor: Roger J. Lewis, MD, PhD, Department of Emergency Medicine, Harbor–UCLA Medical Center, Torrance, CA.
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Address for correspondence and reprints: David M. Schreck, MD, MS, 80 Division Avenue, Summit, NJ 07901. Fax: 908-522-0596; e-mail: schreck@idt.net